NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Patient access scheme submission template

October 2009

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If manufacturers and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a patient access scheme as part of a technology appraisal, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal' (www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp)
- 'Specification for manufacturer/sponsor submission of evidence' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.jsp) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the technology appraisal process, please see NICE's 'Guide to the single technology appraisal (STA) process' and 'Guide to the multiple technology appraisal (MTA) process' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp). The 'Specification for manufacturer/sponsor submission of evidence' provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the 'Guide to the methods of technology appraisal' (www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp).

If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the technology and the disease area to which the patient access scheme applies.

Tecfidera® (dimethyl fumarate) for the treatment of adult patients with relapsing-remitting multiple sclerosis (RRMS).

3.2 Please outline the rationale for developing the patient access scheme.

The objective of the PAS is to make Tecfidera (dimethyl fumarate) available to MS patients in a manner that will be cost effective to the NHS. To achieve this in the simplest way with the minimum of administrative burden to the NHS, patients and Biogen Idec a simple, confidential discount applied at the point of invoice was chosen (a Simple Discount PAS).

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

Simple Discount PAS

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

Scheme applies to the whole licenced population for Tecfidera - adult patients with relapsing-remitting multiple sclerosis (RRMS).

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for

example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

Not applicable – there are no criteria.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

All patients – there are no criteria.

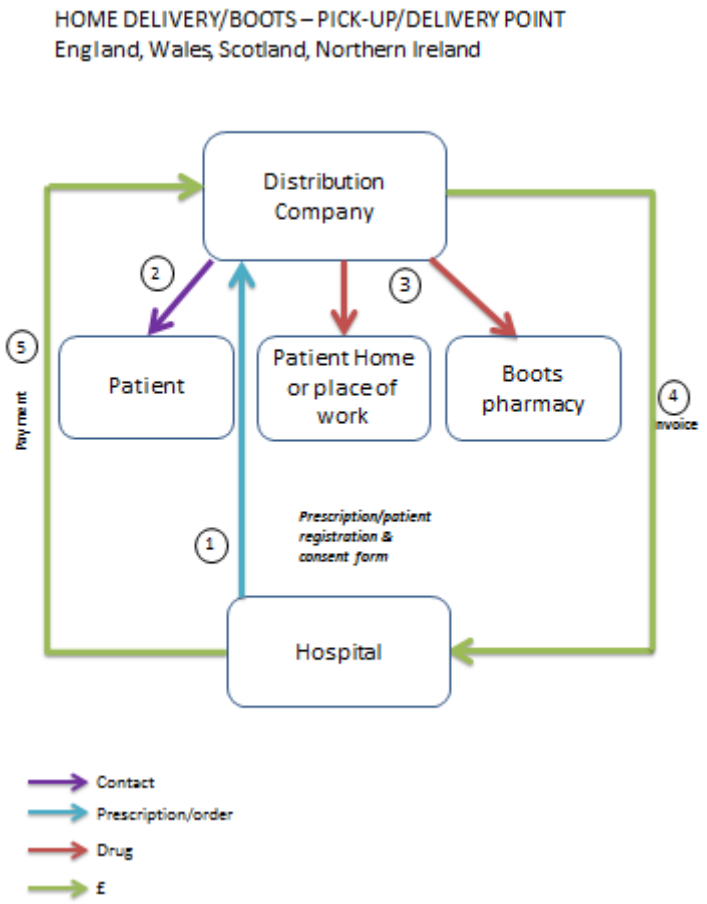
3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

All Tecfidera will be supplied at a discounted price on the original invoice. No rebates are involved.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

No additional administration is required. All Tecfidera will be supplied at the agreed PAS price on the original invoice.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.



3.10 Please provide details of the duration of the scheme.

Until Tecfidera advice is reviewed by NICE.

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

No there are not.

3.12 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

No additional paperwork is involved over and above what would be required to order the drug without a PAS. A simple discount is applied to the original invoice.

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

The population is the same as in the main submission.

4.2 If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

Not applicable – the PAS is being submitted at the start of the TA process.

4.3 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

No changes are required in the structure of the economic model. PAS versus List Price comparisons are made simply by changing the acquisition price. No other costs change.

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

Not applicable. This is not an outcomes based scheme.

4.5 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 6.5 of the 'Specification for manufacturer/sponsor submission of evidence'.

Table 1: Costs associated with the implementation and operation of the patient access scheme (PAS)

	Calculation of cost	Reference source
Stock management	**None**	
Administration of claim forms	**None**	
Staff training	**None**	
Other costs…	**None**	
…		
…		
Total implementation/ operation costs	**None**	**Costs are exactly the same as they would be without a PAS.**

4.6 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

Table 2: Additional treatment-related costs for the intervention both with and without the patient access scheme (PAS)

	Intervention without PAS		Intervention with PAS		Reference source
	Unit cost (£)	**Total cost e.g. per cycle, per patient (£)**	**Unit cost (£)**	**Total cost e.g. per cycle, per patient (£)**	
Interventions					
Monitoring tests					
Diagnostic tests					
Appointments					
Other costs…					
…					
…					
Total treatment-related costs					**All costs are the same with or without the PAS**

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

A suggested format is shown below (table 3).

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

Table 3: Part 1 - Base-case results (list price)

Technologies	Total			Incremental (dimethyl fumarate vs comparator)			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
SC IFNβ-1a 22 µg (Rebif® 22 µg)	£234,103	17.00	5.47	£35,695	0.02	0.26	£142,283
Glatiramer acetate (Copaxone®)	£234,547	17.00	5.50	£35,250	0.02	0.23	£159,295
IM IFNβ-1a 30 µg (Avonex®)	£239,460	17.01	5.50	£30,337	0.01	0.23	£136,452
SC IFNβ-1b 250 µg (Betaferon®/ Extavia®)	£240,159	17.00	5.45	£29,639	0.02	0.28	£106,127
SC IFNβ-1a 44 µg (Rebif® 44 µg)	£242,290	17.01	5.50	£27,507	0.01	0.23	£122,105
Dimethyl fumarate (Tecfidera®)	£269,798	17.02	5.73	-	-	-	-
Fingolimod (Gilenya®)	£282,065	17.00	5.50	-£12,267	0.02	0.23	**Dominant**
Natalizumab (Tysabri®)	£284,763	17.03	5.81	-£14,965	-0.08	-0.06	£173,745

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

Table 4: Part 2 - Base-case results (PAS price)

Technologies	Total			Incremental (dimethyl fumarate vs comparator)			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
SC IFNβ-1a 22 µg (Rebif® 22 µg)							£18,581
Glatiramer acetate (Copaxone®)							£19,057
Dimethyl fumarate (Tecfidera®)							-
IM IFNβ-1a 30 µg (Avonex®)							**Dominant**
SC IFNβ-1b 250 µg (Betaferon®/ Extavia®)							**Dominant**
SC IFNβ-1a 44 µg (Rebif® 44 µg)							**Dominant**
Fingolimod (Gilenya®)							**Dominant**
Natalizumab (Tysabri®)							£534,047

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

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental

[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4.

Table 5: Incremental cost-effectiveness analysis (list price)

Treatment	Total cost	Total QALYs	Inc. costs	Inc. QALYs	ICER
SC IFNβ-1a 22 µg (Rebif® 22 µg)	£234,103	5.4745	-	-	
Glatiramer acetate (Copaxone®)	£234,547	5.5041	£445	0.0296	£15,026
Dimethyl fumarate (Tecfidera®)	£269,798	5.7254	£35,250	0.2213	£159,295
Natalizumab (Tysabri®)	£284,763	5.8115	£14,965	0.0861	£173,745

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.

Table 6: Incremental cost-effectiveness analysis (PAS price)

Treatment	Total cost	Total QALYs	Inc. costs	Inc. QALYs	ICER
SC IFNβ-1a 22 µg (Rebif® 22 µg)	£234,103	5.4745	-	-	-
Glatiramer acetate (Copaxone®)	£234,547	5.5041	£445	0.0296	£15,026
Dimethyl fumarate (Tecfidera®)					£19,057
Natalizumab (Tysabri®)	£284,763	5.8115	£45,998	0.0861	£534,047

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.

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

Table 7: List price univariate sensitivity analysis results part 1

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	-	-£12,267	0.222	**Dominant**	£35,250	0.221	£159,295	£30,337	0.222	£136,452	£29,639	0.279	£106,127
EDSS state costs	+ 20%	-£13,109	0.222	**Dominant**	£34,459	0.221	£155,721	£29,720	0.222	£133,674	£28,749	0.279	£102,942
	- 20%	-£11,426	0.222	**Dominant**	£36,041	0.221	£162,869	£30,955	0.222	£139,229	£30,528	0.279	£109,312
Relapse costs	+ 20%	-£12,062	0.222	**Dominant**	£35,126	0.221	£158,735	£29,974	0.222	£134,817	£29,525	0.279	£105,719
	- 20%	-£12,473	0.222	**Dominant**	£35,374	0.221	£159,855	£30,701	0.222	£138,086	£29,753	0.279	£106,536
Patient utilities	+ 20%	-£12,267	0.259	**Dominant**	£35,250	0.257	£137,279	£30,337	0.251	£121,046	£29,639	0.319	£92,875
	- 20%	-£12,267	0.183	**Dominant**	£35,250	0.183	£192,425	£30,337	0.191	£158,561	£29,639	0.237	£125,276
Natural history relapse rates	+ 20%	-£12,658	0.224	**Dominant**	£35,278	0.221	£159,511	£30,691	0.221	£139,040	£29,639	0.279	£106,128
	- 20%	-£12,539	0.224	**Dominant**	£35,391	0.221	£160,394	£30,780	0.220	£139,701	£29,766	0.279	£106,802
Dimethyl fumarate relapse rate†	+ 20%	-£11,448	0.219	**Dominant**	£36,070	0.218	£165,772	£31,157	0.219	£142,512	£30,458	0.276	£110,527
	- 20%	-£13,087	0.226	**Dominant**	£34,431	0.225	£153,030	£29,518	0.226	£130,590	£28,819	0.283	£101,842
Comparator relapse rate†	+ 20%	-£12,992	0.226	**Dominant**	£34,212	0.226	£151,391	£29,170	0.228	£128,162	£28,494	0.284	£100,175
	- 20%	-£11,542	0.219	**Dominant**	£36,289	0.217	£167,541	£31,504	0.217	£145,144	£30,783	0.274	£112,304
Dimethyl fumarate disability progression rate†	+ 20%	-£10,487	0.038	**Dominant**	£37,031	0.037	£998,178	£32,118	0.038	£842,130	£31,419	0.095	£330,435
	- 20%	-£14,112	0.417	**Dominant**	£33,406	0.415	£80,417	£28,493	0.416	£68,418	£27,794	0.473	£58,712
Comparator disability progression rate†	+ 20%	-£14,205	0.455	**Dominant**	£31,929	0.449	£71,180	£27,517	0.422	£65,247	£26,139	0.530	£49,314
	- 20%	-£10,250	-0.026	**Dominant**	£38,749	-0.021	Dominated	£33,292	0.011	£3,049,522	£33,339	0.010	£3,367,977
Dimethyl fumarate dropouts	+ 20%	-£17,921	0.178	**Dominant**	£29,597	0.177	£166,974	£24,684	0.178	£138,444	£23,985	0.235	£101,960
	- 20%	-£5,380	0.273	**Dominant**	£42,138	0.272	£154,921	£37,225	0.273	£136,337	£36,526	0.330	£110,692
Comparator dropouts	+ 20%	-£6,288	0.243	**Dominant**	£37,187	0.243	£153,174	£32,919	0.247	£133,415	£31,740	0.293	£108,205
	- 20%	-£19,346	0.199	**Dominant**	£32,934	0.197	£167,174	£27,183	0.195	£139,738	£27,190	0.264	£103,085

† 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 8: List price univariate sensitivity analysis results part 2

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	-	£35,695	0.251	£142,283	£27,507	0.225	£122,105	-£14,965	-0.086	Negative
EDSS state costs	+ 20%	£34,866	0.251	£138,979	£26,785	0.225	£118,897	-£14,630	-0.086	Negative
	- 20%	£36,524	0.251	£145,587	£28,230	0.225	£125,313	-£15,300	-0.086	Negative
Relapse costs	+ 20%	£35,379	0.251	£141,025	£27,270	0.225	£121,052	-£14,639	-0.086	Negative
	- 20%	£36,010	0.251	£143,541	£27,744	0.225	£123,157	-£15,291	-0.086	Negative
Patient utilities	+ 20%	£35,695	0.289	£123,720	£27,507	0.258	£106,617	-£14,965	-0.102	Negative
	- 20%	£35,695	0.210	£169,929	£27,507	0.190	£144,892	-£14,965	-0.069	Negative
Natural history relapse rates	+ 20%	£35,955	0.250	£143,995	£27,687	0.224	£123,345	-£15,316	-0.085	Negative
	- 20%	£36,074	0.249	£144,786	£27,791	0.224	£124,068	-£15,365	-0.084	Negative
Dimethyl fumarate relapse rate†	+ 20%	£36,514	0.247	£147,730	£28,327	0.222	£127,844	-£14,145	-0.090	Negative
	- 20%	£34,875	0.255	£136,994	£26,688	0.229	£116,551	-£15,784	-0.082	Negative
Comparator relapse rate†	+ 20%	£34,755	0.255	£136,232	£26,594	0.229	£115,929	-£14,145	-0.090	£157,460
	- 20%	£36,635	0.247	£148,542	£28,420	0.221	£128,511	-£15,784	-0.082	£191,494
Dimethyl fumarate disability progression rate†	+ 20%	£37,475	0.067	£562,011	£29,288	0.041	£712,871	-£13,184	-0.270	Negative
	- 20%	£33,850	0.445	£76,069	£25,663	0.419	£61,190	-£16,809	0.108	**Dominant**
Comparator disability progression rate†	+ 20%	£33,109	0.422	£78,450	£25,022	0.403	£62,023	-£13,184	-0.270	£48,773
	- 20%	£38,394	0.070	£544,827	£30,103	0.037	£807,215	-£16,809	0.108	**Dominant**
Dimethyl fumarate dropouts	+ 20%	£30,041	0.207	£145,242	£21,854	0.181	£120,579	-£20,618	-0.130	Negative
	- 20%	£42,583	0.302	£141,198	£34,395	0.276	£124,627	-£8,077	-0.035	Negative
Comparator dropouts	+ 20%	£38,041	0.278	£136,626	£30,687	0.254	£120,927	-£8,036	-0.038	£210,640
	- 20%	£32,728	0.219	£149,726	£23,534	0.192	£122,493	-£23,320	-0.141	£165,465

† 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 9: PAS price Univariate sensitivity analysis results part 1

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**			£19,057			**Dominant**			**Dominant**
EDSS state costs	+ 20%			**Dominant**			£15,482			**Dominant**			**Dominant**
	- 20%			**Dominant**			£22,631			**Dominant**			**Dominant**
Relapse costs	+ 20%			**Dominant**			£18,497			**Dominant**			**Dominant**
	- 20%			**Dominant**			£19,616			**Dominant**			**Dominant**
Patient utilities	+ 20%			**Dominant**			£16,423			**Dominant**			**Dominant**
	- 20%			**Dominant**			£23,020			**Dominant**			**Dominant**
Natural history relapse rates	+ 20%			**Dominant**			£19,193			**Dominant**			**Dominant**
	- 20%			**Dominant**			£19,751			**Dominant**			**Dominant**
Dimethyl fumarate relapse rate†	+ 20%			**Dominant**			£23,148			£566			**Dominant**
	- 20%			**Dominant**			£15,100			**Dominant**			**Dominant**
Comparator relapse rate†	+ 20%			**Dominant**			£14,065			**Dominant**			**Dominant**
	- 20%			**Dominant**			£24,265			£2,171			**Dominant**
Dimethyl fumarate disability progression rate†	+ 20%			**Dominant**			£181,145			£47,385			£11,659
	- 20%			**Dominant**			£3,876			**Dominant**			**Dominant**
Comparator disability progression rate†	+ 20%			**Dominant**			£1,997			**Dominant**			**Dominant**
	- 20%			£1,612,298			Dominated			£206,886			£232,917
Dimethyl fumarate dropouts	+ 20%			**Dominant**			£9,160			**Dominant**			**Dominant**
	- 20%			**Dominant**			£27,226			£9,128			£5,436
Comparator dropouts	+ 20%			**Dominant**			£25,346			£7,642			£2,409
	- 20%			**Dominant**			£9,646			**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 10: Univariate sensitivity analysis results part 2 (PAS price)

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	-			**£18,581**			**Dominant**			**£534,047**
EDSS state costs	+ 20%			£15,277			**Dominant**			Negative
	- 20%			£21,886			**Dominant**			Negative
Relapse costs	+ 20%			£17,324			**Dominant**			Negative
	- 20%			£19,839			**Dominant**			Negative
Patient utilities	+ 20%			£16,157			**Dominant**			Negative
	- 20%			£22,192			**Dominant**			Negative
Natural history relapse rates	+ 20%			£19,711			**Dominant**			Negative
	- 20%			£20,233			**Dominant**			Negative
Dimethyl fumarate relapse rate†	+ 20%			£22,176			**Dominant**			Negative
	- 20%			£15,092			**Dominant**			Negative
Comparator relapse rate†	+ 20%			£14,589			**Dominant**			
	- 20%			£22,711			**Dominant**			
Dimethyl fumarate disability progression rate†	+ 20%			£107,448			**Dominant**			Negative
	- 20%			£4,617			**Dominant**			Dominant
Comparator disability progression rate†	+ 20%			£4,919			**Dominant**			
	- 20%			£104,456			**Dominant**			
Dimethyl fumarate dropouts	+ 20%			£9,999			**Dominant**			Negative
	- 20%			£26,029			**Dominant**			Negative
Comparator dropouts	+ 20%			£25,170			**Dominant**			
	- 20%			£7,752			**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.

Two-way sensitivity analysis

The results of the two-way sensitivity analysis (PAS price) are shown in Table 11.

Table 11: Two-way sensitivity analysis results

Comparison	Analysis	Change	Dimethyl fumarate	Comparator	List price			PAS price		
					Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
vs fingolimod	**Base case**				-£12,267	0.222	**Dominant**			**Dominant**
	Treatment effect on relapse rate	Lower confidence interval	0.450	0.360	-£12,161	0.222	**Dominant**			**Dominant**
		Upper confidence interval	0.620	0.500	-£11,974	0.221	**Dominant**			**Dominant**
	Treatment effect on disability progression rate	Lower confidence interval	0.470	0.630	-£12,505	0.208	**Dominant**			**Dominant**
		Upper confidence interval	0.890	1.040	-£11,604	0.200	**Dominant**			**Dominant**
	Drop outs	+ 20%	0.151	12.82%	-£11,941	0.199	**Dominant**			**Dominant**
		- 20%	10.04%	8.54%	-£12,459	0.250	**Dominant**			**Dominant**
vs GA	**Base case**				£35,250	0.221	£159,295			£19,057
	Treatment effect on relapse rate	Lower confidence interval	0.45	0.69	£35,111	0.222	£158,216			£18,375
		Upper confidence interval	0.62	0.88	£35,387	0.221	£160,360			£19,729
	Treatment effect on disability progression rate	Lower confidence interval	0.47	0.49	£37,596	0.147	£255,760			£37,695
		Upper confidence interval	0.89	1.16	£32,498	0.290	£111,991			£9,795
	Drop outs	+ 20%	15.10%	15.80%	£31,533	0.199	£158,667			£17,913
		- 20%	10.00%	10.50%	£39,821	0.248	£160,759			£20,542
vs IM IFNβ-1a 30 µg	**Base case**				£30,337	0.222	£136,452			**Dominant**
	Treatment effect on relapse rate	Lower confidence interval	0.450	0.690	£30,392	0.222	£136,850			**Dominant**
		Upper confidence interval	0.620	0.880	£30,285	0.223	£136,072			**Dominant**

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	0.470	0.490	£33,051	0.110	£300,127			£9,046
		Upper confidence interval	0.890	1.160	£26,274	0.395	£66,446			**Dominant**
	Drop outs	+ 20%	0.151	0.158	£27,265	0.203	£134,508			**Dominant**
		- 20%	10.04%	10.50%	£34,071	0.245	£138,930			**Dominant**
vs SC IFNβ-1b 250 µg	**Base case**				£29,639	0.279	£106,127			**Dominant**
	Treatment effect on relapse rate	Lower confidence interval	0.450	0.600	£29,618	0.279	£106,017			**Dominant**
		Upper confidence interval	0.620	0.760	£29,566	0.280	£105,742			**Dominant**
	Treatment effect on disability progression rate	Lower confidence interval	0.470	0.550	£33,510	0.075	£444,510			£19,293
		Upper confidence interval	0.890	1.260	£24,311	0.548	£44,348			**Dominant**
	Drop outs	+ 20%	0.151	10.73%	£26,086	0.249	£104,640			**Dominant**
		- 20%	10.04%	7.15%	£34,078	0.314	£108,365			**Dominant**
vs SC IFNβ-1a 22 µg	**Base case**				£35,695	0.251	£142,283			£18,581
	Treatment effect on relapse rate	Lower confidence interval	0.450	0.620	£35,076	0.254	£138,277			£18,728
		Upper confidence interval	0.620	0.830	£36,391	0.248	£146,898			£18,487
	Treatment effect on disability progression rate	Lower confidence interval	0.470	0.490	£33,231	0.511	£65,029			£31,515
		Upper confidence interval	0.890	1.160	£39,115	-0.100	Dominated			£7,908
	Drop outs	+ 20%	0.151	0.211	£32,388	0.234	£138,174			£18,834
		- 20%	10.04%	14.08%	£39,615	0.269	£147,110			£18,132

Comparison	Analysis	Change	Dimethyl fumarate	Comparator	List price			PAS price		
					Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
vs SC IFNβ-1a 44 µg	**Base case**				£27,507	0.225	£122,105			**Dominant**
	Treatment effect on relapse rate	Lower confidence interval	0.450	0.600	£27,366	0.226	£121,132			**Dominant**
		Upper confidence interval	0.620	0.740	£27,726	0.224	£123,619			**Dominant**
	Treatment effect on disability progression rate	Lower confidence interval	0.470	0.480	£29,705	0.146	£203,088			**Dominant**
		Upper confidence interval	0.890	1.150	£24,338	0.343	£71,024			**Dominant**
	Drop outs	+ 20%	15.06%	19.39%	£25,033	0.210	£119,361			**Dominant**
		- 20%	10.04%	12.93%	£30,421	0.243	£125,278			**Dominant**
vs natalizumab	**Base case**				-£14,965	-0.086	£173,745			£534,047
	Treatment effect on relapse rate	Lower confidence interval	0.450	0.290	-£15,178	-0.085	£178,202			£542,568
		Upper confidence interval	0.620	0.400	-£14,756	-0.087	£169,465			£525,864
	Treatment effect on disability progression rate	Lower confidence interval	0.470	0.430	-£15,479	-0.103	£150,150			£461,103
		Upper confidence interval	0.890	0.840	-£14,203	-0.075	£188,462			£581,969
	Drop outs	+ 20%	15.06%	13.56%	-£13,690	-0.082	£166,569			£506,925
		- 20%	10.04%	9.04%	-£16,432	-0.090	£182,118			£567,056

Abbreviations: ICER, incremental cost-effectiveness ratio; IFN, interferon; IM, intramuscular; SC, subcutaneous; QALY, quality adjusted life year.

4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

List price

Probabilistic sensitivity analysis using the list price produced the incremental cost and QALY ranges shown in Table 131.. The cost-effectiveness planes for the probabilistic sensitivity analyses of dimethyl fumarate, versus each comparator, are shown in Figure 5 and Figure 6. From these results cost-effectiveness acceptability curves were generated (Figure 7 and Figure 8).

Table 12: Incremental cost and QALY range from PSA (list price)

Comparison	Incremental cost range	Incremental QALY range
Dimethyl fumarate vs fingolimod	**Mean SD**	**Mean SD**
	Absolute	
	95% CI	
Dimethyl fumarate vs GA		
	Absolute	
	95% CI	
Dimethyl fumarate vs IM IFNβ-1a 30 µg		
	Absolute	
	95% CI	
Dimethyl fumarate vs SC IFNβ-1b 250 µg		
	Absolute	
	95% CI	
Dimethyl fumarate vs SC IFNβ-1a 22 µg		
	Absolute	
	95% CI	

Comparison	Incremental cost range	Incremental QALY range
Dimethyl fumarate vs SC IFNβ-1a 44 µg		
	Absolute	
	95% CI	
Dimethyl fumarate vs natalizumab		
	Absolute	
	95% CI	

Abbreviations: CI, confidence interval; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; SD, standard deviation.

Figure 1: 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®)

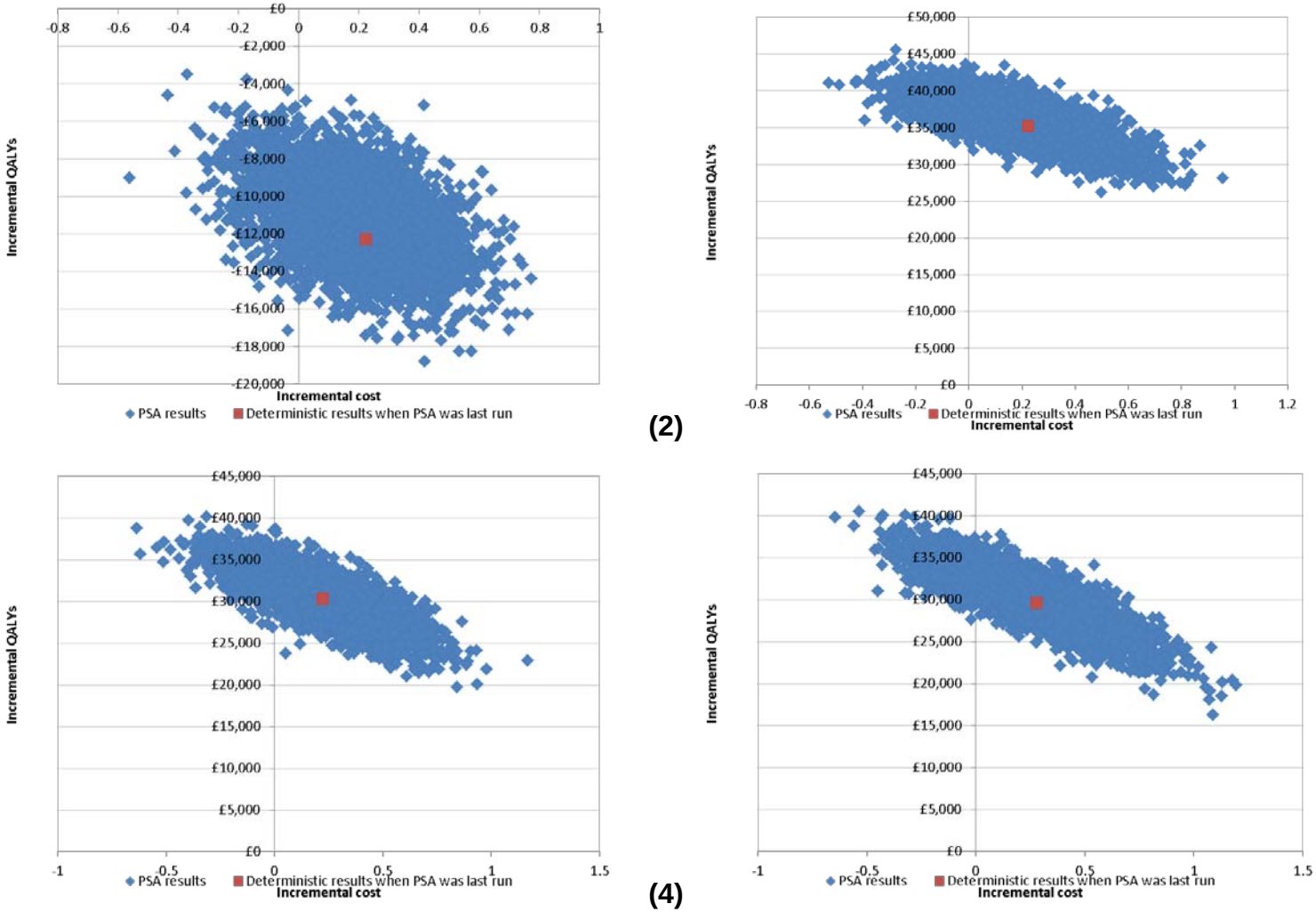
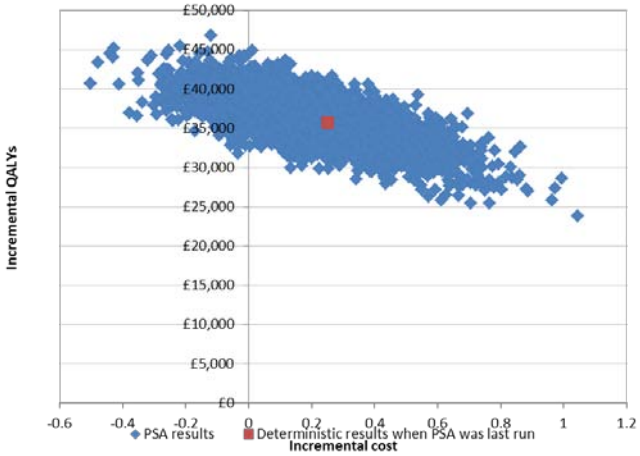


Figure 2: List price cost-effectiveness planes: dimethyl fumarate vs (1) SC IFNβ-1a 22 µg (Rebif® 22 µg), (2) SC IFNβ-1a 44 µg (Rebif® 44 µg), and (3) natalizumab



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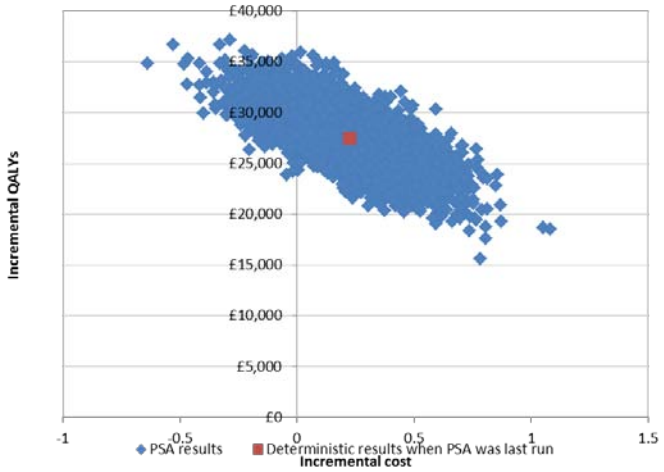
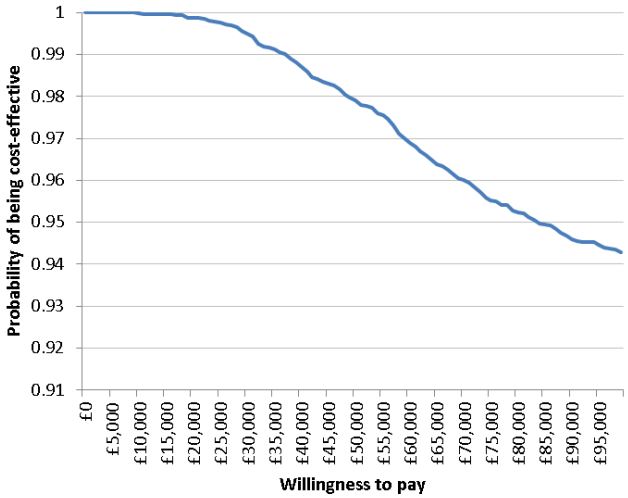


(2)

(3)

Figure 3: 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®)



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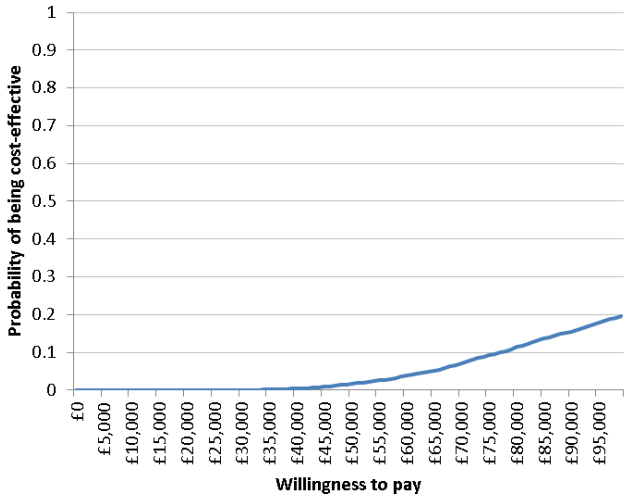

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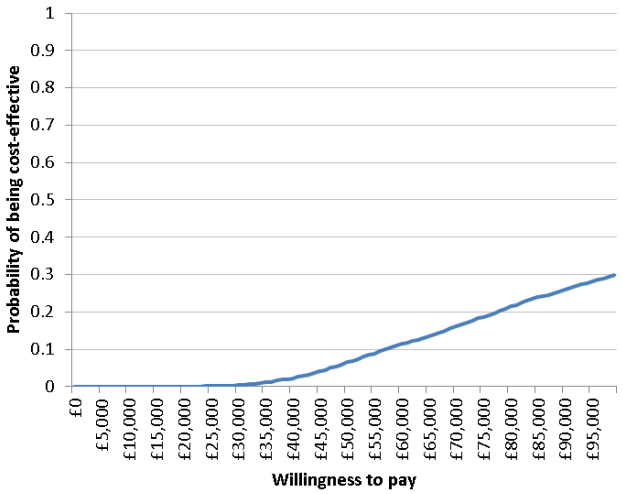

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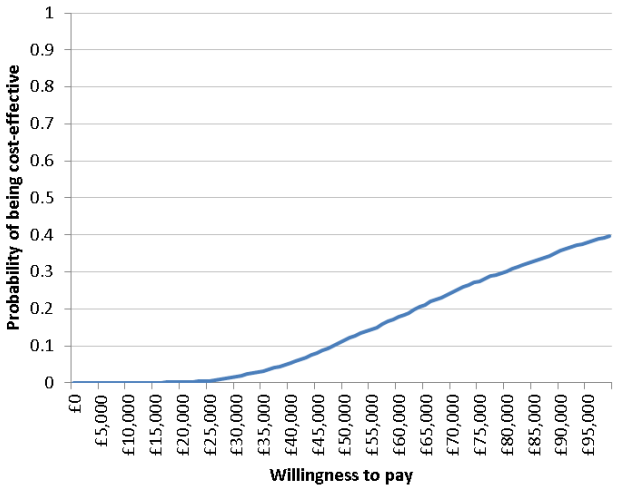

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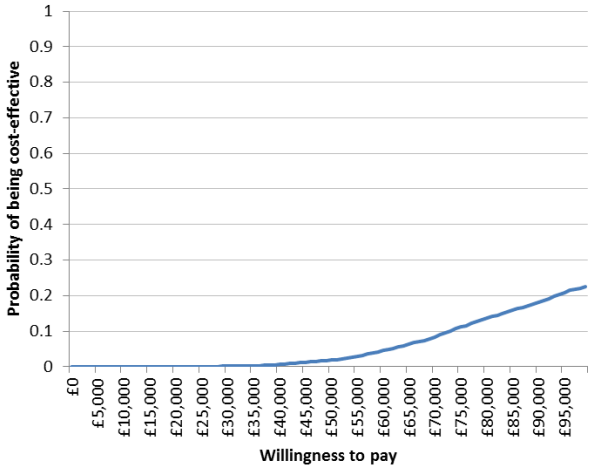
Figure 4: List price cost-effectiveness acceptability curves: dimethyl fumarate vs (1) SC IFNβ-1a 22 µg (Rebif® 22 µg), (2) SC IFNβ-1a 44 µg (Rebif® 44 µg), and (3) natalizumab



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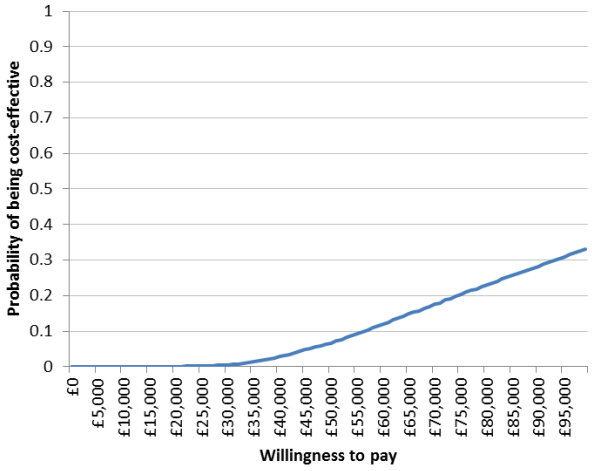

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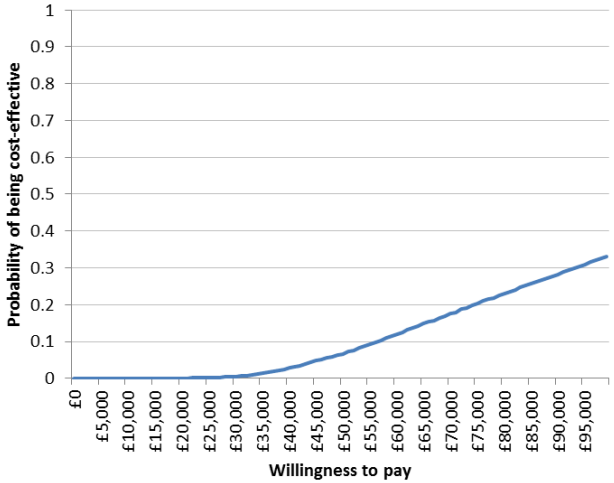


(3)

PAS price

Probabilistic sensitivity analysis using the PAS price produced the incremental cost and QALY ranges shown in Table 13. The cost-effectiveness planes for the probabilistic sensitivity analyses of dimethyl fumarate, versus each comparator, are shown in Figure 5 and Figure 6. From these results cost-effectiveness acceptability curves were generated (Figure 7 and Figure 8), demonstrating that the probability of dimethyl fumarate being cost-effective at £20,000/QALY is ≥70% for all comparators, with the exception of glatiramer acetate.

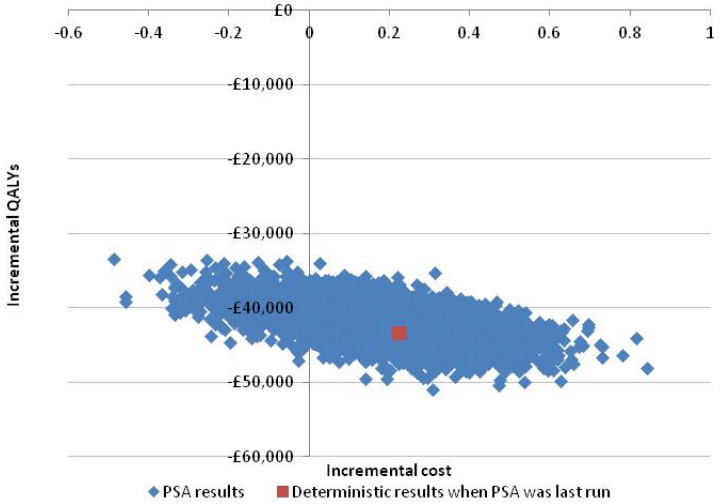
Table 13: Incremental cost and QALY range from PSA (PAS price)

Comparison	Incremental cost range	Incremental QALY range
Dimethyl fumarate vs fingolimod	**Mean SD**	**Mean SD**
	Absolute	
	95% CI	
Dimethyl fumarate vs GA		
	Absolute	
	95% CI	
Dimethyl fumarate vs IM IFNβ-1a 30 µg		
	Absolute	
	95% CI	
Dimethyl fumarate vs SC IFNβ-1b 250 µg		
	Absolute	
	95% CI	
Dimethyl fumarate vs SC IFNβ-1a 22 µg		
	Absolute	
	95% CI	
Dimethyl fumarate vs SC IFNβ-1a 44 µg		
	Absolute	

Comparison	Incremental cost range	Incremental QALY range
	95% CI	
Dimethyl fumarate vs natalizumab		
	Absolute	
	95% CI	

Abbreviations: CI, confidence interval; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; SD, standard deviation.

Figure 5: PAS 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®)



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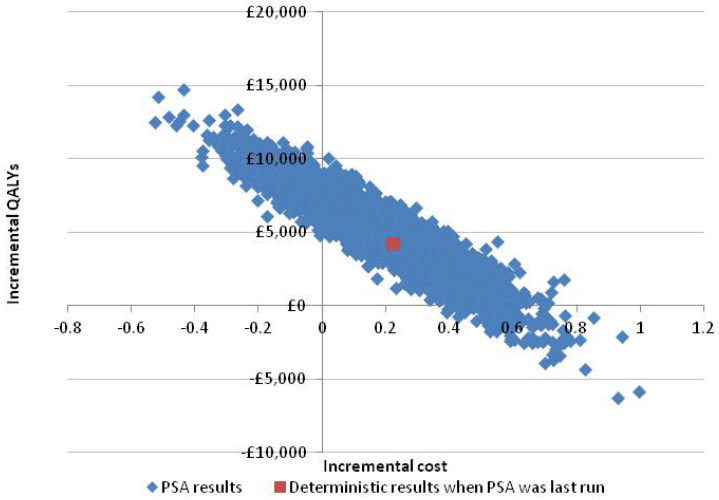

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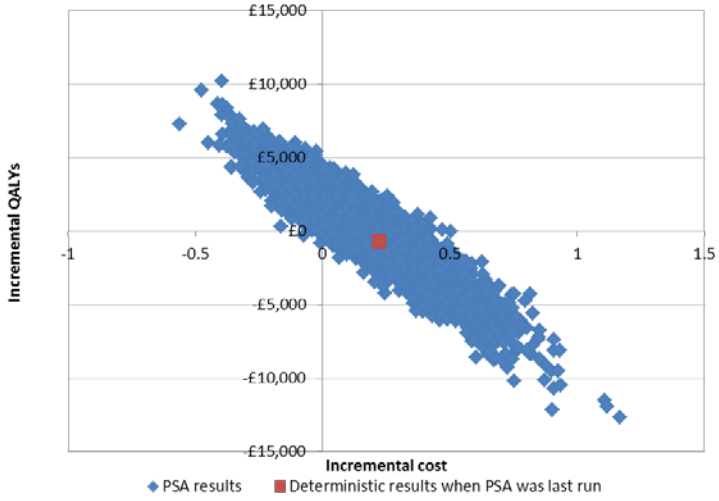

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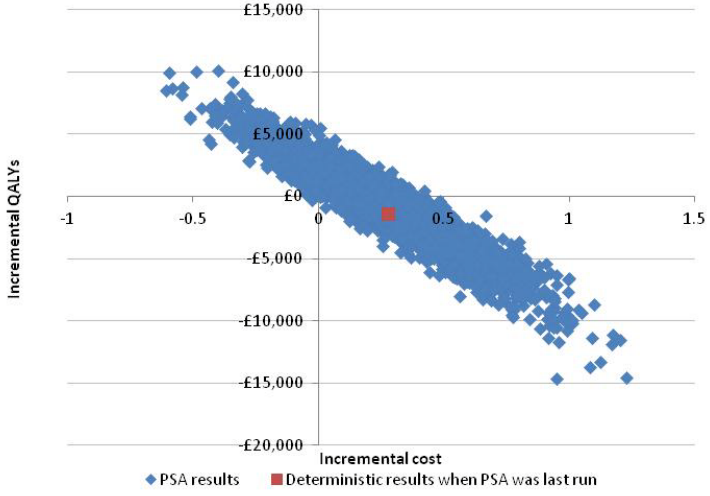

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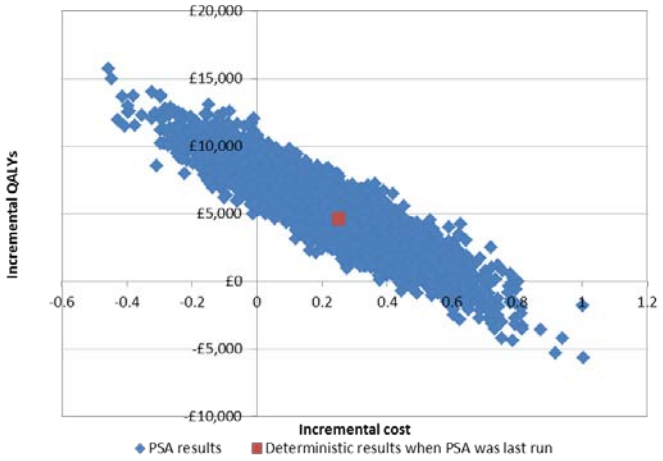
Figure 6: PAS price cost-effectiveness planes: dimethyl fumarate vs (1) SC IFNβ-1a 22 µg (Rebif® 22 µg), (2) SC IFNβ-1a 44 µg (Rebif® 44 µg), and (3) natalizumab



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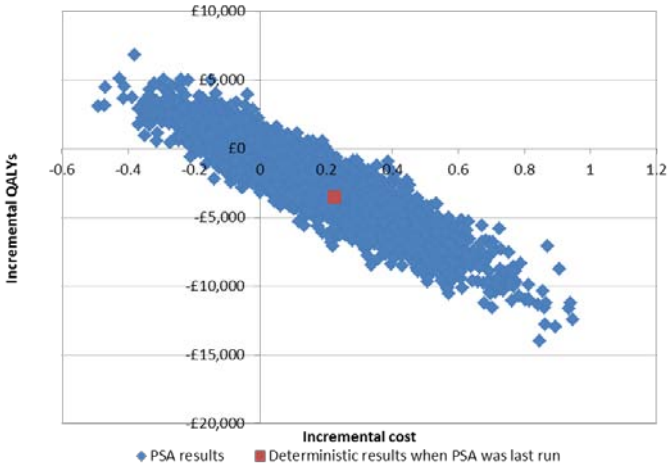

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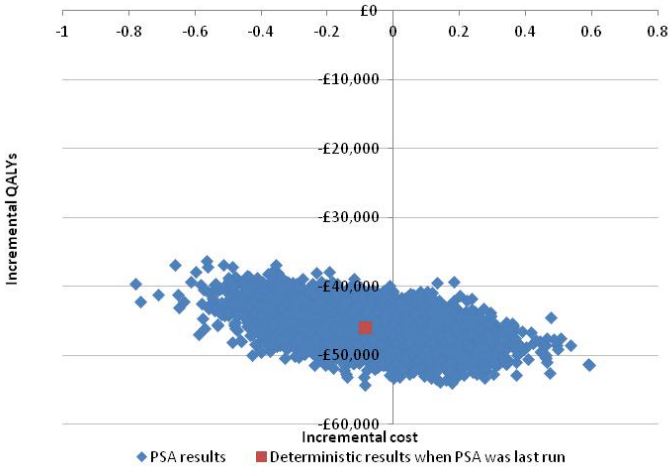

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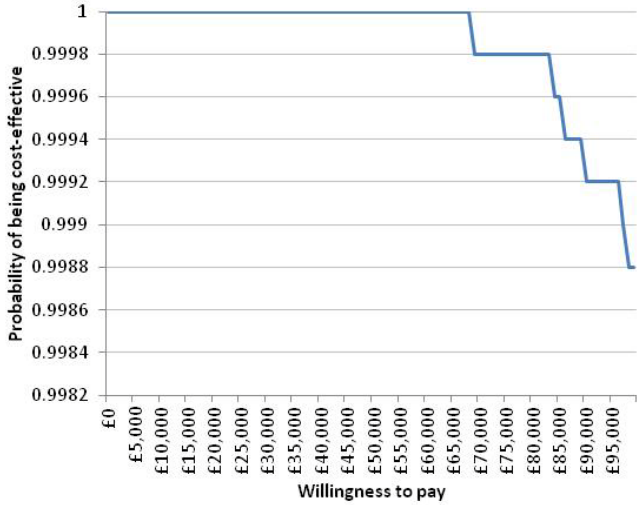
Figure 7: PAS price cost-effectiveness acceptability curves: dimethyl fumarate vs (1) fingolimod, (2) glatiramer acetate, (3) IM IFNβ-1a 30 µg (Avonex®), and (4) SC IFNβ-1b 250 µg (Betaferon®/Extavia®)



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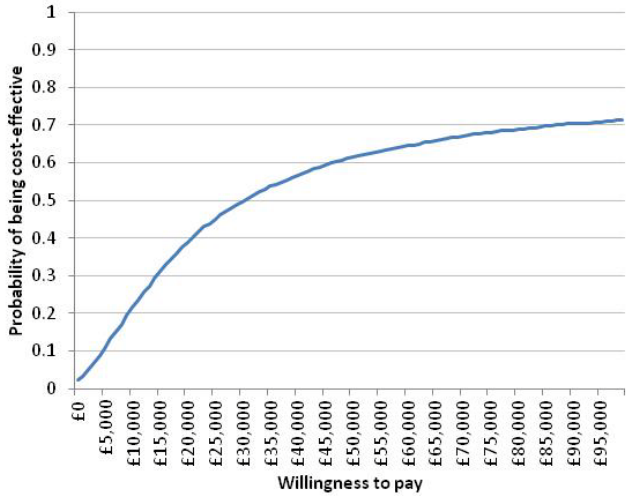

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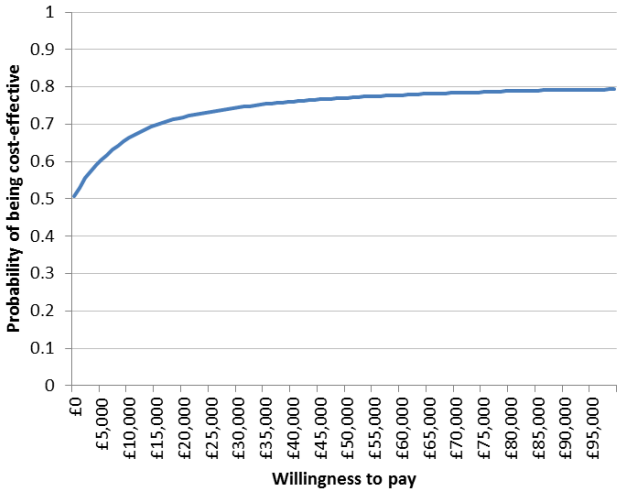

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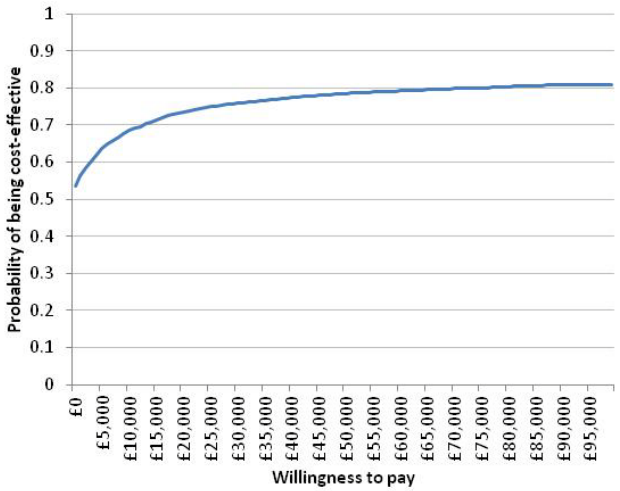

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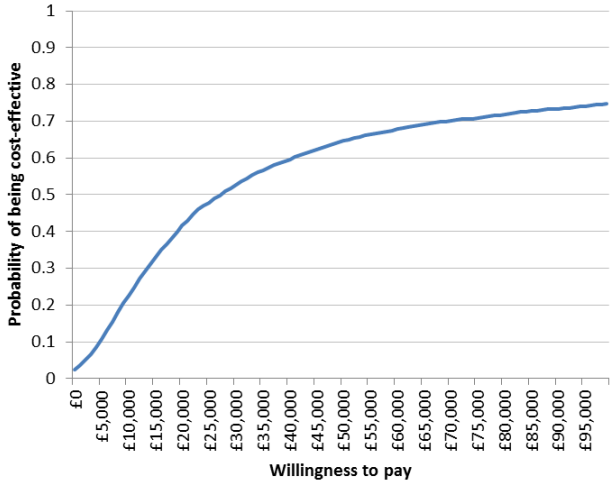
Figure 8: PAS price cost-effectiveness acceptability curves: dimethyl fumarate vs (1) SC IFNβ-1a 22 µg (Rebif® 22 µg), (2) SC IFNβ-1a 44 µg (Rebif® 44 µg), and (3) natalizumab



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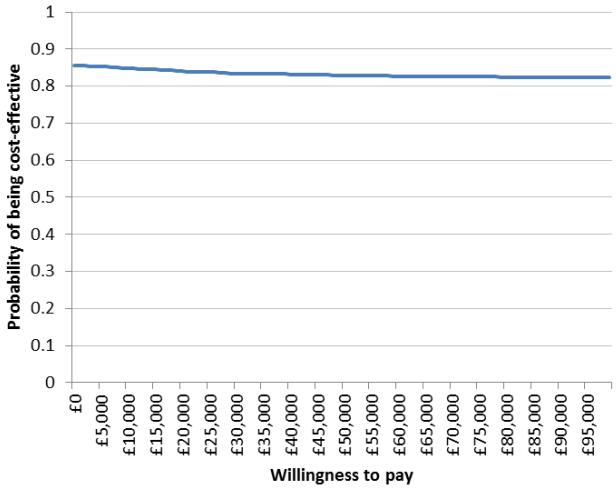

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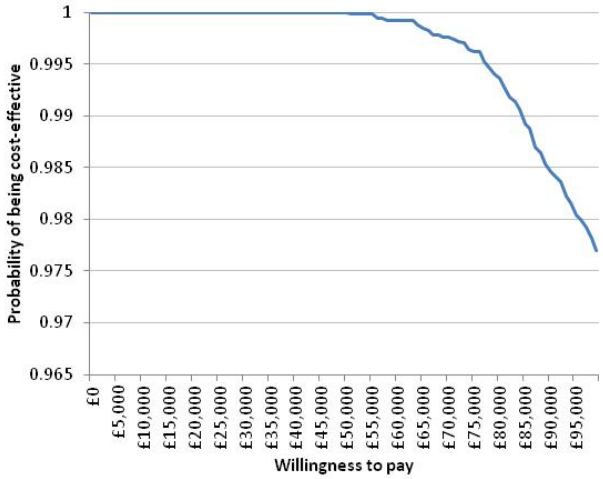

(3)

4.11 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

4.11.1 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

The results of the scenario analyses in which the price of fingolimod was varied are provided in Table 14. The results of the other scenario analyses using the list price are shown in Table 15 and Table 16. The results of the scenario analyses using the PAS price are shown in Table 17 and Table 18.

Table 14: Results of fingolimod simulated PAS price scenario analysis

Fingolimod price reduction	List price			PAS price		
	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
-5%	-£8,593	0.222	**Dominant**	-£39,626	0.222	**Dominant**
-10%	-£4,919	0.222	**Dominant**	-£35,952	0.222	**Dominant**
-15%	-£1,245	0.222	**Dominant**	-£32,278	0.222	**Dominant**
-20%	£2,429	0.222	£10,921	-£28,604	0.222	**Dominant**
-25%	£6,104	0.222	£27,436	-£24,930	0.222	**Dominant**
-30%	£9,778	0.222	£43,952	-£21,256	0.222	**Dominant**
-35%	£13,452	0.222	£60,468	-£17,581	0.222	**Dominant**
-40%	£17,126	0.222	£76,984	-£13,907	0.222	**Dominant**
-45%	£20,800	0.222	£93,499	-£10,233	0.222	**Dominant**
-50%	£24,474	0.222	£110,015	-£6,559	0.222	**Dominant**
-55%	£28,149	0.222	£126,531	-£2,885	0.222	**Dominant**
-60%	£31,823	0.222	£143,047	£789	0.222	£3,549
-65%	£35,497	0.222	£159,562	£4,464	0.222	£20,065
-70%	£39,171	0.222	£176,078	£8,138	0.222	£36,580
-75%	£42,845	0.222	£192,594	£11,812	0.222	£53,096
-80%	£46,519	0.222	£209,110	£15,486	0.222	£69,612
-85%	£50,194	0.222	£225,626	£19,160	0.222	£86,128
-90%	£53,868	0.222	£242,141	£22,834	0.222	£102,643
-95%	£57,542	0.222	£258,657	£26,509	0.222	£119,159

Abbreviations: ICER, incremental cost effectiveness ratio; Incr., incremental; QALY, quality adjusted life year.

Table 15: Results of scenario analysis part 1 (list price)

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%)	-	-£12,654	0.285	**Dominant**	£34,948	0.283	£123,369	£29,709	0.280	£106,185	£29,320	0.343	£85,408
Discount rate costs and benefits	0%	-£16,566	0.358	**Dominant**	£39,492	0.350	£112,695	£34,558	0.333	£103,655	£32,321	0.428	£75,458
Discount rate costs and benefits	6%	-£10,252	0.166	**Dominant**	£32,607	0.167	£195,243	£27,807	0.175	£159,053	£27,769	0.216	£128,767
Discount rate costs Discount rate benefits	0% 6%	-£16,566	0.166	**Dominant**	£39,492	0.167	£236,472	£34,558	0.175	£197,672	£32,321	0.216	£149,874
Discount rate costs Discount rate benefits	6% 0%	-£10,252	0.358	**Dominant**	£32,607	0.350	£93,047	£27,807	0.333	£83,404	£27,769	0.428	£64,831
Discount rate costs and benefits	1.5%	-£14,451	0.289	**Dominant**	£37,598	0.285	£131,982	£32,645	0.277	£117,745	£31,181	0.353	£88,340
Discount rate costs Discount rate benefits	1.5% 3.5%	-£14,451	0.222	**Dominant**	£37,598	0.221	£169,905	£32,645	0.222	£146,832	£31,181	0.279	£111,651
Discount rate costs Discount rate benefits	3.5% 1.5%	-£12,267	0.289	**Dominant**	£35,250	0.285	£123,739	£30,337	0.277	£109,421	£29,639	0.353	£83,969
No caregiver utility	-	-£12,267	0.200	**Dominant**	£35,250	0.200	£176,248	£30,337	0.206	£147,453	£29,639	0.255	£116,090
Time horizon	1 year	-£1,683	0.002	**Dominant**	£9,577	0.005	£1,753,786	£7,292	0.017	£436,425	£8,506	0.012	£682,007
	5 year	-£5,562	0.038	**Dominant**	£28,295	0.045	£628,863	£23,144	0.071	£324,373	£25,318	0.072	£349,525

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
	10 year	-£8,647	0.095	**Dominant**	£34,866	0.101	£346,795	£29,399	0.123	£239,678	£30,424	0.142	£213,540
	20 year	-£11,594	0.185	**Dominant**	£35,605	0.185	£191,994	£30,578	0.193	£158,724	£30,140	0.240	£125,521
	50 year	-£12,176	0.232	**Dominant**	£35,357	0.231	£153,355	£30,421	0.230	£132,086	£29,751	0.289	£102,954
Mortality	General population	-£12,814	0.231	**Dominant**	£34,859	0.229	£152,171	£30,044	0.229	£131,460	£29,168	0.288	£101,238
Annualised relapse rate relative to placebo	Lower 95% CI	-£12,886	0.225	**Dominant**	£34,632	0.224	£154,548	£29,719	0.225	£132,010	£29,020	0.282	£102,883
	Upper 95% CI	-£11,571	0.219	**Dominant**	£35,946	0.218	£164,781	£31,033	0.219	£141,584	£30,335	0.276	£109,856
Disability progression rate relative to placebo	Lower 95% CI	-£14,731	0.483	**Dominant**	£32,786	0.481	£68,102	£27,873	0.482	£57,772	£27,175	0.539	£50,378
	Upper 95% CI	-£8,847	-0.129	£68,676	£38,671	-0.130	Dominated	£33,758	-0.129	Dominated	£33,059	-0.072	Dominated
London Ontario transition matrix for RRMS-RRMS transitions		-£11,372	0.194	**Dominant**	£32,448	0.194	£167,343	£27,655	0.196	£141,234	£27,484	0.247	£111,085

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 16: Results of scenario analysis part 2 (list price)

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%)	-	£34,730	0.336	£103,511	£26,733	0.299	£89,457	-£14,519	-0.128	£113,515
Discount rate costs and benefits	0%	£40,913	0.395	£103,576	£31,582	0.352	£89,717	-£17,893	-0.144	£124,313
Discount rate costs and benefits	6%	£32,575	0.191	£170,861	£25,068	0.172	£145,610	-£13,329	-0.063	£213,065
Discount rate costs Discount rate benefits	0% 6%	£40,913	0.191	£214,594	£31,582	0.172	£183,452	-£17,893	-0.063	£286,020
Discount rate costs Discount rate benefits	6% 0%	£32,575	0.395	£82,468	£25,068	0.352	£71,211	-£13,329	-0.144	£92,604
Discount rate costs and benefits	1.5%	£38,547	0.322	£119,821	£29,736	0.288	£103,389	-£16,532	-0.114	£144,567
Discount rate costs Discount rate benefits	1.5% 3.5%	£38,547	0.251	£153,651	£29,736	0.225	£131,998	-£16,532	-0.086	£191,941
Discount rate costs Discount rate benefits	3.5% 1.5%	£35,695	0.322	£110,956	£27,507	0.288	£95,640	-£14,965	-0.114	£130,863
No caregiver utility	-	£35,695	0.229	£156,124	£27,507	0.206	£133,603	-£14,965	-0.077	£193,887
Time horizon	1 year	£7,882	0.012	£684,710	£5,879	0.011	£515,487	-£2,027	-0.001	£3,368,565
	5 year	£26,335	0.059	£445,295	£20,039	0.056	£355,974	-£9,549	-0.011	£849,040
	10 year	£34,377	0.117	£293,292	£26,452	0.108	£244,106	-£13,614	-0.031	£437,433
	20 year	£36,043	0.209	£172,244	£27,805	0.189	£147,127	-£15,012	-0.068	£220,547
	50 year	£35,803	0.262	£136,423	£27,602	0.235	£117,268	-£15,016	-0.092	£164,082
Mortality	General population	£35,294	0.259	£136,183	£27,152	0.233	£116,775	-£14,816	-0.089	£165,664
Annualised relapse rate relative to placebo	Lower 95% CI	£35,076	0.254	£138,277	£26,889	0.228	£117,896	-£15,583	-0.083	£186,994
	Upper 95% CI	£36,391	0.248	£146,898	£28,203	0.222	£126,966	-£14,269	-0.089	£159,832
Disability progression rate relative to	Lower 95% CI	£33,231	0.511	£65,029	£25,043	0.485	£51,591	-£17,429	0.174	

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
placebo	Upper 95% CI	£39,115	-0.100	Dominated	£30,928	-0.126	Dominated	-£11,545	-0.437	£26,393
London Ontario transition matrix for RRMS-RRMS transitions		£32,253	0.216	£148,986	£24,669	0.195	£126,608	-£13,016	-0.072	£181,019

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

Table 17: Results of scenario analysis part 1 (PAS price)

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**			£11,711			**Dominant**			**Dominant**
Discount rate costs and benefits	0%			**Dominant**			£9,007			**Dominant**			**Dominant**
Discount rate costs and benefits	6%			**Dominant**			£26,985			**Dominant**			**Dominant**
Discount rate costs Discount rate benefits	0% 6%			**Dominant**			£18,900			**Dominant**			**Dominant**
Discount rate costs Discount rate benefits	6% 0%			**Dominant**			£12,860			**Dominant**			**Dominant**
Discount rate costs and benefits	1.5%			**Dominant**			£13,129			**Dominant**			**Dominant**
Discount rate costs Discount rate benefits	1.5% 3.5%			**Dominant**			£16,901			**Dominant**			**Dominant**
Discount rate	3.5%			**Dominant**			£14,803			**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
costs Discount rate benefits	1.5%												
No caregiver utility	-			**Dominant**			£21,085			**Dominant**			**Dominant**
Time horizon	1 year			**Dominant**			£420,018			**Dominant**			£97,977
	5 year			**Dominant**			£125,471			£512			£36,833
	10 year			**Dominant**			£60,578			£6,925			£11,568
	20 year			**Dominant**			£25,454			£5,078			**Dominant**
	50 year			**Dominant**			£18,711			**Dominant**			**Dominant**
Mortality	General population			**Dominant**			£16,371			**Dominant**			**Dominant**
Annualised relapse rate relative to placebo	Lower 95% CI			**Dominant**			£16,059			**Dominant**			**Dominant**
	Upper 95% CI			**Dominant**			£22,521			**Dominant**			**Dominant**
Disability progression rate relative to placebo	Lower 95% CI			**Dominant**			£1,518			**Dominant**			**Dominant**
	Upper 95% CI			£298,886			Dominated			**Dominant**			Dominated
London Ontario transition matrix for RRMS-RRMS transitions				**Dominant**			£19,681			**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 18: Results of scenario analysis part 2 (PAS price)

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

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%)	-			£9,240			**Dominant**			£360,812
Discount rate costs and benefits	0%			£11,587			**Dominant**			£376,755
Discount rate costs and benefits	6%			£23,471			**Dominant**			£662,237
Discount rate costs Discount rate benefits	0% 6%			£24,007			**Dominant**			£866,841
Discount rate costs Discount rate benefits	6% 0%			£11,329			**Dominant**			£287,828
Discount rate costs and benefits	1.5%			£14,574			**Dominant**			£440,647
Discount rate costs Discount rate benefits	1.5% 3.5%			£18,689			**Dominant**			£585,043
Discount rate costs Discount rate benefits	3.5% 1.5%			£14,490			**Dominant**			£402,237
No caregiver utility	-			£20,389			**Dominant**			£360,812
Time horizon	1 year			£52,005			**Dominant**			£15,470,104
	5 year			£62,316			**Dominant**			£2,862,982
	10 year			£47,790			**Dominant**			£1,362,010
	20 year			£24,648			**Dominant**			£674,282
	50 year			£18,136			**Dominant**			£503,289
Mortality	General population			£16,150			**Dominant**			£513,509
Annualised relapse rate relative to placebo	Lower 95% CI			£15,938			**Dominant**			£559,380
	Upper 95% CI			£21,626			**Dominant**			£507,444
Disability progression rate relative to placebo	Lower 95% CI			£2,300			**Dominant**			**Dominant**
	Upper 95% CI			Dominated			**Dominant**			£94,190

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
London Ontario transition matrix for RRMS-RRMS transitions				£16,727			**Dominant**			£579,201

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

4.11.2 What were the main findings of each of the sensitivity analyses?

The results from univariate and two-way sensitivity analysis using the PAS price were generally consistent with those from the base case, demonstrating the robustness of the results. Dimethyl fumarate was dominant in the majority of comparisons, with very few resulting in an ICER above £20,000/QALY.

The scenario analyses indicate that the model is robust to the majority of structural assumptions made, with very few analyses resulting in an ICER ≥£0. When time horizons of 1–10 years were considered the ICER first increased, then decreased, which may appear to be an anomalous result. However, this is a result of a larger accumulation of drug costs in the early period, compared with drug benefits, which become more apparent at later time points

4.11.3 Key drivers of the cost-effectiveness results

Univariate sensitivity analysis demonstrates that the model results are robust, with very few changes resulting in an ICER ≥ £0. The model is most sensitive to changes in the effect of treatment on the disability progression rate; ICERs increased most when the effect of dimethyl fumarate was reduced by 20%, or the effect of the comparator was increased by 20%

4.12 If any of the criteria on which the patient access scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

Not applicable

Impact of patient access scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

Table 5 Results showing the impact of patient access scheme on ICERs

	ICER for intervention versus:				
	Comparator 1		**Comparator 2**		**…**
	Without PAS	**With PAS**	**Without PAS**	**With PAS**	
Scenario 1 (base-case)					
Scenario 2					
Scenario 3					
Scenario 4					
…					

PAS: patient access scheme.

Not applicable

5 Appendices

5.1 Appendix A: Additional documents

5.1.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

No additional forms are required over those that would be required to supply the drug without a PAS.

5.2 Appendix B: Details of outcome-based schemes

5.2.1 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

This Appendix not applicable

5.2.2 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Not applicable

5.2.3 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.

Not applicable

5.2.4 For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Not applicable

5.2.5 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

Not applicable

5.2.6 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered.

Not applicable

5.2.7 Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Not applicable

5.2.8 Please present the cost-effectiveness results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
  - the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

Not Applicable

5.2.9 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

Not Applicable