Articles

Placebo-controlled multicentre randomised trial of interferon β-1b in treatment of secondary progressive multiple sclerosis

*European Study Group on Interferon β-1b in Secondary Progressive MS**

Summary

Background The beneficial effects of interferon β have only been shown for patients in the relapsing-remitting phase of multiple sclerosis (MS). The role of interferon β in the treatment of patients who are in the secondary progressive phase of the disease (SP-MS), and for whom no effective drug treatment is available, has not been assessed.

Methods In this multicentre, double-masked, randomised, placebo-controlled trial, outpatients with SP-MS having scores of 3·0–6·5 on the Expanded Disability Status Scale (EDSS) received either 8 million IU interferon β-1b every other day subcutaneously, or placebo, for up to 3 years. The primary outcome was the time to confirmed progression in disability as measured by a 1·0 point increase on the EDSS, sustained for at least 3 months, or a 0·5 point increase if the baseline EDSS was 6·0 or 6·5. A prospectively planned interim analysis of safety and efficacy of the intention-to-treat population was done after all patients had been in the study for at least 2 years.

Findings 358 patients with SP-MS were allocated placebo and 360 were allocated interferon β-1b; 57 patients (31 placebo, 26 interferon β-1b) were lost to follow-up. There was a highly significant difference in time to confirmed progression of disability in favour of interferon β-1b (p=0·0008). Interferon β-1b delayed progression for 9–12 months in a study period of 2–3 years. The odds ratio for confirmed progression was 0·65 (95% CI 0·52–0·83). This beneficial effect was seen in patients with superimposed relapses and in patients who had only progressive deterioration without relapses. Positive results were also obtained regarding time to becoming wheelchair-bound, relapse rate and severity, number of steroid treatments and hospital admissions, as well as on magnetic resonance imaging variables. The drug was safe and side effects were in line with previous experience with interferon β-1b. The study was stopped after the interim results gave clear evidence of efficacy.

Interpretation Treatment with interferon β-1b delays sustained neurological deterioration in patients with SP-MS. Interferon β-1b is the first treatment to show a therapeutic effect in patients with SP-MS.

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Introduction

In 1993, interferon β-1b emerged as a therapeutic option in multiple sclerosis (MS) and has been hailed as a major advance in the management of this disorder.[1] Three products containing interferon β are available, and phase III trials for each product have shown a reduction in relapse rate by 18–34% in patients with relapsing-remitting MS.[1–3] This reduction in disease activity was associated with a striking effect on abnormalities detected by magnetic resonance imaging (MRI), particularly on the development of new and contrast enhancing lesions.

A major concern of patients with MS and their physicians, is accrual of disability when the disease has reached the secondary-progressive (SP-MS) phase. In SP-MS, disability becomes the dominant factor and determines the level of support required and costs incurred.[4] Three studies[1–3] have given some indication of an effect of interferon β on the accrual of disability but such an effect was difficult to address persuasively: the patient groups studied were in the early stage of the disease with little if any disability, reflected by low Expanded Disability Status Scale (EDSS) scores, and at a time when disability was unlikely to develop over a 2–3 year period. The EDSS measured impairment rather than disability in the group of patients who had scores in the lower part (0–3·0) of the scale.[5,6] The one study[2] in which time to sustained change on the EDSS was used as the primary outcome measure, recruited patients with the lowest EDSS scores and was of the shortest duration.

Disability in MS can result from two distinct, though in many cases, overlapping mechanisms: failure to recover from relapse (incomplete remission) and slow insidious progression. These mechanisms may have different underlying pathologies.[7] In patients with relapsing-remitting disease, the failure to recover from relapse is the sole cause of disability, while patients with secondary progressive MS accrue disability from both relapses and insidious progression.

To address the effects of interferon β-1b on disease progression in patients with SP-MS, we started a large placebo-controlled multicentre European study in 1994.[8] The main clinical findings of a prospectively planned interim analysis are presented here.

Methods

Design

This is a European, multicentre, double-blind, placebo-controlled study of two parallel-treatment groups of outpatients with SP-MS. The study was planned to have a 36-month period of treatment, followed by a drug-free follow-up of 3 months. Regular visits were scheduled for days 1, 3, 5, and 15, months 1–3, and thereafter every 3 months until month 36 (end of

Efficacy variable	Statistical method	Stratification/covariance adjustment	Supportive modelling
Time to confirmed progression	Nonparametric analysis of covariance (primary), Mantel-Cox log-rank test (secondary)	Centre/baseline EDSS Baseline EDSS*	Piecewise logistic model
Time to becoming wheelchair-bound	Mantel-Cox log-rank test	Baseline EDSS*	Piecewise logistic model
Proportion of patients becoming wheelchair bound	Mantel-Haenszel test	Baseline EDSS*	
Annual relapse rate	Nonparametric analysis of covariance	Centre/relapse in previous years	
Percentage change in annual T2 lesion volume	Nonparametric analysis of covariance	Centre/baseline lesion volume	
Number of newly active lesions months 1–6 and months 19–24	Nonparametric analysis of covariance	Centre/baseline number of lesions	
Proportion of patients with confirmed progression	Mantel-Haenszel test	Baseline EDSS*	Logistic model
Change in EDSS from baseline	Extended Mantel-Haenszel test	Baseline EDSS*	
EDSS at endpoint	Extended Mantel-Haenszel test	Baseline EDSS*	
Time to first relapse	Mantel-Cox log-rank test	Centre	
Proportion of patients with moderate or severe relapse	Mantel-Haenszel test	Centre	
Proportion of patients with steroid use	Mantel-Haenszel test	Centre	
Proportion of patients admitted to hospital	Mantel-Haenszel test	Centre	
Number of MS-related hospital admissions per patient	Extended Mantel-Haenszel test	Centre	

*Baseline EDSS categories ⩽3·5, 4·0–5·5, ⩾6·0.

Table 1: **Summary of statistical methods**

treatment) and month 39 (end of drug-free follow-up). Unscheduled visits for assessment and treatment of relapses and other non-MS related medical events were made and documented as required throughout the study. Patients were followed up until the end of the study and underwent regular assessments, unless they withdrew consent or were lost to follow-up.

The study was supervised by a steering committee of investigators and sponsor staff who were masked from the results throughout the study. Data management and all statistical analyses were done by an external institution. An independent advisory committee reviewed the results of regular interim safety analyses and of a prospectively planned interim analysis of efficacy done after all patients had been in the study for at least 24 months.

Patients and treatment

Outpatients eligible for randomisation had a clinically or laboratory supported definite diagnosis of MS.[9] Secondary progression was defined as a period of deterioration, independent of relapses, sustained for at least 6 months, and that followed a period of relapsing-remitting MS. Superimposed relapses were allowed.[10] Patients were aged 18–55 years, with a baseline EDSS score of 3·0–6·5 inclusive and a recorded history of either two relapses or more or 1·0 point or more increase in EDSS in the previous 2 years. Immunosuppressive or immunomodulatory treatment and other putative treatments for MS were not permitted for defined periods before entry into the study. The complete eligibility criteria have been published elsewhere.[8] Patients provided written informed consent.

A central randomisation schedule assigned placebo or interferon β-1b to blocks of six patients in a 1/1 ratio. Access to the code was strictly limited according to study protocol. Patients injected 0·5 mL interferon β-1b (4 million IU) or placebo subcutaneously for the first 2 weeks, thereafter increasing their dose to 1·0 mL (8 million IU interferon β-1b or placebo) every other day. Interferon β-1b was indistinguishable from placebo. Treatment had to be discontinued in cases of intolerable adverse events or clinically relevant laboratory deviations, pregnancy, use of prohibited medication, or if the code was broken.

Non-steroidal anti-inflammatory drugs or paracetamol were recommended to reduce flu-like symptoms or for patients sensitive to changes in body temperature. Systemic steroid treatment was standardised (1 g methylprednisolone intravenously for 3 days—with or without tapering with decreasing oral doses of prednisone or prednisolone) and restricted to treatment of relapses. Courses of steroids were limited to a maximum of three within any year while patients were in the study.

Efficacy and masking

Functional system and EDSS scores were determined as described by Kurtzke.[5] The functional-system scores measure function within individual neurological systems including visual, pyramidal, cerebellar, brainstem, sensory, bowel and bladder, cerebral (mental), and other functions. The EDSS comprises 20 grades from 0 (normal) to 10 (death due to MS) progressing in a single-point step from 0–1 and in 0·5 point steps upward, and is based on the combination of functional-system scores and the patient's degree of mobility, need for walking assistance, or help in the activities of daily living. Because ambiguities in the original definitions resulted in poor inter-rater reliability,[11] physicians rating EDSS underwent training at a central EDSS reference centre that provided standardised rules for assessment of individual functional systems, ambulation distance, and EDSS scoring.[12]

The EDSS reference centre trained raters before the start of the study and in yearly follow-up sessions to reinforce uniformity of assessments, and provided testers with videotapes, manuals, and written guidelines. New EDSS raters underwent training at the EDSS reference centre before assessing patients. Whenever possible, the same EDSS rater did all scheduled neurological assessments for a given patient throughout the study.

To avoid unmasking as a result of the well-characterised side-effects of interferon β-1b,[1,2] designated treating physicians were responsible only for general medical care, safety assessments, and treatment of relapses, while designated EDSS physicians did the standardised neurological tests. EDSS physicians received no potentially unmasking information from the treating physicians, and were allowed to speak to patients only as necessary to carry out neurological tests. During EDSS assessments all potential injection sites were covered. Documentation of neurological examinations and functional system and EDSS scores were kept separately by the EDSS physicians.

A questionnaire to test the success of masking was filled out at the end of the study by treating physicians, EDSS physicians, and patients.

Disability

The primary outcome measure was the time from baseline to the first scheduled quarterly visit at which an increase by at least 1·0 point of the EDSS (0·5 points if the baseline EDSS was 6·0 or 6·5) was recorded, provided the increase was confirmed at the next scheduled study visit 3 months later (at least 70 days apart). The visit at month 33 was the last after which confirmation could be obtained (at month 36). EDSS scores recorded during an investigator-verified relapse were not considered valid except for those collected after day 90 of an ongoing relapse.

Further EDSS-related variables included time to becoming wheelchair-bound (ie, reaching an EDSS score of ⩾7·0). For this criterion no confirmation was required because the number of patients reaching EDSS of 7 or more was expected to be much lower and to occur later, because this criterion was more difficult to reach than the primary endpoint for all those patients who had a baseline EDSS of 6·0 or lower. Additional variables were proportion of patients with confirmed progression, proportion of patients becoming wheelchair-bound, and EDSS at the endpoint.

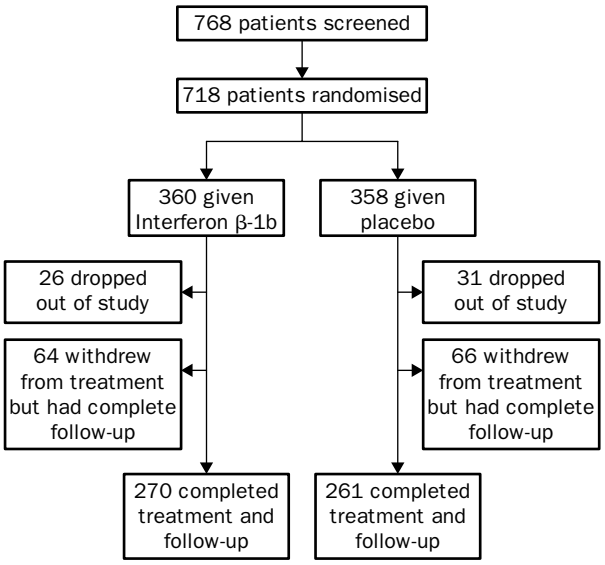

Figure 1: **Trial profile**

Relapse-related variables

A relapse was defined as the acute or subacute appearance or reappearance of a neurological abnormality, immediately preceded by a stable, improving, or slowly progressive neurological state for 30 days before deterioration, present for at least 24 h, and occurring in the absence of fever, known infection, or concurrent steroid withdrawal. Patients were instructed to contact the study centre if any symptom, suggestive of a relapse occurred. The treating physician did the relapse-related assessments including the date of onset, symptoms, and estimate of relapse severity (mild, moderate, or severe), as well as functional-system and EDSS scoring for the relapse assessments. Only relapses verified by the treating physician were considered valid for efficacy analyses.

Relapse-related variables were annual relapse rate (number of relapses divided by days in study, multiplied by 365), time to first relapse, and proportion of patients with moderate or severe relapses.

Other assessments

MS-related steroid use and hospital admissions were assessed. For MRI assessments, all patients had an annual scan, and 125 patients (61 placebo, 64 interferon β-1b) also underwent monthly MRI including T1-weighted gadolinium-enhanced scans in months 0–6 and 18–24. MRI assessments done by one evaluating centre, included annual lesion volume and newly active lesions.

Patients were tested at scheduled visits for titres of neutralising antibodies to interferon β-1b with the MxA protein assay;[13] positivity was defined by two consecutive titres of 1:20 or more.

Safety assessments included adverse events, vital signs, physical examinations, and concomitant medication. Standard laboratory tests were done at all regular visits by a central laboratory. An electrocardiogram was done at the beginning and end of the study. The Montgomery Asberg Depression Rating Scale (MADRS),[14] an observer rating scale, was used to assess mood changes and suicidal risk at all regular quarterly visits.

Statistical analyses

Sample size was determined, assuming that the proportion of patients with confirmed progression in the placebo group would be 50% at 3 years, and a treatment difference of 12·5% was to be detected in a two-sided log-rank test at α=0·029 and 80% power using the Pocock method to adjust for the planned interim analysis. 355 patients per group, including adjustment for an expected 20% loss of patients, were required. α adjustment for the interim analysis of efficacy was later based upon a Lan DeMets adaptation of α spending (α=0·048 for final analysis and α=0·0133 for interim assuming an information fraction of 83% EDSS data). All statistical analyses were based on the intention-to-treat population, including all data of all patients as randomised without any restrictive criteria.

	Placebo (n=358)*	Interferon β-1 (n=360)*
Mean age (SD, years)	40·9 (7·2)	41·1 (7·2)
Women	64·2%	58·1%
Mean disease duration (SD, years)	13·4 (7·5)	12·8 (6·6)
Mean time since diagnosis of relapsing risk MS (SD, years)	8·2 (6·1)	8·1 (5·6)
Mean time since evidence of progressive deterioration (SD, years)	3·8 (3·4)	3·8 (2·7)
Mean time since diagnosis of SP-MS (SD, years)	2·1 (2·2)	2·2 (2·4)
Mean EDSS at baseline (SD)	5·2 (1·1)	5·1 (1·1)
EDSS by category		
⩽3·5	47 (13·1%)	67 (18·6%)
4·0–5·5	142 (39·7%)	140 (38·9%)
⩾6·0	169 (47·2%)	153 (42·5%)
Patients without relapse in 2 years before study†	101 (28·2%)	115 (31·9%)

*No significant differences between treatment groups (p>0·05).
†Data missing for seven patients (four placebo, three interferon β–1b) who were included in the subgroup of patients without relapse.

Table 2: **Patient population (baseline characteristics)**

Baseline characteristics were analysed with the Wilcoxon's rank-sum test for comparison of ordinal and continuous variables, and Fisher's exact test for comparisons of dichotomous or non-ordinal categorical variables.

Efficacy variables were analysed with nonparametric methods addressing the non-linearity of the EDSS scale.[6] The primary method for time to confirmed progression was an analysis of covariance[15] with adjustment for centre and baseline EDSS and stratification adjustment for centre, and covariance-adjusted log-rank scores for the follow-up information on confirmed progression were compared between groups with an extended Mantel-Haenszel test with stratification adjustment for centre.

Life-table estimates were generated and treatment groups compared with the Mantel-Cox log-rank test stratified for baseline EDSS categories (⩽3·5, 4·0–5·5, and ⩾6·0). The odds ratio was estimated from a piecewise logistic regression model including baseline EDSS, centre, and time as factors other than treatment.[16] In expanded models, duration of MS, age, sex, and body-surface area were also included and interaction with treatment was tested. Progression confirmed after 3 and 6 months irrespective of concomitant relapses was also explored. Other efficacy outcomes were analysed with Mantel-Haenszel, extended Mantel-Haenszel, or Mantel-Cox log-rank tests adjusted for baseline EDSS, pre-study relapse, baseline MRI, or centre (table 1).

A longitudinal analysis with the generalised estimating equations approach was used to address the question whether the change from neutralising-antibodies negative to neutralising-antibodies positive status was associated with an attenuation of treatment effects.[17] Tables and analyses were done with SAS software (version 6·12).

Results

Study population

As shown in figure 1, 718 of 768 patients screened in 32 European centres were randomly assigned interferon β-1b (n=360) or placebo (n=358). The mean follow-up time at inerim cut-off was 892 study days in the placebo group and 901 days in the interferon β-1b group, comprising about 85% of EDSS information anticipated over the planned study duration of 3 years. Treatment groups were comparable for all baseline variables (table 2). Of these, 57 patients (31 [8·7%] placebo, 26 [7·2%] interferon β-1b) dropped out of the study (table 3). There were no significant differences for the reasons given between treatment groups. Altogether, 130 patients (66 placebo, 64 interferon β-1b) stopped treatment but were followed up according to the protocol (table 3).

	Placebo (n=358)	Interferon β-1b (n=360)
Reason for drop out		
Adverse event, laboratory deviation	4 (1·1%)	5 (1·4%)
Progression of disease	10 (2·8%)	5 (1·4%)
Death*	1 (0·3%)	3 (0·8%)
Lost to follow-up	4 (1·1%)	8 (2·2%)
Other	12 (3·4%)	5 (1·4%)
Total	31 (8·7%)	26 (7·2%)
Reason for stopping treatment (including drop outs)		
Adverse events†	15(4·2%)	45 (12·5%)
Illness, independent from trial medication	3 (0·8%)	0
Patient uncooperative/rejects treatment*	19 (5·3%)	8 (2·2%)
Deviation from trial protocol	0	3 (0·8%)
Inefficacy of trial medication†‡	44 (12·3%)	23 (6·4%)
Death	0	2 (0·6%)
Pregnancy	0	1 (0·3%)
Other	16 (4·5%)	8 (2·2%)
Total	97 (27·1%)	90 (25·0%)

*One suicide in each group. †p<0·05 two-sided Fisher's Exact Test.
‡Includes two patients (one placebo, one interferon β-1b) who died after premature discontinuation of treatment.

Table 3: **Reasons for dropping out of study and stopping treatment**

Overall, 531 patients (placebo 261 [72·9%], interferon β-1b 270 [75·0%]) either completed 3 years of treatment or were still being treated at interim cut-off (figure 1).

More protocol deviations were reported in the placebo group (73 patients [23·5%]) than in the interferon β-1b group (58 patients [17·2%]). Reasons for protocol deviations were equally distributed between treatment groups except for a significantly more frequent use of prohibited medication, including excessive use of steroids or treatment with immunosuppressants or open label interferon β, in the placebo group (33 *vs* 15 patients, p=0·0071). Only 11 protocol deviations were related to EDSS measurements.

Reasons for treatment discontinuation that differed significantly in frequency between groups were: adverse events (placebo 15 [4·2%] interferon β-1b 45 [12·5%]); patient uncooperative or treatment rejection (placebo 19 [5·3%], interferon β-1b eight [2·2%]); and inefficacy of trial medication as perceived by physician or patient (placebo 44 [12·3%] interferon β-1b 23 [6·4%]; table 3).

Clinical efficacy variables

For the primary efficacy variable, time to confirmed neurological deterioration, the nonparametric analysis of covariance showed a significant difference between the two groups (p=0·0008) in favour of interferon β-1b (figure 2, table 4). Of the 358 patients taking placebo 178 (49·8%) had confirmed progression (days to event [40% quantile] 549, CI 463–642). Of the 360 patients taking interferon β-1b 140 (38·9%) had confirmed progression (days to event [40% quantile] 893, lower CI limit 726, upper CI limit could not be estimated in terms of days within the given study period). Usually, 50% quantile is given, but because this was not reached by both groups we took the next quantile that would reflect the longest period of observation (40% quantile).

Supportive analysis requiring two confirmations (including EDSS assessments at 3 and 6 months) and including scores during relapses, also reached significance (p=0·0016). The primary outcome was confirmed by additional intention-to-treat analyses counting patients lost to follow-up either as progressed after loss to follow-up (p=0·0012) or as not progressed by the end of the study (p=0·0014). Piecewise logistic regression analyses

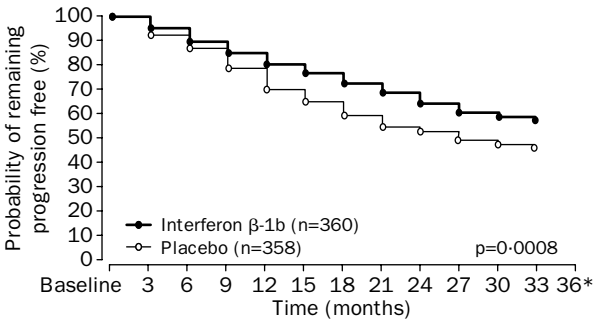

Figure 2: **Time to confirmed progression, life-table estimate**
*Month 36 visit for confirmation only.

also supported the primary analysis with an odds ratio of 0·65 (95% CI 0·52–0·83) and did not reveal any interactions between treatment and the variables included in the expanded model confirming a homogeneous treatment effect over time.

The estimated probabilities of remaining progression free (estimated survival rates) were calculated for each 3-month period throughout 33 months (table 4). Treatment effects became visible after 9 months of treatment (p=0·059) and were significant after 12 months (p=0·003), maintaining significance for each 3-month period throughout the remainder of the study (33 months, p=0·0015). The delay in progression can be described by comparing the periods at which a given estimated probability is reached. Delay ranged from 9 to 12 months for 65% and 60% probability of remaining progression-free (figure 2, table 4). Estimation of quantiles of time to confirmed progression using the Kaplan-Meier method showed increasing delay of progression over time with a difference of 344 days for the 40th quantile.

In the placebo group, 49·7% of patients had confirmed progression compared with 38·9% in the treatment group over the total study period (p=0·0048), which represents a relative reduction of 21·7% in the proportion of patients with progression (table 5). Logistic regression modelling showed that patients on placebo had a 1·6 times higher probability of progression (odds ratio 0·63, 95% CI [0·46–0·85]). The time to becoming wheelchair-bound (ie, reaching EDSS 7·0) was also significantly delayed (odds ratio 0·66, 0·47–0·93; table 5); the comparison of life-table estimates showed a delay of up to 9 months in the interferon β-1b group versus placebo, the difference being significant as of month 12. In the placebo group,

Time period	Placebo		Interferon β-1b		p*
	Survival rate	Number at risk	Survival rate	Number at risk	
Month 1–3	0·93	358	0·95	360	0·1962
Month 4–6	0·87	332	0·89	342	0·3830
Month 7–9	0·79	305	0·85	318	0·0591
Month 10–12	0·71	275	0·81	301	0·0031
Month 13–15	0·65	244	0·77	284	0·0009
Month 16–18	0·60	226	0·73	271	0·0003
Month 19–21	0·55	206	0·69	256	0·0002
Month 22–24	0·53	188	0·65	238	0·0012
Month 25–27	0·50	148	0·61	183	0·0015
Month 28–30	0·48	95	0·60	133	0·0013
Month 31–33	0·47	65	0·58	94	0·0015

*Mantel-Cox log-rank test with stratification adjustment for baseline EDSS categories (secondary method of statistical evaluation); cumulative comparison of survival curves.

Table 4: **Time to confirmed progression: estimated probability to remain progression free by the life-table method**

Efficacy variable	Placebo (n=358)	Interferon β-1b (n=360)	p
Proporportion of patients with confirmed EDSS progression*	49·7%	38·9%	0·0048
Loss of mobility			
Time to becoming wheelchair-bound			0·0133
Estimated probability of not becoming wheelchair-bound			
Year 1	0·90	0·96	0·0129
Year 2	0·81	0·89	0·0094
Year 3	0·66	0·77	0·0133
Mean EDSS			
At endoint	5·84	5·57	0·0750
Change at endpoint†	0·60	0·47	0·0299
Mean annual relapse rate			
Overall	0·64	0·44	0·0002
Year 1	0·82	0·57	0·0095
Year 2	0·47	0·35	0·0201
Year 3	0·35	0·24	0·1624
Median time to first relapse (days)	403	644	0·0030
Proportion of patients with moderate or severe	53·1%	43·6%	0·0083

*Patients lost to follow-up counted as not progressed.
†Endpoint minus baseline.

Table 5: **Results of secondary and tertiary efficacy variables**

88 (24·6%) patients reached an EDSS score of 7 or more, compared with 60 (16·7%) patients in the interferon β-1b group (p=0·0277), which represents a reduction by 32·1% in the proportion of patients becoming wheelchair-bound during the study period. Comparison of EDSS at the endpoint (last visit available) between treatment groups was not significant (p=0·075), but change in EDSS score at endpoint minus baseline showed a significant difference in favour of interferon β-1b (p=0·0227).

The treatment effect on progression was similar, irrespective of baseline EDSS or superimposed relapses before or during the study, with relative reductions of sustained progression of about 20% in the interferon β-1b group (table 6).

Mean annual relapse rate was reduced overall by about 30% in the treatment group (placebo 0·64 *vs* interferon β-1b 0·44, p=0·002). The rates dropped annually in both groups (table 5), maintaining the treatment effect over time, although this was not significant in the third year. The time to first relapse was prolonged in the interferon β-1b group (median 644 days) compared with placebo (median 403 days; p=0·0030) and the proportion of patients with moderate or severe relapses was lower (190 [53·1%] patients on placebo, 157 [43·6%] patients on interferon β-1b, p=0·0083, table 5).

Both the proportion of patients admitted to hospital (189 [52·8%] patients on placebo, 167 [46·4%] patients on interferon β-1b, p=0·0435) and the number of MS-associated hospital admissions per patient were significantly reduced in the patients on active treatment (p=0·0003). The proportion of patients with MS-associated steroid use was significantly lower in the interferon β-1b group (67·9% *vs* 53·6%, p<0·0001).

The questionnaire to assess effectiveness of masking was received from 84–86% of the treating physicians, EDSS physicians, and patients. As expected, treating physicians often guessed correctly whether the patients were on placebo 148 (48·4%) of 306 or interferon β-1b 176 (56·2%) of 313, although they did not know or guessed incorrectly for 225 (36·3%) of 619 and 70 (11·3%) of 619 of patients, respectively. Similarly 165 (54·3%) of 304 patients guessed correctly that they were on placebo and 202 (65·6%) of 308 that they were on active treatment. However, 71 (23·4%) of 304 on placebo thought they were on interferon β-1b, 36 (11·7%) of 308 on interferon β-1b thought they were on placebo, and 138 (22·5%) of 612 did not know. Most importantly, EDSS physicians guessed correctly for only 54 (18·6%) of 291 of patients on placebo and 65 (20·8%) of 312 patients on interferon β-1b. They stated "do not know" for 401 (66·5%) of 603 patients.

MRI variables

Treatment with interferon β-1b resulted in a significant reduction of mean MRI T2 lesion volume, which increased by about 8% in the placebo group and there was a 5% decrease in the interferon β-1b group (p<0·0001). In the frequent MRI cohort (n=125), patients receiving interferon β-1b showed a 65% reduction of newly active lesions from months 1–6 (p<0·0001) and a 78% reduction from months 19–24 (p=0·0008) compared with placebo.

Neutralising antibodies to interferon β-1b

Of 100 (27·8%) patients positive for neutralising antibodies, 66 became so in the first 6 months of treatment. 47 patients positive for neutralising antibodies subsequently had at least one negative titre, and 37 of them remained negative for neutralising antibodies after reverting to a neutralising-antibody-negative status. Longitudinal analyses with the generalised estimating equations approach[17] indicated a significant decrease of the therapeutic effect in terms of relapse rate in patients positive for neutralising antibodies. But for parameters directly associated with the primary endpoint (EDSS changes over time) there was not a decrease in therapeutic effect.

Safety

Clinically relevant and common adverse events significantly associated with interferon β-1b included injection-site events and flu-like symptoms, the latter particularly in the early treatment phase. Injection-site necrosis was observed in 4·7% of patients on interferon β-1b. Other reported adverse events significantly associated with interferon β-1b were muscle hypertonia (37·8% *vs* 27·4%, p=0·0032) and hypertension (3·9% *vs* 0·8%, p=0·0117). Standardised neurological examinations and vital-sign findings associated with

	Placebo (n=358)		Interferon β-1b (n=360)		Δ*
	n	With event‡	n	With event‡	
Baseline EDSS					
⩽3·5	47	20 (42·6%)	67	23 (34·3%)	−19·5%
4·0–5·5	142	73 (51·4%)	140	57 (40·7%)	−20·8%
⩾6·0	169	85 (50·3%)	153	60 (39·2%)	−22·1%
Relapses during study					
With	224	117 (52·2%)	194	81 (41·8%)	−19·9%
Without	134	61 (45·5%)	166	59 (35·5%)	−22·0%
Relapses 2 years before study					
With	257	128 (49·8%)	245	94 (38·4%)	−22·9%
Without	101*	50 (49·5%)	115*	46 (40·0%)	−19·2%

*Relative difference in proportion of patients with event.
†Including seven patients (4 placebo, three interferon β-1b) with missing information, evaluated in the subgroup of patients without relapses.
‡Occurrence of confirmed progression.

Table 6: **Proportion of patients with confirmed progression per baseline EDSS category and per occurrence of relapse before and during study**

Body system/adverse events	Placebo (n=358)	Interferon β-1b (n=360)
Body as a whole		
Flu syndrome	133 (37·2%)	213 (59·2%)
Fever	47 (13·1%)	142 (39·4%)
Chills	26 (7·3%)	79 (21·9%)
Abdominal pain	23 (6·4%)	38 (10·8%)
Chills and fever	1 (0·3%)	13 (3·6%)
Hemic and lymphatic system		
Leucopenia	18 (5·0%)	36 (10·0%)
Cardiovascular system		
Hypertension	3 (0·8%)	14 (3·9%)
Injection site		
Reaction	37 (10·3%)	157 (43·6%)
Inflammation	15 (4·2%)	180 (50·0%)
Necrosis	0	17 (4·7%)
Skin and appendages		
Rash	38 (10·6%)	77 (21·4%)
Musculoskeletal system		
Myalgia	32 (8·9%)	82 (22·8%)
Nervous system		
Hypertonia	98 (27·4%)	136 (37·8%)

Patients were counted for each individual adverse event term so patients who had more than one adverse event are counted more than once. The table does not count multiple occurrences of the same event in one patient.

Table 7: **Adverse events significantly associated with interferon β-1b treatment**

hypertonia and hypertension showed no differences between treatment groups (table 7).

As anticipated from other studies, there were higher proportions of patients with abnormal values of liver enzymes and white-blood-cell counts in the interferon β-1b group. In general, liver-enzyme abnormalities resolved spontaneously or were well managed by dose reduction or intermittent treatment discontinuation. Clinically relevant laboratory abnormalities occurred rarely and were only clearly associated with interferon β-1b for lymphopenia.

There were four deaths in the study, three of which occurred in the interferon β-1b group. Two patients (one on placebo, one on interferon β-1b) committed suicide, one patient had a cardiac arrest, and one a massive pulmonary embolism (55 days after prematurely stopping treatment with interferon β-1b). Patients on interferon β-1b had no increased incidence of new or worsened depression, neither as a spontaneously reported adverse event nor in the quarterly monitoring with the MADRS scale. Suicides or suicide attempts were reported in five patients on placebo and three on interferon β-1b.

Discussion

This phase III study shows a therapeutic benefit of interferon β-1b in SP-MS. SP-MS is reported to be the most common phase of the disease and the one during which major irreversible disabilities most often appear.[17,18]

The cohort studied was representative for this disease group, including patients who progressed with or without superimposed relapses following an initial relapsing-remitting phase.[10] Patients were in the early stage of progression beginning about 10 years after initial diagnosis of MS and had active disease in the 2 years before entry into the study.

The primary outcome measure in this study was sustained progression of disability as measured by EDSS. Although much criticised, the EDSS remains the most widely accepted measure of disease progression in MS.[19] However, the EDSS is poorly responsive at certain levels and particularly between EDSS 6·0 and 7·0. Times spent at these levels are frequently prolonged relative to other points on the scale, a fact that reflects the usually more extended period of deterioration leading to loss of ability to walk. This issue was addressed in the present study by counting 0·5 point steps from a baseline EDSS of 6·0 or 6·5 as full steps. This definition has been suggested[20,21] as a clinically appropriate definition of worsening because each half-point step captures significant progression in this EDSS range. A further limitation of the EDSS scale, its poor inter-rater reliability, was addressed by repeated standardised audiovisual training sessions for the EDSS physicians, which resulted in improved consistency of ratings.[12]

Regarding the primary outcome, a highly significant delay in the time to disease progression ($p=0·0008$) was observed in the interferon β-1b group, as seen in the life-table curves, which show a delay of progression of up to 12 months in the study period. These results are supported by equally clear benefits across the secondary and tertiary variables and led to the independent advisory board's recommendation to stop the study early.

The outcome of any study is invariably influenced by the behaviour of the placebo group. The proportion of treatment failures and time to treatment failure in the placebo arm of this study fell within the range of the results of previous studies including patients with SP-MS.[21,22]

The results of the questionnaire on masking provide encouraging evidence that the specific measures taken—ie, having a separate EDSS physician excluded from patient management and masked from all clinical information, recommending the use of anti-inflammatory drugs, and covering injection sites at all EDSS assessments—were effective.

Interestingly, in this study the therapeutic benefit appeared to be as strong in the severely disabled patients as in those with mild-to-moderate disability. However, it has been suggested that using a more clinically appropriate definition of worsening for patients with baseline EDSS of 6·0 or greater, as described above, essentially removes the dependence of treatment failure on baseline EDSS.[21]

As expected from previous studies of interferon β, the relapse rate was significantly lower in the treated group[1–3] and decreased in both groups over time, as might be anticipated in SP-MS.[18] The effect on disability progression continued to be significant at each time point and similar treatment effects were seen irrespective of on-study relapses, giving further evidence that the effect of interferon β-1b slows the progression of disability in addition to its effect on relapses.

These findings raise important issues in relation to the mechanism of disability progression in MS and the mode of action of interferon β. In this study, an effect was observed on both aspects of deterioration—ie, incomplete recovery from relapse and slow insidious progression. While the former is likely to be associated with demyelination and axonal loss secondary to acute inflammation, the latter may be associated with continuous damage either due to low-grade inflammatory activity or some other independent process. Two possible modes of action may be in play: an impact on disability progression by suppresing low-grade inflammation or, less probably, an additional hitherto unrecognised protective effect on myelin and axonal integrity.

Steroids were more frequently used in the placebo group. This probably reflects the fact that placebo

patients had more disease activity, which is supported by the finding of fewer admissions to hospital as a result of MS in the active treatment group. However, steroid use did not mask the effect of interferon β-1b.

Overall, the side-effect pattern of interferon β-1b seen in this study is in line with the known safety profile and indicates that long-term therapy at a dose of 8 million IU in SP-MS is safe and generally well tolerated. In line with findings from studies of IFNB-1a[2,3] no increased incidence of depression was seen with interferon β-1b treatment in the present study. Muscular hypertonia was reported in a higher proportion of treated patients, but this was not reflected in the detailed neurological assessments.

This study provides convincing evidence that treatment with interferon β-1b delays sustained neurological deterioration in patients with SP-MS. Supportive analyses of disease progression and the consistently positive findings for relapse and MRI-related efficacy variables demonstrate the robustness of the results. Thus, interferon β-1b is the first treatment to show a therapeutic effect in patients with SP-MS.

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