The 11-year long-term follow-up study from the randomized BENEFIT CIS trial

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ABSTRACT

Objective: To assess outcomes for patients treated with interferon beta-1b immediately after clinically isolated syndrome (CIS) or after a short delay.

Methods: Participants in BENEFIT (Betaferon/Betaseron in Newly Emerging MS for Initial Treatment) were randomly assigned to receive interferon beta-1b (early treatment) or placebo (delayed treatment). After conversion to clinically definite multiple sclerosis (CDMS) or 2 years, patients on placebo could switch to interferon beta-1b or another treatment. Eleven years after randomization, patients were reassessed.

Results: Two hundred seventy-eight (59.4%) of the original 468 patients (71.3% of those eligible at participating sites) were enrolled (early: 167 [57.2%]; delayed: 111 [63.1%]). After 11 years, risk of CDMS remained lower in the early-treatment arm compared with the delayed-treatment arm (p = 0.0012), with longer time to first relapse (median [Q1, Q3] days: 1,888 [540, not reached] vs 931 [253, 3,296]; p = 0.0005) and lower overall annualized relapse rate (0.21 vs 0.26; p = 0.0018). Only 25 patients (5.9%, overall; early, 4.5%; delayed, 8.3%) converted to secondary progressive multiple sclerosis. Expanded Disability Status Scale scores remained low and stable, with no difference between treatment arms (median [Q1, Q3]: 2.0 [1.0, 3.0]). The early-treatment group had better Paced Auditory Serial Addition Task–3 total scores (p = 0.0070). Employment rates remained high, and health resource utilization tended to be low in both groups. MRI metrics did not differ between groups.

Conclusions: Although the delay in treatment was relatively short, several clinical outcomes favored earlier treatment. Along with low rates of disability and disease progression in both groups, this supports the value of treatment at CIS.

ClinicalTrials.gov identifier: NCT01795872.

Classification of evidence: This study provides Class IV evidence that early compared to delayed treatment prolongs time to CDMS in CIS after 11 years. *Neurology*® 2016;87:978–987

GLOSSARY

ARR = annualized relapse rate; **BENEFIT** = Betaferon/Betaseron in Newly Emerging MS for Initial Treatment; **CDMS** = clinically definite multiple sclerosis; **CI** = confidence interval; **CIS** = clinically isolated syndrome; **DMT** = disease-modifying therapy; **EDSS** = Expanded Disability Status Scale; **EQ-5D** = EuroQoL–5 Dimension; **FAMS** = Functional Assessment of Multiple Sclerosis; **Gd+** = gadolinium-enhancing; **KM** = Kaplan-Meier; **MS** = multiple sclerosis; **PASAT** = Paced Auditory Serial Addition Task; **Q** = quartile; **RR** = risk ratio; **SDMT** = Symbol Digit Modalities Test; **SPMS** = secondary progressive multiple sclerosis.

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Supplemental data at Neurology.org

Patients with multiple sclerosis (MS), the most common chronic demyelinating disorder of the CNS, often present with an acute or subacute episode of neurologic dysfunction known as a clinically isolated syndrome (CIS).[1,2] Eventually, most of these patients (up to 85%) will be diagnosed with MS once evidence for dissemination of lesions in space and time accumulates.[2,3]

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BENEFIT Study Group coinvestigators are listed at Neurology.org.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article. The Article Processing Charge was paid by Bayer Pharma AG/Bayer HealthCare Pharmaceuticals.

Several controlled studies have shown that conversion to MS can be delayed by starting treatment with disease-modifying therapies (DMTs) at CIS.[4–11] However, data about the effects of starting treatment this early on the long-term disease course, including potential improvements relative to delayed treatment on measures of confirmed disability progression, participation, and quality of life, are scarce.

The 5-year Betaferon/Betaseron in Newly Emerging MS for Initial Treatment (BENEFIT) trial and its 8-year extension have shown improved outcomes in patients who initiated treatment with interferon beta-1b (Betaferon/Betaseron; Bayer HealthCare Pharmaceuticals, Whippany, NJ) immediately after CIS, relative to patients who had started treatment after their second clinical event or 2 years post-CIS at the latest.[6,10] Specifically, we have shown delays in conversion to CDMS and reductions in the annualized relapse rate (ARR) 2, 3, 5, and 8 years after randomization[6,8–10] but only a small change in mean Expanded Disability Status Scale (EDSS) score in both treatment groups up to the 8-year analysis, indicating a relatively mild disease course.[6] The objective of the present study was to examine the longer-term effects of treatment with interferon beta-1b on the disease course at 11 years after occurrence of CIS.

METHODS

Patient selection. The phase 3 BENEFIT trial consisted of a prospective, 2-year, international, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of interferon beta-1b 250 μg administered subcutaneously every other day with a preplanned open-label interferon beta-1b treatment follow-up phase, blinded to the initial treatment allocation and lasting up to 5 years.[10] All patients had experienced a CIS suggestive of MS and had ≥2 clinically silent MRI lesions. Enrollment was completed at centers in Europe, Canada, and Israel between February 2002 and June 2003.[10] The 5-year core and follow-up study was followed by an open-label observational extension study with a maximum follow-up of 8.7 years.[6] Following the extension study, the investigators decided to conduct a prospective, comprehensive, 11-year, cross-sectional reassessment (BENEFIT 11 Study), which is presented here.

Randomization and masking. In the core study, patients were randomized (5:3) by means of a central interactive voice response system within 60 days of CIS to receive either interferon beta-1b 250 μg (early treatment) or placebo (delayed treatment) subcutaneously every other day. After 2 years or conversion to CDMS, all patients could have treatment with interferon beta-1b but could also take another or no DMT.

Assessments. Eleven years after randomization, all patients from participating study centers who were randomized and treated at least once in the placebo-controlled phase were eligible to enter the 11-year follow-up and were approached to participate in a comprehensive reassessment. The battery of assessments included (see figure e-1 at Neurology.org for full list): neurologic history and examination (relapses, current disease course), EDSS,[12] Multiple Sclerosis Functional Composite,[13] employment status and resource use, health-related quality of life (EuroQoL–5 Dimension [EQ-5D],[14] Functional Assessment of Multiple Sclerosis [FAMS]),[15] depressive symptoms (Center for Epidemiologic Studies Depression Scale),[16] fatigue (Fatigue Scale for Motor and Cognitive Functions),[17,18] MS medication history, cognition (Paced Auditory Serial Addition Task [PASAT]-3, Symbol Digit Modalities Test [SDMT]),[19,20] and MRI. Investigators conducted patient assessments at their respective centers but, to include sicker patients who were unable to attend a center in person, a structured interview via phone that included a validated instrument for the assessment of the EDSS[21,22] was offered as an alternative.

CDMS was defined according to slightly modified Poser criteria[23] as (1) a relapse with clinical evidence of ≥1 CNS lesion, and if the first presentation was monofocal, a lesion distinct from the one responsible for the CIS presentation, or (2) sustained progression by ≥1.5 points on the EDSS reaching a total EDSS score of ≥2.5 and confirmed at a consecutive visit 3 months later. Such EDSS progression must have been based on objective clinical evidence of ≥1 neurologic abnormality other than vegetative or cerebral dysfunction.

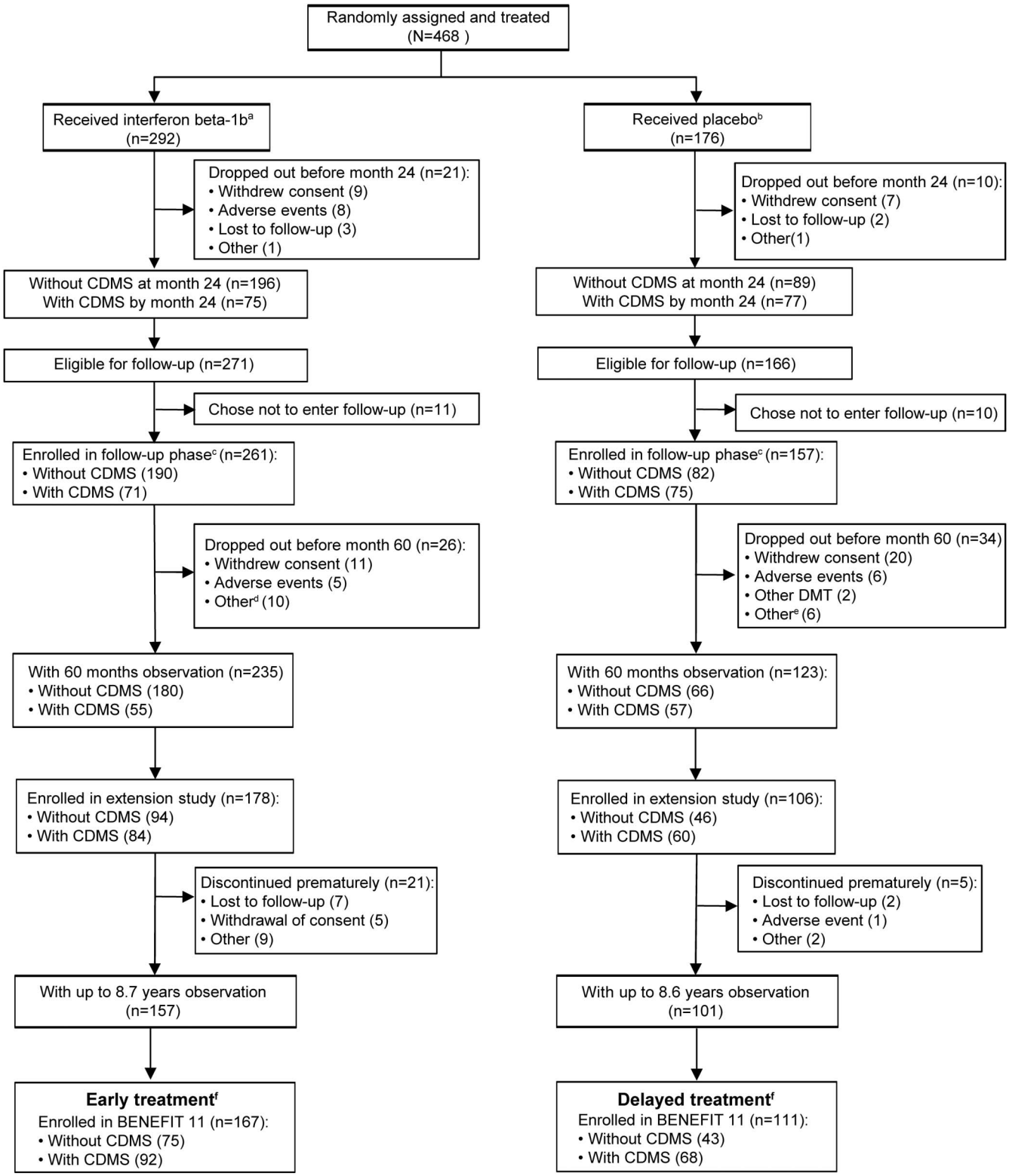
EDSS progression (unrelated to the CDMS definition) was defined as an increase of ≥1 point compared with the initial EDSS score (the lower of the 2 scores obtained during screening and baseline) or an increase of ≥1.5 points if the initial score was 0. A confirmed EDSS progression was defined as a progression confirmed at a scheduled study visit ≥140 days later. A sustained EDSS progression was defined as a progression that had been confirmed in the course of BENEFIT or BENEFIT follow-up and was sustained up to the 11-year visit.

Investigators collected MRI data at study sites according to a standardized MRI protocol. Scans were analyzed at a central reading site (VU University Medical Center, Amsterdam, the Netherlands). Trained readers manually identified and quantified lesions using a local thresholding technique.

Statistical procedures. Statistical modeling was used to estimate treatment effects and explore the relationships of target variables to treatment. The study was exploratory in nature, with the primary objective to describe disease course, particularly time to conversion to CDMS (Class III evidence) and/or secondary progressive MS (SPMS), relapse activity, change in disability, cognitive function, resource use, and working status (Class IV evidence) at year 11. Secondary objectives included assessment of MRI, treatment history, quality of life, depression, and DMT choices. Variables of primary and secondary interest were assessed using proportional hazards regression for time-to-event outcomes and generalized linear regression models, with steroid use during first event (yes or no), multifocal or monofocal onset of disease, and number of T2 lesions at screening (2–4, 5–8, or ≥9) included as the standard set of covariates. An extended set of covariates that included number of gadolinium-enhancing (Gd+) lesions at screening, age, and sex in addition to the standard covariates was used for analysis of time to CDMS, time to first relapse, and ARR. Other variables were analyzed using nonparametric methods. A negative binomial regression model for T1 lesions adjusting for T2 lesions at screening and initial treatment as independent variables was fitted. Changes in imaging hardware and software precluded comparisons of MRI-related outcomes over time. Therefore, only cross-sectional MRI comparisons at year 11 between early and delayed treatment were performed.

Classification of evidence. The primary research question of the study was to assess the effect of treatment with interferon

Figure 1 Study profile for the entire BENEFIT Study



[a]Includes one patient randomized to receive interferon beta-1b but treated with placebo. [b]Includes one patient randomized to receive placebo but treated with interferon beta-1b. [c]Includes one patient entered into the BENEFIT follow-up study after premature discontinuation of the BENEFIT Study. [d]Four lost to follow-up, 2 missing data, 1 noncompliance, 1 treatment failure, 2 refused final visit. [e]Three lost to follow-up, 1 relocated away from site, 1 pregnancy, 1 unable to attend visit because of job. [f]To be eligible for the 11-year follow-up, patients only needed to be randomized and treated in the original BENEFIT Study (i.e., they did not need to be included in the previous BENEFIT analyses). BENEFIT = Betaferon/Betaseron in Newly Emerging MS for Initial Treatment; CDMS = clinically definite multiple sclerosis; DMT = disease-modifying therapy.

beta-1b at CIS or after a short delay on clinical and MRI outcomes after 11 years.

Standard protocol approvals, registrations, and patient consents. The institutional review boards of participating institutions approved the protocol for the study. Patients provided informed consent at enrollment into each phase of the trial. The BENEFIT 11 trial is listed on clinicaltrials.gov under NCT01795872.

RESULTS

Patient disposition. Of the 468 patients originally randomized in BENEFIT, 278 (59.4%) enrolled in BENEFIT 11 (167 [57.2%] from the early-treatment arm and 111 [63.1%] from the delayed-treatment arm) between September 2013 and April 2014 in the 66 of 97 sites in 19 countries that participated in this 11-year follow-up (figure 1). A total of 71.3% of the patients originally randomized and treated in these participating sites were enrolled. Two hundred thirty-seven patients (85.3%) had in-person assessments at study centers; 41 patients (14.7%) had phone assessments.

Baseline characteristics and outcomes of the original cohort vs BENEFIT 11 participants at their last study visits before the 11-year follow-up were generally well comparable (table 1) with the exception of a somewhat higher number converting to CDMS in the 11-year follow-up group. Patients in the early- and delayed-treatment arms of the 11-year follow-up also had similar baseline characteristics. The mean (SD) delay until starting interferon beta-1b treatment was 1.5 (0.73) years in the delayed-treatment group. One hundred seventy-one (61.5%) of the 278 patients enrolled in BENEFIT 11 were on a DMT at the time of assessment; 86 (30.9%) were on interferon beta-1b. Mean (SD) time on interferon beta-1b was 1,523.2 (861.4) days over the 11 years, excluding the BENEFIT Study medication.

Clinical outcomes. After 11 years, the risk of conversion to CDMS was still reduced by 33.0% for patients in the early-treatment arm relative to those in the delayed-treatment arm (hazard ratio 0.670; 95% confidence interval [CI] 0.526–0.854, $p = 0.0012$; figure 2A). One hundred sixty-two patients (66.6% of total early-treatment group; Kaplan-Meier [KM] estimate) in the early-treatment group and 118 (75.0% of total delayed-treatment group [KM estimate]) in the

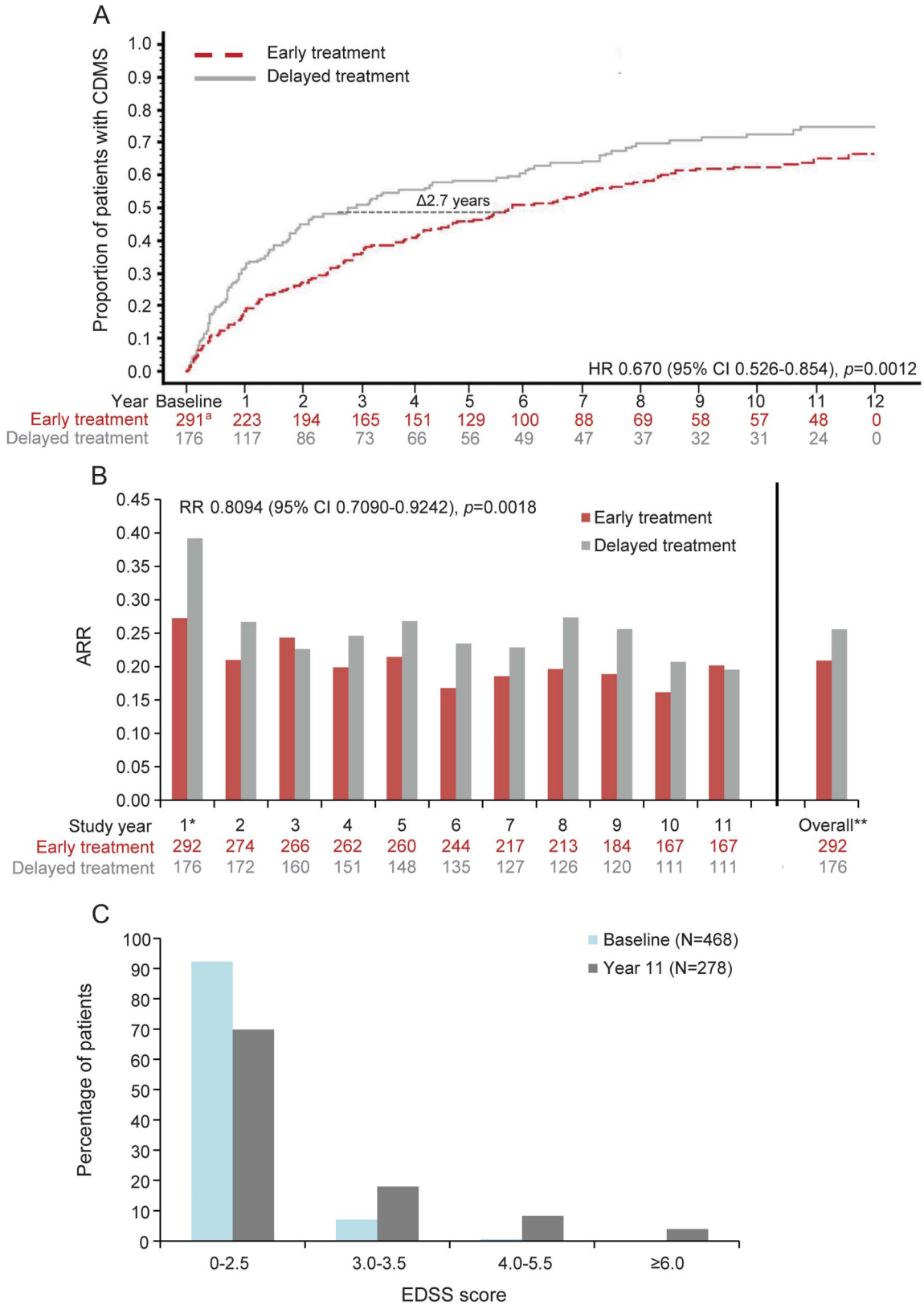
Table 1 Patient characteristics at baseline in the originally randomized BENEFIT population and in those participating in the BENEFIT 11 Study and patient characteristics at last follow-up in patients who did and did not enter BENEFIT 11

	Original BENEFIT population			BENEFIT 11 population		
	Early treatment	Delayed treatment	Overall	Early treatment	Delayed treatment	Overall
Original BENEFIT population, n (%)	292 (100)	176 (100)	468 (100)	167 (57.2)	111 (63.1)	278 (59.4)
Age, y, median (Q1, Q3)	30.0 (24.0, 37.0)	30.0 (25.0, 36.0)	30.0 (24.0, 37.0)	31.0 (24.0, 37.0)	30.0 (25.0, 36.0)	30.0 (25.0, 37.0)
Female, n (%)	208 (71.2)	123 (69.9)	331 (70.7)	122 (73.1)	73 (65.8)	195 (70.1)
Multifocal onset of disease, n (%)	139 (47.6)	83 (47.2)	222 (47.4)	82 (49.1)	56 (50.5)	138 (49.6)
Steroid treatment at CIS, n (%)	210 (71.9)	122 (69.3)	332 (70.9)	119 (71.3)	79 (71.2)	198 (71.2)
EDSS at baseline, median (mean), Q1, Q3	1.50 (1.59), 1.00, 2.00	1.50 (1.49), 1.00, 2.00	1.50 (1.55), 1.00, 2.00	1.50 (1.53), 1.00, 2.00	1.50 (1.57), 1.00, 2.00	1.50 (1.55), 1.00, 2.00
No. of T1 lesions, median (Q1, Q3)	2.0 (0.0, 5.0)	1.0 (0.0, 4.0)	2.0 (0.0, 5.0)	2.0 (0.0, 6.0)	1.0 (0.0, 4.0)	2.0 (0.0, 5.0)
No. of T2 lesions, median (Q1, Q3)	18.0 (7.0, 38.5)	17.0 (7.0, 36.5)	17.0 (7.0, 38.0)	20.0 (7.0, 40.0)	16.0 (7.0, 36.0)	18.0 (7.0, 39.0)
No. of Gd+ lesions, median (Q1, Q3)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)
	At last follow-up before BENEFIT 11[a]					
	Did not enter BENEFIT 11			Participated in BENEFIT 11		
	Early treatment	Delayed treatment	Overall	Early treatment	Delayed treatment	Overall
No.	125	65	190	167	111	278
CDMS, n (%)	48 (38.4)	35 (53.8)	83 (43.7)	92 (55.1)	68 (61.3)	160 (57.6)
ARR	0.1995	0.2653	0.2196	0.1947	0.2517	0.2177
EDSS, median (mean), Q1, Q3	1.5 (1.72), 1.0, 2.0	1.5 (1.52), 1.0, 2.0	1.5 (1.65), 1.0, 2.0	1.5 (1.68), 1.0, 2.0	1.5 (1.69), 1.0, 2.5	1.5 (1.69), 1.0, 2.5
PASAT-3, median (Q1, Q3)	58.0 (53.0, 59.0)	57.0 (49.0, 59.0)	57.0 (52.0, 59.0)	58.0 (54.0, 59.5)	58.0 (51.0, 59.0)	58.0 (53.0, 59.0)

Abbreviations: ARR = annualized relapse rate; BENEFIT = Betaferon/Betaseron in Newly Emerging MS for Initial Treatment; CDMS = clinically definite multiple sclerosis; CIS = clinically isolated syndrome; EDSS = Expanded Disability Status Scale; Gd+ = gadolinium-enhancing; PASAT-3 = Paced Auditory Serial Addition Task–3; Q = quartile.

[a] Last follow-up could have occurred at any time up to the 8-year analysis.[6]

Figure 2 Kaplan-Meier estimates of probability of CDMS (A), ARR (B), and EDSS scores (C) in the BENEFIT 11 population



[a]One patient in the early-treatment arm was excluded from this analysis because diagnosis of CDMS was unclear. Risk of conversion to CDMS was significantly lower for the early-treatment group compared with the delayed-treatment group. Overall ARR was significantly lower in the early-treatment group compared with the delayed-treatment group. As expected, EDSS scores increased from baseline to year 11, but they tended to remain relatively low for both groups. *$p < 0.05$; **$p < 0.01$. ARR = annualized relapse rate; BENEFIT = Betaferon/Betaseron in Newly Emerging MS for Initial Treatment; CDMS = clinically definite multiple sclerosis; CI = confidence interval; EDSS = Expanded Disability Status Scale; HR = hazard ratio; RR = risk ratio.

delayed-treatment group had converted to CDMS at any time until BENEFIT 11. Time to CDMS was shorter in the delayed-treatment arm (log rank $p = 0.0034$) as well as time to first relapse (hazard ratio 0.655 [95% CI 0.517–0.830], $p = 0.0005$). Risk of a first relapse was reduced by 34.5% in the early-treatment compared with the delayed-treatment group. The overall ARR over the 11-year study period was lower in the early-treatment group than in the delayed-treatment group, resulting in a 19.1% reduction in risk of relapses (risk ratio [RR] 0.8094 [95% CI 0.7090–0.9242], $p = 0.0018$; figure 2B). Inspection of figure 2B revealed that the ARR by study year was not only different during the core study but also remained lower in all but 2 of the follow-up years, although after the second year, both groups were similarly exposed to interferon beta-1b treatment.

Overall, only 25 patients had converted to SPMS (5.9%, KM estimate) by year 11 (early 4.5%, delayed 8.3%, KM estimate; log rank $p = 0.4857$). EDSS scores also did not differ between the treatment arms. EDSS scores of study participants remained low and stable with a median (quartile [Q]1, Q3) score of 2.0 (1.0, 3.0) and median change from baseline over 11 years of 0.5 (−0.50, 1.50) in both groups (table 2). By year 11, 69.8% of patients were fully ambulatory with minor or no signs of disability (EDSS score <3.0) (figure 2C).

As a neuropsychological measure, 222 patients had PASAT-3 data available at baseline and year 11. Over the entire study period, the PASAT-3 total score (adjusted for baseline score) was higher in the early-treatment group ($p = 0.0070$) (figure 3). Two hundred thirty-three patients completed the SDMT (early 141, delayed 92). Overall median (Q1, Q3) SDMT score was 53.0 (44.0, 59.0), with little difference between groups. No differences were found between groups on the EQ-5D, FAMS trial outcomes index, Fatigue Scale for Motor and Cognitive Functions, or Center for Epidemiologic Studies Depression Scale with stable values relative to baseline for EQ-5D and FAMS, both of which had also been assessed at baseline. Absence of fatigue (score <43) was reported in

Table 2 EDSS and employment at year 11 in the BENEFIT 11 population

	Early treatment		Delayed treatment		Total BENEFIT 11 population	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
EDSS at year 11						
EDSS score at year 11	2.04 (1.54)	2.0 (1.0, 3.0)	2.22 (1.47)	2.0 (1.0, 3.0)	2.11 (1.51)	2.0 (1.0, 3.0)
Change in EDSS from baseline to year 11	0.55 (1.52)	0.50 (−0.50, 1.50)	0.72 (1.41)	0.50 (−0.50, 1.50)	0.62 (1.47)	0.50 (−0.50, 1.50)
	No. (%)		No. (%)		No. (%)	
Sustained[a] 1-point EDSS progression	31 (18.6)		27 (24.3)		58 (20.9)	
Confirmed[b] 2.5-point EDSS progression	19 (11.4)		14 (12.6)		33 (11.9)	
			Baseline BENEFIT, n (%)		Year 11, n (%)	
Employment status						
Employed			226 (81.3)		204 (73.4)	
≥20 h/wk			211 (75.9)		179 (64.4)	
<20 h/wk			15 (5.4)		25 (9.0)	
Retired or retired early			7 (2.5)		26 (9.4)	
No effect of MS on employment			—		179 (64.4)	
Ceased work because of MS			—		37 (13.3)	
Reduced working hours because of MS			—		54 (19.4)	
Days taken off work because of MS in the last 12 mo[c]						
None			—		178 (64.0)	
1–10			—		19 (6.8)	
11–30			—		17 (6.1)	
>30			—		30 (10.8)	

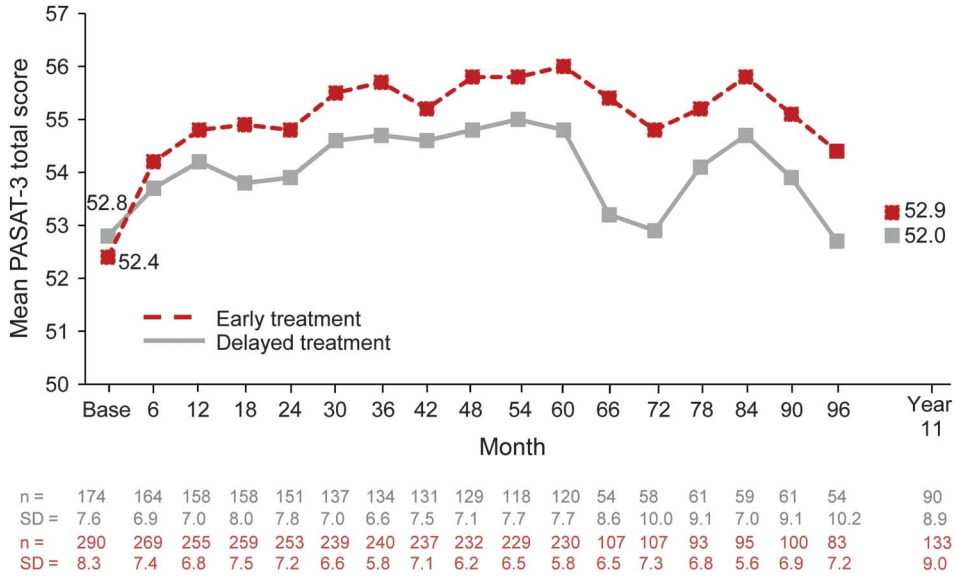
Abbreviations: BENEFIT = Betaferon/Betaseron in Newly Emerging MS for Initial Treatment; EDSS = Expanded Disability Status Scale; IQR = interquartile range; MS = multiple sclerosis.

[a] Sustained EDSS progression defined as a progression that was confirmed in a previous BENEFIT analysis and was again confirmed at year 11.

[b] Confirmed EDSS progression defined as an increase compared with baseline that was confirmed at a scheduled visit ≥140 days later and not within 140 days after a relapse.

[c] Includes lost school days or housework days; data missing from 34 participants (12.2%).

Figure 3 Mean PASAT-3 total score from baseline to year 11



Over the entire study period, the mean PASAT-3 total score was higher in the early- than the delayed-treatment group ($p = 0.0070$). PASAT-3 = Paced Auditory Serial Addition Task–3.

128 patients (46%), and 191 (68.7%) reported no depressive symptoms.

Both groups had similar resource utilization (table 2). Overall, 204 patients (73.4% of all patients in the 11-year follow-up) were still employed, compared with 226 patients (81.3%) at study start. Twenty-six patients (9.4%) were retired at year 11 (22 [7.9%] retired early). Two hundred seventy-one patients (97.5%) were living alone or with a spouse/partner/family, with only 3 (1.1%) living in a long-term care facility. Two hundred fifty-four patients (91.4%) had not been hospitalized because of MS in the 12 months before the 11-year assessment. Sixty-seven patients had used second-line therapy (14.3%, KM estimate: 21.2%) by year 11 (early 38 [13.0%, KM estimate: 19.1%], delayed 29 [16.5%, KM estimate: 24.4%]).

MRI outcomes. One hundred ninety-one patients had MRI scans (early 114, delayed 77). All MRI data are reported as median (Q1, Q3). Relatively little difference in cerebral lesion number or volume was seen between the 2 treatment groups. Brain volume was 1,527.0 cm^3 (1,444.0, 1,595.0) in the early-treatment group and 1,514.0 cm^3 (1,429.0, 1,575.5) in the delayed-treatment group. Ten patients (5.2%) had 1 Gd+ lesion (early 7 [6.1%], delayed 3 [3.9%]) and 6 patients (3.1%) had 2 to 5 Gd+ lesions (early 5 [4.4%], delayed 1 [1.3%]). The number of new T2 lesions since the patient's last study scan was 2.0 (0.0, 6.0) in the early-treatment arm and 2.0 (0.0, 6.5) in the delayed-treatment arm, while T2 lesion volume was 2,237.0 mm^3 (618.0, 5,473.0) and 1,640.5 mm^3 (911.0, 3,419.0), respectively.

T1 hypointense lesion count was 4.0 (1.0, 11.0) in the early-treatment group and 2.0 (1.0, 6.0) in the delayed-treatment group. A regression model identified an effect of baseline T2 lesion count on the number of T1 lesions at year 11 (RR 1.02 [95% CI 1.02, 1.03], $p < 0.0001$), but treatment did not decrease the number of lesions (RR 1.29 [95% CI 0.95, 1.76], $p = 0.1030$).

Safety. 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 reported during BENEFIT 11.

DISCUSSION Performing a comprehensive reassessment after 11 years in a well-characterized group of patients, systematically followed since the initial clinical manifestation, provides a unique opportunity to better understand the benefits of early treatment on outcomes relevant to patients and physicians. This long-term follow-up study provided Class IV evidence that time to CDMS was prolonged and that additional clinical measures (ARR, PASAT score) were improved by early treatment while both groups showed a generally mild disease course. If we consider the length of follow-up, this trial included a sizable proportion (71%) of the originally randomized patients from the centers participating in BENEFIT 11. The comparison of baseline and available follow-up characteristics of patients who did not participate with those who participated in BENEFIT 11 did not reveal sources of systematic bias by selective dropout. A factor that may be

critical to interpretation of these data is the unblinding of the initial randomization that occurred after completion of the year 5 assessments and the uncontrolled nature of treatment after the placebo-controlled phase, a characteristic shared with natural history and observational treatment studies.

Even if we consider this and differences in methodology that make cross-study comparisons difficult, several clinically relevant outcomes in the current study remained relatively stable over 11 years and compare favorably with those reported in natural history cohorts. This is reflected in the high proportion of patients having EDSS score <3.0 and remaining employed through year 11 and in the low rate of conversion to SPMS. A natural history study from Canada found that after 10.2 years, 50% of the patients had reached EDSS score ≥3.0.[24] A group of 1,261 patients from 5 European countries with similar disease duration and demographics had rates of employment ranging from 51% to 63%, with the exception of patients from Italy where 78% remained employed (but in a population that on average was 3 years younger and had a 3-year shorter duration of disease than the BENEFIT 11 population).[25] A cohort of 241 patients with MS from Canada also had lower rates of employment (54%).[24] Natural history studies have reported median times to progressive disease ranging from 15[26] to 19 years[27,28] since the original attack.[29,30]

The more favorable outcomes as compared to natural course studies may be overestimated because of differences in ascertainment[26,30] and temporal shifts with more recent studies showing better outcomes irrespective of treatment allocation.[31] Nevertheless, after 11 years, we observed a relative stability with no apparent difference between the randomization arms. A possible explanation of this relative stability may be found in the fact that both arms can be considered to have received treatment relatively early in the course of the disease as even the delayed-treatment group started treatment within a maximum of 2 years following CIS.

Despite the relatively short delay in treatment initiation in the placebo group, measures reflecting clinical disease activity such as time to CDMS, time to first relapse, and relapse rates, as well as scores on the PASAT, the only neuropsychological test applied from baseline to year 11, still suggest persistent long-term benefits of the earlier treatment. Although the overall lower ARR favoring the earlier-treatment group appears to be mainly driven by differences in the first year of the core study, it is intriguing to see that in the early-treatment group, ARR remained lower in all but 2 of the follow-up years—when treatment with interferon beta-1b was equally available to both groups. This finding suggests the possibility of a more remote decrease in the pathogenic factors that contribute to detectable attacks. This could be an effect on immune regulation or the consequence of better preserved compensation capacity that allowed the consequences of inflammatory attacks to be reduced.

This study adds to the literature on the optimal treatment of patients with MS by supporting and expanding the data on treatment at the earliest clinical manifestation of the disease. Other studies have shown benefits of early treatment for patients with CIS[10,32,33]; however, BENEFIT 11 includes longer follow-up with additional outcome measures that have not previously been described, including resource use, employment status, and patient-reported outcomes. Despite the inherent problems of a comparison with natural course studies, our results indicate that early treatment with interferon beta-1b had a long-lasting, even remote, beneficial effect on disease activity as well as cognitive outcomes, resource utilization, and employment rate. Taken together, the findings of BENEFIT 11 reinforce the importance of starting therapy with interferon beta-1b as soon as possible after the onset of MS symptoms.

AUTHOR CONTRIBUTIONS

L. Kappos: planned the study, reviewed the statistical analysis, interpreted data, and actively contributed to the writing and reviewing of the submitted manuscript. Chair of the study steering committee and study investigator. G. Edan: interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Member of the study steering committee and study investigator. M.S. Freedman: interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Member of the study steering committee and study investigator. X. Montalbán: interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Member of the study steering committee and study investigator. H.-P. Hartung: interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Member of the study steering committee and study investigator. B. Hemmer: interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Member of the study steering committee and study investigator. E. Fox: interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Member of the study steering committee and study investigator. F. Barkhof: collected and analyzed the MRI data, reviewed the statistical analyses, and actively contributed to the writing and reviewing of the submitted manuscript. S. Schippling: interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Member of the study steering committee and study investigator. A. Schulze: developed the statistical analysis plan, conducted the statistical analysis, interpreted data, and actively contributed to the writing and reviewing of the manuscript. D. Pleimes: drafted the statistical analysis plan, interpreted data, and drafted and reviewed the manuscript. C. Pohl: actively involved in drafting the MRI protocol and the statistical analysis plan, reviewed the statistical analyses, and actively contributed to the writing and reviewing of manuscript drafts. Sponsor's responsible clinician for the follow-up study phase. R. Sandbrink: interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Member of the study steering committee. Sponsor's responsible clinician for the placebo-controlled study phase. G. Suarez: drafted the statistical analysis plan, interpreted data, and drafted and reviewed the manuscript. E.-M. Wicklein: drafted the statistical analysis plan, interpreted data, and drafted and reviewed the manuscript. Sponsor's responsible clinician for the extension study phase.

ACKNOWLEDGMENT

The authors thank the patients and the BENEFIT 11 investigators for their continuing contributions to the study. Robert C. Ristuccia, PhD (Precept Medical Communications), provided writing assistance

consisting of medical editing, English-language assistance, formatting of text and figures, and coordinating reviews, which was funded by Bayer HealthCare Pharmaceuticals. This article is dedicated to the memory of our colleague Christoph Pohl who passed away on August 28, 2015. His contributions to the BENEFIT Study have been invaluable and until his last days—although completely paralyzed by his progressive neuromuscular disease and on artificial respiration—he was actively involved in the development of this manuscript and accompanying scientific projects.

STUDY FUNDING

This study was funded by Bayer HealthCare Pharmaceuticals. Representatives of the study sponsor participated in the discussions of the steering committee on the design of the study, including the assessments to be made and the statistical analysis plan. They also provided input on the manuscript, with the understanding that the final decisions related to publication of these data would be made by the study steering committee.

DISCLOSURE

L. Kappos' institution (University Hospital Basel) has received in the last 3 years and used exclusively for research support: steering committee/consulting fees from Actelion, Addex, Bayer HealthCare, Biogen, Biotica, Genzyme, Lilly, Merck, Mitsubishi, Novartis, Ono, Pfizer, Receptos, Sanofi-Aventis, Santhera, Siemens, Teva, UCB, and Xenoport; speaker fees from Bayer HealthCare, Biogen, Merck, Novartis, Sanofi-Aventis, and Teva; support of educational activities from Bayer HealthCare, Biogen, CSL Behring, Genzyme, Merck, Novartis, Sanofi-Aventis, and Teva; royalties from Neurostatus Systems AG; grants from Bayer HealthCare, Biogen, the European Union, Merck, Novartis, Roche, Roche Research Foundations, the Swiss Multiple Sclerosis Society, and the Swiss National Research Foundation. G. Edan has received honoraria for lectures or consulting from Biogen Idec, Merck Serono, and Sanofi-Aventis, and received personal compensation for serving on the BENEFIT scientific advisory board and for speaking from Bayer Pharma AG. He has also received research support from Serono (a grant to University Hospital to support a research program on MRI in MS) and from Teva (a grant to support a research program on anti-IBF neutralizing antibodies). M. Freedman has received compensation from Bayer HealthCare, Biogen Idec, EMD Canada, Genzyme, Merck Serono, Novartis, Sanofi-Aventis, and Teva Canada Innovation for consulting services, and has received research/educational grants from Bayer HealthCare and Genzyme. He also participates in a Genzyme-sponsored speakers bureau. X. Montalbán has received speaking honoraria and travel expenses for scientific meetings and has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Bayer, Biogen Idec, EMD, Genentech, Genzyme, Merck Serono, Neuro-Tec, Novartis, Sanofi-Aventis, Teva Pharmaceuticals, and Almirall. H. Hartung has received honoraria for consulting and speaking at symposia from Bayer Pharma AG, Biogen Idec, Genzyme, Merck Serono, Novartis, Roche, Teva, and Sanofi-Aventis, with approval by the rector of Heinrich-Heine University. B. Hemmer has served on scientific advisory boards for Roche, Novartis, Bayer Schering, Merck Serono, Biogen Idec, GSK, Chugai Pharmaceuticals, Micromet, and Genzyme Corporation; is author on patents re: KIR4.1 antibody testing in MS and genetic determinant of neutralizing antibody development in interferon-beta–treated patients; has received speaker honoraria from Bayer Schering, Novartis, Biogen Idec, Merck Serono, Roche, and Teva Pharmaceutical Industries Ltd.; and has received research support from Biogen Idec, Bayer Schering, Merck Serono, Five Prime, Metanomics, and Novartis. E. Fox has received consulting fees, honoraria, travel, or research support from Acorda, Bayer, Biogen Idec, Eli Lilly, EMD Serono, Genzyme, GlaxoSmithKline, Novartis, Ono, Opexa Therapeutics, Pfizer, Roche, Sanofi, and Teva. F. Barkhof has received compensation for consultancy from Bayer Schering Pharma, Biogen Idec, Merck Serono, Novartis, Sanofi-Aventis, Genzyme, Roche, and Teva, and has received research support from the Dutch Foundation for MS Research (an NGO). S. Schippling has received research grants from Biogen Idec, Bayer Schering Pharma, and Genzyme, and consulting/speaker fees from Bayer Schering Pharma, Biogen Idec, Merck Serono, Novartis, Teva, and Sanofi-Aventis. A. Schulze is a salaried employee of Bayer Pharma AG. At the time this work was conducted, she was a salaried employee of PAREXEL International. D. Pleimes is a salaried employee of Myelo Therapeutics GmbH. He was a salaried employee and is currently a paid consultant for Bayer HealthCare Pharmaceuticals. D.P. owns stock in Bayer AG, the owner of Bayer Pharma AG/Bayer HealthCare Pharmaceuticals. C. Pohl is deceased; disclosures are not included for this author. R. Sandbrink was a salaried employee of Bayer Pharma AG. He owns stock in Bayer AG, the owner of Bayer Pharma AG/Bayer HealthCare Pharmaceuticals. G. Suarez was a salaried employee of Bayer HealthCare Pharmaceuticals. E. Wicklein is salaried employee of Bayer Pharma AG. Go to Neurology.org for full disclosures.

Received September 28, 2015. Accepted in final form April 14, 2016.

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Neurology 2016;87;978-987 Published Online before print August 10, 2016
DOI 10.1212/WNL.0000000000003078