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Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes

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Abstract—*Objective:* To assess efficacy, safety, and tolerability of every-other-day interferon beta-1b treatment in patients with a first clinical event suggestive of multiple sclerosis (MS) (clinically isolated syndrome). *Methods:* We conducted a multicenter, randomized, double-blind, placebo-controlled trial. Patients with a first clinical demyelinating event and at least two clinically silent brain MRI lesions were randomized to interferon beta-1b (IFNB-1b) 250 μg subcutaneously (SC) every other day (EOD) (n = 292) or placebo (n = 176), until clinically definite MS (CDMS) was diagnosed or they had been followed for 24 months. *Results:* After 2 years, 45% of placebo patients had converted to CDMS (Kaplan-Meier estimate; primary outcome measure) and 85% fulfilled the McDonald criteria (co-primary outcome measure). Overall interferon beta-1b delayed the time to diagnosis of CDMS ($p < 0.0001$) and McDonald MS ($p < 0.00001$). Hazard ratios (95% CI) were 0.50 (0.36 to 0.70) for CDMS and 0.54 (0.43 to 0.67) for McDonald MS favoring treatment with IFNB-1b. Treatment was well tolerated, as indicated by the low rate of patients dropping out of the study before CDMS was reached (6.6% overall, 7.2% in the IFNB-1b group). *Conclusions:* Interferon beta-1b 250 μg subcutaneously every other day delayed conversion to clinically definite multiple sclerosis, and should be considered as a therapeutic option in patients presenting with a first clinical event suggestive of multiple sclerosis.

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Two multicenter studies (CHAMPS and ETOMS[1,2]) have shown beneficial effects with once-weekly administered interferon beta-1a on the rate of conversion to clinically definite multiple sclerosis (CDMS) in patients with clinically isolated syndrome (CIS). One single center study also suggested a similar effect with repeated IV immunoglobulin infusions.[3]

The Betaferon in Newly Emerging Multiple Sclerosis for Initial Treatment (BENEFIT) trial was designed to study the efficacy, safety, and tolerability of frequently administered interferon beta-1b in patients with a first clinical event suggestive of MS. We examined the effect of treatment on the rate of conversion to CDMS as defined in the Poser criteria.[4] We also explored therapeutic effects on the rate of conversion to a diagnosis of MS as defined by the diagnostic criteria established by an international panel (the McDonald criteria).[5] These criteria have systematically incorporated paraclinical findings, in particular MRI, to increase sensitivity without compromising specificity.[6-8]

Methods. *Study design, patients, and treatment.* The BENEFIT trial was a double-blind, placebo-controlled, randomized, parallel group, multicenter, phase III study. Between February 2002 and June 2003, patients from 18 European countries, Israel, and Canada were randomized in 98 centers.

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*See the appendix for a list of BENEFIT Investigators.

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Disclosures: L. Kappos has participated and is currently participating as Principal Investigator, Member, or Chair of Planning and Steering committees or Advisory boards in Corporate-sponsored clinical trials in multiple sclerosis. L.K. has also lectured at medical conferences or in public on various aspects of the diagnosis and management of multiple sclerosis and other neurological diseases. In many cases these talks have been sponsored by non-restricted educational grants from one or another of the below listed companies. Honoraria and other payments for all mentioned activities have been exclusively used for funding of research at L.K.'s department. The sponsoring pharmaceutical companies include Biogen Idec, GlaxoSmithKline, Novartis, Sanofi Aventis, Schering, Serono (all > US $10,000 per year); furthermore, Abbott, Bayer, Bayhill, Berlex, Boehringer Ingelheim, Bristol Myers, Centocor, Eisai, Elan, Genzyme, Neurocrine, Roche, Teva, UCB, Wyeth, and others. Research and the clinical operations (nursing and patient care services) of the Multiple Sclerosis Clinic and Research Centre at the University Hospital Basel, led by L.K., have been supported by non-restricted grants from one or more of these companies.

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Patients with a CIS—defined as a first neurologic event suggestive of MS lasting for at least 24 hours and with symptoms and signs indicating either a single lesion (monofocal) or more than one lesion (multifocal) within the CNS—were enrolled. They had to be between 18 and 45 years of age, have presented with a first neurologic event suggestive of MS that lasted for at least 24 hours, and had to have at least two clinically silent lesions on their T2-weighted brain MRI scan with a size of at least 3 mm, at least one of which being ovoid, periventricular, or infratentorial. Baseline Expanded Disability Status Scale (EDSS)[9] score had to be between 0 and 5. Patients in whom any disease other than MS could explain their signs and symptoms, those with any previous episode that could possibly be attributed to an acute demyelinating event, patients with complete transverse myelitis or bilateral optic neuritis, and patients who had received prior immunosuppressive therapy were excluded. Prior to randomization, eligibility of each patient was centrally confirmed (see appendix). Based on the patient's documented signs and symptoms, this group also classified in a standardized manner the first clinical demyelinating event as either monofocal or multifocal.[10] Study treatment had to be started within 60 days after onset of the first clinical event.

Patients were centrally randomized to interferon beta-1b 250 μg (8 MIU) or placebo (both SC EOD) in a 5:3 ratio. A minimization procedure with an element of chance was applied to minimize imbalance of treatment groups for (selected) factors with potential impact on the risk of developing definite MS: 1) steroid use during the first clinical event, 2) investigator's classification of the first event as mono- or polysymptomatic (symptoms indicative of a single lesion, or more than one lesion),[10] 3) number of T2 lesions on the screening MRI, and 4) CSF result.

To ensure blinding, the study medications were identical in appearance, packaging, and labeling. Patients were instructed to cover injection sites during the examination by the masked evaluating neurologist.

In order to optimize the tolerability of the study medication, dose titration was performed (four dose steps of 62.5 μg each, every fourth injection). Concomitant ibuprofen or acetaminophen was given during the first 3 months to reduce flu-like symptoms, and an autoinjector was used in countries where approved. Steroid treatment of the first event and any further relapse during the study was performed at the discretion of the investigator, based on a predefined treatment schedule.

Patients were scheduled to receive double-blinded injections of interferon beta-1b or placebo SC EOD for up to 2 years or until CDMS was reached. CDMS was defined according to slightly modified Poser criteria[4] by 1) a relapse with clinical evidence of at least one CNS lesion, and if the first presentation was monofocal distinct from the lesion 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. All patients completing the double-blind study as planned were eligible to enroll into a single-arm (interferon beta-1b) follow-up study with a total duration of at least 5 years, including the double-blind phase. This follow-up study phase was prospectively designed to explore the long-term impact of early vs delayed treatment with interferon beta-1b on the progression of neurologic disability, on patient-reported outcomes, and on brain MRI findings, including markers of neurodegeneration such as brain atrophy.

The study was conducted in agreement with Good Clinical Practice (GCP) principles according to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use E6.[11] The Institutional Review Boards of all participating centers approved the study protocol and all patients gave written informed consent before trial entry. Overall study conduct and patient safety was overseen by an Independent Advisory Board without access to treatment codes.

Procedures. Regular visits were scheduled for the collection of EDSS, MRI, and other efficacy data, as well as for safety assessments at months 3, 6, 9, 12, 18, and 24. Patient-reported outcomes, including the Functional Assessment of Multiple Sclerosis (FAMS)[12] and EuroQoL-5Dimensional Questionnaire,[13] were evaluated at half-yearly intervals. Neutralizing antibodies (NAbs) were measured every 6 months using the MxA assay.[14]

For exclusion of other diseases that might explain the patient's signs and symptoms, a thorough diagnostic workup was performed during the screening period, including laboratory tests for vasculitis/collagenosis, borreliosis, vitamin B12 deficiency, and neurosarcoidosis. Patients with isolated visual symptoms underwent a complete ophthalmologic examination, and patients with isolated spinal symptoms a spinal MRI or myelography.

In order to preserve blinding, a treating physician was responsible for the overall medical care of the patient and an evaluating physician, who was not otherwise involved in the care of the patients and had no access to the patients' files, conducted all standardized neurologic evaluations and determined the EDSS and Functional System (FS) scores. The effectiveness of blinding was investigated using a blinding questionnaire. Brain MRI results collected during the study were not disclosed to the patient or investigators.

In case of any new, re-occurring, or worsening neurologic symptoms a visit was scheduled and the EDSS was rated by the evaluating physician. Based on the result of this examination and assessment of the possible impact of other factors, such as fever or infection, the treating physician then decided if the criteria for CDMS had been fulfilled. Relapses were defined as the appearance of a new, or reappearance of a neurologic abnormality, separated by at least 30 days from the onset of the preceding event. The abnormality had to be present for at least 24 hours, based on objective clinical evidence and had to occur in the absence of fever or known infection.[4] The diagnosis of CDMS had to be confirmed by a central committee (see appendix). After CDMS confirmation, all evaluations foreseen per protocol for the month 24/end-of-study visit were performed with the exception of an MRI (an MRI was only performed at end-of-study visits that took place within the regular visit schedule because of the limited comparability of MRI data that would have been obtained at these variable time points). At this end-of-study visit—without breaking the randomization code—patients were given the option of participating in the follow-up study with open-label interferon beta-1b treatment.

All MRI scans were performed with 0.1 mmol/kg gadolinium (Gd)-DTPA. The numbers and volumes of hyperintense lesions on T2-weighted images and Gd-enhancing lesions on T1-weighted images were centrally evaluated by the MRI Analysis Centre in Amsterdam (see appendix), which was kept blinded to treatment allocation.

Statistical analysis. Two primary efficacy variables were prespecified: 1) time to CDMS and 2) time to MS according to the McDonald criteria (time to McDonald MS). Assuming similar treatment effects to those observed in the CHAMPS and ETOMS studies, the power of a two-sided ($\alpha = 0.05$) log-rank test for time to CDMS was estimated to be between 88% and 94% when 250 interferon beta-1b-treated patients and 150 placebo-treated patients were randomized.

Evaluation of the co-primary outcomes was based on a sequential, conditional approach. Only if the null hypothesis for time to CDMS could be rejected would the null hypothesis for time to McDonald MS be tested, thus restricting the overall type-I-error probability to 0.05. The prespecified primary analysis intention to treat set comprised all randomized patients who received at least one treatment dose of the study drug.

Primary efficacy variables were analyzed by the log-rank test and by proportional hazards regression. The analysis was adjusted 1) as prospectively defined in the trial protocol for covariates similar to those used for the minimization procedure (steroid use during the first clinical event, onset of the first event as monofocal vs multifocal by central assessment,[10] number of T2 lesions on the screening MRI) and 2) using an extended set of covariates defined post hoc (complete set of covariates), which in addition to the predefined covariates included age and sex as key demographic variables, as well as the number of Gd+ lesions on the screening MRI as one of the most relevant predictors for conversion to CDMS.[15,16] Both hazard ratios and risk reduction (defined as [1 – hazard ratio] x 100%) were calculated by applying proportional hazards regression. For both primary efficacy variables, numbers needed to treat based on the 2-year Kaplan Meier estimates are reported.

To define possible subgroups with differential response to treatment and also to assess the robustness of the treatment effect on the primary outcome time to CDMS, proportional hazards regressions were performed for subgroups of patients stratified by clinical presentation (monofocal vs multifocal) and MRI findings of prognostic relevance[15,16]: number of T2 lesions in the

screening MRI (<9 vs ≥9 T2 lesions) or the presence of at least one Gd+ lesion in the screening MRI.

Two secondary MRI efficacy variables were defined: 1) cumulative number of newly active lesions up to the end of study (last available scan on double-blind treatment)—newly active lesions were defined as new Gd+ lesions and non-enhancing new or enlarging T2-lesions; and 2) change in T2 lesion volume from the screening MRI to end of study. Several other MRI variables were defined as supportive secondary efficacy variables (cumulative number of new T2 lesions, cumulative number of Gd+ lesions, and cumulative volume of Gd+ lesions). MRI efficacy variables were analyzed by nonparametric analysis of covariance, using corresponding MRI parameters from the screening MRI scan as covariates.[17]

For interpretation of the MRI results it has to be noted that due to the design of the study, MRIs of patients who developed CDMS were only available in their initially allocated treatment group up to conversion to CDMS. After this time point patients were switched to active treatment. Because patients who develop CDMS are also likely to have more MRI activity compared with patients who do not develop CDMS, the available MRI data will underestimate lesion activity. Therefore if significantly more patients in one group develop CDMS, this will bias the MRI results in favor of that group.

Change in EDSS, MSFC, and patient reported outcome measures, frequency of adverse events (AEs), and frequency of NAbs were analyzed using descriptive statistics.

In patients randomized to interferon beta-1b, the impact of positive NAb titers (at least one positive NAb titer vs all available NAb titers negative) on the primary outcome was explored post hoc by means of a log-rank test and by proportional hazards regression. Moreover, in order to assess how the exclusion of interferon beta-1b patients with end of study before 24 months influenced the relationship of positive NAb status and time to CDMS, the same analyses were performed for interferon beta-1b patients with end of study after at least 180, 270, or 360 days after start of study treatment.

Baseline characteristics of patients were compared between treatment groups by χ^2 and Wilcoxon tests.

Results. A total of 603 patients were screened for the study (figure 1) and 116 patients were found not to be eligible. Three patients with a relapse subsequent to the first event suggestive of MS were excluded.

A total of 487 patients were randomized, of which 468 started treatment. The 19 patients who were randomized but did not start treatment did not undergo further observation (3 of those patients had reached CDMS before treatment, while other reasons for nontreatment of randomized patients were violation of different inclusion criteria and withdrawal of consent). A total of 437 of the 468 patients (93.6%) who started treatment completed the study as planned (placebo 94.3%; interferon beta-1b 92.8%). A total of 418 (95.6%) of those patients opted to be enrolled in the follow-up study (96.3% of the interferon beta-1b patients).

At baseline, the two randomized groups were similar in terms of demographic, clinical, and MRI characteristics and no significant differences between groups were found for any of the baseline variables shown in table 1. According to the central assessment of patients' signs and symptoms at the first clinical event, 246 patients (52.6%) had clinical evidence of only one lesion in the CNS (monofocal patients). The initial event had been treated with steroids in 332 patients (70.9%). CSF samples were taken from 314 patients (67.1%). Premature discontinuation of study medication was recorded in 62 patients (13.2%). Nearly all patients (97.6% in the interferon beta-1b group and 97.2% in the placebo group) received at least 80% of the treatments scheduled for the double-blind study phase.

Of the 176 placebo patients, 77 progressed to CDMS and 142 fulfilled the criteria for McDonald MS during the course of the study. CDMS was reached by 75 and McDonald MS was reached by 191 of the 292 interferon beta-1b treated patients.

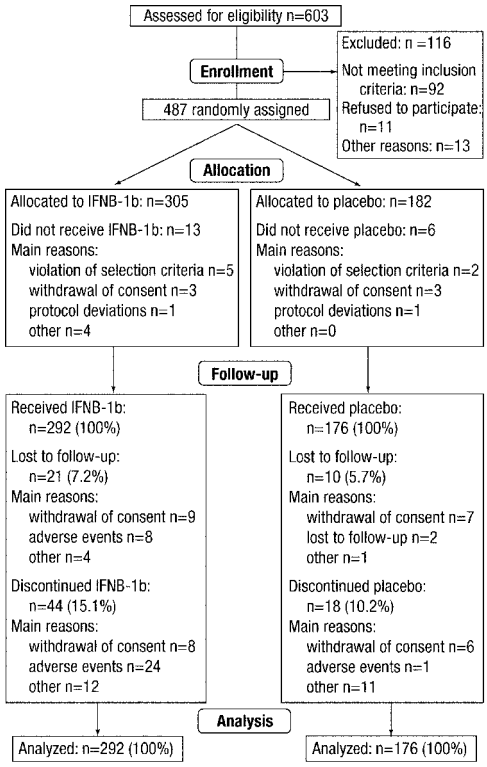

Figure 1. Trial profile.

Results for the primary efficacy variables are outlined in table 2, and figures 2 and 3. For both primary efficacy

Table 1 *Baseline characteristics of patients*

	Interferon beta-1b, n = 292	Placebo, n = 176
Women	207 (70.9)	124 (70.5)
Age at first event, y	30 (24–37.5)	30 (25–36)
White	286 (97.9)	174 (98.9)
Steroid treatment of first event	209 (71.6)	123 (69.9)
Clinical presentation of first event		
Monofocal onset	153 (52.4)	93 (52.8)
Optic nerve	45 (29.4)	35 (37.6)
Brainstem/cerebellar	33 (21.6)	22 (23.7)
Spinal	52 (34.0)	25 (26.9)
Other (cerebral)	23 (15.0)	11 (11.8)
Multifocal onset	139 (47.6)	83 (47.2)
EDSS at baseline	1.5 (0–4.0)	1.5 (0–4.0)
CSF sample taken at first event	198 (67.8)	116 (65.9)
Of these: CSF typical for MS	171 (86.4)	96 (82.8)
MRI at screening		
T2 hyperintense lesions		
No. of T2 lesions	18.0 (7.0–38.5)	17.0 (7.5–36.5)
No. of patients with ≥9 T2 lesions	207 (70.9)	123 (69.9)
Volume of T2 lesions, mm^3	1951.5 (592–5029)	1858.5 (641–3479)
Gadolinium (Gd+) enhancing lesions		
No. of Gd+ lesions	0 (0–1.0)	0 (0–1.0)
Patients with ≥1 Gd+ lesion	127 (43.5)	70 (39.8)
Volume of Gd+ lesions, mm^3	0 (0–155)	0 (0–140)

Values are n (%) or median (Q1–Q3) (1st to 3rd quartile).

EDSS = Expanded Disability Status Scale; MS = multiple sclerosis.

Table 2 *Results for time to clinically definite multiple sclerosis (CDMS) and time to McDonald MS*

			2-Year cumulative probability, %	
	p*	Hazard ratio (95% CI)†	Interferon beta-1b, n = 292	Placebo, n = 176
Time to CDMS	<0.0001	0.50 (0.36–0.70)	28	45
Time to McDonald MS	<0.00001	0.54 (0.43–0.67)	69	85

* Obtained by log rank test.

† Results by proportional hazards regression with complete set of covariates.

variables, the log-rank tests revealed a clear cut advantage of interferon beta-1b ($p < 0.0001$ for time to CDMS, $p < 0.00001$ for time to McDonald MS). According to proportional hazards regression with the complete set of covariates, the risk for CDMS in the interferon beta-1b group was reduced by 50% (hazard ratio with 95% CI: 0.50; 0.36 to 0.70) and for McDonald MS by 46% (0.54; 0.43 to 0.67). The risk reduction in the interferon beta-1b group according to proportional hazards regression with covariates similar to those used in the minimization procedure was 47% for CDMS (0.53; 0.39 to 0.73) and 43% (0.57; 0.46 to 0.71) for McDonald MS.

Based on the Kaplan-Meier estimates, the probability of the development of CDMS over 2 years was reduced by treatment from 45% in the placebo group to 28% in the interferon beta-1b group corresponding to an absolute risk reduction by 17% (figure 2, table 2). Interferon beta-1b prolonged the time to CDMS by 363 days at the 25th percentile, from 255 days in the placebo group to 618 days in the interferon beta-1b group. The patient number needed to be treated (NNT) in order to prevent one case of CDMS within the study period of 2 years is estimated to be 5.9.

Within the first 6 months, the probability of reaching MS according to the McDonald criteria was 51% for placebo and 28% for interferon beta-1b-treated patients. Within 2 years this probability was reduced by treatment from 85% in the placebo group to 69% in the interferon beta-1b group corresponding to an absolute risk reduction of 16% (figure 3, table 2; the corresponding NNT to prevent one case of McDonald MS is 6.3).

There was also a significant treatment effect of interferon beta-1b on time to CDMS in all subgroups defined by different baseline characteristics (table 3). While, according to proportional hazards regression, the individual tests for interactions between the treatment effect and any of the three variables used for subgroup stratification did not reach significance (treatment-by-subgroup interaction terms were associated with p values around/above 0.3), in the total group the treatment effects were more pronounced in patient subgroups with less inflammatory disease activity as documented by Gd enhancement or T2 lesion counts and less dissemination in space at the time of the first event.

Results for the secondary and supportive MRI efficacy variables are presented in table 4. The cumulative number of newly active lesions, the cumulative number of new T2 and Gd+ lesions, as well as the cumulative volume of Gd+ lesions was lower in the interferon beta-1b group compared with patients receiving placebo ($p < 0.0001$ in all cases). There was an overall decrease of the T2 lesion volume from screening to the end of study visit that was more pronounced in the interferon beta-1b than in the placebo group ($p < 0.05$).

Patient-reported physical health and health-related

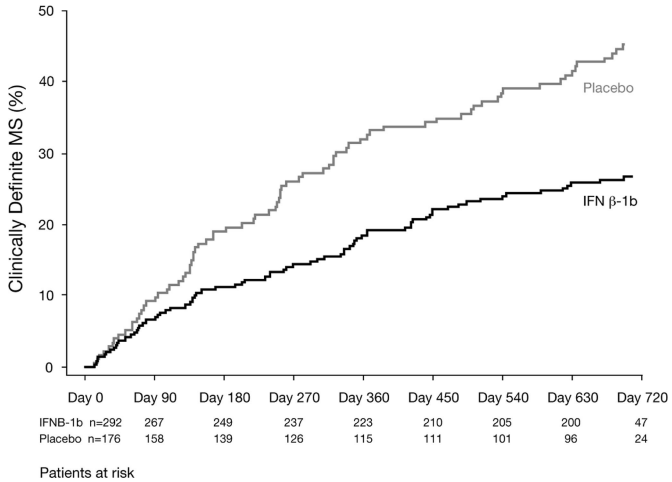

Figure 2. Kaplan-Meier estimates for the probability of clinically definite multiple sclerosis (MS) over 2 years. The cumulative probability of the development of clinically definite MS during the 2-year follow-up period was lower in the interferon beta-1b group than in the placebo group; $p < 0.0001$ by the log-rank test.

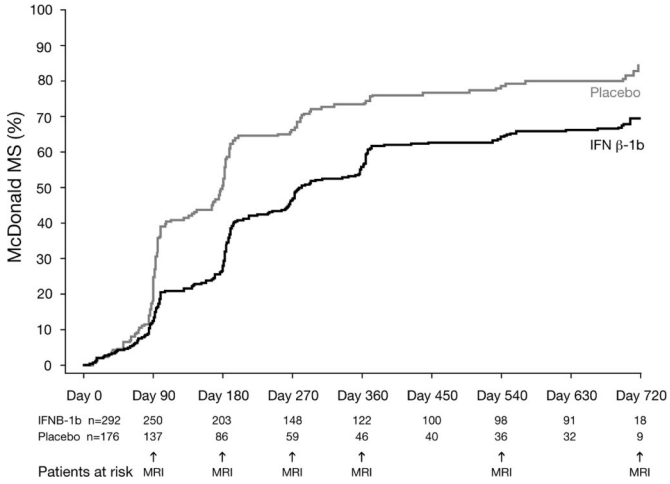

Figure 3. Kaplan-Meier estimates for the probability of McDonald multiple sclerosis (MS) over 2 years. The cumulative probability of the development of McDonald MS during the 2-year follow-up period was lower in the interferon beta-1b group than in the placebo group; $p < 0.00001$ by the log-rank test. The arrows indicate time points when MRI scans were scheduled.

Table 3 *Results for time to clinically definite multiple sclerosis in subgroups according to baseline variables*

			2-Year cumulative probability, %	
	p*	Hazard ratio (95% CI)†	Interferon beta-1b, n = 292	Placebo, n = 176
Monofocal manifestation	0.0004	0.45 (0.29–0.71)	24	47
Multifocal manifestation	0.041	0.63 (0.40–0.99)	31	44
Patients without Gd+ lesions	0.0003	0.43 (0.27–0.69)	20	41
Patients with Gd+ lesions	0.029	0.62 (0.40–0.96)	38	52
Patients with <9 T2 lesions	0.006	0.40 (0.20–0.79)	18	39
Patients with ≥9 T2 lesions	0.002	0.57 (0.40–0.82)	31	48

* Obtained by log rank test.
† Results by unadjusted proportional hazards regression.

quality of life remained essentially unchanged over time, and no differences were observed between interferon beta-1b and placebo (data not shown).

The most common interferon beta-1b-associated AEs were injection site reactions and flu-like syndrome (table 5), the frequency of both AEs being substantially lower in the second year. No deaths occurred during the course of the study. Serious AEs were reported in equal proportions of patients in the two treatment groups (6.8%). The laboratory abnormalities most frequently reported as AEs were increases in liver enzymes. Such increases were transient, however, and were found more frequently in patients treated with interferon beta-1b than in the placebo group during the first 3 months of the study (table 5). Five patients in the interferon beta-1b group discontinued study medication due to abnormal liver test results.

At individual visits after start of therapy, the incidence of positive NAb titers ranged from 16.5% to 25.2% of the interferon beta-1b-treated patients. Neutralizing activity was detected at least once in 75 out of 251 (29.9%) interferon beta-1b patients who provided samples during the treatment phase; of these, 17 (22.7%) converted to negative status later in the study. No significant effect of NAb status on time to CDMS in interferon beta-1b-treated patients was found (log-rank test $p = 0.11$); in this analysis there was a trend toward a lower risk of progressing to CDMS in patients with at least one positive NAb titer (hazard ratio with 95% CI: 0.63; 0.35 to 1.11). When analyses were performed focusing only on interferon beta-1b patients with end of study after at least 180, 270, or 360 days after start of study treatment, no differences were observed between NAb positive and NAb negative patients (log rank tests: $p = 0.97$; $p = 0.71$; $p = 0.84$), and the Kaplan-Meier curves were essentially identical (hazard ratios: 1.01; 0.54 to 1.92 and 1.14; 0.56 to2.30 and 0.91; 0.38 to 2.22).

At the end of the study patients, evaluating physicians, and treating physicians were asked what treatment the patients had received. Evaluating physicians identified interferon beta-1b treatment correctly in 20% and placebo treatment in 10% (wrong answers were given with a frequency of 6% and 14% in these patient groups). In 72% of interferon beta-1b and 76% of the placebo patients the

Table 4 *Secondary and supportive secondary MRI endpoints*

	Interferon beta-1b, n = 292	Placebo, n = 176	p*
Secondary endpoints			
Cumulative no. of newly active lesions†			<0.0001
Mean (SD)	3.7 (8.2)	8.5 (13.9)	
Median (Q1–Q3)	1.3 (0–3.6)	3.2 (1.0–10.4)	
Change in T2 lesion volume [mm^3]‡			<0.05
Mean (SD)	−888.5 (3312.6)	−431.6 (2226.5)	
Median (Q1–Q3)	−206.0 (−827–95)	−93.0 (−624–295)	
Supportive secondary endpoints			<0.0001
Cumulative no. of Gd+ lesions†			
Mean (SD)	1.9 (5.2)	4.3 (7.1)	
Median (Q1–Q3)	0 (0–2)	2.0 (0–5)	
Cumulative volume of Gd+ lesions (mm^3)†			<0.0001
Mean (SD)	203.5 (519.6)	420.6 (680.1)	
Median (Q1–Q3)	0 (0–146)	108.5 (0–516.5)	
Cumulative no. of new T2 lesions†			<0.0001
Mean (SD)	2.9 (4.9)	4.4 (5.7)	
Median (Q1–Q3)	1 (0–4)	2 (1–6)	

* Obtained by non-parametric analysis of variance adjusted for baseline covariates.
† Cumulative scores were obtained for all post-screening visits up to end of study.
‡ From the screening MRI to the study's last MRI.

Q1–Q3 = 1st to 3rd quartile.

Table 5 *Incidence of most frequently reported adverse events (AE) (at least 10% of patients for either/both treatments) and most relevant laboratory findings*

	Interferon beta-1b, n = 292	Placebo, n = 176
Adverse event		
Injection site reaction (during complete study period)	141 (48.3)	15 (8.5)
During first year*	133 (45.5)	14 (8.0)
During second year†	66 (30.0)‡	7 (6.5)§
Flu syndrome (during complete study period)	129 (44.2)	32 (18.2)
During first year*	122 (41.8)	27 (15.3)
During second year†	28 (12.7)‡	11 (10.3)§
Headache	78 (26.7)	30 (17.0)
Asthenia	63 (21.6)	30 (17.0)
Leukopenia¶	53 (18.2)	10 (5.7)
Upper respiratory tract infection	52 (17.8)	34 (19.3)
Paresthesia	48 (16.4)	30 (17.0)
Fever	38 (13.0)	8 (4.5)
Rash	32 (11.0)	5 (2.8)
Depression	30 (10.3)	20 (11.4)
Laboratory finding		
Alanine aminotransferase ≥5 times of baseline	52 (17.8)	8 (4.5)
Aspartate aminotransferase ≥5 times of baseline	18 (6.2)	1 (0.6)

The incidence displayed is the number of patients reporting the respective AE (or having the respective laboratory change) at least once. Values are n (%).

* Start date at or before day 360.

† Ongoing adverse events and adverse events with start date after day 360.

‡ n = 220 Interferon beta-1b patients reached the second year.

§ n = 107 Placebo patients reached the second year.

¶ If reported as AE by the investigator.

answer of the evaluating physician was "don't know." Treating physicians and the patients identified more frequently the actual treatment (for interferon beta-1b: 49% and 67.0%; for placebo: 51% and 52%).

Discussion. Placebo patients in this study were at high risk (85%) of developing MS according to the McDonald criteria within 2 years. Fifty-one percent had reached this co-primary outcome measure after 6 months of study. This indicates that the inclusion criteria helped to identify a population of CIS patients at high risk of developing early active MS and justifies the choice of treating patients with a first clinical event suggestive of MS and at least two clinically silent lesions on brain MRI with disease modifying agents such as interferon beta-1b 250 μg SC EOD. The high probability of developing McDonald MS within just 2 years is also in line with a recent consensus statement that two to three lesions on brain or spinal MRI have a high predictive value for subsequent conversion to clinical MS.[18]

In this study, interferon beta-1b 250 μg SC EOD was effective at slowing the development of recurrent active disease from its onset to the second new event that manifested either clinically or on brain imaging. With the McDonald criteria as an endpoint, the therapeutic effect of interferon beta-1b became apparent after only a few months; at the end of the 2-year treatment period, the probability of not developing McDonald MS was twice as high in the interferon beta-1b group (31%) as with placebo (15%).

As expected from results in established RRMS[19] and SPMS,[20] interferon beta-1b prevented the development of new inflammatory brain lesions also in patients with a first event suggestive of MS. The decrease in the volume of hyperintense T2 lesions observed in both treatment groups from screening to the end of study reflects regression of inflammation that had been associated with the first clinical event. This decrease of T2 lesion volume was more pronounced in interferon beta-1b-treated patients, indicating the efficacy of the treatment. Of note, all group differences with respect to MRI parameters are likely to be underestimated as more patients in the placebo group reached CDMS and switched to active treatment in the extension and, therefore, had no further MRI follow-up in this study.

A robust treatment effect was found throughout all subgroups defined by clinical and MRI measures of disease activity or dissemination in space at onset. We did not find a significant treatment by subgroup interaction between any of the stratification factors and the interferon beta-1b effect. Nevertheless the subgroup analysis (table 3) reveals some interesting trends that deserve further consideration: at first sight a consistently stronger treatment effect is apparent in patients with monofocal clinical presentation, fewer T2 lesions, or no contrast enhancement at baseline, indicating that treatment was particularly beneficial in patients with less active or disseminated disease, e.g., at a time when the disease process is less well established or advanced. This observation is in line with the underlying hypothesis of this and other early intervention studies, that immunomodulatory treatment is more effective the earlier it is started. Apart from pathologic findings and natural history data on the importance of the early disease phase,[21-23] this hypothesis is supported by previous studies that indicate a stronger effect of once-weekly interferon beta-1a in CIS than in established RRMS: in a dose comparison study in RRMS,[24] 22 μg interferon beta-1a once-weekly SC was not different from placebo in suppressing relapse activity, but the same dosage had significant clinical effects in CIS patients.[2] Regarding MRI outcomes, the pivotal study with 30 μg interferon beta-1a once-weekly IM in RRMS failed to show significant effects on change of T2 lesion volume as compared with placebo after 1 and 2 years,[25] while this endpoint was met in patients recruited for the CHAMPS trial and treated with the same interferon beta-1a dose.[1] Partially contrasting to this observation, the post hoc subgroup analysis of CHAMPS[26] and to some extent ETOMS[16] has indicated a higher relative effect of active treatment vs placebo in patients with more inflammatory disease activity at baseline as docu-

mented by higher numbers of T2 and Gad+ enhancing lesions. One possible explanation for the partially contradictory results is a complex interplay of two interfering mechanisms: the amount of disease at baseline might have biologic implications as seen in this study (making early disease more amenable to treatment effects) and a statistical impact (the more disease, the more activity, the better any suppressive effect can be demonstrated). The different selection of patients may also have contributed to different subgroup findings in CHAMPS and BENEFIT, since the BENEFIT study enrolled both patients with a monofocal and multifocal initial manifestation, whereas inclusion criteria in CHAMPS did not foresee enrollment of patients with a multifocal presentation of the disease. By including a higher number of patients with a broader and more representative range of patterns of disease manifestation the BENEFIT study might allow for more informative subgroup analyses. Further analyses of treatment effects in different subgroups of the BENEFIT population are ongoing and will be the subject of a separate publication.

While 16.5 to 25.2% of interferon beta-1b-treated patients had positive NAb titers at each time point in this study no significant impact of NAbs on time to CDMS was found. A comprehensive and more informative analysis of the potential impact of NAbs on clinical outcomes will be part of the open-label follow-up study to this trial.

The percentage of patients who dropped out of the BENEFIT study before reaching the endpoint of CDMS was remarkably low (placebo 5.7%; interferon beta-1b 7.2%). There was also good adherence from patients to interferon beta-1b treatment, and almost all patients opted for open-label treatment after the end of the double-blind study (96%). Safety findings in BENEFIT were in line with the established safety profile of interferon beta-1b. Of note, the frequency of interferon beta-1b related AEs was lower in this than in previous studies with interferon beta-1b (250 μg SC EOD) in relapsing-remitting or secondary progressive disease.[27,28] With respect to the interpretation of patient-reported outcome measures, it has to be taken into consideration that the great majority of patients recover from their initial symptoms, and usually do not sense limitations in daily life. Accordingly, the stable scores obtained during treatment with interferon beta-1b indicate that AEs of treatment had no detectable negative impact on quality of life. The use of a titration scheme and acetaminophen or ibuprofen at the start of therapy might have contributed to these favorable findings and may have helped enhance initial treatment compliance in the critical time before the frequency of drug-related adverse reactions spontaneously decreases. Additionally, the use of an autoinjector might have contributed to lowering the rate of injection site reactions.[29]

Both the significant treatment effect on time to conversion to MS, combined with an acceptable adverse event profile, and the high rate of conversion to MS in the placebo group support the indication of interferon beta-1b treatment in patients who fulfill the inclusion criteria of this study.

Further evidence about the long-term effect of early vs delayed treatment with interferon beta-1b 250 μg SC EOD on relapse rates as well as clinical and MRI measures of disease progression is to be expected from the ongoing open-label follow-up since 96% of the patients after completing the placebo-controlled phase agreed to be enrolled in this preplanned 5-year extension study.

Appendix

Benefit study group. Principal Investigators: Austria—S. Strasser-Fuchs, Graz; T. Berger, Innsbruck; K. Vass, Wien. Belgium—C. Sindic, Brussels; B. Dubois, Leuven; D. Dive, Liège; J. Debruyne, Gent. Canada—L. Metz, Calgary; G. Rice, London (ON); P. Duquette, Y. Lapierre, Montreal; M. Freedman, Ottawa; A. Traboulsee, Vancouver; P. O'Connor, Toronto. Czech Republic—P. Štourač, Brno; R. Taláb, Hradec Kralove; O. Zapletalová, Ostrava; I. Kovárŏvá, E. Medová, Praha; J. Fiedler, Plzen. Denmark—J. Frederiksen, Glostrup. France—B. Brochet, Bordeaux; T. Moreau, Dijon; P. Vermersch, Lille; J. Pelletier, Marseille; G. Edan, Rennes; M. Clanet, Toulouse; P. Clavelou, Clermont Ferrand; C. Lebrun-Frenay, Nice; O. Gout, Paris. Finland—M. Kallela, Helsinki; T. Pirttilä, Kuopio; J. Ruutiainen, Turku; K. Koivisto, Seinäjoki; M. Reunanen, Oulu; I. Elovaara, Tampere. Germany—A. Villringer, H. Altenkirch, Berlin; K. Wessel, Braunschweig; H.-P. Hartung, W. Steinke, Düsseldorf; H. Kölmel, Erfurt; P. Oschmann, Giessen; R. Diem, Göttingen; A. Dressel, Greifswald; F. Hoffmann, Halle/Saale; K. Baum, Hennigsdorf; S. Jung, Homburg/Saar; H. Felicitas Petereit, Köln; M. Sailer, Magdeburg; J. Köhler, Mainz; N. Sommer, Marburg; R. Hohlfeld, München; K.-H. Henn, Offenbach; A. Steinbrecher, Regensburg; H. Tumani, Ulm; R. Gold, P. Rieckmann, Würzburg; R. Kiefer, Münster. Hungary—S. Komoly, G. Gács, G. Jakab, Budapest; L. Csiba, Debrecen; L. Vécsei, Szeged. Israel—A. Miller, Haifa; D. Karussis, Jerusalem; J. Chapman, Tel-Hashomer. Italy—A. Ghezzi, Gallarate; G. Comi, Milano; P. Gallo, Padova; V. Cosi, Pavia; L. Durelli, Torino. The Netherlands—B. Anten, Sittard; L. Visser, Tilburg. Norway—K.-M. Myhr, Bergen. Poland—A. Szczudlik, Kraków; K. Selmaj, Łódź; Z. Stelmasiak, Lublin; R. Podemski, Wrocław; Z. Maciejek, Bydgoszcz. Portugal—L. Cunha, Coimbra. Slovenia—S. Sega-Jazbec, Ljubljana. Spain—X. Montalbán, T. Arbizu, A. Saiz, Barcelona; J. Bárcena, Barakaldo; R. Arroyo, Madrid; O. Fernández, Málaga; G. Izquierdo, Sevilla; B. Casanova, Valencia. Sweden—J. Lycke, Mölndal. Switzerland—L. Kappos, Basel; H. Mattle, Bern; K. Beer, St. Gallen. United Kingdom—R. Coleman, Aberdeen; J. Chataway, London; J. O'Riordan, Dundee; S. Howell, Sheffield. *Steering Committee.* L. Kappos, C.H. Polman, M. Freedman, L. Bauer, G. Edan, M. Ghazi, H.-P. Hartung, D. Miller, X. Montalbán, R. Sandbrink. *Eligibility Review Committee.* C.H. Polman, F. Barkhof, B. Uitdehaag. *CDMS Confirmation Committee.* L. Kappos, A. de Vera, S. Wu. *Central MRI Analysis.* F. Barkhof. *Independent Advisory Board.* H.F. McFarland, J. Kesselring, A.J. Petkau, K.V. Toyka.

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