Long-term effect of early treatment with interferon beta-1b after a first clinical event suggestive of multiple sclerosis: 5-year active treatment extension of the phase 3 BENEFIT trial

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Summary

Background **The Betaferon/Betaseron in newly emerging multiple sclerosis for initial treatment (BENEFIT) trial investigated the effect of treatment with interferon beta-1b after a clinically isolated syndrome. The 5-year active treatment extension compares the effects of early and delayed treatment with interferon beta-1b on time to clinically definite multiple sclerosis (CDMS) and other disease outcomes, including disability progression.**

Methods **Patients with a first event suggestive of multiple sclerosis and a minimum of two clinically silent lesions in MRI were randomly assigned to receive interferon beta-1b 250 µg (n=292; early treatment) or placebo (n=176; delayed treatment) subcutaneously every other day for 2 years, or until diagnosis of CDMS. All patients were then eligible to enter a prospectively planned follow-up phase with open-label interferon beta-1b up to a maximum of 5 years after randomisation. Patients and study personnel remained unaware of initial treatment allocation throughout the study. Primary endpoints were time to CDMS, time to confirmed disability progression measured with the expanded disability status scale, and the functional assessment of multiple sclerosis trial outcomes index (FAMS-TOI) at 5 years. Analysis of the primary endpoints was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00185211.**

Findings **235 (80%) patients from the early treatment and 123 (70%) from the delayed treatment group completed the 5-year study. Early treatment reduced the risk of CDMS by 37% (hazard ratio [HR] 0·63, 95% CI 0·48–0·83; p=0·003) compared with delayed treatment. The risk for confirmed disability progression was not significantly lower in the early treatment group (0·76, 0·52–1·11; p=0·177). At 5 years, median FAMS-TOI scores were 125 in both groups. No significant differences in other disability related outcomes were recorded. Frequency and severity of adverse events remained within the established safety and tolerability profile of interferon beta-1b.**

Interpretation **Effects on the rate of conversion to CDMS and the favourable long-term safety and tolerability profile support early initiation of treatment with interferon beta-1b, although a delay in treatment by up to 2 years did not affect long-term disability outcomes.**

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Introduction

Multiple sclerosis typically presents with a first episode of neurological dysfunction from which most patients eventually recover fully. This episode is known as a clinically isolated syndrome. Over time, most patients with a clinically isolated syndrome in whom additional clinically silent brain lesions on MRI suggest disseminated inflammatory CNS disease develop relapsing-remitting multiple sclerosis and have a substantial risk for later progression of disability.[1–3] Previous studies in patients with clinically isolated syndromes have shown a beneficial effect of early treatment with interferon beta and glatiramer acetate on the risk of conversion to clinically definite multiple sclerosis (CDMS), but they were too short and not prospectively designed to capture any effect on disability.[4–7] Moreover, these trials did not address whether a delay in starting treatment has a long-term effect on disease course.

In the Betaferon/Betaseron in newly emerging multiple sclerosis for initial treatment (BENEFIT) trial, patients who had a clinically isolated syndrome and a minimum of two clinically silent lesions on brain MRI were randomly assigned to receive either interferon beta-1b 250 µg or placebo subcutaneously every other day for 2 years, or until diagnosis of CDMS. Patients were then eligible to enter a prospectively planned follow-up phase with open-label interferon beta-1b for up to 5 years. The effects of early interferon beta-1b treatment were compared with those of delayed treatment initiated after diagnosis of CDMS or after 2 years of study.

At the preplanned 3-year analysis of the BENEFIT study, disability progression was delayed in patients treated early with interferon beta-1b, with a 40% lower relative risk of confirmed progression on the expanded disability status scale (EDSS; p=0·022) and a 41% lower relative risk of conversion to CDMS (p=0·0011).[8] Here we report the 5-year analysis of this trial.

Methods

Patients

Eligible patients had experienced a first neurological event suggestive of multiple sclerosis and had at least two clinically silent lesions on a T2-weighted brain MRI. Patients were aged 18–45 years with a baseline EDSS score[9] of 0–5. Patients in whom any disease other than multiple sclerosis could explain their signs and symptoms were excluded, as were those with any previous episode that could possibly be attributed to an acute demyelinating event, those with complete transverse myelitis or bilateral optic neuritis, and those who had received prior immunosuppressive therapy.

Written informed consent was obtained from all participants for both the original study and the 5-year follow-up phase. The ethics committees and institutional review boards of all participating centres approved the study protocols.

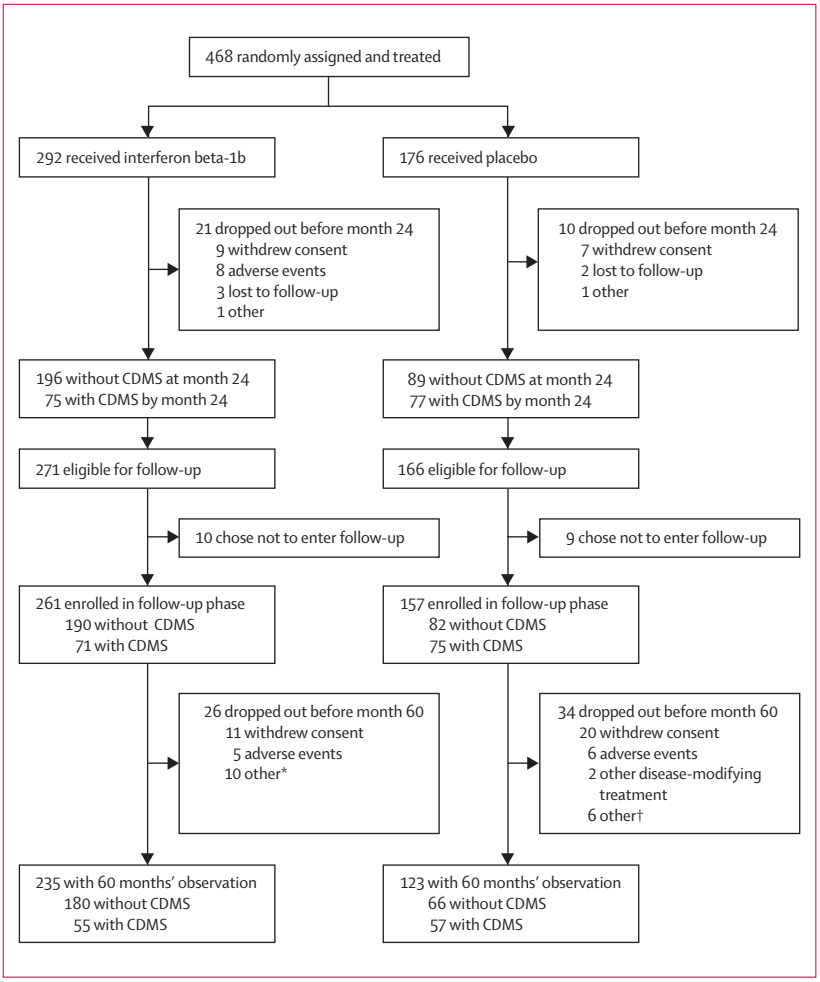

Figure 1: **Study profile**

*Three lost to follow-up, one relocated away from site, one pregnancy, one unable to attend visit because of job. †Four lost to follow-up, two missing data, one non-compliance, one treatment failure, two refused final visit.

Randomisation and masking

Within 60 days of onset of the first clinical event, patients were randomly assigned to receive either interferon beta-1b 250 µg or placebo subcutaneously every other day. Allocation was by means of a central interactive voice response system provided and maintained by Perceptive Informatics (Berlin, Germany). The procedure was designed to keep the overall treatment allocation ratio for interferon beta-1b and placebo close to five to three, respectively. A minimisation procedure with an element of randomisation[10] was used to minimise imbalances of treatment groups with respect to steroid use during first clinical demyelinating event (no or yes), classification of first demyelinating event (monosymptomatic or polysymptomatic), number of T2 lesions in screening MRI (two to four, five to eight, or at least nine T2 lesions), and CSF results (positive for oligoclonal bands or raised IgG index, negative, or not done).

Original treatment allocation was masked throughout the trial for all but 13 patients: 12 on placebo who did not develop any clinical or MRI activity for 2 years and were informed accordingly after a recommendation of the study's independent advisory board; and one patient for whom the treatment code was unblinded by the investigator because of a serious adverse event.

Procedures

Patients completed the placebo-controlled phase when CDMS was diagnosed and centrally confirmed with modified Poser criteria[9] or after 2 years in the study, and were eligible to enter the follow-up phase. Patients were offered interferon beta-1b 250 µg subcutaneously every other day for up to 5 years from randomisation. Every effort was made to obtain full follow-up assessments of all patients, including those who did not opt for ongoing treatment.

Details of assessments in the follow-up phase have been reported previously.[8] Neurological assessments (EDSS[11] and multiple sclerosis functional composite [MSFC][12]) were done at 6-monthly intervals. Brain MRI data and quality of life (QoL) assessments including the functional assessment of multiple sclerosis (FAMS),[13] EuroQol-5 dimensional questionnaire (EQ-5D), and a visual analogue scale (VAS)[14] were recorded every 12 months. To ensure maximum concealment throughout the whole trial, until end of year 5, a treating physician was responsible for the overall medical care of patients and a specially trained evaluating physician, who was not otherwise involved in the care of the patients and had no access to the patient files, did all standardised neurological assessments and determined the EDSS and functional system (FS) scores.[15] Interaction of the evaluating physician with patients was restricted to the neurological assessment. Relapses were assessed and defined in accordance with established guidelines[10] and the diagnosis of CDMS was confirmed by a central

committee. Neutralising antibodies were measured every 6 months with the in-vitro MxA assay.[16]

Statistical analysis

As previously reported,[8] the prespecified intention-to-treat analysis set comprised all patients who received at least one dose in the placebo-controlled phase after randomisation. The group of patients initially assigned interferon beta-1b (the early treatment group) was compared with the group allocated placebo with the option of starting interferon beta-1b after confirmation of CDMS or after 2 years (the delayed treatment group).

Analyses of all integrated data collected up to 3 years and all integrated data collected up to 5 years after randomisation were planned before completion of the placebo-controlled phase. To adjust for multiple testing, a nominal two-sided significance level of 0·0253 (with Šidàk's adjustment for multiple comparisons) was assigned to the 3-year and this 5-year analysis, thus allowing for an overall type 1 error probability of 0·05 for testing the primary efficacy measures.[17]

Three prespecified primary efficacy measures were tested in a sequential, conditional approach in the following order: time to CDMS, time to confirmed EDSS progression (not previously tested in the placebo-controlled phase), and the health-related QoL FAMS-trial outcome index (FAMS-TOI) score.

EDSS progression was defined as an increase in the EDSS score by ≥1·0 step compared with the lowest score obtained during screening and baseline. This progression had to be confirmed 6 months later. Only EDSS values obtained at scheduled visits were taken into account for the prespecified main analysis of this outcome but various sensitivity analyses were done as previously described.[8]

Prespecified secondary clinical outcome measures included time to multiple sclerosis as defined by the McDonald criteria,[18] risk for recurrent relapses, neurological status as measured by the MSFC, time to secondary progressive multiple sclerosis, number of admissions to hospital related to multiple sclerosis, and health-related QoL as rated on the EQ-5D. Secondary outcomes obtained by brain MRI included cumulative number of newly active lesions (new T2 or new gadolinium-enhancing lesions), change in lesion burden (on T1-weighted and T2-weighted images), and percentage change in brain volume as measured by the structural image evaluation using normalisation of atrophy method.[19] The annualised relapse rate over the entire study and within each study year as well as MSFC subtests were analysed as supportive endpoints.

For time-to-event outcomes, differences between the early and the delayed interferon beta-1b treatment groups were analysed by the log-rank test (primary analysis) and by adjusted Cox proportional hazards regression. Prespecified covariates were steroid use during the first clinical event, onset of disease (monofocal *vs* multifocal), age, sex, and number of T2 lesions and gadolinium-enhancing lesions at screening. The FAMS-TOI was analysed with non-parametric ANCOVA. The treatment effect on the annualised relapse rates was evaluated by a generalised linear Poisson regression model (covariates were steroids, onset of disease, and T2 lesions). The treatment effect on recurrent relapses and multiple-sclerosis-related admissions to hospital was analysed with the Andersen–Gill proportional hazards regression model with the same covariates as for time-to-event outcomes. Treatment effects on patient-reported outcome measures, MSFC, and MRI efficacy variables were analysed by use of non-parametric ANCOVA, with corresponding parameters from baseline (for patient-reported outcome) or screening (for MRI) assessments as covariates. Analyses on visit-based outcomes were done with data after 5 years of observation. Sensitivity analyses were done for all clinical outcome measures at the end of study visits and included all patients who dropped out before year 5. Apart from the primary outcomes, statistical analyses were not adjusted for multiple testing.

Role of the funding source

The steering committee members and the sponsor designed the study. The authors had access to all data, participated in the analysis and interpretation of data,

	Placebo-controlled phase		Follow-up phase		BENEFIT 5-year completers	
	Interferon beta-1b (n=292)	Placebo (n=176)	Early treatment (n=261)	Delayed treatment (n=157)	Early treatment (n=235)	Delayed treatment (n=123)
Women (%)	207 (71%)	124 (70%)	186 (71%)	108 (69%)	166 (71%)	83 (67%)
Age, years	30 (24·0–37·5)	30 (25·0–36·0)	30 (24·0–37·0)	30 (25·0–36·0)	30 (24·0–38·0)	30 (25·0–36·0)
Monofocal disease onset (%)	153 (52%)	93 (53%)	134 (51%)	84 (54%)	118 (50%)	63 (51%)
Had used steroids (%)	209 (72%)	123 (70%)	180 (69%)	108 (69%)	158 (67%)	86 (70%)
Number of T2 lesions	18 (7·0–38·5)	17 (7·5–36·5)	18 (7·0–39·0)	17 (8·0–37·0)	18 (7·0–39·0)	17 (8·0–36·0)
Number of gadolinium-enhancing lesions	0 (0·0–1·0)	0 (0·0–1·0)	0 (0·0–1·0)	0 (0·0–1·0)	0 (0·0–1·0)	0 (0·0–2·0)
EDSS score	1·5 (1·0–2·0)	1·5 (1·0–2·0)	1·5 (1·0–2·0)	1·5 (1·0–2·0)	1·5 (1·0–2·0)	1·5 (1·0–2·0)

Data are number (%) or median (IQR). EDSS=expanded disability status scale.

Table 1: **Baseline characteristics of patients entering the BENEFIT placebo-controlled phase and follow-up phase, and those completing the 5-year study**

	Number of patients with event at 5 years		Risk (Kaplan–Meier estimates) at 5 years		Hazard ratio (95% CI)	p value (log-rank test)	Absolute risk reduction (95% CI)
	Early treatment (n=292)	Delayed treatment (n=176)	Early treatment (n=292)	Delayed treatment (n=176)			
CDMS	124	94	46%	57%	0·63 (0·48 to 0·83)	0·003	11% (1·2% to 20·9%)
McDonald MS	224	151	81%	89%	0·55 (0·45 to 0·68)	<0·0001	8% (0·7% to 14·5%)
EDSS progression*	65	47	25%	29%	0·76 (0·50 to 1·17)	0·177	4% (–4·8% to 12·8%)

CDMS=clinically definite multiple sclerosis. EDSS=expanded disability status scale. *EDSS progression was defined as an increase in the EDSS score of ≥1·0 step compared with the lowest score obtained during the screening period (ie, at the screening or at the baseline visit).

Table 2: **Time to clinically definite multiple sclerosis, time to multiple sclerosis according to the McDonald criteria, and time to confirmed EDSS progression**

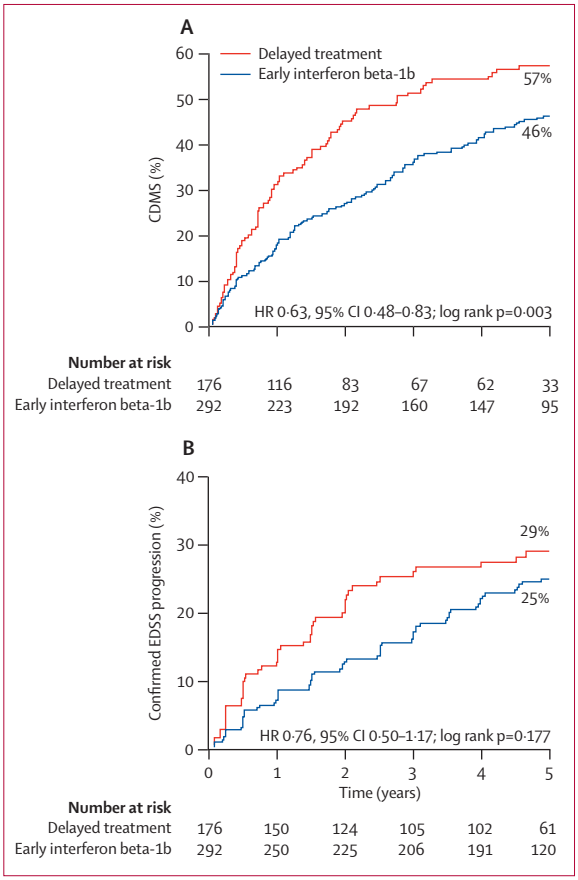

Figure 2: **Kaplan–Meier estimates for the probability of clinically definite multiple sclerosis (A) and time to confirmed disability progression (B) at 5 years**

Hazard ratio for clinically definite multiple sclerosis (CDMS) calculated with proportional hazards regression adjusted for age, sex, steroid use during first event, monofocal *vs* multifocal disease onset, T2 lesions, and gadolinium-enhancing lesions. Disability progression was recorded with the expanded disability status scale (EDSS). Hazard ratio for EDSS progression calculated with proportional hazards regression adjusted for T2-lesion volume.

and were members of the publication committee. The academic authors vouch for the completeness and veracity of the data and analyses. The decision to submit the article for publication was made jointly by the members of the study steering committee.

See Online for webappendix

Results

418 (89%) of the 468 patients who had started placebo-controlled treatment between February, 2002, and June, 2003, entered the follow-up phase (261 in the early treatment group, 157 in the delayed treatment group; of these, 235 and 147 patients received active treatment in the follow-up phase; figure 1).[8] 235 (80%) of 292 patients from the interferon beta-1b group and 123 (70%) of 176 from the placebo group completed the full 5 years of the study (of these, 191 and 90 respectively were receiving active treatment at the end of the follow-up phase). Median length of placebo exposure in the delayed treatment group was 1 year 11 months (mean 1 year 4 months; range 0 year 1 month to 2 years 1 month). Median duration of interferon beta-1b exposure was 5 years for the early treatment group (3 years 11 months; 0 years 0 months to 5 years 5 months), and 2 years and 11 months for the delayed treatment group (2 years 4 months; 0 years 0 months to 4 years 11 months). The two randomised groups of the double-blind study were largely similar in terms of demographic, clinical, and MRI characteristics (table 1). Key baseline characteristics were much the same in the patients from both groups who entered and completed the follow-up phase.

At the end of the 5-year observation period, the risk for CDMS (table 2 and figure 2) was lower in the early treatment group (46%) than in the delayed treatment group (57%; hazard ratio [HR] 0·63, 95% CI 0·48–0·83; log-rank test p=0·003), resulting in a number needed to treat of nine to prevent one diagnosis of CDMS.

At the end of the 5-year observational period, the risk for confirmed EDSS progression was 25% in the early treatment group and 29% in the delayed treatment group (table 2 and figure 2); the number needed to treat to prevent one EDSS progression was 25. However, the difference between early and delayed treatment in the time to confirmed EDSS progression over 5 years was not statistically significant (HR 0·76, 95% CI 0·50–1·17; log rank test p=0·177). Similar results were obtained for this outcome measure in various sensitivity analyses done for all patients (webappendix p 1) or in predefined subgroups (table 3). Patients with multifocal initial presentation, those with higher T2 lesion numbers, and

those with no gadolinium-enhancing lesions at baseline tended to benefit more from early treatment (table 3).

Group average EDSS values changed little over 5 years (table 4, figure 3). In both treatment groups, the median EDSS remained 1·5 from baseline to 5 years, and the median change in EDSS from baseline to any follow-up visit remained 0·0. Most patients had low EDSS values at the end of the 5-year observation period (table 4). Comparing EDSS values at baseline with those at 5 years (table 4), the percentages of patients with worsened (increase ≥1·0), stable (no change beyond 0·5), and improved EDSS (decrease ≥1·0) were 21%, 53%, and 26% in the early treatment group, and 23%, 56%, and 21% in the delayed treatment group (p=0·567). EDSS scores did not differ significantly when the last available EDSS in the study was analysed instead of EDSS at 5 years (to account for possible bias from early drop outs).

Benefits of early interferon beta-1b treatment were also found for time to multiple sclerosis diagnosed with McDonald criteria (HR 0·55, 95% CI 0·46–0·68; p<0·0001; table 2). The number of recurrent relapses in the early treatment group was 277 in 127 (44%) of 292 patients compared with 203 in 98 (56%) of 176 in the delayed treatment group. Annualised relapse rates were lower in the early treatment group than in the delayed treatment group in the first year of the study (p=0·014), but were not different from year 2 onwards (figure 4).

Mean MSFC score improved over the 5 years in most patients and there was no significant difference between treatment groups (p=0·608; table 5). Improvement of the overall MSFC score was largely due to improvement in the cognitive subtest, the paced auditory serial addition test (PASAT). In the subtests for arm function (nine-hole peg test, p=0·442) and leg function (25-foot walk, p=0·941), results did not differ significantly between treatment groups. In the PASAT, improvement was more pronounced in the early treatment as compared with the delayed treatment group; the difference increased during the course of the study until year 5 (year 3, p=0·064; year 5, p=0·005; figure 3; webappendix p 2).

Over the 5-year observation period, the numbers of patients who converted to secondary-progressive multiple sclerosis were low in both treatment groups: five (2%) of 292 in the early treatment group and four (3%) of 176 in the delayed treatment group (log rank p=0·6457). The difference between the early and delayed treatment for the risk of recurrent multiple-sclerosis-related admissions to hospital was not statistically significant (HR 0·82, 95% CI 0·55–1·24; p=0·350).

Throughout the 5 years of observation, QoL assessed with the FAMS-TOI and the EQ-5D rating scales remained high and without significant differences between the two groups (table 5). The early treatment group developed fewer newly active lesions (new or enlarging T2 lesions or gadolinium-enhancing lesions) over 5 years than did the delayed treatment group (p=0·006; table 5). T2-lesion volume decreased from screening to month 12 and remained stable in most patients in both groups with no significant differences between the two groups (p=0·780). There were only small changes and no differences between groups when the volume of hypointense T1 lesions (p=0·662) and brain volume (p=0·121) at 5 years were compared with those at baseline (table 5, webappendix p 3).

The frequency of adverse events was within the established safety and tolerability profile of interferon beta-1b 250 µg subcutaneously every other day, and did not differ from that reported previously for the placebo-controlled phase[6] (webappendix p 4). The percentage of patients experiencing at least one serious adverse event was similar in each group: 61 (21%) in the early treatment group and 42 (24%) in the delayed

	Hazard ratio (95% CI)*	p value†
Monofocal at first event suggestive of MS	0·968 (0·58–1·61)	0·959
Multifocal at first event suggestive of MS	0·555 (0·31–0·98)	0·052
<9 T2 lesions at screening MRI	0·851 (0·41–1·76)	0·609
≥9 T2 lesions at screening MRI	0·713 (0·46–1·11)	0·192
No gadolinium-enhancing lesions at screening MRI	0·685 (0·41–1·16)	0·195
≥1 gadolinium-enhancing lesion at screening MRI	0·804 (0·47–1·40)	0·460

Subgroups were predefined in the statistical analysis plan according to key clinical and MRI features that, according to published work, would best characterise dissemination and activity of the disease at the time of the first event.[20] MS=multiple sclerosis. *Additional covariates: steroid use, interferon beta-1b treatment, T2 lesion categories >9 or ≤9, age categories >30 or ≤30 years, sex, presence of gadolinium-enhancing lesions. †Log-rank test.

Table 3: **Treatment effect of early versus delayed interferon beta-1b on confirmed EDSS progression in subgroups at time of first event**

	Early treatment (n=235)		Delayed treatment (n=122)*		p value
	Mean	Median (IQR)	Mean	Median (IQR)	
EDSS at year 5					
EDSS score (SD)	1·46 (1·16)	1·5 (1·0 to 2·0)	1·51 (1·12)	1·5 (1·0 to 2·0)	0·547†
Patients in EDSS by category at year 5					
EDSS ≤1·0	102 (43%)	..	51 (42%)	..	0·602‡
EDSS 1·5–2·5	107 (46%)	..	53 (43%)	..	
EDSS ≥3·0	26 (11%)	..	18 (15%)	..	
Change in EDSS from baseline to year 5					
Change to year 5 (SD)	–0·03 (1·19)	0·0 (–1·0 to 0·5)	0·07 (1·08)	0·0 (–0·5 to 0·5)	
Patients with EDSS change from baseline to year 5					
Worsened EDSS (≥1·0)	49 (21%)	..	28 (23%)	..	0·567‡
Stable EDSS (–0·5 to 0·5)	124 (53%)	..	68 (56%)	..	
Improved EDSS (≤–1·0)	62 (26%)	..	26 (21%)	..	
Patients with EDSS change from baseline to last available EDSS score§					
Worsened EDSS (≥1·0)	60 (21%)	..	44 (25%)	..	0·255‡
Stable EDSS (–0·5 to 0·5)	160 (55%)	..	99 (56%)	..	
Improved EDSS (≤–1·0)	72 (25%)	..	33 (19%)	..	

*5-year EDSS record missing for one patient. †Non-parametric analysis of covariance. ‡Fisher's exact test. EDSS=expanded disability status scale. §For early treatment n=292; for delayed treatment n=176.

Table 4: **EDSS score at and up to 5 years**

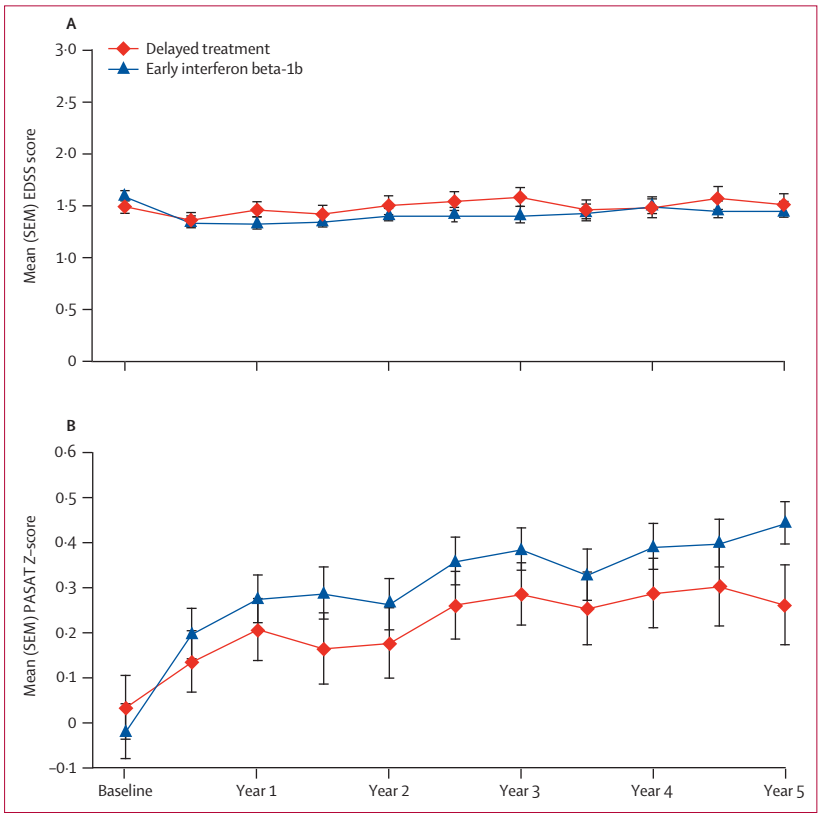

Figure 3: **Mean expanded disability status scale score (A) and mean PASAT *Z* scores (B) over 5 years**
EDSS scores did not differ significantly at 5 years (p=0·547 by non-parametric analysis of covariance). PASAT Z scores were different (p=0·005 by non-parametric analysis of covariance; higher scores indicate better performance). SEM=standard error of the mean.

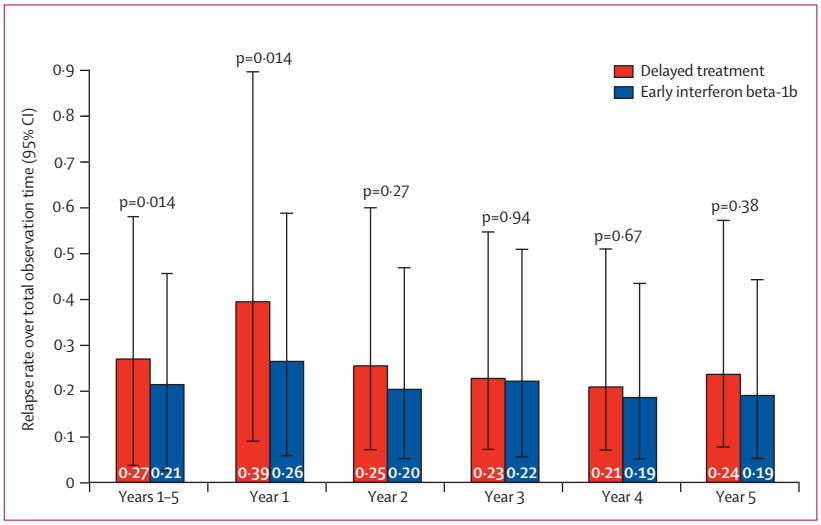

Figure 4: **Annualised relapse rate over 5-years**
p calculated with generalised linear Poisson regression model adjusted for steroids, disease onset, and T2-lesions.

treatment group). Most serious adverse events were not related to the study drug (as assessed by the investigator). No deaths were reported during the study period. During the 5 years, 88 (32%) of 277 patients in the early treatment group and 40 (23%) of 173 patients in the delayed treatment group, who had post-baseline blood samples investigated, had at least one blood sample positive for neutralising antibodies (titre ≥20 NU/mL). Of these, 53 patients (60%) in the early treatment and 18 patients (45%) in the delayed treatment group had reverted to having negative titres by the end of the 5 years. Occurrence of neutralising antibodies, irrespective of titre, was not associated with either shorter time to CDMS or higher annualised relapse rates.

Discussion

The 5-year analysis of the BENEFIT study substantiates some findings in favour of early intervention that had already been observed at the 3-year timepoint.[8] An earlier initiation of interferon beta-1b reduced the risk for a diagnosis of multiple sclerosis with clinical or McDonald criteria at 5 years, even though both treatment groups had received active intervention for at least 3 years. Likewise, the annualised relapse rate over 5 years was significantly lower in the early treatment group; an effect which was primarily due to differences in relapse rates in the placebo-controlled first 2 years of the study when interferon beta-1b exposure was different in the two treatment groups. Early treatment was also associated with a substantial reduction in the cumulative number of newly active lesions on brain MRI and had favourable effects on the PASAT, a cognitive performance measure, over 5 years.

Including BENEFIT, four placebo-controlled studies have addressed the value of early immunomodulatory treatment in clinically isolated syndromes.[4–7] Across different designs, preparations, and dosing schedules all have shown a significant delay in conversion to CDMS with active treatment (table 6). Whether this translates to long-term benefits for patients can be addressed only in long-term studies. Prospectively planned long-term studies on the difference between early and delayed intervention in chronic diseases are rare. Many published long-term extensions of clinical trials (one in clinically isolated syndromes [table 7],[22] two in relapsing-remitting multiple sclerosis[23,24]) have severe methodological restrictions—eg, non-prospective design, high and possibly selective dropout rates, unblinded assessments, and poor monitoring—that limit their interpretation.[25] In designing and doing the long-term follow-up of the present BENEFIT study, major efforts were made to address these issues by strictly applying the intention-to-treat principle, keeping the blinding for the original treatment allocations, retaining the same standards of assessment, and by prospectively planning the statistical analyses. Thus, this trial should provide methodologically sound evidence that might help in treatment decisions in the earlier stages of relapsing-remitting multiple sclerosis. Assessment of the balance between burden of treatment

	Early treatment (n=261)			Delayed treatment (n=157)			p value*
	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)	
FAMS-TOI score	169	118·9 (24·9)	125·0 (107·0 to 139·0)	91	118·7 (26·1)	125·0 (104·8 to 140·0)	0·888
EQ-5D HRQoL score	222	0·8 (0·2)	0·8 (0·7 to 1·0)	114	0·8 (0·2)	0·9 (0·7 to 1·0)	0·721
Overall MSFC score	228	0·08 (0·71)	0·23 (–0·16 to 0·50)	120	0·12 (0·72)	0·23 (–0·21 to 0·62)	0·608
PASAT	229			120			0·005
Raw score		56·14 (5·70)	58·00 (55·00 to 60·00)		54·68 (7·80)	58·00 (53·50 to 59·00)	
Z score		0·44 (0·71)	0·67 (0·30 to 0·92)		0·26 (0·97)	0·67 (0·12 to 0·80)	
Nine-hole peg test	230			120			0·442
Raw score		0·054 (0·009)	0·054 (0·049 to 0·059)		0·055 (0·009)	0·056 (0·050 to 0·060)	
Z score		0·05 (1·06)	0·07 (–0·57 to 0·72)		0·23 (1·09)	0·26 (–0·41 to 0·81)	
Timed 25-foot walk	229			120			0·941
Raw score		5·09 (1·80)	4·70 (4·10 to 5·45)		4·93 (1·49)	4·68 (4·13 to 5·50)	
Z score		–0·22 (1·16)	0·03 (–0·46 to 0·41)		–0·13 (0·96)	0·04 (–0·49 to 0·40)	
Cumulative number of newly active lesions	219	9·7 (14·7)	4·0 (1·0 to 12·0)	114	12·9 (15·7)	7·0 (2·0 to 18·0)	0·006
Absolute change in T2-lesion volume (mL)	215	–0·6 (4·1)	–0·1 (–0·8 to 0·2)	112	–0·3 (2·4)	–0·2 (–0·7 to 0·4)	0·780
Change in brain volume (%)	141	–2·7 (2·4)	–2·3 (–3·7 to –1·1)	80	–2·0 (2·1)	–1·8 (–3·3 to –0·7)	0·121
Absolute change in hypointense T1 (black holes) lesion volume (mL)	217	–0·03 (0·9)	0·0 (–0·2 to 0·04)	114	0·01 (0·8)	0·0 (–0·09 to 0·05)	0·662

*Non-parametric analysis of covariance. MSFC=multiple sclerosis functional composite. PASAT=paced auditory serial addition test. FAMS-TOI=functional assessment of multiple sclerosis-trial outcome index. EQ-5D=EuroQoL 5-dimensional questionnaire. HRQoL=health-related quality of life.

Table 5: **Other efficacy measures over 5 years**

and effects on outcome in patients with clinically isolated syndromes is clinically important because most patients will develop CDMS and eventually progress to substantial disability in the following years. However, about 15–20% might not develop CDMS at all, not even after 20 years.[3]

On the basis of the preplanned 3-year analysis, we reported that a delay of interferon beta-1b treatment for up to 2 years was associated with a significantly higher risk of developing confirmed disability progression as measured by the EDSS.[8] The results of the 5-year final analysis of the trial presented here expand on these observations and put them into perspective. After 5 years, the absolute numbers of patients with confirmed EDSS progression were still lower in the early treatment group, although the difference in the delayed treatment group was less pronounced and no longer statistically significant. In years 4 and 5 of observation, fewer patients showed disease progression in the delayed than in the early interferon beta-1b treatment group. The risk for disease progression from year 3 to year 5 only increased by 5% (from 24% to 29%) in patients with delayed treatment, compared with 9% (from 16% to 25%) for early treatment. As discussed previously,[26] in the setting of inhomogeneous populations and only partially effective interventions, survival-type measures offer a limited time frame for the detection of differences: patients with clinically isolated syndromes who had a naturally more progressive disease course had a higher chance of confirmed EDSS progression during the initial phase of the trial if assigned placebo than if assigned interferon beta-1b. Therefore EDSS progression might be more common in the early treatment group in the later phases of the study. Thus, a partly effective treatment that delays but not necessarily prevents the event will result in a seemingly decreasing effect of early intervention.

If we assume that treatment with interferon beta-1b prevents at least part of further damaging autoimmune attacks, we expect the effect of earlier treatment to be diluted as the duration of active treatment in the delayed group increases relative to the placebo phase. In the early phase of multiple sclerosis, the capacity for repair and compensation of impaired CNS functions is not exhausted[27,28] and can contribute to recovery of overt neurological deficits.

At the 5-year time point, average EDSS scores of both treatment arms were still slightly lower than at baseline; only a few patients had reached moderate-to-severe disability and a quarter of the cohort had improved neurological status measured with the EDSS (26% and 21% in the early and delayed treatment groups, respectively). In view of the overall low progression rate it is not surprising that for the outcome of disability, the search for subgroups of responders to treatment yielded less clear findings and only partly confirmed the analysis for the outcome of CDMS.[29,30]

Disease activity might also cause functional deficits not assessed in the routine neurological examination with EDSS assessments. This limitation might be true especially for neuropsychological deficits that substantially contribute to the disease burden of patients

	BENEFIT[6] (n=468)	ETOMS[5] (n=309)	CHAMPS[4,21] (n=383)	PreCISe[7] (n=481)
Study characteristics				
Comparison	Interferon beta-1b *vs* placebo	Interferon beta-1a *vs* placebo	Interferon beta-1a *vs* placebo	Glatiramer acetate *vs* placebo
Dose	250 µg subcutaneous every other day	22 µg subcutaneous once a week	30 µg intramuscular once a week	20 mg subcutaneous once a day
Mean age (years)	30·7	28·5	33·0	31·1
Women (%)	331 (71%)	197 (64%)	289 (75%)	326 (67%)
Time from first symptoms to treatment (days)	52 (mean), 55 (median)	79 (mean)	19 (median)	74 (mean), 79 (median)
Received steroids for first event (%)	332 (71%)	217 (70%)	383 (100%)	308 (64%)
Disease onset (%)	246 (53%) monofocal onset; 222 (47%) multifocal	121 (39%) multifocal onset	115 (30%) multifocal disease at baseline according to post-study analysis[21]	481 (100%) monofocal only
Main clinical outcomes				
Conversion to CDMS (%)	At 2 years: 28% *vs* 45%; p=0·0001	At 2 years: 34% *vs* 45%; p=0·047	At 3 years: 35% *vs* 50%; p=0·002	At 2·4 years: 25% *vs* 43%; p=0·0001
CDMS risk reduction	HR 0·50 (0·36–0·70)	OR 0·61 (0·37–0·99)	RR 0·56 (0·38–0·81)	HR 0·55 (0·40–0·77)
Main MRI outcomes				
Number of new gadolinium-enhancing lesions, median (IQR)	Up to 2 years: 0·0 (0–2) *vs* 2 (0–5); p=0·0001	At 2 years: 0·5 (0·0–1·0) *vs* 0·0 (0·0–1·0); p=0·809	At 18 months (mean, SD): 0·4 (1·5) *vs* 1·4 (3·6); p<0·001	At 2·4 years: 0·46 *vs* 1·19 p<0·001
Number of new T2 lesions, median (IQR)	Up to 2 years: 1·0 (0–4) *vs* 2 (1–6); p=0·0001	At 2 years: 2·00 (0·50–4·50) *vs* 3·00 (1·50–6·25); p<0·001	At 18 months (mean, SD): 2·1 (3·2) *vs* 5·0 (7·7); p<0·001	At 2·4 years: 0·7 *vs* 1·8 p<0·0001

EDSS=expanded disability status scale. GA=glatiramer acetate. CDMS=clinically definite multiple sclerosis. HR=hazard ratio. RR=rate ratio. OR=odds ratio.

Table 6: **Comparison of controlled studies in patients with clinically isolated syndromes, main baseline characteristics and outcomes of placebo-controlled phase**

	BENEFIT 5-year (n=468)	CHAMPIONS 5-year[22] (n=383)
Study characteristics		
Study design	Full-scale, prospectively planned extension phase, double-blind as to initial randomisation	Open-label extension, not prospectively planned
Eligible population	All randomised patients after completing the 2-year, double-blind phase or converting to CDMS	All randomised patients after completing the 3-year, double-blind phase or converting to CDMS
Number (% of initially randomised) entering follow-up study	418 (89%)	203 (53%)
Number (% of initially randomised) completing 5-year follow-up	357 (76%)	195 (51%)
Main clinical outcomes		
Conversion to CDMS, early *vs* delayed (%)	46% *vs* 57%; HR: 0·63 (0·48–0·83); p=0·003	36% *vs* 49%; HR: 0·65 (0·43–0·97) p=0·03
Risk of confirmed EDSS progression, early *vs* delayed (%)	At 3 years: (16 *vs* 24; HR 0·60; p=0·022)[8] At 5 years: (25 *vs* 29; HR 0·76; p=0·177)	At 3 years: not available At 5 years: 68% *vs* 74% of patients had EDSS ≤1·5 (p=0·73)
HRQoL, early *vs* delayed	HRQoL as assessed by FAMS-TOI remained stable over 5 years (mean [SD] 118·7 [24·9] *vs* 118·7 [26·1]; p=0·888)	Not available
Other outcomes		
MRI, early *vs* delayed	Median (IQR) cumulative number of newly active lesions (new or enlarging T2 lesions, gadolinium-enhancing lesions): 4·0 (1·0–12·0) *vs* 7·0 (2·0–18·0; p=0·0062)	Median (IQR) cumulative number of new or enlarging T2 lesions early *vs* delayed treatment: 3·5 (0·5–8·5) *vs* 6·0 (2·0–13·0; p=0·05)
Reduction in annualised relapse rate (%)	0·21 *vs* 0·27; p=0·014	0·17 *vs* 0·32; p=0·02
Neurological status as assessed by MSFC	Mean MSFC score improved over 5 years; no difference between treatment groups (p=0·608). No difference in upper (nine-hole peg test, p=0·442) and lower (25-foot walk, p=0·941) extremity function tests between treatment groups. Improvement in PASAT with early treatment (p=0·005).	Not available

HR=hazard ratio. CDMS= clinically definite multiple sclerosis. EDSS=expanded disability status scale. HRQoL=health-related quality of life.

Table 7: **Comparison of published study extensions of controlled studies in patients with clinically isolated syndromes**

with multiple sclerosis as time goes by.[31] Comprehensive neuropsychological and functional MRI studies have shown impaired cognitive function in up to 60% of patients with clinically isolated syndromes.[32–34] The observations in BENEFIT with repeated measurements of the PASAT, a standardised measure of working memory and attention, seem to suggest that in follow-up tests with the PASAT, most control patients improve but

reach a plateau after the third session. The fact that in the BENEFIT study improvement in this cognitive measure was more pronounced in the early treatment group over a 5-year observation period suggests additional effects of recovery or compensation, and indicates that this capacity might have been better preserved with early treatment. Because this was not a primary outcome, the difference in improvement in favour of early treatment could be a chance observation, although the persistence of the difference up to year 5 is intriguing.

We recorded no differences in the two other subscores of the MSFC measuring arm and leg function. As with the EDSS results, function in these two subscores did not substantially change over time, indicating that neurological symptoms causing readily detectable motor disturbances were rare with interferon beta-1b treatment in this early phase of the disease. Likewise, patients in both groups reported high and stable ratings in various QoL questionnaires over 5 years, suggesting that neither the disease nor the treatment had a substantial negative effect on their physical and mental wellbeing. In line with these patient-reported outcomes, the adverse event profile emerging from this 5-year study was benign and compatible with reports from other interferon beta-1b trials and the 2-year and 3-year analysis of BENEFIT.[6,8] The longer observation period allowed for a more comprehensive analysis of the role of neutralising antibodies to interferon beta but failed to show any negative effect on the main outcomes.[35]

As in the first 2 years,[36] MRI findings over 5 years are in accordance with the clinical observations. In both groups, overall disease burden, as depicted by T2-lesion volumes, was lower at 5 years than at baseline, indicating recovery from the initial inflammatory event.

Brain volume and T1-hypointense lesion volume—MRI surrogates thought to reflect neuronal loss and axonal degeneration rather than inflammation[37]—did not show strong changes over time, again reflecting the favourable disease course of the entire cohort with respect to the evolution of irreversible pathological changes. We recorded little decrease in brain volume in both groups of patients (median decrease of 2·3% and 1·8% in the early *vs* delayed treatment groups after 5 years) without significant differences between early and delayed treatment. A post-hoc analysis of a 2-year study of low-dose interferon beta-1a subcutaneously every other day in clinically isolated syndromes (ETOMS)[38] showed a significant effect of treatment (median 2-year decrease in brain volume of 0·88 in interferon beta-1a *vs* 1·37 in the placebo group). We can only speculate about the reasons for this discrepancy, but contributing factors might include: different selection of patients with more active disease as indicated by the higher annual rate of atrophy, the lower dose and perhaps therefore less anti-inflammatory effect of interferon, and methodological issues such as differences in MRI technology.[39]

The low progression of neurological deficits contrasts with the high conversion rate to a diagnosis of multiple sclerosis defined by McDonald criteria[18] that occurred within the first year of the BENEFIT study,[6] and was mainly based on the depiction of new MRI lesions. This discrepancy illustrates the low short-term and mid-term correlation of conventional MRI defined inflammatory events and clinical (especially disability-related) outcomes.[40,41] It also suggests that the McDonald criteria[18]—notwithstanding their contribution to an improved and more reliable diagnostic process—do not necessarily predict disease outcome.

The relative benefits of starting treatment immediately after the first episode of symptoms highly suggestive of multiple sclerosis, versus a delay by several months up to 2 years, tended to decrease with the length of observation and of ongoing interferon beta-1b treatment as far as disability progression was concerned. After 5 years, the overall rate of progression of disability as measured by the EDSS was low in both treatment groups, which indicates that a delay in treatment initiation by up to 2 years does not result in irreversible clinically relevant deficits in most patients. Nevertheless, persistence of significant favourable effects on the rate of conversion to CDMS, on inflammatory disease activity in MRI, and on cognitive performance after 5 years, together with a well established long-term safety profile, should be taken into account when making decisions on early initiation of immunomodulatory treatment with interferon beta-1b.

Contributors

LK was actively involved in drafting and amending the statistical analysis plan, was responsible for the central CDMS confirmation during the study, and reviewed the statistical analysis. MSF reviewed the statistical analysis. CHP was responsible for the central eligibility assessment during the study and reviewed the statistical analysis. GE, H-PH, DHM, and XM reviewed the statistical analysis. FB was responsible for the central MRI analysis (apart from brain volume analysis) of the study and reviewed the statistical analysis. EWR was responsible for the central MRI brain volume analysis of the study and reviewed the statistical analysis. LB reviewed the statistical analysis; he was also the study manager of the placebo-controlled study phase. CM was actively involved in data collection and reviewed the statistical analysis. VL was responsible for biometrical analyses in the study and created the statistical analysis plan. RS was actively involved in drafting and amending the statistical analysis plan and reviewed the statistical analysis; he was the sponsor's responsible clinician for the placebo-controlled study phase and oversaw the conduct and analyses of the whole study programme. CP was actively involved in amending the statistical analysis plan and reviewed the statistical analysis; he was the sponsor's responsible clinician for the follow-up study phase and led the conduct of follow-up study phase as well as the integrated analyses. LK, MSF, CHP, GE, H-PH, DHM, XM, FB, EWR, LB, and RS were actively involved in drafting and amending the study protocol. All authors actively contributed to the writing and reviewing of the submitted manuscript, and have seen and approved the final version.

Conflicts of interest

University Hospital Basel (LK) has received research support from Bayer Schering, Biogen Idec, GlaxoSmithKline, Merck Serono, Novartis Pharmaceuticals, Sanofi-Aventis, Teva Pharmaceuticals, and Wyeth Pharmaceuticals; LK has been principal investigator, member, or chair of steering committees or advisory boards in multiple sclerosis clinical trials sponsored by Abbott Laboratories, Bayer, Bayhill, Berlex, Biogen

Idec, Boehringer-Ingelheim, Bristol-Myers Squibb, Centocor, Eisai, Genzyme, GlaxoSmithKline, Immune Response, Medicinova, Neurocrine, Novartis Pharmaceuticals, Sanofi-Aventis, Bayer Schering, Merck Serono, Roche, Teva Pharmaceuticals, UCB Pharma, and Wyeth, and has received lecture fees from Bayer, Biogen Idec, GSK, Novartis, Sanofi-Aventis, Bayer Schering, Merck Serono, Roche, Teva. These payments and consultancy fees have been exclusively used for the support of research activities. MSF is a consultant and advisory board member for Bayer Schering Pharma, Pfizer, Merck Serono, BioMS, Novartis, and Teva Neuroscience. CHP has received: consulting fees from Biogen Idec, Bayer Schering Pharma AG, Teva, Merck Serono, Novartis Pharmaceuticals, GlaxoSmithKline, UCB, AstraZeneca, Roche and Antisense therapeutics; lecture fees from Biogen Idec, Bayer Schering Pharma AG, Novartis, and Teva Pharmaceuticals; grant support from Biogen Idec, Bayer Schering Pharma, GlaxoSmithKline, Novartis, Merck Serono, and Teva. GE received personal compensation for serving on an advisory board and for speaking from Bayer Schering Pharma AG. H-PH has received honoraria and consultancy fees from, and participated as an investigator in phase 2 and 3 trials for, Biogen Idec, Bayer Vital, Bayer Schering, Merck Serono, and Teva Pharmaceuticals, and has received research grant support from Biogen Idec. DHM has received grant support from Biogen Idec, Elan, Bayer Schering, and GlaxoSmithKline for performance of MRI analyses in clinical trials, as well as honoraria for advisory or consultancy work, lectures, and related travel expenses from Aventis, Biogen Idec, Bristol Myers Squibb, GlaxoSmithKline, Bayer Schering, Merck Serono, UCB Pharma, and Wyeth. XM has received honoraria for consultation and speaking from Serono, Bayer Schering Pharma AG, Biogen Idec, Sanofi-Aventis, Teva, and Novartis. FB received consultancy fees from Bayer Schering Pharma for performing the central MRI analysis in the BENEFIT study. EWR received grant support from Biogen Idec, Bayer Schering, Novartis, Sanofi-Aventis, and GlaxoSmithKline for evaluation of multicentre multiple sclerosis studies. Payments for advisory board and steering committee membership, as well as speaker honoraria by the above mentioned companies to EWR were exclusively used for research projects at the Department of Neuroradiology, University Hospital, Basel, Switzerland. LB, CM, VL, CP, and RS are or have been (LB) salaried employees of Bayer Schering Pharma AG, which also contracted medical writing support.

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