Appendix 7 _Additional safety data

Question 1

Study ID (original trial) (N†)	Length of exposure	FU*	Discontinuation	Mortality	Side effects
Kappos 2007 (BENEFIT) n=418	Early: 2.96 years (median) Delayed: 1 year (median)	3 yrs	**Due to any reason** Early interferon: 12 **(4.6%)** Delayed interferon: 14 **(8.9%)** **Due to adverse events** Early interferon: 1 **(0.4%)** Delayed interferon: 4 **(2.5%)**	No deaths were reported during the study period.	**Injection site reaction** Early IFN: 158 (54%) Delayed IFN: 68 (39%)
Kappos 2009 (BENEFIT) n=392	Early: 5 years (median) Delayed: 2.9 years (median)	5 yrs	**Due to any reason** Early interferon: 26 **(9.96%)** Delayed interferon: 34 **(21.6%)** **Due to adverse events** Early interferon: 5 **(1.9%)** Delayed interferon: 6 **(3.8%)**	No deaths were reported during the study period.	**Injection site reaction** Early IFN: 164 (56%) Delayed IFN: 71 (40%)
Edan 2014 (BENEFIT) n=284	Early: 7 years (median) Delayed: 4.5 years (median)	8 yrs	Not 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."*	
Kappos 2016 (BENEFIT)	NR	11 yrs	Not reported	"*The frequency and type of adverse events reported were consistent with the known profile of interferon beta-1b. There were no new safety signals detected at year 11. No serious adverse events were*	

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n=278				*reported during BENEFIT 11."*	
REFLEXION (unpublished;NCT00813709) (REFLEX) n=155	NR	5 yrs	***Due to any reason*** Interferon (qw): 20 **(39.2%)** Interferon (tiw): 11 **(23.9%)** Delayed interferon: 20 **(34.5%)** ***Due to adverse events*** Interferon (qw): 4 **(7.8%)** Interferon (tiw): 3 **(6.5%)** Delayed interferon: 5 **(8.6%)**	No deaths were reported during the study period.	**Injection site erythema** Early IFN: 2 (4.35%) Delayed IFN: 4 (6.9%)
Kinkel 2006 (CHAMPS) n=204	NR	5 yrs	*"No new safety concerns with IFN -1a therapy arose during the CHAMPIONS Study"*		
Comi 2013 (PRECISE) n=409	Early: 4.7 years (median) Delayed: 3.5 years (median)	5 yrs	*"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."*		
†Number of participants who started the extension phase, *Number of years follow-up from start of original trial ‡ adjusted for age, CHAMPS qualifying event, CHAMPS baseline brain MRI T2 lesions volume, and baseline number of Gd+ lesions					

Question 2_Additional safety data

Study ID (original trial) N†	Length of exposure‡	FU*	Discontinuation	Mortality	Side effects
Kieseier 2015 (ADVANCE) n=1332	Early= 2 years Delayed= 2 years	2 yrs	**Due to any reason** (during extension) PegIFN (2 weeks): 27/438 **(6.2%)** PegIFN (4 weeks): 47/439 **(10.7%)** Delayed pegIFN (2 weeks): 32/228 **(14%)** Delayed pegIFN (4 weeks): 28/227 **(12.3%)** **Due to adverse events** (during extension) PegIFN (2 weeks): 7/438 **(1.6%)** PegIFN (4 weeks): 9/439 **(2%)** Delayed pegIFN (2 weeks): 8/228 **(3.5%)** Delayed pegIFN (4 weeks): 9/227 **(3.96%)**	**Mortality** PegIFN (2 weeks): 3/438 **(0.68%)** PegIFN (4 weeks): 0/439 Delayed pegIFN (2 weeks): 0/228 Delayed pegIFN (4 weeks): 2/227	**Injection site erythema** PegIFN and delayed (2 weeks): 470 **(64%)** PegIFN and delayed (4 weeks): 433 **(59%)**
PRISMS-4 2001 (PRISMS) n=506	NR	4 yrs	**Due to any reason** (during extension) IFN beta-1a (22ug): 28 **(11%)** IFN beta-1a (44ug): 45 **(18%)** Delayed 22ug: 37 **(11%)** Delayed 44ug: 36 **(21%)** **Due to adverse events** (during extension) IFN beta-1a (22ug): 3 **(1.8%)** IFN beta-1a (44ug): 9 **(5.4%)** Delayed 22ug: 3 **(14%)** Delayed 44ug: 12 **(13.8%)**	Adverse events during the extension were similar to those observed in PRISMS-2 (table 4), and most were mild. Fifty-four patients experienced 67 serious adverse events during years 3 and 4, and the incidence of serious adverse events was similar between groups. One patient in the Rx22 group died after a myocardial infarction.	
Kappos 2006 (PRISMS) n=382	NR	7-8	NR	**Mortality** IFN beta-1a (22ug): 5/189 **(2.7%)** IFN beta-1a (44ug): 1/184 **(<1%)** Delayed treatment: 2/187 **(1%)**	NR

Study ID (original trial) N†	Length of exposure‡	FU*	Discontinuation	Mortality	Side effects
Rudick 2005/ Rudick 2010 (MSCRG) n=172	Early= 4.2 years¥ Delayed= 4.9 years¥	8 yrs	**Due to any reason** (during extension) Early IFN: 32 (27.8%) Delayed IFN: 34 (33%)	NR	NR
Ebers 2010/ Reder 2010 (IFNB MS trial) n=260	The median total length of exposure to IFNB-1b since the start of the pivotal trial was 7.9 years	16 yrs	NR	**Mortality** IFN 250ug vs. placebo: p=0.0049 IFN 50ug vs. placebo: p=0.0402 IFN beta-1b (250ug): 6 (5.4%) IFN beta-1b (50ug): 9 (8.3%) Placebo: 20 (18.4%)	**Injection-site reactions** Interferon beta-1b (250ug): 83 **(86.5%)** Placebo: 33 **(41.8%)**
Goodin 2012 (IFNB MS trial) n=366	NR	21 years	NR	**Mortality** HR=0.53 (0.31-0.9); p=0.017 (IFN 250ug vs. placebo) HR=0.54 (0.32-0.91); p=0.0202 (IFN 50ug vs. placebo) IFN beta-1b (250ug): 22 **(18%)** IFN beta-1b (50ug): 22 **(17.9%)** Placebo: 37 **(30.6%)**	NR
Johnson 2000 (Johnson 1995)	Early= 5.8 years Delayed= NR	6 yrs	**Due to any reason** (during open-label phase) Early treatment: 24 **(23.8%)**	NR	**Injection-site reactions** (during open-label phase) Early treatment: 2.4%

Study ID (original trial) N†	Length of exposure‡	FU*	Discontinuation	Mortality	Side effects
n=208			Delayed treatment: 32 **(30%)**		Delayed treatment: 0.9%
Gold 2016 (DEFINE and CONFIRM) n=1736	NR	5 yrs	Rates of discontinuation due to individual AEs in were low (≤2% for individual AEs in each treatment group).	**Mortality** Dimethyl fumarate (BID): 2 /501 **(<1%)** PBO/BID: 1/249 **(<1%)** GA/BID: 0/118 **(0%)**	**Infections** Dimethyl fumarate (BID): 327/501 **(65%)** PBO/BID: 141/249 **(57%)** GA/BID: 61/118 **(52%)** **Malignancies** Dimethyl fumarate (BID): 10/501 **(2%)** PBO/BID: 5/249 **(2%)** GA/BID: 0/118 **(0%)** **Progressive multifocal leukoencephalopathy*** Dimethyl fumarate (BID): 0/501 PBO/BID: 0/249 GA/BID: 0/118
O'Conner 2016 (TEMSO) n=742	T (14mg) = 6.2 years (median) T (7mg) = 5.7 years (median) Delayed (14mg) = 3.8 years	Up to 9 yrs	**Due to adverse events** Teriflunomide 14mg: 24 **(9.6%)** Delayed teriflunomide 14mg: 11 **(10.4%)**	**Adverse events leading to death** Teriflunomide 14mg: 1 **(<1%)** Delayed teriflunomide 14mg: 0 **(0%)**	**Serious adverse events** Teriflunomide 14mg: 55 **(22%)** Delayed teriflunomide 14mg: 19 **(17.9%)** *Peripheral neuropathy confirmed via electrophysical nerve conduction tests*

Study ID (original trial) N†	Length of exposure‡	FU*	Discontinuation	Mortality	Side effects
	(median) Delayed (7mg) = 3.7 years (median)				*was reported for 9 patients receiving teriflunomide 14 mg (1 of whom had 2 events) and 5 patients receiving 7 mg.*
Kappos 2015 (FREEDOMS) n=920	Fingolimod 0.5mg= 3.8 years Fingolimod 1.25mg= 3.8 years Delayed= 1.8 years	4-6 yrs	**Due to any reason** (during extension) Early (0.5mg): 41 **(12.4%)** Delayed treatment (0.5mg): 29 **(18.7%)** **Due to adverse event** (including abnormal laboratory values) Early (0.5mg): 15 **(4.5%)** Delayed treatment (0.5mg): 16 **(10.3%)**	NA	**Infections** Fingolimod (0.5mg): 240 **(72.5%)** Fingolimod (1.25mg): 204 **(70.6%)** Delayed treatment: 209 **(69.7%)** **Serious adverse events** Fingolimod (0.5mg): 31 **(9.4%)** Fingolimod (1.25mg): 31 (10.7%) Delayed treatment: 28 **(9.3%)** **Neoplasms** Fingolimod (0.5mg): 7 **(2.1%)** Fingolimod (1.25mg): 5 **(1.7%)** Delayed treatment: 5 **(1.67%)** **Herpesvirus infection** Fingolimod (0.5mg): 40 **(12.1%)** Fingolimod (1.25mg): 31 **(10.7%)** Delayed treatment: 28 **(9.3%)** **Bradyarrhythmia** Fingolimod (0.5mg): 0 **(0%)** Fingolimod (1.25mg): 1 **(0.4%)** Delayed treatment: 0 **(0%)**

Study ID (original trial) N†	Length of exposure‡	FU*	Discontinuation	Mortality	Side effects
					Bradycardia Fingolimod (0.5mg): 1 **(0.3%)** Fingolimod (1.25mg): 1 **(0.4%)** Delayed treatment: 3 **(1%)** **Macular edema** Fingolimod (0.5mg): 1 **(0.3%)** Fingolimod (1.25mg): 1 **(0.4%)** Delayed treatment: 1 **(0.3%)**
NCT00355134 (unpublished) (FREEDOMS II) n=632	NR	4.5 yrs	**Due to any reason** (during extension) Fingolimod (0.5mg): 37 **(17%)** Fingolimod (1.25mg): 31 **(15.3%)** Delayed treatment: 35 **(16.5%)** **Due to adverse event** (including abnormal laboratory values) Fingolimod (0.5mg): 11 **(5%)** Fingolimod (1.25mg): 17 **(8.4%)** Delayed treatment: 12 **(5.7%)**	NA	Reported only for whole group only
Khatri 2011 (TRANSFORMS) n=1027	Early= 2 years Delayed= 1 year	2 yrs	**Of study drug due to any reason** Fingolimod (0.5mg): 38 **(10.7%)** Delayed fingolimod (0.5mg): 28 **(16.7%)** **Of study drug due to adverse event** (including abnormal laboratory values) Fingolimod (0.5mg): 21 **(5.9%)** Delayed fingolimod (0.5mg): 9 **(5.4%)**		**Infectious adverse events (during extension)** Fingolimod (0.5mg): 204 **(47.6%)** Delayed fingolimod (0.5mg): 91 **(54%)** **Serious adverse event (during extension)** Fingolimod (0.5mg): 19 **(4.4%)**

Study ID (original trial) N†	Length of exposure‡	FU*	Discontinuation	Mortality	Side effects
					Delayed fingolimod (0.5mg): 8 **(5%)** **Neoplasms (during extension)** (benign, malignant, unspecified including cysts and polyps) Fingolimod (0.5mg): 6 (**1.4%)** Delayed fingolimod (0.5mg): 0 (**0%)** **Herpes zoster (during extension) (disseminated and ophthalmic)** Fingolimod (0.5mg): 0 **(0%)** Delayed fingolimod (0.5mg): 1 (**0.06%)** **Bradycardia (during extension)** Fingolimod (0.5mg): 0 **(0%)** Delayed fingolimod (0.5mg): 1 (**0.06%)** **Macular oedema (during extension)** Fingolimod (0.5mg): 0 **(0%)** Delayed fingolimod (0.5mg): 1 (**0.06%)**

Study ID (original trial) N†	Length of exposure‡	FU*	Discontinuation	Mortality	Side effects
Cohen 2015 (TRANSFORMS) n=1027	NR	4.5 yrs	**Of study drug due to any reason** Fingolimod (0.5mg): 75 **(21.1%)** Delayed fingolimod (0.5mg): 44 **(26%)** **Of study drug due to adverse event** (including abnormal laboratory values) Fingolimod (0.5mg): 35 **(9.8%)** Delayed fingolimod (0.5mg): 11 **(6.6%)**		**Malignancies** (basal cell carcinoma, breast cancer) Fingolimod (0.5mg): 8/356 (2.24%) Delayed fingolimod (0.5mg): 1/167 (0.6%) **Serious adverse events** Fingolimod (0.5mg): 55 (**15.4%)** Delayed fingolimod (0.5mg): 21 **(12.6%)** **Herpes viral infection** Fingolimod (0.5mg): 36 **(10.1%)** Delayed fingolimod (0.5mg): 25 **(15%)** **Herpes zoster (disseminated)** Fingolimod (0.5mg): 0 **(0%)** Delayed fingolimod (0.5mg): 1 **(0.23%)**
Giovannoni 2014 (SELECT) n=517	Early= 2 years Delayed= 1 year	2 yrs	**Of study drug due to any reason** (during open-label phase) Daclizumab (150mg): 27 **(15.7%)** Delayed treatment: 20 **(11.8%)** **Of study drug due to adverse events** (during open-label phase) Daclizumab (150mg): 9 **(5.2%)** Delayed treatment: 3 **(1.8%)**	**Mortality** One patient in the washout and re-initiation group died because of autoimmune hepatitis after re-initiation of 300 mg daclizumab HYP. A contributory role of daclizumab HYP could not be excluded.	**Autoimmune disorders** (autoimmune hepatitis, Grave's disease or hyperthyroidism, ulcerative colitis) Continuous treatment: 3/173 **(1.7%)** Washout and re-initiation: 1/174 **(<1%)** Delayed treatment: 0/170 **(0%)**

Study ID (original trial) N†	Length of exposure‡	FU*	Discontinuation	Mortality	Side effects
					Malignancy Continuous treatment: 0/173 **(0%)** Washout and re-initiation: 0/174 **(0%)** Delayed treatment: 1/170 **(<1%)** **Serious Infections** Continuous treatment: 4/173 **(2.3%)** Washout and re-initiation: 4/174 **(2.4%)** Delayed treatment: 5/170 **(2.9%)** **Serious cutaneous events** Continuous treatment: 3/173 **(1.73%)** Washout and re-initiation: 1/174 **(0.57%)** Delayed treatment: 2/170 **(1.17%)**

‡Mean number of years on study drug
¥Combined interferon beta-1a and interferon beta-1b
*Subsequent to the data cutoff for this report, a fatal case of progressive multifocal leukoencephalopathy (PML) in a patient treated with DMF 240 mg TID was reported in the setting of severe, prolonged lymphopenia (~290–580 cells/mL3 over 3.5 years)

Study ID (original trial) (N†)	FU*	Discontinuation	Mortality	Side effects
Giovannoni 2010 (CLARITY) n=1326	3 yrs	**Due to any reason** Cladribine 3.5mg: 35 **(8.1%)** Cladribine 5.25mg: 50 **(11%)** Placebo: 57 **(13%)** **Due to adverse events** Cladribine 3.5mg: 5 **(1.1%)** Cladribine 5.25mg: 9 **(2%)** Placebo: 5 **(1.1%)**	Cladribine 3.5mg: 2 **(0.46%)** Cladribine 5.25mg: 2 **(0.44%)** Placebo: 0 **(0%)**	**Any serious adverse event** Cladribine 3.5mg: 36 **(8.4%)** Cladribine 5.25mg: 41 **(9%)** Placebo: 28 **(6.4%)** **Infections or infestations (number of participants with any)** Cladribine 3.5mg: 205 **(47.7%)** Cladribine 5.25mg: 222 **(48.9%)** Placebo: 185 **(42.5%)** **Serious infections or infestations (number of participants with any)** Cladribine 3.5mg: 10 **(2.3%)** Cladribine 5.25mg: 13 **(2.9%)** Placebo: 7 **(1.6%)** **Neoplasms (number of participants with any)** Cladribine 3.5mg: 6 **(1.4%)** Cladribine 5.25mg: 4 **(0.9%)** Placebo: 0 **(0%)**