

Supplementary Tables

Supp Table 1: LIST OF SUPPLEMENTARY ANALYSES UNDERTAKEN AND RATIONALE

Pre-specified?	Problem to be addressed	Analysis undertaken	Results at
	<i>Sensitivity analyses</i>		
Yes	Comparability with year 6 analysis, in which EDSS scores recorded after a patient had switched to a non-scheme DMT were excluded	Exclude such scores, including those for patients who switch to a non-scheme DMT before the first annual review.	Tables 6, 7
Yes	Assess implications of excluding EDSS scores after any switch to a different DMT	Exclude such scores.	Tables 6, 7
Yes	Possible bias due to incomplete follow-up in RSS cohort	Impute missing year 10 values using the MLM model to extrapolate from the available data (single and multiple imputations). As a sensitivity analysis, add 0.5 EDSS points to each imputed value	Tables 6, 7
Yes	As above	Supplement available data by using "out of window" year 10 scores to impute the value for year 10.	Tables 6, 7
Yes	Possible bias due to patterns of availability of data in BCMS dataset	Use MLM to "enrich" BCMS dataset by imputing additional EDSS scores for patients with relatively sparse follow-up; re-estimate transition matrices and use in Markov model	Tables 6, 7
No	Possible bias due to slight difference in the distribution of disease duration at baseline between the BCMS and RSS datasets	Estimate a time -variant Markov model for the BCMS data (ie a model in which the transition probabilities can vary with time from baseline) and apply to the RSS data adjusting for the difference in mean disease duration at baseline	Tables 6, 7; appendix 8
	<i>Subgroup analyses</i>		
Yes	Variation of treatment effect with baseline EDSS	Patients starting at EDSS 3.5 or below versus those starting at (a) EDSS 4-5.5, (b) EDSS 6 and above	Tables 9, 10
Yes	Effect of gender	Male versus female (with further analysis using gender-specific transition matrices derived from the BCMS data)	Table 11
Yes	Possible bias due to patients who had been waiting for treatment for some years before the start of the RSS ("prevalent patients") and who may therefore not be typical of a normal cohort of patients starting treatment ("incident patients")	Patients recruited during the first quartile (first 12 months) or before the median (first 18 months) versus those recruited later	Tables 9-11
Yes	Effect of disease duration at baseline	Patients with disease duration at baseline below the lower quartile (3 years) or median (6 years) versus those with longer disease duration	Tables 9-11
Yes	Effect of disease course at baseline	Patients with SPMS at baseline versus RRMS at baseline	Tables 9, 10
Yes	Whether patients who drop off treatment have worse outcomes than those on treatment throughout	Patients dropping off treatment versus those staying on treatment throughout	Table 11
No	Reduce confounding due to correlation between baseline EDSS and other factors	A number of 2-way subgroup analyses- by EDSS at baseline and (i) recruitment date, (ii) disease duration, and (iii) type of MS.	Tables 9-11
	<i>Other supplementary analyses</i>		
Yes	Apparent "waning" of treatment effect	Estimate a Markov model in which the treatment effect (the relative hazard ratio for forward transitions) is allowed to vary with time from baseline	Appendix 6
Yes	As above	Direct comparison of MLM models fitted to BCMS and RSS data	Appendix 3
Yes	As above	Direct estimation of a Markov model from the RSS data and comparison with parameters estimated from BCMS data	Appendix 3
No	Possible bias due to variation of natural history transition matrices with time from baseline	Repeat of key analyses using the time-variant Markov model	Appendix 7

Supp Table 2: AVAILABLE DATA BY YEAR FROM BASELINE

	----- Total cohort -----				----- Subgroup with RRMS at baseline -----				
	"In-window" scores ^(a)		Including imputed year 10 ^(b) scores		"In-window" scores ^(a)		Including imputed year 10 ^(b) scores		
	Number	%	Number	%	Number	%	Number	%	
Data available at least to:									
Year 1	4,862	100.0%	4,862	100.0%	4,217	100.0%	4,217	100.0%	
Year 2	4,748	97.7%	4,748	97.7%	4,131	98.0%	4,131	98.0%	
Year 3	4,632	95.3%	4,633	95.3%	4,051	96.1%	4,052	96.1%	
Year 4	4,518	92.9%	4,523	93.0%	3,973	94.2%	3,978	94.3%	
Year 5	4,398	90.5%	4,407	90.6%	3,880	92.0%	3,889	92.2%	
Year 6	4,290	88.2%	4,307	88.6%	3,797	90.0%	3,814	90.4%	
Year 7	4,141	85.2%	4,174	85.8%	3,674	87.1%	3,704	87.8%	
Year 8	3,984	81.9%	4,045	83.2%	3,538	83.9%	3,588	85.1%	
Year 9	3,743	77.0%	3,867	79.5%	3,341	79.2%	3,442	81.6%	
Year 10	3,139	64.6%	3,507	72.1%	2,811	66.7%	3,129	74.2%	

a) All scores are allocated to the nearest anniversary of the date of the patient's baseline assessment. For the primary analysis, scores recorded more than 6 months after the 10th anniversary of baseline were regarded as "out of window" and disregarded

(b) For one sensitivity analysis, a further 371 scores collected at year 11 or later were used to impute an "in window" year 10 score.

Supp Table 3: BASELINE STATISTICS - COMPARISON OF BCMS AND RSS DATASETS

	----- BCMS dataset -----				----- RSS analysis cohort ^a -----		
	RRMS at baseline	SPMS at baseline	Total		RRMS at baseline	SPMS at baseline	Total
Number	735	163	898	Number	4,217	645	4,862
% of cohort	82%	18%		% of cohort	87%	13%	
Mean(SD) and Median (IQR) :							
Age at onset	28.6(8.1) 27.4(22.6-33.8)	32.1(10.3) 31.5(24.5-37.5)	29.2(8.6) 28.0(22.8-34.6)	Age at onset	31.0(8.4) 30.2(24.8-36.5)	31.9(9.05) 31.3(25.3-38.5)	31.1(8.5) 30.3(24.9-36.8)
Age at baseline	35.8(8.4) 35.1(29.6-41.4)	43.5(10.5) 41.9(35.9-51.5)	37.2(9.3) 36.2(30.3-42.9)	Age at baseline ^b	38.7(8.6) 38.4(32.5-44.5)	46.8(8.4) 46.9(40.7-52.9)	39.8(9.0) 39.5(33.3-45.9)
Disease duration	7.2(6.4) 5.4(2.1-10.4)	11.4(7.9) 9.9(5.3-16.4)	7.9(6.9) 5.9(2.5-11.5)	Disease duration	7.7(6.6) 5.7(2.6-11.0)	15.0(9.1) 13.7(7.7-20.6)	8.7(7.4) 6.5(2.9-12.4)
MSSS at baseline	3.45(2.3) 2.92(1.66-5.07)	6.28(2.1) 6.64(4.78-7.93)	3.96(2.5) 3.79(1.85-5.85)	MSSS at baseline ^c	4.81(2.50) 4.82(2.82-6.81)	6.48(1.91) 6.54(5.09-7.98)	5.04(2.46) 5.09(3.10-6.99)
EDSS at baseline	1.98(1.4) 2.0(1.0-2.5)	4.48(1.6) 4.5(3.0-6.0)	2.44(1.7) 2.0(1.0-3.5)	EDSS at baseline	3.07(1.5) 3.0(2.0-4.0)	5.54(1.1) 6.0(5.0-6.5)	3.40(1.69) 3.5(2.0-4.5)
Relapses in previous 2 yrs	2.9(1.2) 2(2-3)	2.8(1.2) 2(2-3)	2.9(1.2) 2(2-3)	Relapses in previous 2 yrs ^d	3.0(1.3) 3(2-3)	2.8(1.3) 2(2-3)	2.9(1.33) 3(2-3)
% female	77	61	74%	Female	75%	72%	75%

a Patients eligible and treated, with EDSS score at baseline and available age at onset

b Where available (n = 4205/644)

c Where available (n = 4212/644)

d Where available (n = 4217/644)

Supp Table 4: SENSITIVITY ANALYSES (UTILITY BASIS)

Variant	Number of patients	Mean years		Absolute treatment effect (utility)		Relative treatment effect (utility)	
		follow up	on treatment	Markov model	MLM	Markov model	MLM
Primary analysis	4,862	8.7	7.0	0.039 (0.034, 0.044)	0.037 (0.031, 0.042)	76% (73%, 79%)	77% (74%, 80%)
RRMS only subgroup	4,217	8.9	7.3	0.051 (0.046, 0.056)	0.037 (0.031, 0.042)	69% (66%, 72%)	76% (72%, 79%)
Supplementary/sensitivity analyses (including patients with SPMS at baseline except where noted)							
Excluding EDSS scores recorded after a patient has switched to a non-scheme DMT (a):							
Primary analysis cohort	4,799	8.0	6.4	0.039 (0.034, 0.044)	0.039 (0.034, 0.044)	73% (70%, 77%)	74% (71%, 77%)
RRMS only subgroup (b)	4,157	8.1	6.7	0.050 (0.045, 0.055)	0.039 (0.033, 0.044)	66% (63%, 70%)	72% (68%, 76%)
Excluding EDSS scores recorded after a patient has switched to any other DMT (a)							
Primary analysis cohort	4,475	7.0	5.7	0.038 (0.033, 0.042)	0.040 (0.035, 0.045)	71% (67%, 75%)	70% (66%, 74%)
RRMS only subgroup	3,871	7.0	5.9	0.048 (0.043, 0.053)	0.040 (0.035, 0.045)	64% (60%, 67%)	68% (64%, 72%)
Imputation - Markov model, using imputed values derived from the MLM							
- "on treatment" assumption	4,862	7.0	5.7	0.039 (0.034, 0.044)	n/a	79% (76%, 81%)	n/a
- "off treatment" assumption	4,862	7.0	5.9	0.036 (0.031, 0.041)	n/a	80% (77%, 83%)	n/a
Imputation - multilevel model							
- "on treatment" assumption	4,862	9.9	9.9	n/a	0.042 (0.036, 0.047)	n/a	77% (74%, 80%)
- "off treatment" assumption:							
single imputation	4,862	9.9	9.9	n/a	0.039 (0.033, 0.044)	n/a	79% (74%, 80%)
multiple imputation	4,862	9.9	9.9	n/a	0.036 (0.030, 0.043)	n/a	80% (77%, 83%)
single imputation + 0.5 EDSS points for each imputed value	4,862	9.9	9.9	n/a	0.016 (0.010, 0.021)	n/a	92% (88%, 95%)
Supplement RSS data with imputed values derived from out-of-window year 10 scores (c)	4,862	8.9	7.0	0.038 (0.033, 0.043)	(c)	77% (74%, 80%)	(c)
Use transition matrices from BCMS dataset supplemented by imputing additional data for patients with sparse follow up (c)							
Including patients with SPMS at baseline	4,862	8.7	7.0	0.052 (0.047, 0.057)	(c)	70% (67%, 73%)	(c)
Excluding patients with SPMS at baseline	4,217	8.9	7.3	0.065 (0.060, 0.071)	(c)	63% (60%, 66%)	(c)
Alternative Markov model with time-varying natural history transition matrices	4,862	8.7	7.0	0.070 (0.065, 0.075)	n/a	64% (61%, 66%)	n/a
Year 1 baseline [see appendix 6]	4,360	7.9	6.2	0.034 (0.029, 0.039)	0.032 (0.027, 0.037)	77% (74%, 81%)	79% (75%, 82%)

a) Patients switching before year 1 are also excluded from the analysis b) This was the primary analysis for the interim year 6 analysis
c) These variants were only carried out for the Markov model

Supp Table 5: SUBGROUP ANALYSES BY TYPE OF MS, DATE OF BASELINE ASSESSMENT AND BASELINE EDSS (BOTH MODELS) – UTILITY OUTCOMES

Population	n	Mean years		Mean baseline EDSS	----- Markov model -----		----- Multi-level model -----		----- Multi-level model with imputation -----	
		at risk	on treatment		Absolute treatment effect	Relative rate of progression	Absolute treatment effect	Relative rate of progression	Absolute treatment effect	Relative rate of progression
Primary analysis population	4,862	8.7	7.0	3.18	0.039(0.034, 0.044)	76% (73%, 79%)	0.037 (0.031, 0.042)	77% (74%, 80%)	0.039 (0.033, 0.044)	78.9% (76.0%, 81.8%)
Baseline EDSS ≤3.5	2,940	9.0	7.4	2.02	0.052 (0.046, 0.058)	69% (65%, 73%)	0.027 (0.021, 0.033)	81% (77%, 85%)	0.021 (0.015, 0.028)	86.5% (82.5%, 90.5%)
Baseline EDSS 4 to 5.5	1,275	8.6	6.7	4.42	0.038 (0.028, 0.048)	75% (69%, 82%)	0.024 (0.013, 0.034)	83% (76%, 90%)	0.021 (0.010, 0.032)	87.3% (81.0%, 93.5%)
Baseline EDSS ≥6	647	8.0	5.5	6	-0.018 (-0.035, -0.002)	112% (102%, 123%)	0.105 (0.086, 0.123)	61% (56%, 67%)	0.156 (0.138, 0.174)	56.4% (51.7%, 61.2%)
RRMS at baseline	4,217	8.9	7.3	2.86	0.051 (0.046, 0.056)	69% (66%, 72%)	0.037 (0.031, 0.042)	76% (72%, 79%)	0.035 (0.029, 0.041)	79.3% (76.1%, 82.6%)
SPMS at baseline	645	7.8	5.1	5.29	-0.041 (-0.056, -0.026)	129% (118%, 139%)	0.036 (0.019, 0.053)	83% (76%, 91%)	0.066 (0.047, 0.084)	77.2% (71.1%, 83.3%)
RRMS at baseline and:										
baseline EDSS ≤3.5	2,882	9.0	7.5	2.00	0.055 (0.049, 0.061)	67% (64%, 71%)	0.030 (0.024, 0.036)	79% (75%, 83%)	0.025 (0.018, 0.031)	84.3% (80.2%, 88.3%)
baseline EDSS 4 to 5.5	1,093	8.7	7.0	4.40	0.048 (0.037, 0.058)	70% (63%, 76%)	0.032 (0.020, 0.043)	78% (70%, 85%)	0.028 (0.016, 0.040)	82.5% (75.8%, 89.3%)
baseline EDSS ≥6	242	8.4	6.2	6	0.020 (-0.007, 0.047)	87% (70%, 105%)	0.138 (0.107, 0.169)	49% (40%, 59%)	0.187 (0.156, 0.219)	46.2% (38.6%, 53.7%)
SPMS at baseline and:										
baseline EDSS ≤3.5	58	8.2	5.9	2.69	-0.099 (-0.144, -0.053)	179% (142%, 217%)	-0.128 (-0.174, -0.081)	232% (176%, 288%)	-0.155 (-0.207, -0.102)	233.1% (187.7%, 278.5%)
baseline EDSS 4 to 5.5	182	7.8	5.1	4.55	-0.020 (-0.045, 0.005)	115% (96%, 133%)	-0.021 (-0.049, 0.006)	116% (96%, 135%)	-0.023 (-0.052, 0.006)	113.2% (95.7%, 130.7%)
baseline EDSS ≥6	405	7.8	5.1	6	-0.041 (-0.061, -0.022)	129% (115%, 142%)	0.085 (0.063, 0.108)	69% (61%, 76%)	0.137 (0.115, 0.159)	62.3% (57.0%, 67.6%)
Date of baseline assessment:										
on or before 28/8/2003	2,351	8.7	6.9	3.32	0.033 (0.025, 0.040)	79% (75%, 84%)	0.033 (0.026, 0.041)	79% (74%, 84%)	0.037 (0.029, 0.045)	80.2% (76.0%, 84.4%)
after 28/8/2003	2,511	8.8	7.0	3.05	0.044 (0.037, 0.052)	73% (69%, 77%)	0.040 (0.032, 0.047)	75% (71%, 79%)	0.041 (0.033, 0.048)	77.6% (73.4%, 81.8%)
Baseline at or before 31/8/2003 and										
baseline EDSS ≤3.5	1,352	8.9	7.5	2.07	0.048 (0.039, 0.057)	71% (65%, 76%)	0.022 (0.013, 0.031)	84% (78%, 90%)	0.017 (0.007, 0.026)	89.1% (83.0%, 95.1%)
baseline EDSS 4 to 5.5	631	8.6	6.6	4.42	0.030 (0.016, 0.044)	81% (72%, 90%)	0.018 (0.003, 0.033)	87% (78%, 97%)	0.012 (-0.003, 0.027)	92.5% (84.0%, 101.0%)
baseline EDSS ≥6	368	7.9	5.4	6	-0.017 (-0.038, 0.003)	112% (98%, 126%)	0.102 (0.078, 0.126)	62% (54%, 70%)	0.154 (0.129, 0.178)	57.0% (51.1%, 62.9%)
Baseline after 31/8/2003 and										
baseline EDSS ≤3.5	1,588	9.0	7.4	1.97	0.055 (0.047, 0.064)	67% (63%, 72%)	0.031 (0.023, 0.040)	79% (73%, 85%)	0.025 (0.016, 0.034)	84.4% (78.9%, 89.8%)
baseline EDSS 4 to 5.5	644	8.5	6.8	4.43	0.046 (0.031, 0.060)	70% (61%, 79%)	0.030 (0.015, 0.045)	78% (68%, 89%)	0.029 (0.013, 0.045)	82.2% (72.5%, 91.9%)
baseline EDSS ≥6	279	8.2	5.6	6	-0.020 (-0.045, 0.005)	114% (97%, 131%)	0.108 (0.080, 0.137)	61% (51%, 71%)	0.159 (0.131, 0.186)	55.6% (48.6%, 62.7%)