Supplementary Appendix

Table S1. Baseline demographics and clinical characteristics[6]

Characteristic	**Placebo (n=500)**	**Peginterferon beta-1a every 2 weeks (n=512)**	**Peginterferon beta-1a every 4 weeks (n=500)**
Age, years	36.3 (9.7)	36.9 (9.8)	36.4 (9.9)
Gender, n (%) female	358 (72)	361 (71)	352 (70)
Race, n (%) Caucasian	412 (82)	416 (81)	409 (82)
Geographic regions, n (%)			
India	56 (11)	58 (11)	56 (11)
North America	17 (3)	19 (4)	16 (3)
Western Europe	38 (8)	41 (8)	39 (8)
Eastern Europe	354 (71)	355 (69)	355 (71)
Rest of World	35 (7)	39 (8)	34 (7)
Time since first MS symptoms, years	6.3 (6.3)	6.9 (6.6)	6.5 (6.1)
Time since MS diagnosis, years	3.5 (4.6)	4.0 (5.1)	3.4 (4.4)
Relapses within the previous 3 years	2.6 (1.00)	2.6 (0.99)	2.5 (0.77)
Relapses within the previous 12 months	1.6 (0.67)	1.6 (0.67)	1.5 (0.62)
EDSS Score	2.44 (1.18)	2.47 (1.26)	2.48 (1.24)
EDSS <4, n (%)	432 (86)	423 (83)	413 (83)
EDSS ≥4, n (%)	68 (14)	89 (17)	87 (17)
Patients absent Gd+ lesions, n (%)	296 (59)	334 (65)	297 (59)
Number of Gd+ lesions	1.6 (3.8)	1.2 (3.4)	1.8 (5.4)
Number of new or newly-enlarging T2	50.6 (35.7)	48.7 (36.8)	51.4 (36.0)

Characteristic	**Placebo (n=500)**	**Peginterferon beta-1a every 2 weeks (n=512)**	**Peginterferon beta-1a every 4 weeks (n=500)**
lesions			
Prior medication, n (%)			
Glatiramer acetate	24 (5)	27 (5)	28 (6)
IFN beta-1b	6 (1)	8 (2)	5 (1)
IFN beta-1a	5 (1)	4 (<1)	6 (1)

Data are presented as mean (standard deviation), unless otherwise stated.

EDSS=Expanded Disability Status Scale. Gd+=gadolinium-enhancing. IFN=interferon. MS=multiple sclerosis.

Table S2. Adverse events, serious adverse events, and discontinuations – Year 1 and Year 2

	Year 1 (Calabresi et al 2014)			**Year 2**				
Event, n (%)	Placebo (n=500)	Peginterferon beta-1a every 2 weeks (n=512)	Peginterferon beta-1a every 4 weeks (n=500)		Delayed treatment: peginterferon beta-1a every 2 weeks[a] (n=228)	Delayed treatment: peginterferon beta-1a every 4 weeks[a] (n=227)	Peginterferon beta-1a every 2 weeks (n=438)	Peginterferon beta-1a every 4 weeks (n=439)
Any adverse event	417 (83)	481 (94)	472 (94)		210 (92)	206 (91)	392 (89)	391 (89)
Most common adverse events (≥10% in any treatment group)								
Injection site erythema	33 (7)	315 (62)	282 (56)	Injection site erythema	135 (59)	119 (52)	212 (48)	211 (48)
Influenza like illness	63 (13)	239 (47)	234 (47)	Influenza like illness	106 (46)	95 (42)	192 (44)	199 (45)
Pyrexia	76 (15)	228 (45)	218 (44)	Pyrexia	66 (29)	66 (29)	136 (31)	138 (31)
Headache	165 (33)	224 (44)	204 (41)	Headache	64 (28)	70 (31)	126 (29)	122 (28)
MS relapse	159 (32)	96 (19)	111 (22)	MS relapse	52 (23)	52 (23)	64 (15)	101 (23)
Myalgia	30 (6)	97 (19)	97 (19)	Myalgia	27 (12)	27 (12)	58 (13)	60 (14)

Chills	23 (5)	88 (17)	92 (18)	Chills	29 (13)	28 (12)	41 (9)	52 (12)
Injection site pain	15 (3)	77 (15)	67 (13)	Nasopharyngitis	17 (7)	22 (10)	47 (11)	45 (10)
Asthenia	38 (8)	68 (13)	70 (14)	Injection site pain	25 (11)	25 (11)	45 (10)	32 (7)
Back pain	57 (11)	61 (12)	64 (13)	Injection site pruritus	26 (11)	17 (7)	47 (11)	24 (5)
Injection site pruritus	6 (1)	68 (13)	56 (11)	Asthenia	10 (4)	24 (11)	40 (9)	39 (9)
Nasopharyngitis	77 (15)	53 (10)	69 (14)	Arthralgia	14 (6)	23 (10)	33 (8)	33 (8)
Arthralgia	35 (7)	57 (11)	54 (11)	--		--		
Fatigue	49 (10)	51 (10)	55 (11)	--		--		
Pain in extremity	49 (10)	44 (9)	54 (11)	--		--		
Severe adverse events[b]	53 (11)	90 (18)	82 (16)	**Severe adverse events**[b]	39 (17)	34 (15)	56 (13)	62 (14)
AEs related to study treatment	266 (53)	459 (90)	449 (90)	**AEs related to study treatment**	198 (87)	179 (79)	350 (80)	357 (81)

AEs leading to discontinuation	7 (1)	25 (5)	24 (5)	**AEs leading to discontinuation**	8 (4)	9 (4)	8 (2)	9 (2)
Any serious adverse events	76 (15)	55 (11)	71 (14)	**Any serious adverse events**	36 (16)	42 (19)	39 (9)	67 (15)
Deaths	2 (<1)[c]	1 (<1)[d]	1 (<1)[e]	**Deaths**	0 (0)	2 (<1)[f]	3 (<1)[g]	0 (0)

[a]Delayed treatment groups: patients who received placebo in Year 1 and switched to peginterferon beta-1a in Year 2.

[b]Severe adverse events were defined as symptom(s) that cause severe discomfort; incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) could be given and/or subject hospitalized.

[c]n=1 sudden death of unknown cause, n=1 subarachnoid hemorrhage.

[d]n=1 cause unknown.

[e]n=1septicemic shock.

[f]n=1 squamous cell carcinoma oral cavity, n=1 aspiration pneumonia

[g]n=1 sudden death, cause unknown, n=1 car accident, n=1 pneumonia/septicaemia

Table S3: Potentially clinically significant hematology lab abnormalities – Year 2

Parameters/criterion	**Delayed treatment: peginterferon beta-1a every 2 weeks[a] (n=228[b])**	**Delayed treatment: peginterferon beta-1a every 4 weeks[a] (n=227[b])**	**Peginterferon beta-1a every 2 weeks (n=438[b])**	**Peginterferon beta-1a every 4 weeks (n=439[b])**
Patients with any post-baseline value, total n	227	227	438	438
WBC, n (%)				
$<3 \times 10^9$/L	23 (10)	7 (3)	42 (10)	22 (5)
Lymphocytes, n (%)				
$<0.8 \times 10^9$/L	13 (6)	7 (3)	35 (8)	23 (5)
PMN, n (%)				
$\leq 1.0 \times 10^9$/L	2 (<1)	0 (0)	4 (<1)	6 (1)
Hemoglobin, n (%)				
≤100 g/L	15 (7)	9 (4)	19 (4)	20 (5)
Platelet count, n (%)				
$\leq 100 \times 10^9$/L	3 (1)	2 (<1)	5 (1)	4 (<1)

PMN=polymorphonuclear leukocytes. WBC=white blood cell.

[a]Delayed treatment groups: patients who received placebo in Year 1 and switched to peginterferon beta-1a in Year 2.

[b]Total n is the number of patients in the safety population dosed in year 2 with at least one post-baseline value. This is the denominator for percentages in parentheses.

Table S4: Maximum post-baseline liver transaminases – Year 2

Parameters/Criterion	**Delayed treatment: peginterferon beta-1a every 2 weeks[a] (n=228[b])**	**Delayed treatment: peginterferon beta-1a every 4 weeks[a] (n=227[b])**	**Peginterferon beta-1a every 2 weeks (n=438[b])**	**Peginterferon beta-1a every 4 weeks (n=439[b])**
Patients with any post-baseline value, total n	227	227	438	438
ALT, n (%)				
>1 x ULN	111 (49)	70 (31)	162 (37)	124 (28)
≥3x ULN	9 (4)	8 (4)	14 (3)	15 (3)
>5 x ULN	2 (<1)	2 (<1)	7 (2)	7 (2)
AST, n (%)				
>1 x ULN	72 (32)	36 (16)	119 (27)	73 (17)
≥3x ULN	4 (2)	1 (<1)	9 (2)	10 (2)
>5 x ULN	2 (<1)	0 (0)	6 (1)	5 (1)

ALT=alanine transaminase. AST=aspartate transaminase. ULN=upper limit of normal.

[a]Delayed treatment groups: patients who received placebo in Year 1 and switched to peginterferon beta-1a in Year 2.

[b]Total n is the number of patients in the safety population dosed in year 2 with at least one post-baseline value. This is the denominator for percentages in parentheses. Baseline is Year 1 baseline for patients previously treated with peginterferon beta-1a, and year 2 baseline for patients previously treated with placebo, during year 1.

Table S5. Potentially clinically significant hematology lab abnormalities over 2 years – All patients who received peginterferon beta-1a any time over 2 years

Parameters/criterion	**Peginterferon beta-1a every 2 weeks (n=740)**	**Peginterferon beta-1a every 4 weeks (n=728)**
WBC, n (%)		
<3 x 10^9/L	80 (11)	43 (6)
Lymphocytes, n (%)		
<0.8 x 10^9/L	64 (9)	48 (7)
PMN, n (%)		
≤1.0 x 10^9/L	11 (1)	11 (2)
Hemoglobin, n (%)		
≤100 g/L	42 (6)	35 (5)
Platelet count, n (%)		
≤100 x 10^9/L	13 (2)	7 (<1)

PMN=polymorphonuclear leukocytes. WBC=white blood cell.

Table S6. Maximum post-baseline liver transaminases over 2 years – All patients who received peginterferon beta-1a any time over 2 years

Parameters/Criterion	**Peginterferon beta-1a every 2 weeks (n=740)**	**Peginterferon beta-1a every 4 weeks (n=728)**
ALT, n (%)		
>1 x ULN	399 (54)	292 (40)
≥3x ULN	56 (8)	38 (5)
>5 x ULN	21 (3)	17 (2)
AST, n (%)		
>1 x ULN	293 (40)	171 (24)
≥3x ULN	23 (3)	21 (3)
>5 x ULN	11 (1)	8 (1)

ALT=alanine transaminase. AST=aspartate transaminase. ULN=upper limit of normal.

Table S7: Incidence of positive antibody tests over 2 years – All patients who received peginterferon beta-1a any time over 2 years

Antibody type	**Peginterferon beta-1a every 2 weeks (n=740)**	**Peginterferon beta-1a every 4 weeks (n=728)**	**Total (n=1468)**
Number of antibody positive/number at risk (%)– Post-baseline to Week 96			
IFN binding (BAbs) positive	54/706 (8)	36/706 (5)	90/1412 (6)
IFN neutralizing (NAbs) positive	7/715 (<1)	6/716 (<1)	13/1431 (<1)
Anti-PEG positive	40/681 (6)	55/682 (8)	95/1363 (7)

IFN=interferon. PEG=polyethylene glycol.

Entries are number of antibody positive/number at risk. Number at risk is the number of patients whose baseline antibody was not positive and who had at least one post-baseline antibody value for any time post baseline. Numbers in parentheses are percentages based on number at risk.