NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single technology appraisal (STA)

Fingolimod for the Treatment of Relapsing-Remitting Multiple Sclerosis in Adults

Manufacturer response to Evidence Review Group request for an analysis of Population “1b but not 2”

Novartis Pharmaceuticals UK Ltd.

Updated 13 May 2011

Table 1 and Table 2 state the numbers of patients for the population “1b but not 2”. Table 3 and Table 4 describe the baseline characteristics for the population “1b but not 2”.

Table 1 Number of patients - FREEDOMS

	Fingolimod 0.5mg (N=425)	**Placebo (N=418)**
Population 1b[1]	[redacted]	[redacted]
Population 2[2]	77	63
Population “1b but not 2”	[redacted]	[redacted]

Table 2 Number of patients - TRANSFORMS

	Fingolimod 0.5mg (N=429)	**Interferon-beta-1a (N=431)**
Population 1b[1]	[redacted]	[redacted]
Population 2[2]	56	65
Population “1b but not 2”	[redacted]	[redacted]

[1] Defined as: “Patients who have had prior therapy and have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year.”
[2] Defined by NICE as: “2 or more relapses in 1 year and with 1 or more gadolinium enhancing lesions on brain MRI.”

Table 3 Baseline characteristics - FREEDOMS - "Population 1b but not 2"

Baseline characteristic	**Fingolimod 0.5mg (n=[redacted])**	**Placebo (n=[redacted])**
Age, years		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]
Clinical characteristics		
Time since onset of symptoms to randomisation (years)		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Relapses in previous year		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Relapses in previous 2 years		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
EDSS score		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
EDSS score, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
1.5	[redacted]	[redacted]
2	[redacted]	[redacted]
2.5	[redacted]	[redacted]
3	[redacted]	[redacted]
3.5	[redacted]	[redacted]
4	[redacted]	[redacted]
4.5	[redacted]	[redacted]
5	[redacted]	[redacted]
5.5	[redacted]	[redacted]
Treatment history		
Any therapy (%)	[redacted]	[redacted]
MRI findings		
Patients with no gadolinium-enhancing lesions on T_1-weighted images, number/total (%)	[redacted]	[redacted]
Number of gadolinium-enhancing lesions on T_1-weighted images		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Volume of lesions on T_2-weighted images, mm^3		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Normalised brain volume, cm^3		
Mean (SD)	[redacted]	[redacted]

Baseline characteristic	Fingolimod 0.5mg (n=[redacted])	Placebo (n=[redacted])
Median (range)	[redacted]	[redacted]

Table 4 Baseline characteristics - TRANSFORMS - "Population 1b but not 2"

Baseline characteristic	Fingolimod 0.5mg (n=[redacted])	Interferon-beta-1a (n=[redacted])
Age, years		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]
Clinical characteristics		
Time since onset of symptoms to randomisation (years)		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Relapses in previous year		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Relapses in previous 2 years		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
EDSS score		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
EDSS score, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
1.5	[redacted]	[redacted]
2	[redacted]	[redacted]
2.5	[redacted]	[redacted]
3	[redacted]	[redacted]
3.5	[redacted]	[redacted]
4	[redacted]	[redacted]
4.5	[redacted]	[redacted]
5	[redacted]	[redacted]
5.5	[redacted]	[redacted]
Treatment history		
Any therapy (%)	[redacted]	[redacted]
MRI findings -		
Patients with no gadolinium-enhancing lesions on T_1-weighted images, number/total (%)	[redacted]	[redacted]
Number of gadolinium-enhancing lesions on T_1-weighted images		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Volume of lesions on T_2-weighted images, mm^3		

Baseline characteristic	Fingolimod 0.5mg (n=[redacted])	Interferon-beta-1a (n=[redacted])
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Normalised brain volume, cm^3		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]

Table 5 and Table 6 states the outcome data for the population "1b but not 2" for the trials FREEDOMS and TRANSFORMS. Table 7 and Table 8 states the relative effect measures data for the population "1b but not 2" for the trials FREEDOMS and TRANSFORMS.

Table 5 Outcome data - FREEDOMS - Population "1b but not 2"

	Fingolimod 0.5mg (n=[redacted])	Placebo (n=[redacted])
Annualised Relapse Rate (95% CI)[3]	[redacted]	[redacted]
Number(%) patients with confirmed relapse up to Month 24	[redacted]	[redacted]
Number(%) patients with 3-month confirmed disability progression up to Month 24	[redacted]	[redacted]
Time to first 3-month confirmed disability progression. K-M estimate(SE) of free progression at Month 24. [95% CI)	[redacted]	[redacted]
Number (%) of patients discontinuing due to adverse event	[redacted]	[redacted]

Table 6 Outcome data - TRANSFORMS - Population "1b but not 2"

	Fingolimod 0.5mg (n=[redacted])	Interferon-beta-1a (n=[redacted])
Annualised Relapse Rate (95% CI)[3]	[redacted]	[redacted]
Number(%) patients with confirmed relapse up to Month 12	[redacted]	[redacted]
Number(%) patients with 3-month confirmed disability progression up to Month 12	[redacted]	[redacted]
Time to first 3-month confirmed disability progression. K-M estimate(SE) of free progression at Month 12. [95% CI)	[redacted]	[redacted]
Number (%) of patients discontinuing due to adverse event	[redacted]	[redacted]

[3] Negative binomial (NB) regression model, log-link, adjusted for treatment for the overall result, and for treatment subgroup, and treatment by subgroup interaction for subgroup analyses. Log(time on study) was used as an offset variable

Table 7 Relative effect measures - FREEDOMS - Population "1b but not 2"

	Fingolimod 0.5mg compared to placebo	p
Annualised Relapse Rate ratio (95% CI) [confirmed relapses only, up to Month 24]	[redacted]	[redacted]
Hazard Ratio 3-month confirmed disability progression (95% CI) [Month 24]	[redacted]	[redacted]

Table 8 Relative effect measures - TRANSFORMS - Population "1b but not 2"

	Fingolimod 0.5mg compared to interferon-beta-1a	p
Annualised Relapse Rate ratio (95% CI) [confirmed relapses only, up to Month 12]	[redacted]	[redacted]
Hazard Ratio 3-month confirmed disability progression (95% CI) [Month 12]	[redacted]	[redacted]

Table 9 shows the incremental analysis of the cost-effectiveness results for fingolimod compared to Avonex (Interferon-beta-1a). Novartis believes that Fingolimod is cost-effective in Population 1b and this sub-analysis of Population 1b which the ERG and NICE have requested is consistent with this.

Table 9 Cost-effectiveness results (discounted)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Avonex	£58,590	-0.827	-	-	-
Fingolimod	£97,010	1.223	£38,420	2.050	£18,741

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.