Fingolimod for multiple sclerosis

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Fingolimod

- First oral treatment for relapsing remitting MS

Multiple Sclerosis - Background

- One of the most common chronic disabling neurological condition affecting young adults
  - ~85,000 people in the UK (pop=c60m) have MS
- Autoimmune T-cell mediated reaction to myelin
- Onset in early adulthood (20-30)
- Female:Male 2:1
- 85% have Relapsing Remitting MS.
- 15% Primary Progressive MS
- Extremely variable course
- Life expectancy may be shortened, however many people with MS have the same life expectancy as that of the general population

Disease Characteristics

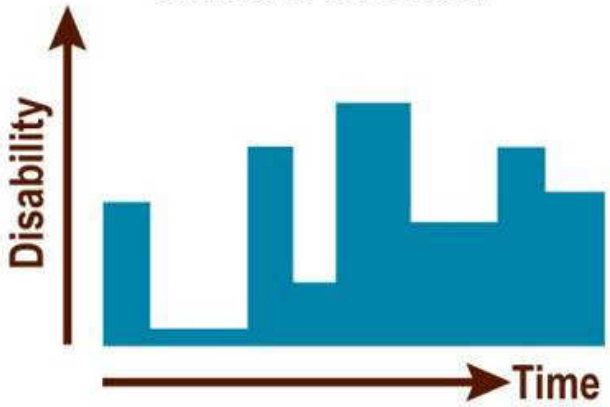
80 - 85% of people with MS

Relapsing Remitting (RRMS)

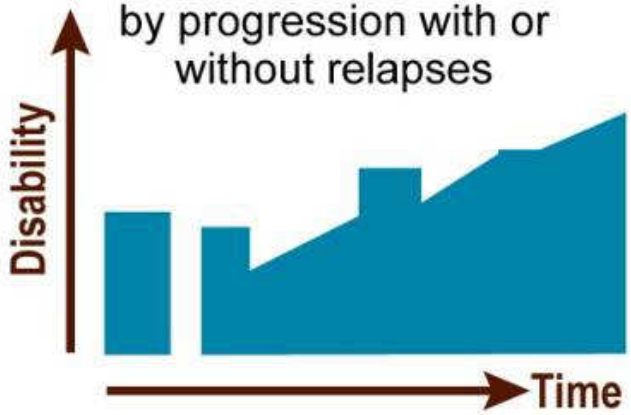
Secondary Progressive (SPMS)

Majority of people with RRMS develop SPMS

Acute relapses with full or partial recovery; stable in between



Begins with RR, followed by progression with or without relapses



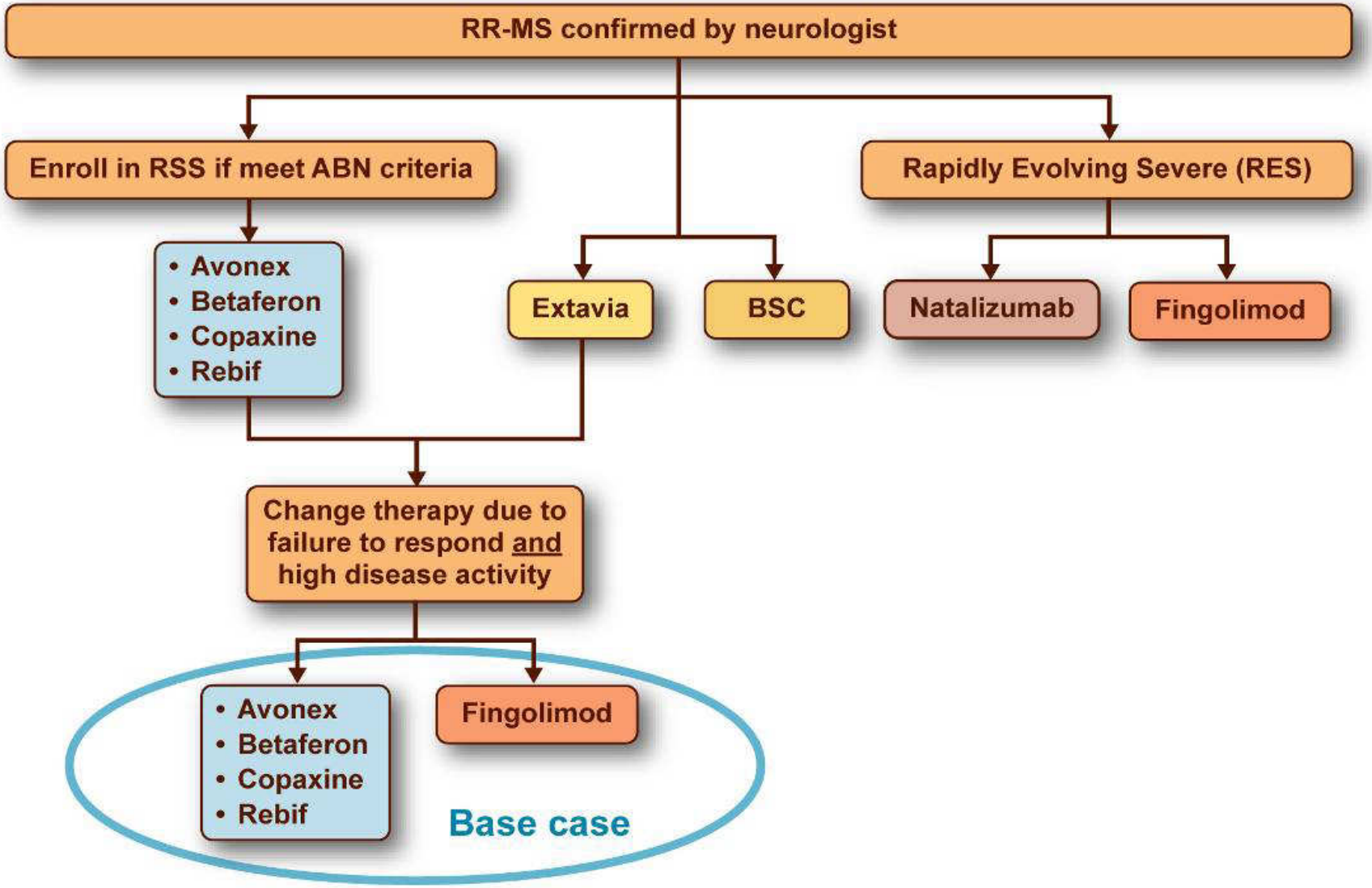
Patient populations in marketing authorisation and manufacturer's submission

Fingolimod has a UK marketing authorisation as a single disease modifying therapy in highly active relapsing-remitting multiple sclerosis for:

Marketing Authorisation	Manufacturer's Submission	Referred to as population:
Rapidly evolving severe RRMS (RES)	≥ 2 disabling relapses in 1 year, and with ≥ 1 gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to previous MRI	**2***
High disease activity despite treatment with beta-interferon	≥ 1 relapse in previous year while on therapy and ≥ 9 T2-hyperintense lesions brain MRI or ≥ 1 Gadolinium enhancing lesion	**1a***
	"Non-responders" with unchanged or increased relapse rates, compared to previous year	**1b***

There is a high level of overlap between 1a and 1b. Some patients in population 2, also meet criteria for 1a or 1b

Current Management



Source: Manufacturer's submission

Clinical effectiveness evidence

- 2 phase III RCTs
  - FREEDOMS trial and TRANSFORM trial
- Adults aged 18 to 55 years with RRMS

- FREEDOMS trial: 24 months
  - Oral fingolimod 0.5 mg (n=425) vs placebo (n=418)
- TRANSFORMS trial: 12 months
  - Oral fingolimod 0.5 mg (n=431) vs IM interferon-beta-1a (Avonex) 30 µg (n=435)

- Populations in TRANSFORMS and FREEDOMS trials broader than those in marketing authorisation
- Manufacturer provided data for subgroups which approximated (post-hoc) populations in marketing authorisation
- Submission focused on population 1b (largest subgroup)
  - No economic evaluation of populations 1a or 2 was provided

Results: Annualised Relapse Rate and Rate Ratio

	FREEDOMS (24 months)			TRANSFORMS (12 months)		
Population	Fingolimod 0.5 mg	Placebo	Rate Ratio (95% CI)	Fingolimod 0.5 mg	Avonex	Rate Ratio (95% CI)
1b, some of whom may also meet criteria for 2	0.21 (CI not reported)	0.54 (CI not reported)	0.38 (0.24 to 0.62)	0.25 (CI not reported)	0.51 (CI not reported)	0.50 (0.33 to 0.74)

Data on 1b not 2 populations “academic in confidence”

Disability Progression

Absence of disability progression after **six** months				
	Placebo	***Avonex***	***Fingolimod***	
All patients (%)	81.0 (77.1 to 84.9)		87.5 (84.3 to 90.7)	P = 0.01 NNT = 7
All patients (%)		92.1 (89.4 to 94.7)	94.1 (91.8 to 96.3)	P = 0.25 NNT = 50
Hazard Ratio for Disability Progression (patients with DMT in previouos year)				
	Placebo	***Avonex***	***Fingolimod***	
Population 1b	Comparator		0.59 (0.29 to 1.20)	P = 0.142
Population 1a	Comparator		0.63 (0.31 to 1.26)	P = 0.188
Population 1b		Comparator	0.71 (0.31 to 1.62)	P = 0.421
Population 1a		Comparator	0.76 (0.35 to 1.68)	P = 0.497

Adverse events

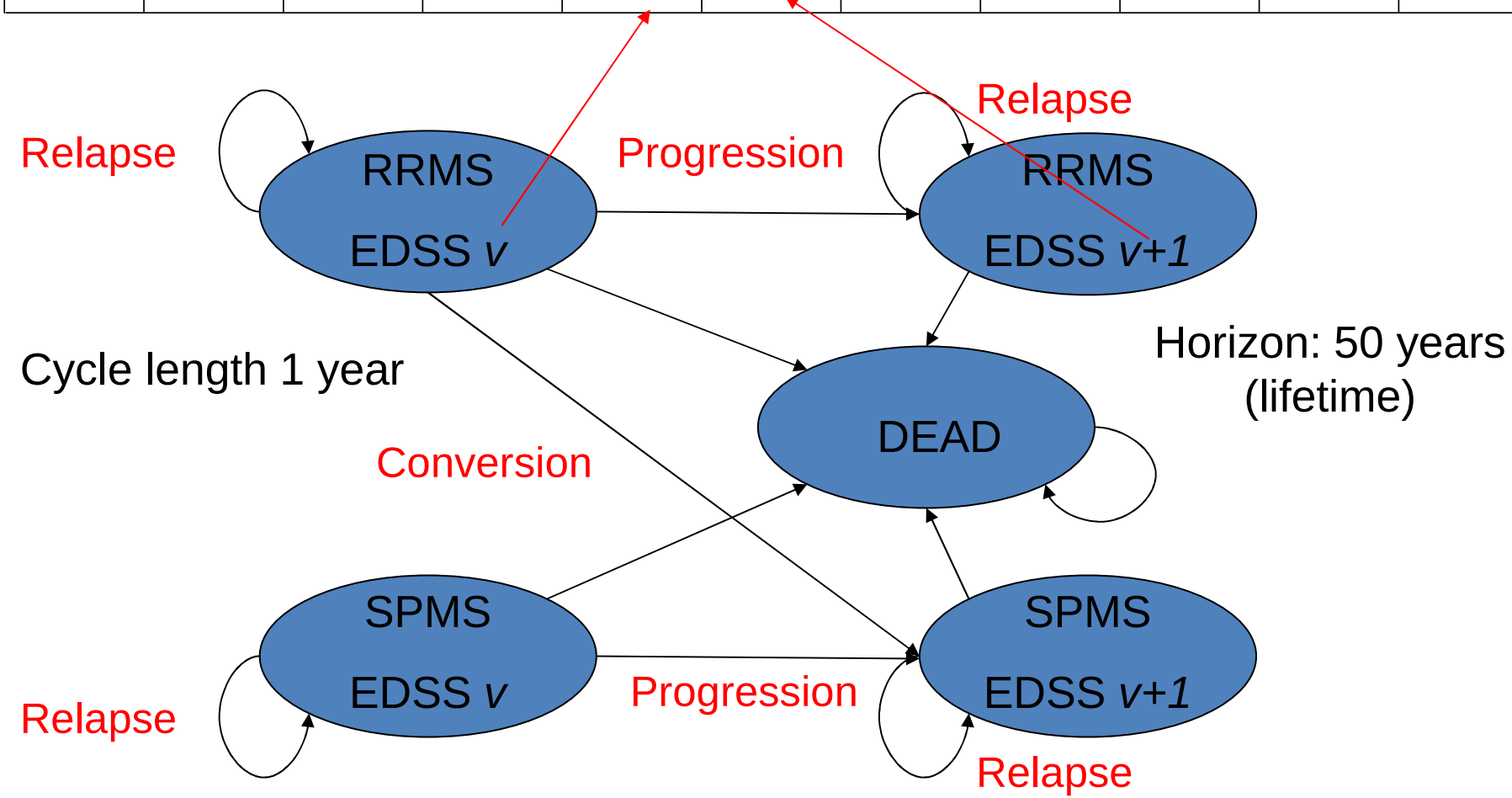
- Majority of adverse events FREEDOMS and TRANSFORMS trials showed no statistically significant differences between the fingolimod 0.5 mg and comparison
- The submission combined the fingolimod 0.5 mg arms from the two trials for the assessment of safety outcomes
- Fingolimod was associated with significantly more influenza-type illness than placebo (FREEDOMS trial), but the incidence was still significantly lower than in the Avonex arm (TRANSFORMS trial)
- People treated with fingolimod showed higher incidence of raised hepatic enzymes than those in either the Avonex or the placebo groups

Expanded Disability Severity Scale

0.0	**Normal neurological examination**
1.0	No disability, minimal signs in one FS
2.0	Minimal disability in one FS
3.5	Fully ambulatory but with moderate disability in one FS and more than minimal disability in several others
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability; able to walk without aid or rest some 300 meters.
5.0	Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (work a full day without special provisions)
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting
7.0	Unable to walk beyond approximately five meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms
9.0	Confined to bed; can still communicate and eat.
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow
10.0	Death due to MS

Markov Model

EDSS	0	0.5-1	1.5-2	2.5-3	3.5-4	4.5-5	5.5-6	6.5-7	7.5-8	8.5-9.5



RRMS = Relapsing-remitting multiple sclerosis
SPMS = 2° progressive multiple sclerosis
EDSS = Expanded Disability Status Scale

Assumptions (i)

- Patients enter at EDSS 0 to 6
- Patients with EDSS 0 to 6 may receive a disease modifying tx
- Patient on reaching EDSS ≥7 receive best supportive care
- Progression RRMS to SPMS – London, Ontario cohort
- No disease regression, progression risk has no “memory”
- No conversion from SPMS to RRMS
- Relapse rate = *f*(EDSS)
- Mortality risk = *f*(EDSS, RRMS, SPMS)
- Treatment effects directly only relapse and progression
- EDSS state determines mortality via a relative risk of death
- No treatment disutility assumed for fingolimod

Assumptions (ii)

- Constant treatment effect (relative risk) for up to 50 years on treatment (i.e do not increase or decrease over time)
- Implicit assumption that Avonex is a representative comparator
- EQ-5D = *f(*EDSS) despite trial evidence
- Equal adherence to fingolimod and Avonex
- NHS and PSS costs are equal for RRMS and SPMS
- Costs = *f*(EDSS)
  - only costs of severe adverse events included in model

Clinical Data in Model

Variable	Value
Population	
Age at treatment start	37.3 years
Female to Male ratio	2.3 : 1
Years since diagnosis	6.25 years
Clinical inputs (for population 1b)	
RR confirmed progression	Academic in confidence
RR of relapse	FREEDOMS (direct) Fingolimod vs placebo = 0.559 TRANSFORMS (indirect) Avonex vs placebo = 0.933
Discontinuations due to AEs	TRANSFORMS Fingolimod = 6/191 Avonex = 3/183

Health-related quality of life

- Patient-reported outcomes with EQ-5D in FREEDOMS trial

EQ-5D *change from baseline* (24 months) in the FREEDOMS trial

Change in score from baseline, mean +/- SD	n	Placebo	Fingolimod 0.5 mg
EQ-5D utility score	AiC	AiC	AiC

- Trial shows no significant difference in EQ5D utility between arms
- Manufacturer used EDSS-based EQ-5D scores from published literature (Orme et al. 2007) in economic model

Manufacturer's Deterministic (Base-case) Results (pop 1b)

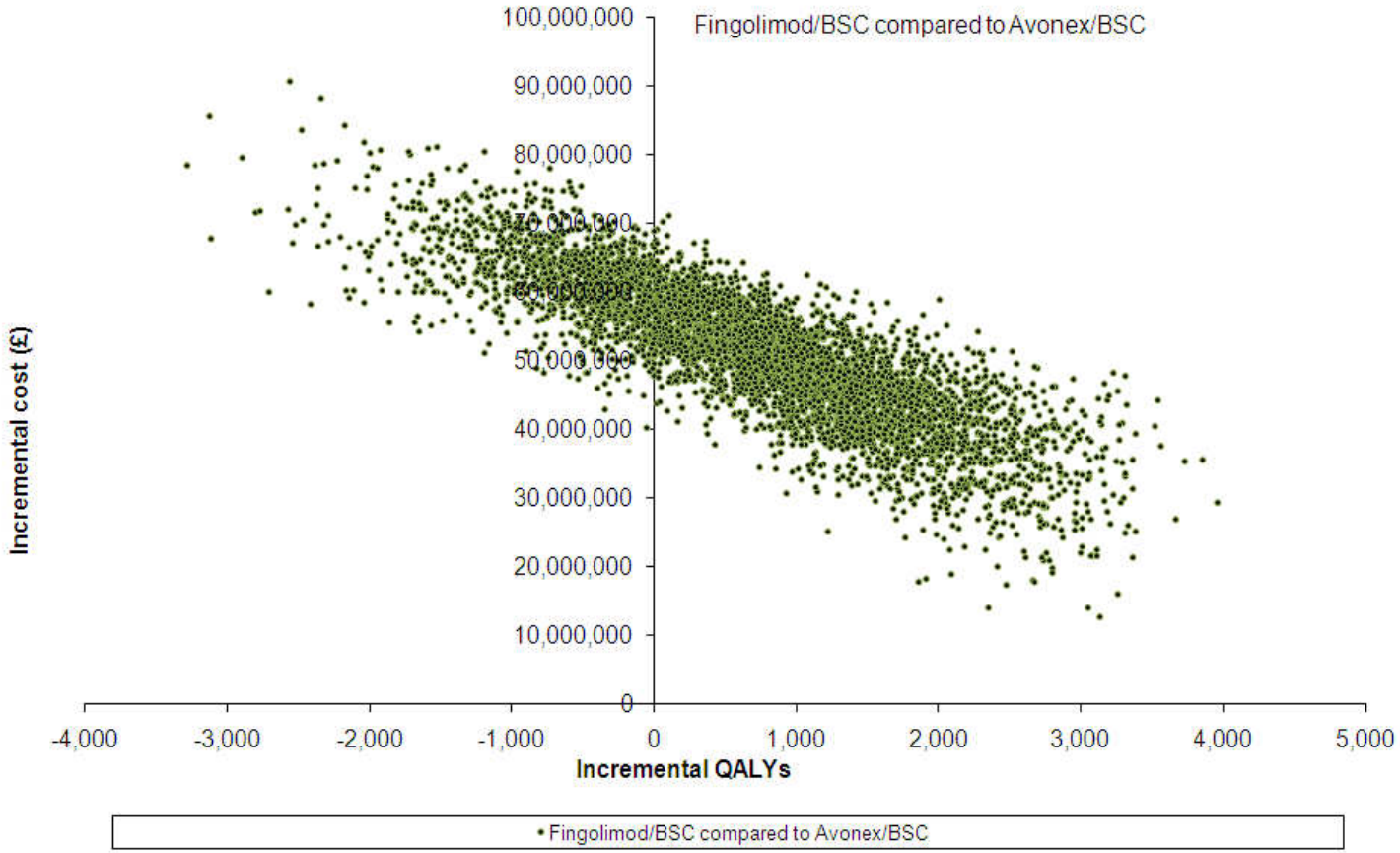
Discounted Deterministic Cost-Effectiveness Results

Tech-nologies	Total costs (£)	Total QALYs	Incre-mental costs (£)	Incre-mental QALYs	ICER £ per QALY gained
Avonex	271,647	3.98	—	—	—
Fingolimod	321,721	4.88	50,084	0.90	55,634

- **ICER was most sensitive to changes in:**
  1. Relative risks of disease progression (lower to upper CI bounds)
     - Fingolimod (£25k per QALY to £107k per QALY)
     - Avonex (A dominates F to £6k per QALY for F)
  2. Relative risk of relapse for Avonex (£69k to £40k per QALY)
  3. Discount rate (£43k and £64k per QALY for 0% and 6%)

- Uncertainty in other parameter values led to only small changes in ICER
- In PSA, 26% probability that the ICER is less than £30,000/QALY gained

Manufacturer's submission: PSA scatter plot



- In majority (75%) of PSA runs, fingolimod had additional cost over Avonex but additional QALY benefits
- 26% probability that the ICER for fingolimod vs Avonex is less than £30,000 per QALY threshold

ERG critique - main concerns

- Populations defined by manufacturer are not mutually exclusive
  - Population 1b constituted 44% of participants in TRANSFORMS trial and fewer than 20% participants in FREEDOMS trial
  - Power calculations may not give good indication of trials' ability to assess fingolimod relative to comparators in licensed population
- Concerned that RRs rather than HRs were used when adjusting natural history estimates of progression to account for use of treatments
- Lack of justification for structural assumptions in base case
- Comparators other than Avonex should have been considered
  - Considered best supportive care may have been more appropriate
- Considers there to be a high degree of uncertainty around model predictions
- Concerned that utility data from trials not used in model
- Administrative and monitoring costs of fingolimod and Avonex were not well justified by manufacturer

Committee's Considerations (i)

- Available evidence shows that fingolimod improves outcomes for the whole population in the clinical trials
  - however the magnitude of the relative effect of fingolimod in the subgroups defined by the marketing authorisation remains uncertain
- Limiting the analyses to comparisons with Avonex only appears inappropriate
- It was not unsurprising to see non-significant changes in health-related quality of life measures in the FREEDOMS and TRANSFORMS trials, but the impact of fingolimod on health-related quality of life remained uncertain
- Concerned that the treatment effect observed for the duration of the trials (1 or 2 years) was maintained at the same level during the on-treatment periods in the model
  - Considered that it would be more prudent to assume some waning of treatment effect over time

Committee's Considerations (ii)

- Concerned that the natural history progression data were a source of considerable uncertainty in the model
- Uncertainties in the manufacturer's model were thought to lead to an underestimation of the most plausible ICER
- Even an analysis that relied on a combined set of plausible assumptions would be certain to produce ICERs that substantially exceed the range it could consider to represent a cost-effective use of NHS resources
- Most plausible ICERs for fingolimod for population 1b are likely to be:
  - above £94,000 per QALY gained compared with best supportive care
  - above £79,000 per QALY gained in population 1b excluding population 2 (people with rapidly evolving severe disease)

ACD section 4.17

- base case ICER for fingolimod of £55,600 per QALY gained compared with Avonex subject to considerable uncertainty/ underestimation because:
  - Avonex is not the only relevant comparator
  - Assumptions about long term treatment effectiveness optimistic
  - Administration costs employed in the model (number of neurologists visits)
  - Natural history of disease progression unrepresentative of the current UK population with MS
  - Utility data

ACD Preliminary Recommendation

- Fingolimod is not recommended for the treatment of relapsing–remitting multiple sclerosis

Consultation on ACD

- Responses received from:
  - Novartis Pharmaceuticals UK (manufacturer)
  - Royal College of Physicians
  - MS Society
  - MS Trust
  - Royal College of Nursing
  - Kings Neurosciences Centre
  - Merck Serono
  - Clinical expert on behalf of Royal College of Physicians, Association of British Neurologists and British Society of Rehabilitation Medicine
  - Collective response from several UK neurologists
  - Members of Parliament
  - Public (63 web responses)

Comments on ACD – Patient Organisations (i)

- Extremely disappointed with draft recommendation
- None of the Committee members have specific neurological experience
  - Unreasonable to expect the two clinical experts at the meeting to discuss all the key issues
- Denying access to fingolimod is unethical and perverse
- MS Society considers their survey reporting the experiences of over 1000 people with MS was not adequately discussed by the Committee
- Physical and emotional impact of relapses not adequately described in ACD
- Avonex is a suitable comparator. Best supportive care is not a suitable comparator because:
  - Not reflective of best practice or professional guidelines
  - TA127 did not consider BSC to be an appropriate comparator (inconsistent decision-making)
- Trial demonstrates people who receive fingolimod experience significantly less deterioration in their ability to carry out daily activities than those treated with beta-interferon

Comments on ACD – Commentators

- A negative recommendation will exacerbate the 'postcode' lottery of MS treatment that already exists
- UK is ranked 13th out of 14 countries in terms of access to new treatments for MS, a negative recommendation on the use of fingolimod will widen this gap further
- Committee's decision does not seem to take the wider social and economic benefits of fingolimod into account
- Given the incomplete submission of evidence for all patient subgroups considered and uncertainties surrounding the economic evaluation, the preliminary recommendation is justified
- Evidence of serious adverse events associated with fingolimod treatment are emerging including delayed asystole, complete heart block, retinal vein occlusion and malignancy
  - Consideration of further monitoring may be warranted

Comments on ACD – General Public (ii)

- Socio-economic benefits of reduced number of relapses with fingolimod treatment has not been given due consideration
- There is wide variation in patients response to existing treatments
- Committee didn't understand the significance of the statements from the patients perspective relating to adverse effects of treatment and the value of fingolimod to patients, their carers and families
- Interferon treatment causes severe side effects which have a considerable impact on daily living
- Hidden costs of fingolimod such as disability benefits, hospital admissions, and carer's allowance have not been considered
- Fingolimod gives patients back their independence
- Avonex is a reasonable comparator and can be justified on the basis that neurologists accept that all beta-interferons are comparable in efficacy

Patient Access Scheme from Manufacturer

- Patient Access Scheme proposed by manufacturer
  - Simple confidential discount to the list price offered
  - Not dependent on any criteria
  - Applies to all supplies and preparations of fingolimod

Base-case (no PAS)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Avonex	271,647	3.98	—	—	—
Gilenya	321,721	4.88	50,084	0.90	**55,634**

Base-case with PAS

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Avonex	271,647	3.98	—	—	—
Gilenya	281,404	4.88	9,758	0.90	**10,839**

Scenario Analyses including PAS (i)

- **Comparison with Rebiff-44**

No PAS

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Rebif-44	263,055	4.17	—	—	—
Gilenya	326,751	4.94	63,697	0.766	**£83,120**

With PAS

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Rebif-44	263,055	4.17	—	—	—
Gilenya	284,338	4.94	21,284	0.766	**£27,774**

- Manufacturer notes that efficacy data to derive analyses based on all patients with RRMS, not those who meet the criteria for population 1b
  - Efficacy data likely to overestimate effect of Rebif-44, therefore ICER likely to be lower

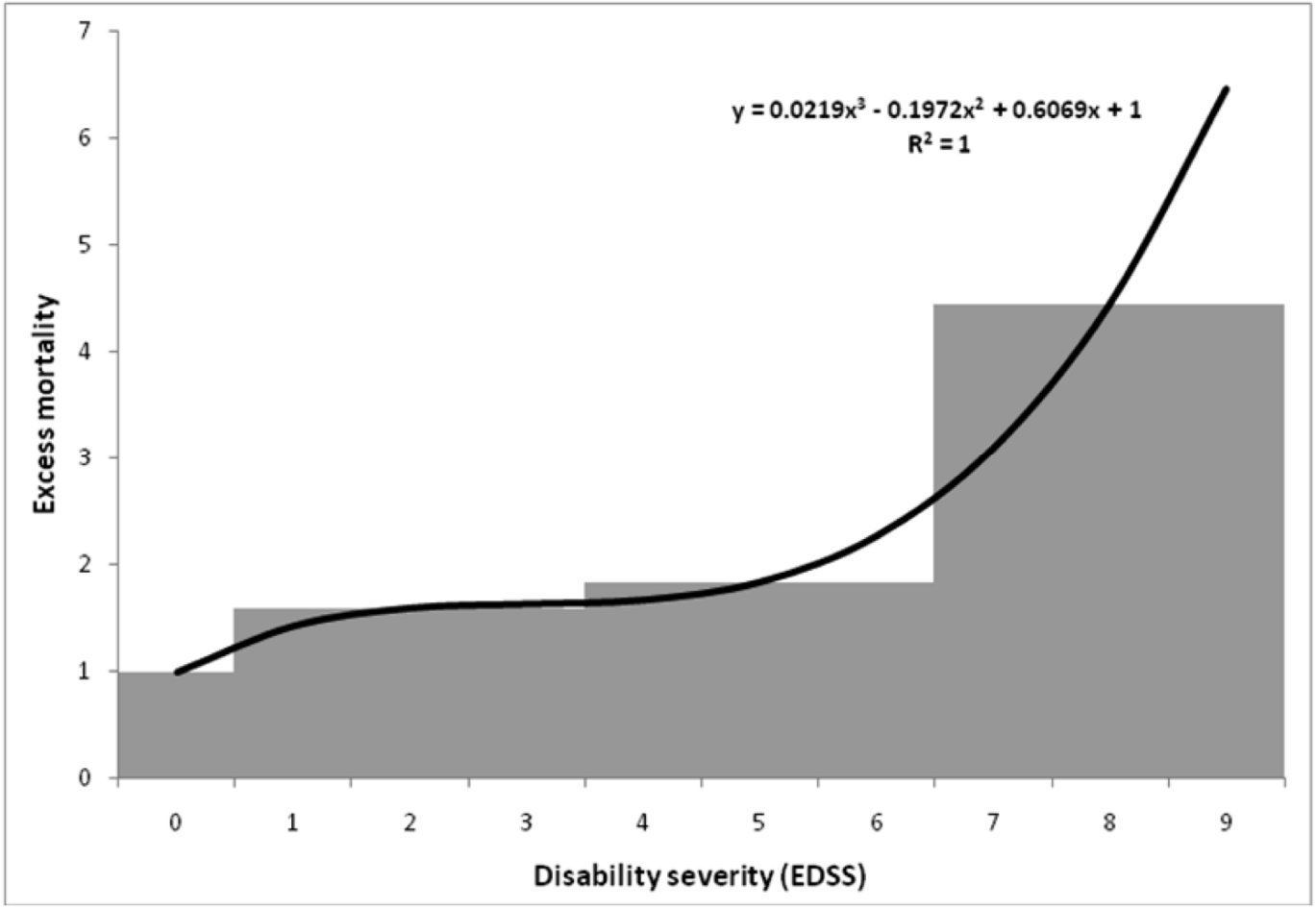
Issues

- Is Avonex/beta interferon the most appropriate comparator for population 1b?
- Is there sufficient evidence that fingolimod has a meaningful impact on patient quality of life?
- The ERG explored numerous key uncertainties in the model. Have all of the key uncertainties in the model been explored by the ERG and/or the manufacturer?

- *How do you think this appraisal would be dealt with in the Bulgarian health system?*
- *What are the advantages and disadvantages from your perspective of the approach taken by NICE?*

Uncertainties

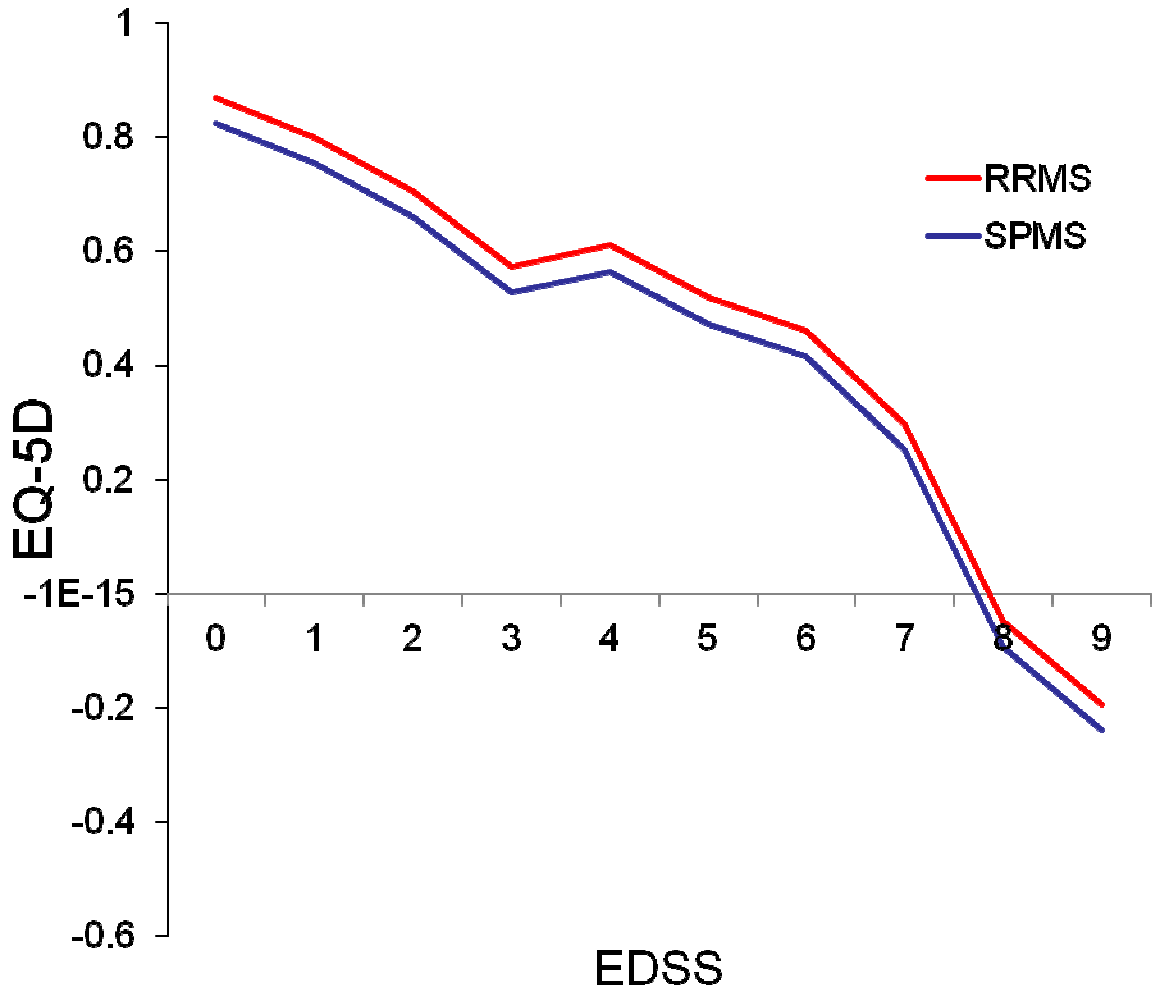
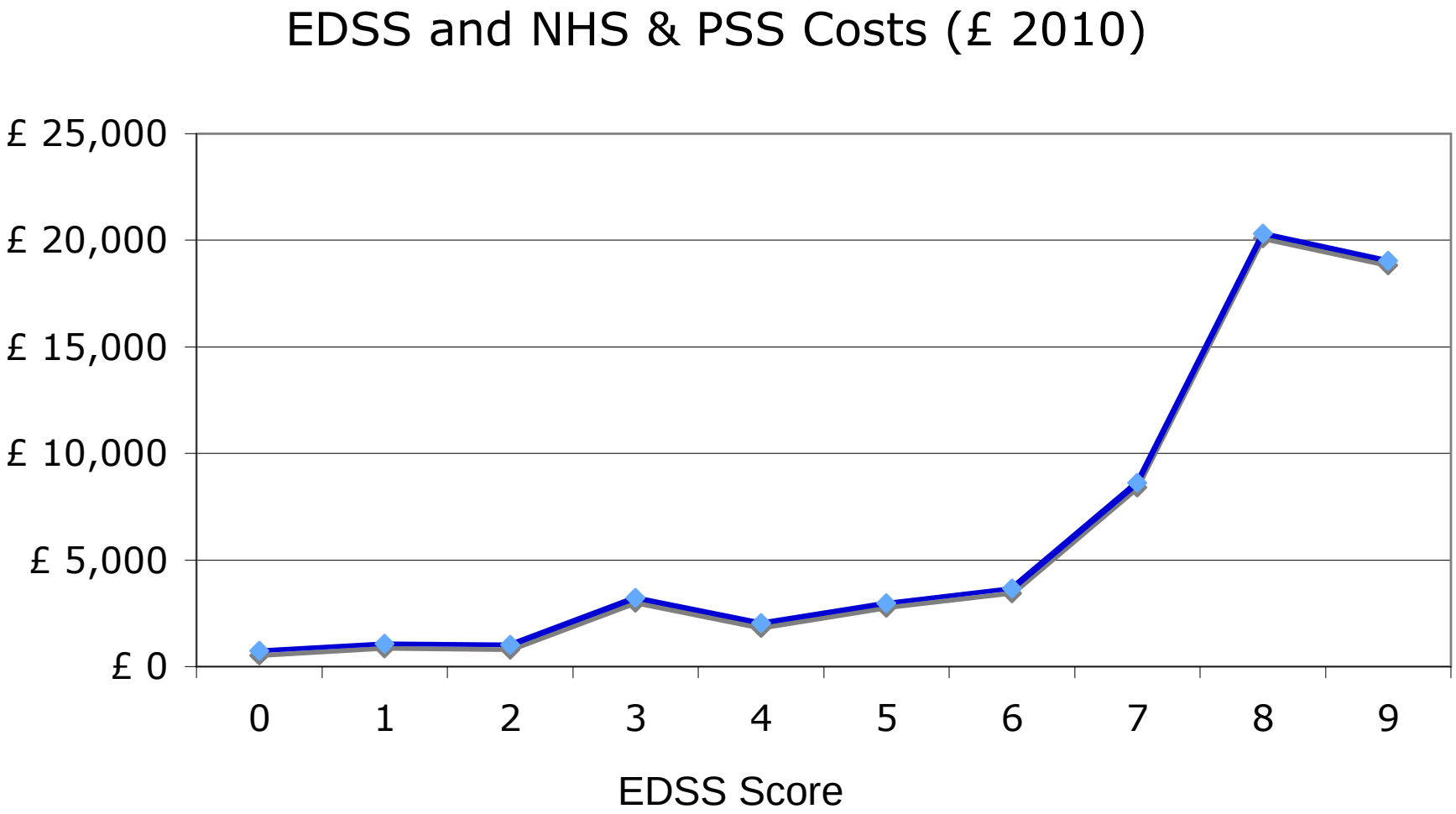
Effect of EDSS score on mortality



EDSS	RR Death
0	1.00
1	1.43
2	1.60
3	1.64
4	1.67
5	1.84
6	2.27
7	3.10
8	4.45
9	6.45

Ref: Page 207 MS. References cited: Sadovnick et al (1992) Pokorski (1997)

EDSS and EQ-5D



EDSS and Costs