Appendix 2: Meta-regression Analyses Controlling for Baseline Relapse Rate: Clinical Efficacy and Safety of Disease-modifying Therapies for Multiple Sclerosis

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METHODS SUMMARY

Meta-regressions allow one to investigate whether study characteristics are related to absolute or relative treatment effects. In the present investigation, we test whether baseline prior relapse rate (i.e., the rate of relapses over the 12 months prior to study entry) is related to the relative treatment effects versus placebo for the annualized relapse rate (ARR) ratio, sustained accumulation of disability at 3 months (SAD3) and 6 months (SAD6) in the all-years, at least 80% relapsing-remitting multiple sclerosis (RRMS) subset of multiple sclerosis (MS) studies. In statistical terms, the heart of the model is changing the simple specification of the log-effect (where that effect can be a hazard ratio, a rate ratio, or an odds ratio):

$$\text{Log(treatment effect)} = \theta$$

to a specification that allows the log-effect for placebo-controlled studies to vary based on a mean-centered regressor, in this case, prior relapse rate over the last year:

$$\text{Log(treatment effect)} = \theta + \gamma^{*}[\text{Prior Relapse Rate[i]-Prior Relapse Rate (mean)}].$$

Some studies did not have data on the 1-year prior relapse rate but did have data on the relapse rate over the previous 2 years. Analysis of the subset of studies with data on both the 1-year and 2-year rates found a relatively consistent relationship between the two; we estimated that the 2-year rate is, on average, 1.49 times higher than the 1-year rate (see Table 2). This ratio was used to impute 1-year rates from studies with 2-year data.

Studies with missing data at both 1 year and 2 years could still be included in the analysis if they were not placebo-controlled, as the meta-regression assumed that any effect of prior relapse rate was limited to the relationship to placebo. A more complex model would be possible (i.e., one in which each treatment was affected differently by prior relapse rate) if there were more studies; however, the dataset was too sparse to power such a model.

Studies that were placebo-controlled and did not have a 1-year or 2-year rate were dropped from analyses. Fortunately, only a few studies were lost: Jacobs (1996; Avonex®); Kappos (2008; BG-12 [dimethyl fumarate]); Vollmer (2011; Avonex® and laquinimod); Hauser (2008; rituximab); and Polman (2005; laquinimod). No comparators were dropped from analyses due to the loss of these studies. Further details are shown in Table 3. A sample of WinBUGs code is shown for SAD3 in Appendix A.

RESULTS

Annualized Relapse Rate

Initial analyses using the “All-Years, 80%+ RRMS” inclusion criteria found homogeneous results for ARR ratios, with a sqrt(tau) of 0.038. This was lower than the estimate found in the base-case results (0.061, post-2000, 80%+ RRMS), suggesting that the greater clinical heterogeneity present after the inclusion of the pre-2000 studies did nothing to increase statistical heterogeneity.

A meta-regression was conducted to investigate whether prior relapse rate would explain significant variation in ARR ratios. As noted above, the meta-regression investigates whether there is an interaction effect between active treatment efficacy and placebo efficacy.

The estimate of gamma (the relationship between the prior relapse rate and the log-ARR ratios for active treatment vs. placebo) was estimated at 0.056 [-0.351, 0.262]. This is both substantively and statistically non-significant (in a Bayesian sense). The result is not surprising when one considers the study effects that are driving the estimate – studies have similar ratios, even as their prior relapse rate varies.

For instance, consider the fingolimod trials and glatiramer acetate (GA) trials, which drive the meta-regression, as these are the trials for which there is the most variation in prior relapse rate within treatment comparison:

Table 1. Example ARR Ratios and Prior Relapse Rates (for Fingolimod and GA Trials)

	Fingolimod	**Placebo**	**ARR Ratio**	**Prior Relapse Rate**
FREEDOM	0.18	0.4	0.45	1.47
Kappos (2006)	0.35	0.77	0.45	1.27
	GA	**Placebo**	**ARR Ratio**	**Prior Relapse Rate**
Comi (2001)	0.81	1.21	0.67	1.78
Johnson (1995)	0.59	0.84	0.7	1.95
CONFIRM (2012)	0.29	0.4	0.73	1.38

Abbreviations: ARR = Annualized relapse rate; GA = Glatiramer acetate

The ratios are extremely stable even as the prior relapse rate (and placebo response rate) varies. This is in part why the estimate of random-effects variation was so low in the original (non meta-regression) mixed treatment comparison (MTC) analyses.

Table 4 shows that point estimates of the rate ratios for treatments relative to placebo (and thus, to each other) change very little after the effect of prior relapse rate is accounted for by the meta-regression analyses.

Three-month Sustained Accumulation of Disability

Initial analyses using the “All-Years, 80%+ RRMS” inclusion criteria found relatively homogeneous results for SAD3 hazard ratios, with a sqrt(tau) of 0.069. This was the same as the estimate found in the base-case results (0.069, post-2000, 80%+ RRMS), suggesting that the greater clinical heterogeneity present after the inclusion of the pre-2000 studies did nothing to increase statistical heterogeneity. A meta-regression was conducted to investigate whether prior relapse rate would explain significant variation in SAD3 hazard ratios.

The estimate of gamma (the relationship between the log-hazard ratio (HR) and treatment efficacy vs. placebo) was estimated at -0.50 [-1.10, 0.08]. This is statistically marginally significant (the frequentist p-value with this confidence interval would be 0.08; the Bayesian interpretation would be that if our model assumptions are true, there is a 95.8% chance that the effect of prior relapse rate is a negative one [i.e., the higher the baseline relapse rate, the greater the advantage for most active treatments versus

placebo]) and is substantively of moderate importance. For example, consider the PRISMS study, which found an HR of Rebif vs. placebo of 0.65, with a prior relapse rate of 2.01 relapses per year. The predicted HR for this study with a prior relapse rate of 1.51 relapses per year (common of newer studies) would be exp[ln(0.65)+0.5*0.50)] = 0.83, or a reduction in efficacy relative to placebo of over 50%.

Investigation of the studies driving this estimate found 3 studies with substantively higher-than-average prior relapse rates (Bornstein, 1987, GA vs. placebo, 2.58; IFNB study group, IFNB-250 vs. placebo, 2.30; PRISMS, Rebif vs. placebo, 2.01). All 3 studies found higher active treatment vs. placebo rates than the other direct evidence (in the case of Bornstein, the other GA vs. placebo studies found weaker GA effects) or indirect evidence (the indirect evidence for IFNB 250 vs. placebo and for Rebif vs. placebo suggested a weaker relationship than found in the IFNB study and PRISMS, respectively).

A sensitivity analysis was conducted to determine if the Bornstein study was the primary driver of the effect. As it has the highest prior relapse rate and is the only study for which there is direct evidence contradicting it, it might be reasoned that this study alone is the reason for the almost significant effect. However, the size of the effect diminished only slightly after dropping the Bornstein study (from -0.50 to -0.42), suggesting that other studies also are contributing to the effect of baseline relapse rate on the estimate of treatment effect for the SAD3 outcome.

Table 4 shows that point estimates of the HRs for treatments relative to placebo (and thus, to each other) change slightly after the effect of prior relapse rate is accounted for.

Six-month Sustained Accumulation of Disability

Initial analyses using the “All-Years, 80%+ RRMS” inclusion criteria found a moderately high result for SAD6 hazard ratios, with a sqrt(tau) of 0.14. This was somewhat lower than the estimate found in the base-case results (0.21, post-2000, 80%+ RRMS), suggesting that the greater clinical heterogeneity present after the inclusion of the pre-2000 studies did nothing to increase statistical heterogeneity. A meta-regression was conducted to investigate whether prior relapse rate would explain significant variation in SAD6 hazard ratios.

The estimate of gamma (the relationship between the log-hazard ratio (HR) and treatment efficacy vs. placebo) was estimated at -0.33 [-2.31, 1.70]. This is statistically insignificant (the frequentist p-value with this confidence interval would be >0.50), and the sqrt(tau) returned to a value almost as high as found for the base-case analysis: 0.20.

Investigation of the studies driving the finding of heterogeneity in the SAD6 analyses suggests that there is potentially heterogeneity in the alemtuzumab vs Rebif results. While the overall meta-analysis did not have significant heterogeneity (p=0.11), the value of I^2 was relatively high (74%), in part because the hazard ratio found for CAMMS223 (0.25) was considerably lower than it was for CARE MS I or CARE MS-I or CARE MS-II (0.7 and 0.58, respectively). There also was a sign of inconsistency in the results for EVIDENCE, REGARD, and CombiRx; simply put, EVIDENCE found an advantage for Rebif over Avonex, but REGARD found GA to be superior to Rebif, while CombiRx found GA to be inferior to Avonex. This inconsistency also was a cause of the higher-than-optimal estimate of heterogeneity. While the estimate of sqrt(tau) is accounted for in the credible intervals for the estimates of the hazard ratios, it remains the case that caution should be taken in generalizing the results.

Table 4 shows that point estimates of the HRs for treatments relative to placebo (and thus, to each other) change slightly after the effect of prior relapse rate is accounted for.

DISCUSSION/SUMMARY

Meta-regressions were conducted for three of the key outcomes for the health-economic model, investigating whether prior relapse rate was related to the relative treatment effects versus placebo for the ARR ratio, SAD3, or SAD6. No effect was found for prior relapse rate on ARR ratios or SAD6 hazard ratios, but a marginally significantly negative effect was found for SAD3. It is unknown whether the effects are due to prior relapse rate itself or differences in study protocols/methods between older studies (which tend to have higher prior relapse rates) and newer studies. Point estimates change slightly for SAD3 when prior relapse rate is accounted for, primarily due to the adjustment for prior relapse rate, but in part because placebo-controlled studies with missing data on prior relapse rate were dropped from analyses.

Table 2. Comparison of 1-year and 2-year Prior Relapse Rate Across Trials

Author, Year	Trial Name	Treatment	Prior Relapse Rate, 1-year	Prior Relapse Rate, 2-year	Calculated 2-year to 1-year Ratio
Comi, 2012	ALLEGRO	Laquinimod	1.2	1.9	1.58
Comi, 2012	ALLEGRO	Placebo	1.3	1.9	1.46
Comi, 2011	FORTE	GA 20 mg	1.5	2	1.33
Comi, 2011	FORTE	GA 40 mg	1.4	2	1.43
Kappos, 2010	FREEDOMS	Fingolimod 1.25 mg	1.5	2.1	1.40
Kappos, 2010	FREEDOMS	Fingolimod 0.5 mg	1.5	2.1	1.40
Kappos, 2010	FREEDOMS	Placebo	1.4	2.2	1.57
Calabresi, 2012	FREEDOMS II	Fingolimod 1.25 mg	1.5	2.3	1.53
Calabresi, 2012	FREEDOMS II	Fingolimod 0.5 mg	1.4	2.2	1.57
Calabresi, 2012	FREEDOMS II	Placebo	1.5	2.2	1.47
Kappos, 2006	FTY720 D2201 Study	Fingolimod 1.25 mg	1.3	1.9	1.46
Kappos, 2006	FTY720 D2201 Study	Fingolimod 5 mg	1.3	1.9	1.46
Kappos, 2006	FTY720 D2201 Study	Placebo	1.2	1.8	1.50
Saida, 2012	Japanese Phase II	Placebo	1.7	2.8	1.65
Saida, 2012	Japanese Phase II	Fingolimod 0.5 mg	1.4	2.2	1.57
Saida, 2012	Japanese Phase II	Fingolimod 1.25 mg	1.5	2.3	1.53
O'Connor, 2011	TEMSO	Placebo	1.4	2.2	1.57
O'Connor, 2011	TEMSO	Teriflunomide 7 mg	1.4	2.3	1.64
O'Connor, 2011	TEMSO	Teriflunomide 14 mg	1.3	2.2	1.69
Vermersch, 2012	TENERE	IFNβ-1a 44 µg	1.3	1.7	1.31
Vermersch, 2012	TENERE	Teriflunomide 7 mg	1.4	1.7	1.21
Vermersch, 2012	TENERE	Teriflunomide 14 mg	1.2	1.7	1.42
Kappos, 2012	TOWER	Placebo	1.4	2.1	1.50
Kappos, 2012	TOWER	Teriflunomide 7 mg	1.4	2.1	1.50

Author, Year	Trial Name	Treatment	Prior Relapse Rate, 1-year	Prior Relapse Rate, 2-year	Calculated 2-year to 1-year Ratio
Kappos, 2012	TOWER	Teriflunomide 14 mg	1.4	2.1	1.50
Cohen, 2010	TRANSFORMS	Fingolimod 1.25	1.5	2.2	1.47
Cohen, 2010	TRANSFORMS	Fingolimod 0.5 mg	1.5	2.3	1.53
Cohen, 2010	TRANSFORMS	IFNβ-1a 30 µg	1.5	2.3	1.53

Abbreviations: GA = Glatiramer acetate; IFNβ-1a = Interferon beta-1a; mg = milligram; µg = microgram

Table 3. Prior Relapse Rates Among Analyzed Trials (All Years with 80% RRMS)

Trial Name	Treatment	1-year rate	2-year rate	3-year rate	ARR Analysis	SAD3 Analysis	SAD 6 Analysis
AFFIRM	Natalizumab	1.53			Yes	Yes	Yes
AFFIRM	Placebo	1.5			Yes	Yes	Yes
ALLEGRO	Laquinimod	1.2	1.9		Yes	Yes	Yes
ALLEGRO	Placebo	1.3	1.9		Yes	Yes	Yes
BECOME	GA 20 mg	NR			Yes	--	--
BECOME	Interferon β-1b 250 ug	NR			Yes	--	--
BEYOND	Interferon β-1b 500 ug	1.6			Yes	Yes	--
BEYOND	Interferon β-1b 250 ug	1.6			Yes	Yes	--
BEYOND	GA 20 mg	1.6			Yes	Yes	--
BG-12 Phase Iib Study	BG-12 120mg qd	NR			Excluded	--	--
BG-12 Phase Iib Study	BG-12 120 tid	NR			Excluded	--	--
BG-12 Phase Iib Study	BG-12 240mg tid	NR			Excluded	--	--
Bornstein 1987	GA 20 mg	2.58*	3.8		--	Yes	--
Bornstein 1987	Placebo	2.58*	3.9		--	Yes	--
BRAVO	Laquinimod 0.6 mg	NR			Excluded	--	--
BRAVO	Interferon β-1a 30 ug	NR			Excluded	--	--
BRAVO	Placebo	NR			Excluded	--	--
CAMMS223	Interferon β-1a 44 ug	NR			Yes	Yes	Yes
CAMMS223	Alemtuzumab 12 mg	NR			Yes	Yes	Yes

Trial Name	Treatment	1-year rate	2-year rate	3-year rate	ARR Analysis	SAD3 Analysis	SAD 6 Analysis
CAMMS223	Alemtuzumab 24 mg	NR			Yes	Yes	Yes
CARE MS I	Interferon β-1a 44 ug	1.8			Yes	Yes	Yes
CARE MS I	Alemtuzumab 12 mg	1.8			Yes	Yes	Yes
CARE-MS II	Interferon β-1a 44 ug	1.5			Yes	Yes	Yes
CARE-MS II	Alemtuzumab 12 mg	1.7			Yes	Yes	Yes
CARE-MS II	Alemtuzumab 24 mg	1.6			Yes	Yes	Yes
CombiRx	Interferon β-1a 30 ug	1.7		2.6	Yes	--	Yes
CombiRx	GA 20 mg	1.6		2.4	Yes	--	Yes
CONFIRM	Placebo	1.4			Yes	Yes	--
CONFIRM	BG-12 240 mg bid	1.3			Yes	Yes	--
CONFIRM	BG-12 240 tid	1.4			Yes	Yes	--
CONFIRM	GA 20 mg	1.4			Yes	Yes	--
Copolymer 1 Multiple Sclerosis Study Group	GA 20 mg	1.95*	2.9		Yes	Yes	--
Copolymer 1 Multiple Sclerosis Study Group	Placebo	1.95*	2.9		Yes	Yes	--
DEFINE	placebo	1.3			Yes	Yes	--
DEFINE	BG-12 240 mg bid	1.3			Yes	Yes	--
DEFINE	BG-12 240 mg tid	1.3			Yes	Yes	--
Dose Comparison 9006 Study Group	GA 20 mg	1.5			Yes	--	--
Dose Comparison 9006 Study Group	GA 40 mg	1.5			Yes	--	--

Trial Name	Treatment	1-year rate	2-year rate	3-year rate	ARR Analysis	SAD3 Analysis	SAD 6 Analysis
European/Canadian Glatiramer Acetate Study	GA	1.78*	2.8		Yes	--	--
European/Canadian Glatiramer Acetate Study	Placebo	1.78*	2.5		Yes	--	--
EVIDENCE	Interferon β-1a 44 ug	1.74*	2.6		Yes	Yes	Yes
EVIDENCE	Interferon β-1a 30 ug	1.74*	2.6		Yes	Yes	Yes
FORTE Study Group	GA 20 mg	1.5	2		Yes	--	--
FORTE Study Group	GA 40 mg	1.4	2		Yes	--	--
FREEDOMS	Fingolimod 1.25 mg	1.5	2.1		Yes	Yes	Yes
FREEDOMS	Fingolimod 0.5 mg	1.5	2.1		Yes	Yes	Yes
FREEDOMS	Placebo	1.4	2.2		Yes	Yes	Yes
FREEDOMS II	Fingolimod 1.25 mg	1.5	2.3		Yes	Yes	Yes
FREEDOMS II	Fingolimod 0.5 mg	1.4	2.2		Yes	Yes	Yes
FREEDOMS II	Placebo	1.5	2.2		Yes	Yes	Yes
FTY720 D2201 Study Group	Fingolimod 1.25 mg	1.3	1.9		Yes	--	--
FTY720 D2201 Study Group	Fingolimod 5 mg	1.3	1.9		Yes	--	--
FTY720 D2201 Study Group	Placebo	1.2	1.8		Yes	--	--
HERMES	Rituximab 1000 mg	NR			Excluded	--	--
HERMES	Placebo	NR			Excluded	--	--
IFNB MS Study Group	Interferon β-1b 1.6 MIU	2.3*	3.3		Yes	Yes	--
IFNB MS Study Group	Interferon β-1b 8 MIU	2.3*	3.4		Yes	Yes	--

Trial Name	Treatment	1-year rate	2-year rate	3-year rate	ARR Analysis	SAD3 Analysis	SAD 6 Analysis
IFNB MS Study Group	Placebo	2.3*	3.6		Yes	Yes	--
Japanese Phase II study	Placebo	1.7	2.8		Yes	--	--
Japanese Phase II study	Fingolimod 0.5 mg	1.4	2.2		Yes	--	--
Japanese Phase II study	Fingolimod 1.25 mg	1.5	2.3		Yes	--	--
LAQ/5062	Laquinimod 0.3 mg	1.46			Yes	--	--
LAQ/5062	Laquinimod 0.6 mg	1.51			Yes	--	--
LAQ/5062	Placebo	1.37			Yes	--	--
Laquinimod in Relapsing MS	Laquinimod 0.3 mg	NR			--	--	--
Laquinimod in Relapsing MS	Laquinimod 0.1 mg	NR			--	--	--
Laquinimod in Relapsing MS	Placebo	NR			--	--	--
MSCRG	Interferon β-1a 30 ug	NR			Excluded	--	--
MSCRG	Placebo	NR			Excluded	--	--
PRISMS	Interferon β-1a 22 ug	2.01*	3		--	Yes	--
PRISMS	Interferon β-1a 44 ug	2.01*	3		--	Yes	Yes
PRISMS	Placebo	2.01*	3		--	Yes	Yes
REGARD	Interferon β-1a 44 ug	1.33*	Unclear		Yes	--	Yes
REGARD	GA 20 mg	1.33*	Unclear		Yes	--	Yes
SELECT	Daclizumab HYP 300 mg	1.3			Yes	Yes	--
SELECT	Daclizumab HYP 150 mg	1.4			Yes	Yes	--
SELECT	Placebo	1.3			Yes	Yes	--

Trial Name	Treatment	1-year rate	2-year rate	3-year rate	ARR Analysis	SAD3 Analysis	SAD 6 Analysis
TEMSO	Placebo	1.4	2.2		Yes	Yes	Yes
TEMSO	Teriflunomide 7 mg	1.4	2.3		Yes	Yes	Yes
TEMSO	Teriflunomide 14 mg	1.3	2.2		Yes	Yes	Yes
TENERE	IFNβ-1a 44 µg	1.3	1.7		Yes	Yes	Yes
TENERE	Teriflunomide 7 mg	1.4	1.7		Yes	Yes	Yes
TENERE	Teriflunomide 14 mg	1.2	1.7		Yes	Yes	Yes
Teri in MS	Placebo	1.47			Yes	--	--
Teri in MS	Teriflunomide 7 mg	1.47			Yes	--	--
Teri in MS	Teriflunomide 14 mg	1.47			Yes	--	--
TOWER	Placebo	1.4	2.1		Yes	Yes	Yes
TOWER	Teriflunomide 7 mg	1.4	2.1		Yes	Yes	Yes
TOWER	Teriflunomide 14 mg	1.4	2.1		Yes	Yes	Yes
TRANSFORMS	Fingolimod 1.25	1.5	2.2		Yes	Yes	
TRANSFORMS	Fingolimod 0.5 mg	1.5	2.3		Yes	Yes	
TRANSFORMS	IFNβ-1a 30 µg	1.5	2.3		Yes	Yes	

Abbreviations: ARR = Annualized relapse rate; GA = Glatiramer acetate; IFN = Interferon; pbo = placebo; SAD = Sustained accumulation of disability; µg = microgram

Note: Prior relapse rate is only important for placebo-controlled trials. Active controlled trials with missing data were still included in the analysis. Grayed out trials are those placebo-controlled trials not reporting prior relapse rate or reporting only the median prior relapse rate.

*Indicates 1-year imputation from 2-year rate.

Table 4. Summary of MTC, Meta-regression, and Literature Results

Comparison	Base Case – Post-2000, 80% RRMS (MTC)	All Years with 80% RRMS	All Years with 80% RRMS Controlling for Relapse (Meta-regression)	Direct Evidence	Trial Name	Author, Year
ARR						
GA vs. pbo	0.64 [0.53, 0.76]	[redacted]	[redacted]	0.72 [0.61, 0.87] 0.7 [0.57, 0.86] 0.67 [0.48, 0.93]	CONFIRM Copolymer 1 MS Study* European/Canadian GA Study*	Fox, 2012 Johnson, 1995 Comi, 2001
Rebif 44 µg vs. pbo	0.62 [0.51, 0.76]	[redacted]	[redacted]	--	--	--
Rebif 22 µg vs. pbo	--	--	--	--	--	--
Avonex vs. pbo	0.78 [0.67, 0.91]	[redacted]	[redacted]	0.73 [0.62, 0.86] 0.82 [0.68, 0.98]	BRAVO MSCRG*	Vollmer, 2012 Jacobs, 1996
Betaferon vs. pbo	0.68 [0.52, 0.88]	[redacted]	[redacted]	0.66 [0.56, 0.79]	IFNB MS Study*	Duquette, 1993
Alemtuzumab 12 vs. pbo	[redacted]	[redacted]	[redacted]	--	--	--
SAD3						
GA vs. pbo	0.93 [0.59, 1.45]	[redacted]	[redacted]	0.93 [0.63, 1.37] 0.32 [0.09, 1.09] 0.86 [0.51, 1.45]	CONFIRM Bornstein, 1987* Copolymer 1 MS Study*	Fox, 2012 Bornstein, 1987 Johnson, 1995
Rebif 44 µg vs. pbo	0.79 [0.51, 1.24]	[redacted]	[redacted]	0.65 [0.45, 0.94]	PRISMS*	Ebers, 1998
Rebif 22 µg vs. pbo	--	[redacted]	[redacted]	0.75 [0.53, 1.08]	PRISMS*	Ebers, 1998
Avonex vs. pbo	0.91 [0.61, 1.33]	[redacted]	[redacted]	--	--	--
Betaferon vs. pbo	1.21 [0.68, 2.16]	[redacted]	[redacted]	0.68 [0.4, 1.17]	IFNB MS Study*	Duquette, 1993
Alemtuzumab 12 vs. pbo	[redacted]	[redacted]	[redacted]	--	--	--

Comparison	Base Case – Post-2000, 80% RRMS (MTC)	All Years with 80% RRMS	All Years with 80% RRMS Controlling for Relapse (Meta-regression)	Direct Evidence	Trial Name	Author, Year
			SAD6			
GA vs. pbo	0.89 [0.24, 3.21]	[redacted]	[redacted]	--	--	--
Rebif 44 µg vs. pbo	0.94 [0.30, 2.91]	[redacted]	[redacted]	0.73 [0.47, 1.14]	PRISMS*	Ebers, 1998
Rebif 22 µg vs. pbo	--	--	--	--	--	--
Avonex vs. pbo	0.92 [0.25, 3.49]	[redacted]	[redacted]	0.62 [0.37, 1.03]	MSCRG*	Jacobs, 1996
Betaferon vs. pbo	--	--	--	--	--	--
Alemtuzumab 12 vs. pbo	[redacted]	[redacted]	[redacted]	--	--	--

Abbreviations: ARR = Annualized relapse rate; GA = Glatiramer acetate; ICER = Incremental cost-effectiveness ratio; MTC = Mixed treatment comparison; pbo = placebo; RRMS = Relapsing remitting multiple sclerosis; SAD = Sustained accumulation of disability; µg = microgram
*Study enrolled patients prior to 2000.

** Correct values. Those in Table AA2.7 in Additional Appendix 2 of STA submission wrong (misread off Table AA2.9.) although correct values entered in HE model

APPENDIX A. WINBUGS CODE FOR META-REGRESSION ANALYSES

Below is the model code for the SAD3 meta-regression analyses modeling placebo-controlled studies as having effects equal to a grand mean, modified by gamma01, the slope for the effect of (a mean-centered) prior relapse rate.

```
model {

for (i in 1:N) {
prec.Prog3HR[i] <- 1/(Prog3HR.se[i]*Prog3HR.se[i])
Prog3HR[i]~dnorm(theta[i],prec.Prog3HR[i])
theta[i] <- delta[i] + gamma01*(PriorRR[i]-PriorRR.bar)*step(1.1-nb[i])
                delta[i] ~ dnorm(md[i],prec)
                md[i] <-  dd[ntreat[i]] - dd[nb[i]]

        }

gamma01~dnorm(0.0,0.0001)

PriorRR.bar<-1.64076923076923

tau<-1/prec
tau.sqrt<-sqrt(tau)


# Prior for between-study precision/sd
prec <- 1/(sd*sd)
sd ~ dunif(0,1)

#Give priors for differences
            dd[1]<-0
            for (k in 2:19){dd[k] ~ dnorm(0,0.0001) }


#All pairwise comparisons
for (c in 1:19-1){
            for (k in (c+1):19){
                        logHR[c,k] <- dd[k] - dd[c]
                        logHRprob[c,k] <- step(logHR[c,k])
                        HR[c,k] <- exp(logHR[c,k])
                        }
            }

gamma01better<-step(gamma01)
```