Appendix 8_ Results of extension studies

Table 1: Results of extension studies comparing early and delayed treatment with interferon in CIS

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety	
	Findings favouring early treatment	**Findings indicating no between group differences (or descriptive results)**	**Findings favouring early treatment**	**Findings indicating no between group differences (or descriptive results)**	**Findings favouring delayed treatment**	**Findings indicating no between group differences**
Kappos 2007	**Conversion to CDMS** HR=0.59; 95% CI, 0.44-0.80; p=0.0011 RR= 0.70; 95% CI, 0.56-0.88; p=0.002 Early treatment: 99/292 (34%) Delayed treatment: 85/176 (48%) **EDSS Progression** HR= 0.60; 95% CI, 0.39-0.92; p=0.022 RR= 0.63; 95% CI, 0.43-0.94; p=0.02 Early treatment: 42/292 (14%) Delayed treatment: 40/176 (23%)		**Cumulative number of newly active lesions** Fewer newly active lesions developed in the early treatment group over 3 years than in the delayed treatment group (p<0·0001).	**Absolute change in T2 lesion volume** No significant difference between groups (p=0·070) **Change in brain volume (%)** No significant difference between groups (p=0.15)	**Injection site reaction** RR=1.38, 95% CI, 1.11-1.71, p=0.003 158 (54%) patients in the early group 68 (39%) patients in the delayed group **Leucopenia** RR=1.69, 95% CI, 1.08-2.64, p=0.003 65 (22%) patients in the early group 22 (13%) patients in the delayed group **Raised alanine aminostransferase concentrations** RR=2.28, 95% CI, 1.25-4.19, p=0.008 46 (16%) patients in the early group 12 (7%) in the delayed group	**Flu-like symptoms** RR=1.00, 95% CI, 0.82-1.21, p=0.97 144 (49%) patients in the early group 86 (49%) patients in the delayed group

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety	
Kappos 2009	**Conversion to CDMS** HR=0.63; 95% CI, 0.48-0.83; p=0.003 RR= 0.70; 95% CI, 0.56-0.88; p=0.002 Early treatment: 124/292 (42%) Delayed treatment: 94/176 (53%)	**EDSS Progression** HR= 0.76; 95% CI, 0.50-1.17; p=0.177 RR=0.83; 95% CI, 0.60-1.15; p=0.27 Early treatment: 65/292 (22%) Delayed treatment: 47/176 (27%)	**Cumulative number of newly active lesions** Early treatment group: 9.7, 14.7 (mean, SD) Delayed group: 12.9, 15.7 (mean, SD) Significant when authors controlled for baseline scores, p=0.006	**Absolute change in T2 lesion volume** Early treatment group: -0.6, 4.1 (mean, SD) Delayed group: -0.3, 2.4 (mean, SD) **Change in brain volume (%)** Early treatment group: -2.7, 2.4 (mean, SD) Delayed group: -2.0, 2.1 (mean, SD) Not significant when authors controlled for baseline scores, p=0.121	**Injection site reaction** RR=1.39, 95% CI, 1.13-1.71, p=0.002 164 (56%) patients in the early group 71 (40%) patients in the delayed group **Leucopenia** RR=1.69, 95% CI, 1.13-2.54, p=0.01 73 (25%) patients in the early group 26 (15%) patients in the delayed group	**Flu-like syndrome complex** RR=1.05, 95% CI, 0.88-1.25, p=0.97 158 (54%) patients in the early group 91 (52%) patients in the delayed group
Edan 2014	**Conversion to CDMS** HR=0.678; 95% CI, 0.525-0.875; p=0.003 Early treatment: 55.5% Delayed treatment: 65.8%	**EDSS Progression** RR=1.19; 95% CI, 0.83-1.72; p=0.35 Early treatment: 60/178 (34%) Delayed treatment: 30/106 (28%)				*The authors reported no difference between groups in the total number of patients experiencing ≥1 serious adverse event: 12 patients (6.7%) in the early treatment group and eight patients (7.5%) in the delayed treatment group.*
REFLEXION (NCT00813709)	**Conversion to CDMS** Interferon tiw vs delayed - HR=0.56, 95% CI, 0.38-0.82, p=0.002 Interferon qw vs delayed - HR=0.57, 95% CI, 0.39-0.84, p=0.006 **Percentage of Relapse-Free**			**Percent Change From Baseline in Brain Volume**** Interferon (qw): -0.86 (1.073), mean (SD) Interferon (tiw): -1.14 (1.321), mean (SD) Delayed interferon: -1.02 (1.248), mean (SD)		

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety	
	Participants Interferon (qw): 102/175 (58.3%) Interferon (tiw): 88/171 (51.5%) Delayed interferon: 73/171 (42.7%)			**Number of new T2 Lesions**** Interferon (qw): 1.39 (2.573), mean (SD) Interferon (tiw): 1.19 (4.217), mean (SD) Delayed interferon: 0.83 (1.545), mean (SD) **Number of new gadolinium enhanced (Gd+) Lesions**** Interferon (qw): 0.40 (1.354), mean (SD) Interferon (tiw): 0.41 (1.754), mean (SD) Delayed interferon: 0.17 (0.506), mean (SD)		
REFLEXION (NCT00813709)	**Percentage of Relapse-Free Participants** Interferon (qw): 79/175 (45.1%) Interferon (tiw): 70/171 (40.9%) Delayed interferon: 59/171 (34.5%)	**Conversion to CDMS**** (cumulative % of participants with CMDS) Interferon (qw): 40.7%, 95% CI, 32.8 to 48.6 Interferon (tiw): 39.2%, 95% CI, 30.8 to 47.6 Delayed interferon: 44.6%, 95% CI, 36.6 to 52.6		**Percent Change From Baseline in Brain Volume**** Interferon (qw): -0.86 (1.073), mean (SD) Interferon (tiw): -1.14 (1.321), mean (SD) Delayed interferon: -1.02 (1.248), mean (SD) **Number of new T2 Lesions**** Interferon (qw): 1.17 (2.628), mean (SD) Interferon (tiw): 1.35 (3.284), mean (SD) Delayed interferon: 1.17 (2.576), mean (SD)		**Discontinuation due to any reason**** Interferon (qw): 20/51 (39.2%) Interferon (tiw): 11/46 (23.9%) Delayed interferon: 20/58 (34.5%) **Discontinuation due to adverse events**** Interferon (qw): 4/51 (7.8%) Interferon (tiw): 3/46 (6.5%) Delayed interferon: 5/58 (8.6%)

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety	
				Number of new gadolinium enhanced (Gd+) Lesions** Interferon (qw): 0.36 (1.225), mean (SD) Interferon (tiw): 0.48 (1.618), mean (SD) Delayed interferon: 0.24 (0.823), mean (SD)		
Kinkel 2006	**Conversion to CDMS** HR= 0.65, 95% CI, 0.43-0.97; p=0.03 (unadjusted) HR= 0.57, 95% CI, 0.38-0.86; p=0.008 (adjusted for age, CHAMPS qualifying event, CHAMPS baseline brain MRI T2 lesions volume, and baseline number of Gd+ lesions)			**New or enlarging T2 lesions** Early treatment: 3.5 (0.5-8.5); median (IQR) Delayed treatment: 6.0 (2-13); median (IQR) Wilcoxon rank sum test indicated no significant difference (p=0.05), as the 0.01 level of significance was not met. **Gad lesions (% of participants with ≥1 lesion)** Early treatment: 29% Delayed treatment: 30% Wilcoxon rank sum test indicated no significant difference between groups (p=0.81) **Change in T2 lesions volume (mm3)** Early treatment: 646 (-105, 2,599); median (IQR) Delayed treatment: 827 (107, 4,112); median (IQR) Wilcoxon rank sum test		*"No new safety concerns with IFN -1a therapy arose during the CHAMPIONS Study."*

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety	
				indicated no significant difference between groups (p=0.10)		
Comi 2013	**<u>Conversion to CDMS</u>** HR= 0.59, 95% CI, 0.44-0.86; p=0.008 (adjusted baseline values) Early treatment: 55/163 (34%) Delayed treatment: 71/126 (56%)		**<u>Cumulative number of T2 lesions per year</u>** Early treatment group: 1.74, 2.67 (mean, SD) Delayed group: 2.99, 4.36 (mean, SD) **<u>Cumulative number of new GAD lesions per year</u>** Early treatment group: 0.68, 1.41 (mean, SD) Delayed group: 1.45, 2.76 (mean, SD) **<u>Percent brain volume change from baseline to last observed value</u>** Early treatment group: -0.99, 1.27 (mean, SD) Delayed group: -1.28, 1.31 (mean, SD)			*Aurthors reported that GA was well tolerated, with only 71 patient withdrawals (14.8%) over five years due to AEs. AE type, frequency, and severity were consistent with the known safety profile of GA. No significant differences were detected in the incidence of any AE between the early- and delayed-treatment groups. The most common treatment-associated AEs were injection site reactions. Serious AEs were reported in 28 patients in the early-treatment group (including one death during the double-blind phase) and 32 patients in the delayed-treatment group.*

*From trial baseline

†Proportion of original cohort who completed the extension phase

¥Actual N not reported, baseline N used

**No statistical analysis reported

HR= Hazard ratio

RR= relative risk

CI= confidence intervals

FAMS-TOI= Funtional Assessment of multiple sclerosis
SMD= Standard mean difference
CDMS = Clinically Definite Multiple Sclerosis

Table 2: Results of extension studies comparing early and delayed treatment with interferon in RRMS

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety		
	Findings favouring early treatment	Findings indicating no between group differences (or descriptive results)	Findings favouring early treatment	Findings indicating no between group differences (or descriptive results)	Findings favouring early treatment	Findings favouring delayed treatment	Findings indicating no between group differences
Kieseier 2015 1332 (88%)	**<u>Annualised relapse rate</u>** RR¥= 0.629; 95% CI, 0.50-0.79; p<0.0001 Peginterferon (2 weeks): 0.22; 95% CI, 0.183-0.267 Delayed treatment: 0.351, 95% CI, 0.295-0.418 **<u>Disability progression</u>** (24 week confirmed) RR= 0.58; 95% CI, 0.39-0.87, p=0.009 Peginterferon (2 weeks): 34/512 (6.6%) Delayed treatment: 57/500 (11.4%)	**<u>Annualised relapse rate</u>** RR¥= 0.829; 95% CI, 0.666-1.030; p=0.0906 Peginterferon (4 weeks): 0.291, 95% CI, 0.244-0.348 Delayed treatment: 0.351, 95% CI, 0.295-0.418 **<u>Disability progression</u>** RR= 0.91; 95% CI, 0.64-1.30, p=0.61 Peginterferon (4 weeks): 52/500 (10.4%) Delayed treatment: 57/500 (11.4%)	**<u>New or newly enlarging T2-weighted hyperintense lesions at 2 years</u>** Lesion mean ratio: 0.84, 95% CI, 0.69-1.03, p=0.0973[β] Peginterferon (4 weeks): 12.5 (adjusted mean number of lesions) Delayed treatment: 14.8 (adjusted mean number of lesions) **<u>Gd+ lesions at 2 years</u>** p=0.2169[δ] Peginterferon (2 weeks): 0.7 (0.12), mean (SE) Delayed treatment: 0.5	**<u>New or newly enlarging T2-weighted hyperintense lesions at 2 years</u>** Lesion mean ratio: 0.84, 95% CI, 0.69-1.03, p=0.0973[β] Peginterferon (4 weeks): 12.5 (adjusted mean number of lesions) Delayed treatment: 14.8 (adjusted mean number of lesions) **<u>Gd+ lesions at 2 years</u>** p=0.2169[δ] Peginterferon (2 weeks): 0.7 (0.12), mean (SE) Delayed treatment: 0.5			**<u>Mortality</u>** Peginterferon (2 weeks): 3/438 Peginterferon (4 weeks): 0/439 Delayed peginterferon (2 weeks): 0/228 Delayed peginterferon (4 weeks): 2/227 **<u>Serious adverse events</u>** Peginterferon (2 weeks): 56/438 (13%) Peginterferon (4 weeks): 62/439 (14%) Delayed peginterferon (2 weeks): 39/228 (17%) Delayed peginterferon (4 weeks): 34/227 (15%)

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety		
			(0.08), mean (SE)	(0.08), mean (SE)			
Gold 2016		**Annualised relapse rate** (cumulative from baseline to year 5)** BID/BID: 0.163; 95% CI, 0.14-19 PBO/BID: 0.24; 95% CI, 0.196-0.296 GA/BID: 0.199; 95% CI, 0.148, 0.269 **Disability progression** (proportion progressed at 5 years, confirmed at 24 weeks)** BID/BID: 18.6%; 95% CI, 15.3%-22.4% TID/TID: 21.4% PBO/BID: 21.1%; 95% CI, 16.2%-22.4% PBO/TID: 26% GA/BID: 25.7%; 95% CI, 18.4%-35.2% GA/TID: 20.3%		**Brain atrophy** (only 23% of participants entering ENDORSE included in MRI analyses presented here) BID/BID (N=129): -0.85 (0.958), mean (SD) PBO/DMF (N=103): -1.19 (1.252), mean (SD) GA/DMF (N=57): -1.07 (1.272), mean (SD) Authors report that adjusted percent brain volume change from baseline was not significantly different in BID/BID compared with PBO/DMF (p=0.168) or GA/DMF (p=0.500)		**Mortality** BID/BID: 2/501 (<1%) TID/TID: 2/501 (<1%) PBO/BID: 1/249 (<1%) PBO/TID: 0/248 (0%) GA/BID: 0/118 (0%) GA/TID: 0/119 (0%) **Malignancies**** BID/BID: 10/501 (2%) TID/TID: 8/501 (2%) PBO/BID: 5/249 (2%) PBO/TID: 0/248 (0%) GA/BID: 0/118 (0%) GA/TID: 3/119 (3%)	**Infections**** BID/BID: 327/501 (65%) TID/TID: 322/501 (64%) PBO/BID: 141/249 (57%) PBO/TID: 139/248 (56%) GA/BID: 61/118 (52%) GA/TID: 55/119 (46%) **Serious infections**** BID/BID: 18/501 (4%) TID/TID: 13/501 (3%) PBO/BID: 8/249 (3%) PBO/TID: 7/248 (3%) GA/BID: 2/118 (2%) GA/TID: 4/119 (3%)
Kappos 2015	**Annualised relapse rate** Fingolimod (0.5mg) vs delayed treatment - ARR ratio= 0.52; 95 % CI, 0.42-0.64; p<0.0001¤ Fingolimod (1.25mg) vs delayed treatment -		**New or newly enlarging T2-weighted hyperintense lesions at 2 years‡** Fingolimod (0.5mg) vs delayed treatment - p<0.0001 Fingolimod (1.25mg) vs delayed treatment -				**Infections** Fingolimod (0.5mg): 240/331 (72.5%) Fingolimod (1.25mg): 204/289 (70.6%) Delayed treatment: 209/300 (69.7%) **Serious adverse events**

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety		
	ARR ratio= 0.46; 95 % CI, 0.37-0.57; p<0.0001¤ Fingolimod (0.5mg): 0.19; 95% CI, 0.16-0.22 Fingolimod (1.25mg): 0.16; 95% CI, 0.14-0.20 Delayed treatment: 0.36; 95% CI, 0.31-0.41 **Disability progression** (12 week confirmed)Δ Fingolimod (0.5mg) vs delayed treatment - p<0.0171 Fingolimod (1.25mg) vs delayed treatment - p<0.0165 Fingolimod (0.5mg): 73.9%; 95% CI, 69.4%-78.4% Fingolimod (1.25mg): 74.2%; 95% CI, 69.5-79.8% Delayed treatment: 66.3%; 95% CI, 61.3%-71.3%		p<0.0001 Fingolimod (0.5mg): 4.5; 95% CI, 4.27-4.68 Fingolimod (1.25mg): 4.0; 95% CI, 3.80-4.21 Delayed treatment: 11.0; 95% CI, 10.68-11.36 **Gd+ lesions at 2 years**Æ Fingolimod (0.5mg) vs delayed treatment - p<0.0001 Fingolimod (1.25mg) vs delayed treatment - p<0.0001 Fingolimod (0.5mg): 1.1; 95% CI, 0.98-1.23 Fingolimod (1.25mg): 0.8; 95% CI, 0.70-0.94 Delayed treatment: 3.7; 95% CI, 3.42-3.91 **Percent brain volume change**ð Fingolimod (0.5mg) vs delayed treatment - p<0.0013 Fingolimod (1.25mg) vs delayed treatment - p<0.0010 Fingolimod (0.5mg): -1.7; 95% CI, -1.91, -1.43 Fingolimod (1.25mg): -				Fingolimod (0.5mg): 31/331 (9.4%) Fingolimod (1.25mg): 31/289 (10.7%) Delayed treatment: 28/300 (9.3%) **Neoplasms** Fingolimod (0.5mg): 7/331 (2.1%) Fingolimod (1.25mg): 5/289 (1.7%) Delayed treatment: 5/300 (1.67%)

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety		
			1.6; 95% CI, -1.88, -1.40 Delayed treatment: -2.2; 95% CI, -2.51, -1.97				
NCT00355134 (unpublished)	**Aggregate Annualized Relapse Rate (ARR)** (trial baseline until end of extension, up to approximately 54 months) Fingolimod (0.5mg): 0.19, 95% CI, 0.157-0.234 Fingolimod (1.25mg): 0.18, 95% CI, 0.147-0.222 Delayed treatment: 0.36, 95% CI, 0.305-0.431 **Percentage of Participants Relapse-free*** (trial baseline until end of extension, up to approximately 54 months) Fingolimod (0.5mg): 66.57%, 95% CI, 60.86-72.28 Fingolimod (1.25mg): 63.88%; 95% CI, 56.19-71.57 Delayed treatment: 49.12% , 95% CI, 43.35-54.89			**Number of New or Newly Enlarged T2 Lesions** (from month 24 to 36; N=319) Fingolimod (0.5mg): 0.45 (1.360), mean (SD) Fingolimod (1.25mg): 0.63 (2.856), mean (SD) Delayed treatment: 0.63 (1.455), mean (SD) **Number of Gadolinium-enhanced T1 Lesions** (during extension study, up to approximately 54 months; N=562) Fingolimod (0.5mg): 0.09 (0.308), mean (SD) Fingolimod (1.25mg): 0.46 (2.381), mean (SD) Delayed treatment: 0.45 (3.618), mean (SD) **Percent Change From Baseline in Brain Volume** (during extension study, up to approximately 54			**Discontinuation due to any reason** (during extension) Fingolimod (0.5mg): 37/217 (17%) Fingolimod (1.25mg): 31/203 (15.3%) Delayed treatment: 35/212 (16.5%) **Discontinuation due to adverse event** (including abnormal laboratory values) Fingolimod (0.5mg): 11/217 (5%) Fingolimod (1.25mg): 17/203 (8.4%) Delayed treatment: 12/212 (5.7%%)

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety		
	*generated from Kaplan-Meier curves of the time to first relapse			months; N=547) Fingolimod (0.5mg): -1.27% (1.69), mean (SD) Fingolimod (1.25mg): -1.13% (1.64), mean (SD) Delayed treatment: -1.69% (1.96) , mean (SD)			
PRISMS-4 506 (90%)	**Annualised relapse rate** (relapse count/year) *Years 1-4* RR=0.70, 0.59-0.82; p<0.001 (44ug) RR=0.76, 0.66-0.89; p<0.001 (22ug) *Years 3-4* RR=0.73, 0.58-0.94; p=0.014 (44ug) RR=1.01, 0.80-1.28; p=0.946 (22ug) **Proportion of participants relapse free** Interferon beta-1a (22ug): 14.4% (p=0.02) Interferon beta-1a (44ug): 19% (p<0.001) Delayed treatment: 6.7%	**Disability progression** (number of participants free from) Interferon beta-1a (22ug): 88/173 (51%) - ns Interferon beta-1a (44ug): 92/164 (54.3%) - ns Delayed treatment: 74/161 (46%)	**New T2 lesions per patient per scan** *Years 1-4* Interferon beta-1a (22ug): 1.3 (1-1.75) (p<0.001) Interferon beta-1a (44ug): 0.5 (0.33-0.67) (p<0.001) Delayed 22ug: 2 (1.67-3.25) Delayed 44ug: 2.7 (2-3.5) *Years 3-4* Interferon beta-1a (22ug): 1 (0.5-1) (p<0.001) Interferon beta-1a (44ug): 0 (0-0 (p<0.001) Delayed 22ug: 0.5 (0.5-1) Delayed 44ug: 1 (0.5-1.5)				**Discontinuation due to any reason during extension** Interferon beta-1a (22ug): 28/251 (11%) Interferon beta-1a (44ug): 45/251 (18%) Delayed 22ug: 37/331 (11%) Delayed 44ug: 36/171 (21%) *(excluding patients who took no drug in years 3 and 4)*

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety		
Kappos 2006	**Disability progression** (confirmed at 3 months; 4 years' follow-up) *Participants with missing data are assumed to have progressed* HR=0.71; p=0.007 (44ug) HR=0.77; p=0.036 (22ug) Interferon beta-1a (22ug): 128/189 (67.7%) Interferon beta-1a (44ug): 118/184 (64.1%) Delayed treatment: 137/187 (73.3%) **Progression to EDSS score 6.0**** Interferon beta-1a (22ug): 42/189 (22.2%) Interferon beta-1a (44ug): 36/182 (19.8%) Delayed treatment: 32/186 (17.2%)	**Disability progression** (confimred at 3 months; 4 years' follow-up) *Participants with missing data are assumed to not have progressed* HR=0.80; p=0.119 (44ug) HR=0.89; p=0.379 (22ug) Interferon beta-1a (22ug): 108/189 (57.1%) Interferon beta-1a (44ug): 100/184 (54.3%) Delayed treatment: 104/187 (55.6%)	**Relative percentage change in T2 burden of disease (summed cross-sectional area of lesions in T2 scans)** (from baseline to LTFU) Interferon beta-1a (44ug): 5.0 (–64.7, 1055) Delayed treatment: 24.5 (–56.3, 869.2) p=0.002Ω ΩANCOVA adjusted for study site and T2 BOD at baseline. Includes baseline, 4 year data and LTFU data.	**Relative percentage change in T2 burden of disease (summed cross-sectional area of lesions in T2 scans)** (from baseline to LTFU) Interferon beta-1a (22ug): 17.4 (–52.5, 774.8) Delayed treatment: 24.5 (–56.3, 869.2) p=0.114Ω ΩANCOVA adjusted for study site and T2 BOD at baseline. Includes baseline, 4 year data and LTFU data.			**Mortality** Interferon beta-1a (22ug): 5/189 (2.7%) Interferon beta-1a (44ug): 1/184 (<1%) Delayed treatment: 2/187 (1%)
Rudick 2005/Rudic	**Disability progression** *Number of participants*	**Disability progression** *Number of participants*					**Discontinuation due to any reason** (during open-

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety		
k 2010/Herndon 2005	*reaching EDSS score 4.0* RR= 0.57, 95% CI, 0.43-0.75, p<0.0001 Early treatment: 35/79 (44.3%) Delayed treatment: 53/81 (65.4%)	*reaching EDSS score 6.0* RR= 0.69, 95% CI, 0.45-1.07, p=0.09 Early treatment: 23/79 (29%) Delayed treatment: 34/81 (42%) *Sustained progression∂ for 6 months* RR= 0.68, 95% CI, 0.41-1.14, p=0.14 Early treatment: 18/79 (22.8%) Delayed treatment: 27/81 (33.3%) ∂ Defined as a 1-point or greater worsening from baseline sustained for at least 6 months					label phase) Early treatment: 32/115 (27.8%) Delayed treatment: 34/103 (33%)
Ebers 2010 260 (69.9%)		**Disability progression** *Proportion reaching EDSS score 6*** Interferon beta-1b (250ug): 44/96 (45.8%) Interferon beta-1b (50ug): 33/85 (38.8%) Placebo: 36/79 (45.6%%) *Proportion reaching secondary progressive*			**Mortality** IFN 250ug vs. placebo: p=0.0049 IFN 50ug vs. placebo: p=0.0402 Interferon beta-1b (250ug): 6/111 (5.4%) Interferon beta-1b (50ug): 9/108 (8.3%) Placebo: 20/109 (18.4%)		**Fever** Interferon beta-1b (250ug): 58/96 (60.4%) Placebo: 31/79 (39.2%) **Injection-site reactions** Interferon beta-1b (250ug): 83/96 (86.5%) Placebo: 33/79 (41.8%) **Flu-like symptoms** Interferon beta-1b (250ug):

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety		
		*MS*** Interferon beta-1b (250ug): 42/96 (43.8%) Interferon beta-1b (50ug): 28/85 (32.9%) Placebo: 34/79 (43%)					55/96 (57.3%) Placebo: 45/79 (57%) **Increased liver transaminases** Interferon beta-1b (250ug): 23/96 (24%) Placebo: 5/79 (6.3%)
Goodin 2012 366 (98.4%)					**Mortality** HR=0.532, 95% CI, 0.314-0.902; p=0.0173 (IFN 250ug vs. placebo) HR=0.540, 95% CI, 0.318-0.915; p=0.0202 (IFN 50ug vs. placebo) Interferon beta-1b (250ug): 22/122 (18%) Interferon beta-1b (50ug): 22/123 (17.9%) Placebo: 37/121 (30.6%)		
Johnson 2000		*Results only presented for early treatment group* **Annual relapse rate** ARR=0.42; 95% CI, 0.34-0.51					**Discontinuation due to any reason** (during open-label phase) Early treatment: 24/101 (23.8%) Delayed treatment: 32/107 (30%)
Freedmans 2005		**Disability progression** (proportion with 1 point EDSS increase)		**T2 active lesions** Interferon 44mcg vs delayed interferon			**Discontinuation due to adverse event during extension**

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety		
		22mcg vs delayed 22mcg (p=0.94) 44mcg vs delayed 44mcg (p=0.17) Interferon 22mcg: 39 Interferon 44mcg: 35 Delayed interferon (22mcg): 46 Delayed interferon (44mcg): 40 **Mean relapse rate** 22mcg vs delayed 22mcg (p=0.96) 44mcg vs delayed 44mcg (p=0.32) Interferon 22mcg: 0.83 Interferon 44mcg: 0.77 Delayed interferon (22mcg): 0.84 Delayed interferon (44mcg): 0.86		44mcg (p=0.15) Interferon 22mcg vs delayed interferon 22mcg (p=0.69) Interferon 22mcg: 1.7 (3.3), median (mean) Interferon 44mcg: 1.3 (2.6), median (mean) Delayed interferon (22mcg): 1.7 (3.4), median (mean) Delayed interferon (44mcg): 2.0 (3.6), median (mean)			(N in each group unclear) Interferon 22mcg: 2 Interferon 44mcg: 4 Delayed interferon (22mcg): 0 Delayed interferon (44mcg): 1 Serious adverse events were balanced between groups. Those SAEs considered at least possibly related to medication included one patient on 22 mcg qw (vomiting) and five patients on 44 mcg qw (gastroenteritis, depression with suicide attempt, psychosis, MS exacerbation and Grave's disease). All SAEs were unique events except for three cases of depression on 22 mcg qw and two cases of cholelithiasis on 44 mcg qw.
Giovannoni 2014		**Annualised relapse rate** (during extension phase) Continuous treatment: 0.165; 95% CI, 0.105-0.259 Washout and re-initiation: 0.179; 95% CI, 0.123-0.261		**Number of gadolinium-enhancing T1 lesions** (during extension phase; 252 weeks' follow-up) Teriflunomide 14mg: 0.21 (0.62); mean, (SD) Delayed teriflunomide 14mg: 0.18 (0.55);			**Serious adverse events** Teriflunomide 14mg: 55/250 (22%) Delayed teriflunomide 14mg: 19/106 (17.9%) Teriflunomide 7mg: 62/254 (24.4%) Delayed teriflunomide 7mg: 30/130 (23.1%)

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety		
		Delayed treatment: 0.302; 95% CI, 0.215-0.423 **<u>Proportion of patients who relapsed</u>** (during extension) Continuous treatment: 0.136; 95% CI, 0·087–0·209 Washout and re-initiation: 0.241, 95% CI, 0·175–0·327 Delayed treatment: 0.176, 95% CI, 0·125–0·245 **<u>Number with confirmed disability progression</u>** (during extension) Continuous treatment: 7/129 (5.4%) Washout and re-initiation: 10/132 (7.6%) Delayed treatment: 8/163 (4.9%)		mean, (SD) Teriflunomide 7mg: 0.56 (1.58); mean, (SD) Delayed teriflunomide 7mg: 0.6 (2.32); mean, (SD) **<u>T2 lesion volume (mL)</u>** (during extension phase; 252 weeks' follow-up) Teriflunomide 14mg: 14.67 (12.55); mean, (SD) Delayed teriflunomide 14mg: 17.36 (17.85); mean, (SD) Teriflunomide 7mg: 17.7 (19.35); mean, (SD) Delayed teriflunomide 7mg: 16.09 (14.74); mean, (SD)			**<u>Adverse events leading to death</u>** Teriflunomide 14mg: 1/250 (<1%) Delayed teriflunomide 14mg: 0/106 Teriflunomide 7mg: 1/254 (<1%) Delayed teriflunomide 7mg: 1/130 (<1%) **<u>Malignancies</u>** (neoplasms, glioma, cervical carcinoma, breast cancer, hepatic cancer, basal cell carcinoma, metastatic colon cancer) Teriflunomide 14mg: 4/250 (1.6%) Delayed teriflunomide 14mg: 1/106 (<1%) Teriflunomide 7mg: 3/254 (1.2%) Delayed teriflunomide 7mg: 2/130 (1.5%) **<u>Discontinuation due to adverse events</u>** Teriflunomide 14mg: 24/250 (9.6%) Delayed teriflunomide 14mg: 11/106 (10.4%) Teriflunomide 7mg: 29/254 (11.4%) Delayed teriflunomide 7mg:

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety		
							18/130 (13.8%)
Khatri 2011	**Estimated annualised relapse rate*** Continuous fingolimod (0.5mg): 0.18, 95% CI, 0.14-0.22 Continuous fingolimod (1.25mg): 0.20, 95% CI, 0.16-0.25 Delayed fingolimod: 0.33, 95% CI, 0.27-0.39 p<0.0001 for continuous treatment groups vs. delayed fingolimod group Continuous fingolimod (0.5mg) vs delayed fingolimod HR**=0·58; 95% CI, 0·45–0·74 Continuous fingolimod (1.25mg) vs delayed fingolimod HR=0·64; 95% CI, 0·50–0·82 *Months 0–24, estimated from a negative binomial regression model adjusted for treatment, country, number of			**Number of new or enlarged T2 lesions** Fingolimod (0.5mg): 0.9 (1.65), mean (SD) Delayed fingolimod (0.5mg): 0.7 (1.54), mean (SD) Fingolimod (1.25mg): 1.0 (2.3), mean (SD) Delayed fingolimod (1.25mg): 1.0 (1.87), mean (SD) **Number of gad-enhancing lesions on T1-weighted images** Fingolimod (0.5mg): 0.1 (0.44), mean (SD) Delayed fingolimod (0.5mg): 0.1 (0.34), mean (SD) Fingolimod (1.25mg): 0.2 (0.96), mean (SD) Delayed fingolimod (1.25mg): 0.2 (1.11), mean (SD) **Change in normalised brain volume** Fingolimod (0.5mg): -0.37 (0.67), mean (SD) Delayed fingolimod (0.5mg): -0.22 (0.64),	**Infectious adverse events** Fingolimod (0.5mg): 204/429 (47.6%) Delayed fingolimod (0.5mg): 91/167 (54%) Fingolimod (1.25mg): 199/420 (47.4%) Delayed fingolimod (1.25mg): 91/174 (52%) **Serious adverse event** Fingolimod (0.5mg): 19/429 (4.4%) Delayed fingolimod (0.5mg): 8/167 (5%) Fingolimod (1.25mg): 21/420 (5%) Delayed fingolimod (1.25mg): 21/174 (12%)	**Neoplasms** (benign, malignant, unspecified including cysts and polyps) Fingolimod (0.5mg): 6/429 (1.4%) Delayed fingolimod (0.5mg): 0/167 Fingolimod (1.25mg): 3/420 (0.7%) Delayed fingolimod (1.25mg): 1/174 (0.6%)	

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety		
	relapses in the 2 years before enrolment, and core baseline EDSS score. **Calculated from a Cox proportional hazard model adjusted by treatment, country, number of relapse in the previous 2 years before enrolment and core baseline EDSS			mean (SD) Fingolimod (1.25mg): -0.35 (0.67), mean (SD) Delayed fingolimod (1.25mg): -0.14 (0.60), mean (SD)			
Cohen 2015	**Risk of relapse** Continuous fingolimod (0.5mg) vs delayed fingolimod HR=0·65; p<0.001	**Estimated annualised relapse rate*** Continuous fingolimod (0.5mg): 0.16, 95% CI, 0.12-0.19 Delayed fingolimod: 0.20, 95% CI, 0.16-0.25 p=0.101 for continuous treatment vs. delayed treatment **Disability progression (confirmed at 3 months)**** HR=0.94, 95% CI, 0.71-1.26); p=0.687 Continuous fingolimod (0.5mg): 94 (22%) Delayed fingolimod: 91 (21%) **Disability progression (confirmed at 6**		**Number of new/newly enlarging T2 lesions** Continuous fingolimod (0.5mg): 0.9 (2.7), mean (SD) Delayed fingolimod: 1.0 (4.4), mean (SD) **Number of GAD T1 lesions** Continuous fingolimod (0.5mg): 0.3 (1.1), mean (SD) Delayed fingolimod: 0.4 (2.7), mean (SD) **Mean percent change in brain volume** Continuous fingolimod (0.5mg): -1.01 Delayed fingolimod: -0.96 p=0.937		**Malignancies (basal cell carcinoma, breast cancer)** Fingolimod (0.5mg): 8/356 (2.24%) Delayed fingolimod (0.5mg): 1/167 (0.6%)	**Discontinuation of study drug due to any reason** Fingolimod (0.5mg): 75/356 (21.1%) Delayed fingolimod (0.5mg): 44/167 (26.3%) Fingolimod (1.25mg): 85/330 (25.8%) Delayed fingolimod (1.25mg): 51/174 (29.3%) **Discontinuation of study drug due to adverse event** (including abnormal laboratory values) Fingolimod (0.5mg): 35/356 (9.8%) Delayed fingolimod (0.5mg): 11/167 (6.6%) Fingolimod (1.25mg): 35/330 (10.6%) Delayed fingolimod (1.25mg): 32/174 (18.4%)

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety		
		<u>months)</u> HR=1.08, 95% CI, 0.77-1.51); p=0.674 Continuous fingolimod (0.5mg): 73 (17%) Delayed fingolimod: 63 (15%) *From start of extension to end of study. P-value from negative binomial regression model, adjusted for treatment, pooled country, number of relapses in the previous 2 yeas before enrollment and original trial baseline EDSS **From original trial baseline to end of extension study. HRs and p values from the Cox proportional hazards model adjusted for treatment, pooled country, core baseline EDSS and age					**<u>Serious adverse events</u>** Fingolimod (0.5mg): 55/356 (15.4%) Delayed fingolimod (0.5mg): 21/167 (12.6%)

HR= Hazard ratio
RR= relative risk
CI= confidence intervals
DMF= BID and TID dimethyl dumarate groups confirmed
†Proportion of original cohort who completed the extension phase
**No statistical anaysis reported/carried out
¥Based on negative binomial regression, with adjustment for baseline EDSS (<4 vs. ≥4), baseline relapse rate, age (<40 vs. ≥40).

[β]Based on negative binomial regression, adjusted for baseline number of new or newly enlarging T2 lesions
[δ]Percent reduction based on group mean and p-value based on multiple logit regression, adjusted for baseline number of Gd+ lesions
¤Annualized relapse rate (ARR) estimated from a negative binomial model adjusted for treatment, pooled country, number of relapses in the 2 years before enrollment, and FTY720 Research Evaluating Effects of Daily Oral Therapy in MS (FREEDOMS) baseline Expanded Disability Status Scale score; p values are for the ARR ratio between active treatment ARR and placebo ARR.
ΔTime to 3-month confirmed disability progression based on EDSS score with Kaplan-Meier estimate of patients free from progression at EoS
‡Cumulative number of new or newly enlarged T2 lesions compared using a negative binomial model adjusted for treatment, FREEDOMS baseline volume of T2 lesions, and pooled country
[Æ]Cumulative number of gadolinium (Gd)-enhancing T1 lesions from month 0 to EoS, including patients with all assessments during that time interval; p values are for comparisons with the placebo–fingolimod group
δBetween-group comparisons of changes in brain volume from month 0 to end of study in the FTY720 Research Evaluating Effects of Daily Oral Therapy in MS (FREEDOMS) intent-to-treat (ITT) population. Percentage brain volume change was compared using a rank analysis of covariance adjusted by treatment, normalized brain volume at FREEDOMS baseline, and country

Table 3: Results of extension studies comparing early and delayed treatment with interferon in PPMS

Study ID N (% of original cohort)†	Relapse and disability progression	MRI	Safety
Tur 2011	**Disability progression*** (from original trial baseline to end of extension) Early treatment: 70.97% Delayed treatment: 67.74% Signed rank test indicated not significant between group difference (p=0.78) **Cognitive performance** (from original trial baseline to end of extension) *PASAT* Wilcoxon rank sum test indicated no difference between groups on the PASAT for changes from baseline to 5 year follow-up (p=0.24) *at least 1–EDSS point increase if the baseline EDSS score was 5 or lower or 0.5-point increase if the baseline EDSS score was 5.5 or higher (1 step change)	**Change in T2 lesion volume** (from original trial baseline to end of extension) Early treatment: 2265.9 (−303.30 to 12 754.40); median change (range) Delayed treatment: 2986.90 (−9773.30 to 13 226.50); median change (range) Signed rank test indicated no significant differnce between treatment groups (p=0.78) **Change in brain parenchymal fraction** (from original trial baseline to end of extension) Early treatment: -1.78 (−6.99 to 1.29); median change (range) Delayed treatment: −3.16 (−6.87 to 2.37); median change (range) Signed rank test indicated significantly lower brain atrophy in the early treatment group (p=0.004)	Not reported

Study ID N (% of original cohort)†	Relapse and disability progression	MRI	Safety