CME

A randomized, double-blind, dose-comparison study of weekly interferon β-1a in relapsing MS

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Abstract—*Background:* Interferon β-1a (IFNβ-1a; Avonex) is effective for the treatment of relapsing MS; however, the optimal dose of IFNβ-1a is not known. *Objective:* To determine whether IFNβ-1a 60 μg IM once weekly is more effective than IFNβ-1a 30 μg IM once weekly in reducing disability progression in relapsing MS. *Methods:* In a double-blind, parallel-group, dose-comparison study, 802 patients with relapsing MS from 38 centers in Europe were randomized to IFNβ-1a 30 μg (n = 402) or 60 μg (n = 400) IM once weekly for ≥36 months. The primary endpoint was disability progression, defined as time to a sustained increase of ≥1.0 point on the Expanded Disability Status Scale (EDSS) persisting for 6 months. Additional endpoints included relapses, MRI, safety, immunogenicity, and subgroup analyses of disability progression. *Results:* Both groups showed equal rates of disability progression (hazard ratio, 0.96; 95% CI, 0.77 to 1.20; $p = 0.73$). In both groups the proportion of subjects with progression of disability by 36 months estimated from Kaplan–Meier curves was 37%. No dose effects were observed on any of the secondary clinical endpoints. Only one MRI measure at one time point, number of new or enlarging T2 lesions at month 36 compared with month 24, showed a difference favoring the 60-μg dose. Both doses were well tolerated; however, slightly higher incidences of flulike symptoms and muscle weakness were observed in the 60-μg group. The incidences of neutralizing antibodies (titers ≥ 20) were 2.3% in the 30-μg group and 5.8% in the 60-μg group. *Conclusion:* There was no difference between IFNβ-1a 30 μg and 60 μg IM in clinical or MRI measures.

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Interferon beta-1a (IFNβ-1a; Avonex, Biogen, Inc., Cambridge, MA) is one of three IFNβ preparations available for the treatment of relapsing MS. In the pivotal phase III study, a once-weekly 30 μg IM dose of this IFNβ-1a product was shown to significantly prolong the time to sustained worsening of disability as defined by an increase in Expanded Disability Status Scale (EDSS) score of at least one point maintained for at least 6 months.[1] Significant beneficial effects of treatment were also reported for relapses,[1] MRI measures,[1,2] and cognitive function.[3] Recent results have shown that a once-weekly 30 μg dose also significantly reduced the rate of developing clinically definite MS and MRI activity in patients with a first demyelinating event.[4] However, the optimal dose of IFNβ-1a has not been established. The results of multiple-dose studies with the two other IFNβ preparations, IFNβ-1b (Betaseron or Betaferon, Berlex Laboratories, Montvale, NJ/Schering AG, Berlin, Germany) and IFNβ-1a given SC (Rebif, Serono, Geneva, Switzerland), have been interpreted to suggest that there may be a dose-response effect below a certain threshold dose for each IFNβ preparation.[5-9] In addition, these data suggest that there is a ceiling effect such that once the threshold dose is attained, higher doses do not provide added clinical benefit.[5,6,8]

The purpose of this study was to determine whether IFNβ-1a 60 μg is more effective than IFNβ-1a 30 μg IM once weekly in reducing sustained disability progression in patients with relapsing MS. The 60 μg dose was chosen for comparison to the commercially available dose because pharmacodynamic data have shown that increasing the IFNβ-1a dose from 30 μg to 60 μg led to a greater level of induction of biologi-

See also pages 1480, 1482, and 1496

*See the Appendix on page 1516 for a list of European IFNβ-1a (Avonex) Dose-Comparison Study Investigators.

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cal markers (i.e., neopterin and β2-microglobulin), without a notable increase in side effects.[10] This is the first double-blind, controlled study specifically designed and powered as a superiority trial to determine whether a higher dose of IFNβ-1a is clinically more effective than a lower dose. In addition, it is currently unclear whether a higher dose of IFNβ should be given to patients with more advanced disease. By enrolling patients with baseline EDSS scores from 2.0 to 5.5, this study also aimed to determine whether the dose of IFNβ-1a should be varied according to the level of disability. Another objective was to develop long-term safety profiles for IFNβ-1a 30 μg and 60 μg.

Methods. The full methodology and design of this double-blind, randomized, dose-comparison study have been published separately[11] and are reviewed below.

Subjects. Men and women 18 to 55 years of age (inclusive) with a relapsing form of MS were enrolled in the study from April 1996 to May 1997. Subjects were included in the study if they had a clinical diagnosis or a laboratory-supported clinical diagnosis of definite MS[12] for at least 1 year, at least two medically documented relapses within the 3 years before randomization, and an EDSS score between 2.0 and 5.5, inclusive. Recovery from relapses could be either complete or incomplete, although disease course was required to be stable or improving at time of study entry. Patients were excluded from the study if they had progressive disease (defined as a continuous deterioration in neurologic function during the previous 6 months, without superimposed relapses during the previous 1 year), had a relapse within 2 months before randomization, or were pregnant or breast-feeding. Women of childbearing potential were required to use an adequate method of contraception. Patients with a history of uncontrolled seizures, suicidal ideation, or an episode of severe depression within 3 months before randomization were not eligible for enrollment. Patients were also excluded if they received treatment with any of the following within 3 months of randomization: other IFN products, investigational products intended to treat either MS disease activity or progression (symptomatic therapies were acceptable) or non-MS indications, chronic immunosuppressant therapy, or chronic steroid therapy.

Before enrollment, all aspects of the study protocol were reviewed with each subject and informed written consent was obtained. The study protocol was approved by local Institutional Review Boards and was carried out according to the Declaration of Helsinki.

Study design. This was a randomized, double-blind, parallel-group, dose-comparison study conducted at 38 centers in Europe. Subjects who met inclusion criteria were randomized to receive IFNβ-1a 30 μg or IFNβ-1a 60 μg IM once weekly for at least 36 months.

Each study site designated a primary examining neurologist and one or more treating neurologists. The examining neurologist was responsible for performing EDSS evaluations and neurologic examinations during all scheduled study visits, was not involved with any other aspect of subject care, and did not have access to clinical information that might compromise blinding or to the results of prior examinations.

To ensure consistency across sites, examining neurologists attended a standard training session before enrollment of subjects and again after approximately 2 years. Treating neurologists were responsible for all other aspects of subject care and management, including the assessment and treatment of adverse events and relapses.

Subjects were required to visit the clinic every 3 months for evaluation of primary and secondary endpoints, relapses, and adverse events. A subset of subjects from 28 participating sites received MRI scans at baseline and at months 12, 24, and 36. To avoid selection bias, all recruited patients from these centers were included sequentially in the MRI cohort until the required sample size was achieved. A smaller subset of the MRI cohort from 12 of the 28 participating MRI sites received more frequent MRI; these data will be published separately. MRI endpoints included number of new or enlarging T2 lesions compared to previous scan and to baseline, number and volume of gadolinium (Gd)-enhanced lesions, change from baseline in T2 lesion volume, and change from baseline in T1 hypointense lesion volume.

In addition to 3-month evaluations, patients were seen at any time throughout the study for evaluation of relapses or adverse events. Safety was assessed by the incidence of adverse events and the results of blood chemistry, hematology, and urine testing. Serum levels of neutralizing antibodies (NAB) were measured at baseline and every 3 months throughout the study at a central laboratory at Biogen, Inc., using a two-step ELISA-cytopathic effect assay.[13] We report the incidence of titers ≥1:20—the level that has been associated with reduced biological activity of IFNβ1a.[13]

Outcome variables. The primary endpoint was disability progression, defined as time to a sustained increase of ≥1.0 point on the EDSS persisting for 6 months for subjects with baseline EDSS scores ≤4.5, or a 0.5-point increase for subjects with a baseline EDSS score ≥5.0. Additional outcome variables included the following: disability progression defined as a 1.5-point increase from baseline EDSS score maintained for 6 months; change in EDSS score at 36 months following treatment initiation; and sustained progression to an EDSS score of ≥4.0 and ≥6.0. Furthermore, disability progression was also analyzed according to the following baseline disease characteristics: presence of Gd-enhanced lesions at baseline (0 or ≥1); EDSS score at baseline (≤3.5 or ≥4.0); and type of relapsing MS (relapsing-remitting or relapsing progressive). Further endpoints included self-reported relapses, IV steroid use (surrogate marker for relapses), and progression on the Nine-Hole Peg Test (9HPT). Because relapses do not fully represent the extent of disease activity, and do not correlate with disability progression,[14] they were not predefined in the protocol as an efficacy endpoint. The 9HPT was performed twice at each visit for both the dominant and nondominant hand and progression was defined as a worsening from baseline of at least 20% of the better value on either hand, which was sustained over three consecutive scheduled visits and a period of at least 6 months. All primary and secondary endpoints were predefined before the start of the trial.

MRI. The MRI included axial double echo T2-weighted images and pre- and post–contrast-enhanced T1-weighted images. Recommended MRI specifications were 1 Tesla or

higher field strength, 23 contiguous 5-mm slices without gaps, 230-mm field of view with a 256 × 256 matrix, phase-encoding direction of left-right, and conventional spin echo sequences. Acceptable acquisition parameters at all field strengths were a repetition time (TR) of 2,000 to 2,800 ms for T2 images dual echo, an echo time (TE) of 40 to 45 ms for the first echo (CSF isointense to normal brain tissue), and a TE of 80 to 100 ms (CSF bright) for the second echo. For T1-weighted images, TR was 500 to 700 ms and TE was 15 to 20 ms. Enhanced and unenhanced T1-weighted images were acquired at each imaging time point. Acquisition of enhanced T1-weighted scans began 5 minutes after IV injection of Gd-DTPA 0.1 mmol/kg. Imaging parameters were kept constant in each patient over the entire study. Repositioning was achieved by using standardized anatomic landmarks.

All images were transferred to the MS-MRI Evaluation Center in Basel, Switzerland, where analyses were performed by experienced raters who were blinded to treatment. Scans were checked for artifacts, consistency of MRI measures, and repositioning; nonsatisfactory scans were repeated. Gd+ lesions on T1-weighted images were counted and marked on the hard copies; T2 lesions were marked on hard copies of the short TE- long TR-weighted images.

Gd+ lesion volume on T1-weighted images and lesion load on T2-weighted images were measured using a computed semiautomated thresholding technique.[15,16] Digital images were analyzed by a group of technicians after comprehensive training to ensure a median intrarater coefficient of variation of 2.5% and interrater variation of <5%. Raters and technicians checked the consistency of lesion identification from hard copy to computer image, and missing lesions were segmented by the original technician. Lesion volume was calculated by multiplying lesion area with slice thickness (5 mm in all cases).

Subject randomization. Subjects were randomized to receive weekly injections of IFNβ-1a 30 μg or 60 μg in a 1:1 ratio. To achieve balance between the treatment groups with respect to baseline EDSS, prestudy relapse rate based on the 3 years before study entry, duration of disease, and age at diagnosis, the minimization procedure[17] was used to assign subjects to the two dose groups; the minimization variables were categorized. Each subject's treatment assignment was individually determined using a phone-in interactive voice response software program developed and administered by the contract research organization. The probability of assigning a subject to a group to correct for existing imbalances was 1.0.[18]

Study drug and intervention. IFNβ-1a (Avonex), a natural sequence, glycosylated, recombinant protein derived from Chinese hamster ovary cell line, was provided by Biogen, Inc. IFNβ-1a was packaged as a lyophilized powder in vials containing either 30 μg or 60 μg per vial. Drug was administered in equal volumes by IM injection once weekly. The 30-μg and 60-μg injections were indistinguishable, and neither the subjects nor medical personnel were aware of the dose of drug administered.

Concomitant medications and dosing modifications. Paracetamol (1 gram 2 hours postinjection, then 1 gram every 4 to 6 hours to a maximum of 4 grams within 24 hours) could be administered for 24 hours following each injection to treat flulike symptoms. In case of intolerable flulike symptoms, the dose of IFNβ-1a could be reduced by 50% for up to 8 consecutive weeks. If symptoms continued, treatment could be interrupted for up to 4 weeks, following which, if the symptoms persisted on retreatment at 50% dosage, the treatment was discontinued. Subjects who prematurely discontinued study treatment were followed as per protocol for the remainder of the study.

Relapses could be treated at the discretion of the investigator, with the following treatment regimen recommended: 1 gram methylprednisolone once daily or 0.50 grams twice daily via IV infusion over 30 to 60 minutes for 3 or 4 days. Additionally, subjects could be given a 2-week tapering course of prednisone or prednisolone. All steroid use was recorded.

Statistical analysis. The primary outcome measure was sustained EDSS progression at 36 months. A sample size of approximately 800 subjects (400 per treatment group) was required to detect a difference between survival distributions for which the cumulative percentage of subjects progressing by 36 months was estimated to be 21% in the 30-μg group and 13% in the 60-μg group, with 80% power, an overall two-sided significance level of 0.05, and 25% dropouts. A subset of subjects had annual MRI. The sample size estimation for the MRI cohort was based on a cumulative logit model that assumes proportional odds. A sample size of approximately 358 subjects was required to detect a log-OR of 1.87 based on the number of Gd+ lesions at 36 months in the 30-μg group compared with the 60-μg group with 80% power, an overall two-sided significance level of 0.05, and 10% dropouts.

All statistical analyses included all randomized subjects, following the intent-to-treat principle. All reported *p* values are based on two-tailed statistical tests, with a significance level of 0.05. No imputation was performed for missing data.

The primary endpoint, the cumulative probability of sustained disability progression, was calculated for each treatment group using the Kaplan–Meier product-limit method. The difference between treatment groups was compared using the Cox proportional hazards model using baseline EDSS score, prestudy relapse rate, duration of disease, age, and sex as preplanned covariates. Covariates that did not reach a significance level of 0.05 were dropped from the Cox proportional hazards model. All time-to-event endpoints were analyzed in a similar way. The treatment difference on the extent of change in EDSS was analyzed using the rank-based analysis of covariance (ANCOVA) models at each predefined time point using baseline EDSS score as the covariate. Annualized relapse rates and steroid courses were compared between doses using the likelihood ratio test for a Poisson model. Percentages of relapse-free patients within months 12, 24, and 36 were estimated using the Kaplan–Meier method and the difference between treatment groups was compared using the log-rank test. For MRI, ANCOVA models based on the ranked outcome were used to assess dose effect on change in T2 lesion volume and volume of Gd+ lesions. For the number of new or enlarging T2 lesions and the number of Gd+ lesions, logistic regression for ordinal variables, which assumes proportional odds, was used to assess the dose effect. The baseline covariates for these models included age, sex, EDSS group, number of Gd+ lesions, logarithm of T2 lesion volume, logarithm of relapse rate, and

Table 1 *Baseline patient demographic and clinical characteristics*

Characteristic	IFNβ-1a 30 μg, n = 402	IFNβ-1a 60 μg, n = 400
Age, y, mean ± SD	36.9 ± 7.9	36.7 ± 7.9
% Women	68	68
% White	97	98
Classification of MS, %		
Relapsing-remitting	85.0	85.5
Relapsing-progressive*	15.0	14.5
Disease duration, y, mean ± SD	6.6 ± 5.6	6.5 ± 5.3
Age at diagnosis, y, mean ± SD	31.3 ± 7.8	31.3 ± 7.8
EDSS score, mean ± SD	3.6 ± 1.0	3.6 ± 1.0
No. (%) of patients with EDSS score:		
≤3.5	235 (58)	228 (58)
4.0 to 5.5	167 (42)	171 (41)
≥6.0	0 (0)	1 (<1)
Prestudy relapse rate,† mean ± SD	1.3 ± 0.6	1.3 ± 0.6

* Patients with early progressive disease who experienced relapses; patients with confirmed progressive disease and no relapses were excluded from the study.

† Relapse rate per year during the 3 years before study enrollment.

IFN = interferon; EDSS = Expanded Disability Status Scale.

logarithm of years since diagnosis. Covariates that were not significant were dropped from the models.

Two preplanned interim analyses of the primary endpoint were conducted at months 12 and 24 after the last patient was enrolled. Each interim analysis was conducted at a significance level of 0.001 and the final analysis at a level of 0.05. This testing strategy preserved an overall 0.05 type 1 error rate.[19] The Data Monitoring Committee reviewed the results of the two interim analyses and did not recommend early termination of the study.

Results. *Subjects.* A total of 802 patients (545 women and 257 men) were randomized; 402 subjects received IFNβ-1a 30 μg and 400 received IFNβ-1a 60 μg IM once weekly. Demographic and baseline clinical disease characteristics are shown in table 1. There were no differences between treatment groups with regard to age, sex, race, duration of MS, EDSS scores, or prestudy relapse rates.

Of 802 subjects randomized, 634 (79%) completed 36 months on study (figure 1). Thirty-two percent of subjects in the 30-μg group and 31% in the 60-μg group discontinued study drug before 36 months. Twenty-one percent of subjects in each dose group discontinued the study before 36 months. The most common reasons for discontinuation of study drug/study were adverse events/intolerance to study drug (13%/4%), perceived worsening disease (10%/8%), and other (9%/9%). There were no significant differences between treatment groups in the reasons for study drug or study discontinuation. Only one difference, the percentage of patients who discontinued study drug owing

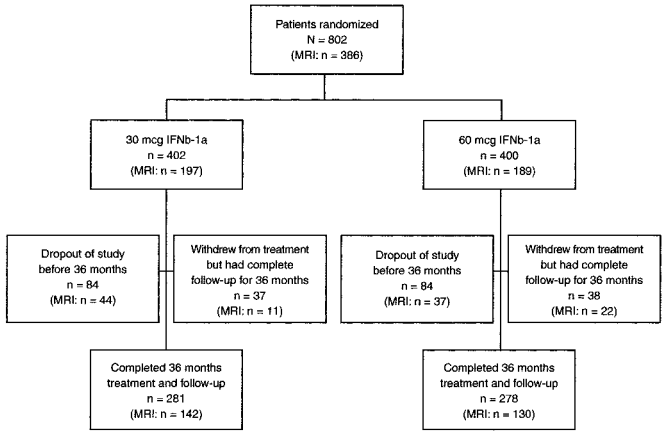

Figure 1. Trial profile. The number of subjects who remained on study for 36 months (≥156 weeks) was 318 and 316 in the 30- and 60-μg treatment groups (MRI: n = 153 and 152). IFN = interferon.

to perceived worsening disease, approached significance, being higher in the 30-μg group (30 μg vs 60 μg, 12% vs 8%; $p = 0.058$).

Clinical efficacy. Figure 2 shows the Kaplan–Meier curve of the cumulative percentage of subjects whose disability progressed for each treatment group. The cumulative rate of sustained disability progression was not different between the IFNβ-1a 30-μg and 60-μg groups (hazard ratio, 0.96; 95% CI, 0.77 to 1.20; $p = 0.73$). The cumulative percentage of subjects with progression by 36 months was 37% in both the IFNβ-1a 30-μg and 60-μg groups. The cumulative percentages of subjects with progression at 24 months were 29% in the 30-μg group and 28% in the 60-μg group, and at 12 months 18% in the 30-μg group and 15% in the 60-μg group.

Figure 3 shows Kaplan–Meier curves of the primary

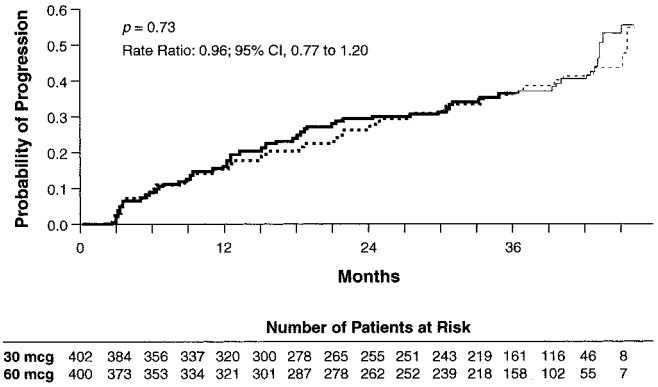

*Figure 2. Kaplan-Meier curve of the cumulative probability of disability progression according to treatment group (all subjects). The 36-month cumulative probability of developing progression in disability was 37% in the interferon (IFN)β-1a 30-μg group and 37% in the IFNβ-1a 60-μg group (*p *= 0.73). The Kaplan–Meier curves become thinner after the 36-month time point to indicate that a high number of patients dropped out of the study after they were on treatment for 3 years and that these data should be interpreted with caution. Dotted line = IFNβ-1a 30 μg, solid line = IFNβ-1a 60 μg.*

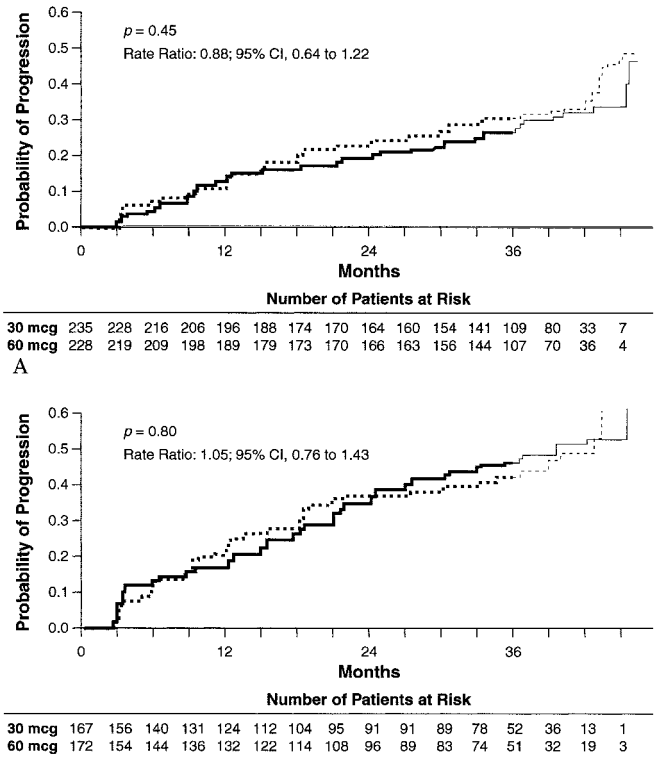

Figure 3. Kaplan-Meier curves of the cumulative probability of disability progression in subjects with baseline Expanded Disability Status Scale (EDSS) scores ≤3.5 (A) and baseline EDSS scores ≥4.0 (B). No differences were observed between interferon (IFN)β-1a 30 μg and IFNβ-1a 60 μg for subjects with baseline EDSS scores ≤3.5 (p = 0.45) or baseline EDSS scores ≥4.0 (p = 0.80). The Kaplan–Meier curves become thinner after the 36-month time point to indicate that a high number of patients dropped out of the study after they were on treatment for 3 years and that these data should be interpreted with caution. Dotted line = IFNβ-1a 30 μg, solid line = IFNβ-1a 60 μg.

endpoint in subgroups, based on baseline EDSS score. No differences were observed between IFNβ-1a 30 μg and IFNβ-1a 60 μg for subjects with baseline EDSS scores ≤3.5 (mean EDSS score 2.8) (hazard ratio, 0.88; 95% CI, 0.64 to 1.22; $p = 0.45$) or baseline EDSS scores ≥4.0 (mean EDSS score 4.5) (hazard ratio, 1.05; 95% CI, 0.76 to 1.43; $p = 0.80$). For subjects with baseline EDSS ≤3.5, the proportions of subjects with disability progression by 36 months were 31% in the IFNβ-1a 30-μg group and 29% in the 60-μg group (figure 3A); by 24 months, 24% of subjects in the 30-μg group and 19% of subjects in the 60-μg group had disability progression. For subjects with baseline EDSS ≥4.0, the proportions of subjects with disability progression by 36 months were 44% in the 30-μg and 47% in the 60-μg group (figure 3B). Subgroup analyses based on presence or absence of Gd-enhanced lesions at baseline also showed no significant difference between IFNβ-1a 30 μg and 60 μg on progression of disability (table 2). At baseline, 15% of patients in the 30-μg group and 14.5% in the 60-μg group were considered to have a progressive form of relapsing MS. There was no difference between IFNβ-1a doses on progression of disability in subjects with relapsing-remitting MS ($p = 0.75$) or relapsing-progressive MS ($p = 0.99$).

A total of 160 patients (75 in the 30-μg group and 85 in the 60-μg group) did not receive the full dose of treatment for ≥6 weeks at any time during the study. A post hoc analysis was performed to rule out the possibility that the data of these patients masked a dose effect in the primary efficacy analysis. There was no difference in the progression of disability observed between the IFNβ-1a 30-μg group and the 60-μg group ($p = 0.68$), if data of these patients were excluded.

No differences were observed between IFNβ-1a 30 μg and IFNβ-1a 60 μg in disability progression defined as a 1.5-point increase in EDSS ($p = 0.58$). Subgroup analyses of this endpoint based on level of disability at baseline also demonstrated no difference between IFNβ-1a doses (baseline EDSS ≤3.5, $p = 0.48$; baseline EDSS ≥4.0, $p = 0.89$). There were also no differences between treatment groups

Table 2 *Results on secondary endpoints**

Secondary endpoint	IFNβ-1a 30 μg, n = 402	IFNβ-1a 60 μg, n = 400	Hazard ratio (95% CI)	*p* Value
Subgroup analysis of primary endpoint, % of patients				
0 Gd+ lesions at baseline	49	43	0.83 (0.51, 1.36)	0.47
≥1 Gd+ lesion at baseline	40	41	0.96 (0.64, 1.43)	0.83
Progression to a 1.5-point increase in EDSS, % of patients	27	27	0.93 (0.71, 1.21)	0.58
Progression to an EDSS ≥4.0, % of patients	23	24	1.00 (0.69, 1.45)	0.99
Progression to an EDSS ≥6.0, % of patients	18	19	0.93 (0.68, 1.29)	0.68
Progression on the 9HPT, % of patients	17	17	1.00 (0.71, 1.42)	0.99
Change in EDSS	n = 273	n = 271		
Mean ± SEM	0.36 ± 0.07	0.33 ± 0.07	NA	1.0
Median (range)	0.5 (−2.5, 4.5)	0.5 (−4.0, 3.5)		

* Over 36 months.

IFN = interferon; EDSS = Expanded Disability Status Scale; Gd+ = gadolinium-enhanced lesions; 9HPT = Nine-Hole Peg Test.

Table 3 *Annualized relapse rates, IV steroid use, and percentages of relapse-free patients**

Variable	IFNβ-1a 30 μg, n = 402	IFNβ-1a 60 μg, n = 400	*p* Value
Relapse rate			
Prestudy mean	1.3	1.3	
Annualized relapse rate over study	0.77	0.81	0.33
Annualized IV steroid use	0.68	0.70	0.52
Percentage of relapse-free patients†			0.83
Within 6 mo	67	66	
Within 12 mo	53	49	
Within 24 mo	33	33	
Within 36 mo	23	23	
Median time to first relapse, d	402	347	

* Relapse rates and courses of steroid were analyzed by the Likelihood ratio test; relapse-free rates derived from a Kaplan-Meier analysis.
† Relapse free from enrollment through 6, 12, 24, and 36 months.

IFN = interferon.

on relapse rate ($p = 0.33$), percentage of relapse-free patients ($p = 0.83$), and the proportion of patients who received IV steroids for relapses ($p = 0.52$) (table 3). No other clinical endpoints evaluated demonstrated a significant dose effect (see table 2).

MRI. Subjects. Of 386 patients who received annual MRI scans, 197 were randomized to receive IFNβ-1a 30 μg and 189 to receive IFNβ-1a 60 μg. A total of 305 subjects (79%) completed 36 months on study (see figure 1). There were no significant differences between treatment groups of the MRI cohort in the reasons for discontinuation of study or study drug. The two treatment groups were similar with respect to baseline MRI characteristics (table 4).

Gd-enhanced lesions. The mean number of Gd+ lesions was not different between the IFNβ-1a 30-μg and IFNβ-1a 60-μg groups at month 12 ($p = 0.99$), month 24 ($p = 0.67$), or month 36 ($p = 0.76$) (figure 4A). With both doses of IFNβ-1a, similar reductions in the number of Gd+ lesions were observed at all time points. For example, the reduction from baseline in mean number of Gd+ lesions at month 36 was 78% in the 30-μg group and 64% in the 60-μg group ($p = 0.76$, 30 vs 60 μg).

Measuring the volume of enhancing lesions ensures that large lesions are not equated with small lesions in the process of counting the number of enhancing lesions. No differences between IFNβ-1a 30 μg and IFNβ-1a 60 μg in mean volume of Gd+ lesions were observed at month 12 ($p = 0.92$), month 24 ($p = 0.79$), or month 36 ($p = 0.58$) (figure 4B). In both doses of IFNβ-1a, the mean volume of Gd+ lesions from baseline was similarly reduced throughout the study; at month 36, IFNβ-1a 30 μg showed a 75% reduction and IFNβ-1a 60 μg a 68% reduction ($p = 0.58$, 30 vs 60 μg).

T2-hyperintense lesions. No differences were observed between IFNβ-1a 30 μg and IFNβ-1a 60 μg on change from baseline in T2-hyperintense lesion volume at month 12 ($p = 0.71$), month 24 ($p = 0.97$), or month 36 ($p = 0.52$). The median change in T2 lesion volume at month 12 was -450 mm^3 (range -16034.8, 13544.7) in the 30-μg group and -377 mm^3 (range -17814.7, 13193.5) in the 60-μg group. By month 36, the median reductions in T2 volume were smaller, with -198 mm^3 (range -17298.1, 18642.1) and -26 mm^3 (range -30265.6, 43168.5) observed in the IFNβ-1a 30-μg and 60-μg groups ($p = 0.52$, 30 vs 60 μg).

The number of new or enlarging T2 lesions is a measure of the cumulative individual pathologic events that occurred since the previous scan was performed. An analysis of the number of new or enlarging T2 lesions at each year compared with baseline was performed and is shown in figure 5. There were no differences between 30 μg and 60 μg in number of new or enlarging T2 lesions compared with baseline at month 12 ($p = 0.30$), month 24 ($p = 0.35$), or month 36 ($p = 0.11$). Table 5 summarizes the mean

Table 4 *Baseline MRI characteristics*

Characteristics	IFNβ-1a 30 μg	IFNβ-1a 60 μg
No. of subjects in annual	197	189
MRI cohort		
Gd+ lesion number		
n	195	187
Mean	3.0	2.3
SD	4.93	3.49
Gd+ lesion volume, mm^3		
n	195	187
Median	64.6	40.4
Range	0–4,003.7	0–4,003.7
T2 lesion volume, mm^3		
n	195	187
Median	15364.9	12963.5
Range	399.6–87,418.8	169.5–151,061.5
T1 lesion volume, mm^3		
n	182	174
Median	988.8	855.6
Range	0–14,606.1	0–19,897.2

IFN = interferon; Gd+ = gadolinium-enhanced.

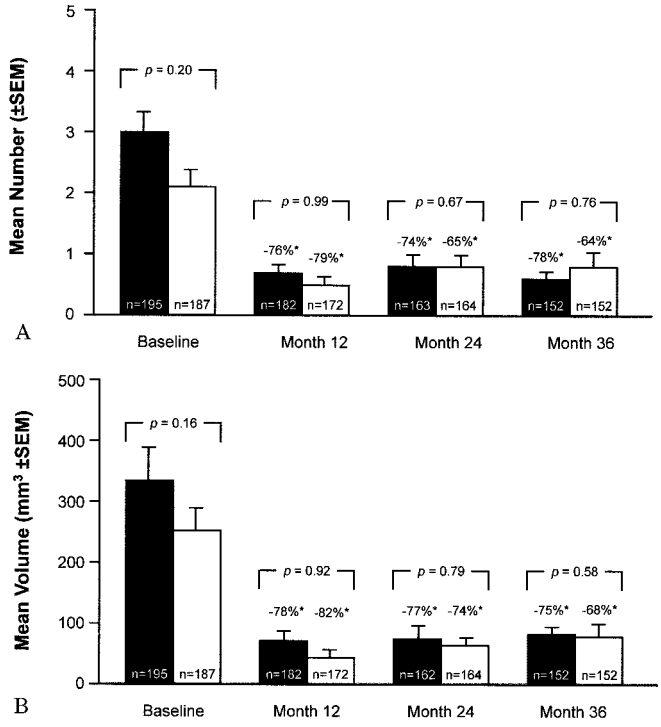

*Figure 4. Mean number (A) and volume (B) of gadolinium (Gd+) lesions (A). Mean number and volume of Gd+ lesions were not different between interferon (IFN)β-1a 30 μg and IFNβ-1a 60 μg at any time point. Black bars = IFNβ-1a 30 μg, white bars = IFNβ-1a 60 μg. *Percent reduction vs baseline.*

number of new or enlarging T2 lesions at each year; *p* values are based on comparisons of lesions at each year with those of the previous year (e.g., month 36 scan compared with month 24 scan). There were no differences between IFNβ-1a 30 μg and 60 μg in the number of new or enlarging T2 lesions, except for month 36 compared with month 24 ($p = 0.004$). At month 36, the proportion of subjects with 0 or 1 new or enlarging T2 lesions was higher in the 60-μg group (59%) than in the 30-μg group (35%). In contrast, the proportion of subjects with ≥4 new or enlarging T2 lesions was lower in the 60-μg group (20%) than in the 30-μg group (30%).

T1-hypointense lesions. No differences were observed between IFNβ-1a 30 μg and IFNβ-1a 60 μg on change from baseline in T1-hypointense lesion volume at month 36 ($p = 0.41$). The median change from baseline to month 36 in T1 lesion volume was 190 mm^3 in the 30-μg group (a 19% increase from baseline) and 85 mm^3 in the 60-μg group (a 10% increase from baseline).

Safety. Both doses of IFNβ-1a were well tolerated. Adverse events that led to discontinuation of study drug or withdrawal from the study were reported by 45 (11%) subjects in the IFNβ-1a 30-μg group and 64 (16%) subjects in the 60-μg group. The most frequent adverse events that led to withdrawal of study drug or study discontinuation in the IFNβ-1a 30-μg and 60-μg groups included symptoms of MS (3% and 6%), flulike syndrome (2% and 7%), and depression (2% and 3%).

Overall, the safety profile of IFNβ-1a was consistent with that observed in other clinical studies and from postmarketing surveillance. The incidence and severity of adverse events known to be associated with the administration of IFNβ products were similar between the two groups. Adverse events for which the incidences differed by ≥5% between dose groups were flulike symptoms (92% vs 85%, $p = 0.001$) and muscle weakness (20% vs 14%, $p = 0.039$), which occurred more frequently in the 60

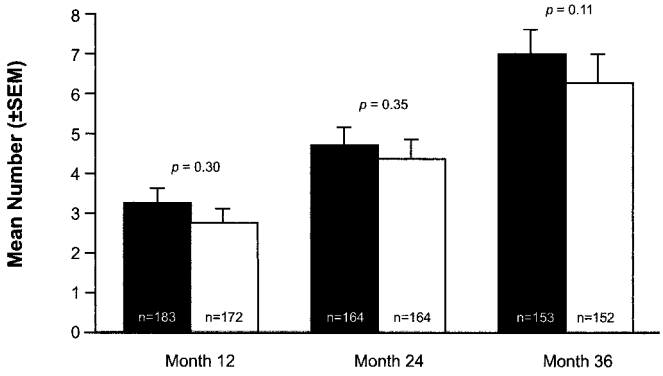

Figure 5. Mean cumulative number of new or enlarging T2 lesions at months 12, 24, and 36 compared with baseline. No significant differences between interferon (IFN)β-1a 30 μg and IFNβ-1a 60 μg in mean number of new or enlarging T2 lesions were observed at any time point. Black bars = IFNβ-1a 30 μg, white bars = IFNβ-1a 60 μg.

Table 5 *Number of new or enlarging T2 lesions per year*

Time point	IFNβ-1a 30 μg	IFNβ-1a 60 μg	*p* Value*
Month 12, n (%)			
0	46 (25)	44 (26)	
1	40 (22)	48 (28)	
2–3	44 (24)	39 (23)	
≥4	53 (29)	41 (24)	
n	183	172	
Mean ± SEM	3.3 ± 0.34	2.8 ± 0.37	0.30
Month 24, n (%)			
0	44 (27)	56 (34)	
1	39 (24)	37 (23)	
2–3	40 (24)	38 (23)	
≥4	41 (24)	33 (20)	
n	164	164	
Mean ± SEM	2.5 ± 0.25	2.3 ± 0.27	0.15
Month 36, n (%)			
0	35 (23)	59 (39)	
1	38 (25)	29 (19)	
2–3	34 (22)	35 (23)	
≥4	46 (30)	29 (20)	
n	153	152	
Mean ± SEM	3.2 ± 0.33	2.9 ± 0.45	0.004

* *p* Values are based on comparisons of number of new or enlarging lesions at each year with measurements during the previous year (e.g., month 36 compared with month 24).

IFN = interferon.

μg group than in the 30 μg group, and headache (36% vs 28%, $p = 0.015$) and accidental injury (22% vs 16%, $p = 0.058$), which occurred more frequently in the 30 μg group than in the 60 μg group. There was no significant difference in the number of subjects who did not receive the full dose as per protocol owing to adverse events or intolerability.

The incidence of self-reported depression was similar between the two treatment groups (35% in the 30-μg group and 31% in the 60-μg group). The percentage of patients considered depressed according to the Beck Depression Inventory was similar between the two dose groups at each time point, as was the overall incidence of patients considered depressed at any time after baseline (English language questionnaire, 9% vs 10%, French language questionnaire, 10% vs 10%, for 30 μg and 60 μg). The incidences of suicidal tendencies, suicide attempts, and manic-depressive reactions were all <1% in both treatment groups.

There were no significant differences between the two dose groups in the proportions of subjects who had clinically notable changes in laboratory values. There were no differences between dose groups in the incidence of serious adverse events. Two deaths were reported; one subject in the 30-μg group died during the study as a result of drowning and one subject in the 60-μg group died after the study ended from cervical carcinoma. The proportions of patients who had NAB (titers ≥ 20) at any time during the study were 2.3% in the 30-μg group and 5.8% in the 60-μg group.

Discussion. The results of the current study showed that there was no difference between IFNβ-1a 30 μg and IFNβ-1a 60 μg IM once weekly in the rate of accumulation of physical disability in subjects with relapsing MS. In addition, there were no differences or trends between doses on any of the clinical secondary endpoints, including subgroup analyses of the primary endpoint based on EDSS, presence of Gd-enhanced lesions, and type of relapsing MS at baseline. There were no differences between IFNβ-1a 30 μg and 60 μg in producing substantial reductions from baseline in all MRI measures at all time points. Only one MRI parameter at one time point, number of new or enlarging T2 lesions at month 36 compared with month 24, showed a difference between the IFNβ-1a 30- and 60-μg doses ($p = 0.004$). Counting of new and enlarging T2 lesions is the most sensitive of standard MRI measures of inflammatory disease activity and was the only one suggesting some dose effect in the PRISMS 2-year analysis.[6] Counting new and enlarging T2 lesions on a yearly basis detects more lesions than comparing 2- or 3-year scans with baseline.[20] Therefore, this finding may indicate a minor dose effect. However, it is difficult to explain why this effect occurs only during the third and not during the first and especially the second year of continuing IFN treatment (see table 5). Thus, another explanation is that this effect is due to chance, which is a distinct possibility when multiple comparisons are made.

Although it would have been desirable to have performed a placebo-controlled study to determine the absolute clinical efficacies of the two doses, in view of ethical and practical difficulties, no placebo control was used.[11] The clinical benefit of IFNβ in relapsing MS has already been demonstrated,[1,5,6] and the use of a placebo in a study with a projected treatment duration of 3 years creates ethical concerns. The efficiency of blinding was not formally analyzed in the current study. However, this study, besides using a "double physician design" with one treating and one examining neurologist (the latter was not involved in any issues of daily patient care), did not compare against placebo, and there were only small differences in the adverse events observed between the two treatment groups. Small differences in adverse events between treatment groups would help maintain blinding to a greater extent than in published placebo-controlled studies. In addition, if blinding was compromised, we would have expected to see a difference between doses because there most likely would have been a physician and patient bias for the higher dose to be more effective than the lower dose.

The current study was specifically designed to determine whether IFNβ-1a 60 μg once weekly was superior to IFNβ-1a 30 μg once weekly. We compared the current results with those of the phase III trial of IFNβ-1a, in which the 30-μg dose was compared with placebo, to determine whether the magnitude of treatment effects is consistent between the two studies. Owing to differences in entry criteria based on EDSS scores at baseline, subjects in the current study had more severe physical disability (mean EDSS = 3.6) than those in the phase III trial of IFNβ-1a vs placebo, which used baseline EDSS ≤3.5 as an entry criterion (mean EDSS = 2.4).[1] In the subset of subjects with baseline EDSS scores ≤3.5 (mean EDSS = 2.8) in the current study, the proportion of subjects with progression of disability by 24 months in the IFNβ-1a 30-μg group (24%) was similar to that observed in the phase III study. In the phase III study, 22% of subjects (all had EDSS scores ≤3.5) showed progression of disability by 2 years, compared with 35% of placebo subjects (table 6).[1] Overall, IFNβ-1a 30 μg produced a 74% reduction from baseline in the mean number of Gd+ lesions at month 24 in the current study, which is similar to the 75% reduction observed in the IFNβ-1a phase III trial.[1,21] Reductions from baseline in volume of Gd+ lesions were 71% in the phase III trial and 77% in the current study.[1] Although the validity of comparisons between studies is limited, this analysis suggests that both the 30 μg and 60 μg once-weekly doses showed a similar treatment effect to that observed in the placebo-controlled phase III study, and thus that they are equally effective in slowing the accumulation of disability in patients with relapsing MS.

Overall, the subgroup of subjects with EDSS scores ≥4.0 at baseline had greater progression of disability compared with those with baseline EDSS ≤3.5, which is to be expected given the bimodal distribution of the EDSS. Based on a post hoc analysis

Table 6 *Comparison of disability progression* and percentage of relapse-free patients using interferon β-1b and interferon β-1a products compared on a weekly microgram dose basis*

Product	Dose regimen	N	Weekly dose, μg	Years studied	Baseline EDSS, mean (SD)	Cumulative progression,† %		Reduction in progression, %	Relapse-free patients, %
						Treatment	Placebo		
IFNβ-1a	30 mcg IM once weekly[1]	158	30	2	2.4 (0.8)	22	35	37.2‡	35
(Avonex)	30 mcg IM once weekly	235	30	2	2.8 (0.57)	24	NA	NA	
	(baseline EDSS ≤3.5)			3		31	NA	NA	
	30 mcg IM once weekly	402	30	2	3.6 (1.03)	29	NA	NA	33
	(all subjects)			3		37	NA	NA	23
	60 mcg IM once weekly	228	60	2	2.9 (0.56)	19	NA	NA	
	(baseline EDSS ≤3.5)			3		29	NA	NA	
	60 mcg IM once weekly	400	60	2	3.6 (1.00)	28	NA	NA	33
	(all subjects)			3		37	NA	NA	23
IFNβ-1a	22 mcg SC three times per	189	66	2	2.5 (1.2)	30	39	23.1	27
(Rebif)	week[6,9,22]	167		4		49	NA	NA	14
	44 mcg SC three times per	184	132	2	2.5 (1.3)	27	39	30.8‡	32
	week[6,9,22]	167		4		44	NA	NA	19
IFNβ-1b	50 mcg SC every other day[5,23]	125	175	2	2.9 (1.1)				21
(Betaseron)				3		28§	28§	0	18
				5		47	46	0	
	250 mcg SC every other day[5,23]	124	875	2	3.0 (1.1)				31
				3		20§	28§	28.6	22
				5		35	46	25.5	

* Confirmed disability defined as an increase from baseline of EDSS score ≥1.0 to be maintained for a minimum of 3 months[5,6,9,22,23] or 6 months.[1]

† Kaplan-Meier estimate.

‡ $p < 0.05$.

§ Percentage of patients who progressed within the first 3 years.

EDSS = Expanded Disability Status Scale; NA = not applicable.

of data from another study,[6] it had been suggested that a higher dose of IFNβ-1a has significant advantages over lower doses in patients with a baseline EDSS ≥4.0. However, in our study, IFNβ-1a 30 μg and 60 μg once weekly were equally effective in the subgroup of subjects who had higher EDSS scores at baseline (EDSS ≥ 4.0). Hence, the efficacy of IFNβ-1a 30 μg IM was not limited to subjects with lower EDSS scores, and furthermore, more disabled patients did not require higher doses.

There were no differences between doses in annualized relapse rates or the percentages of patients who remained relapse free at any yearly time point during the course of the study. The median time to first relapse ranged from 12 to 14 months and was similar between the two dose groups. The percentages of relapse-free patients with IFNβ-1a IM are similar to those from the phase III studies of IFNβ-1b and IFNβ-1a SC (see table 6).[5,6] In addition, the median time to first relapse with IFNβ-1a IM compares favorably with those observed with IFNβ-1b and IFNβ-1a SC.[5,22] For IFNβ-1b, the median time to first relapse was 153 days (5.5 months) in the placebo group, 180 days (6.4 months) in the 50-μg group, and 295 days (10.5 months) in the 250-μg group.[5] For IFNβ-1a SC, the median time to first relapse was 135 days (4.5 months) in the placebo group, 228 days (7.6 months) in the 22-μg group, and 288 days (9.6 months) in the 44-μg group.[22] In addition, the annual rate of IV steroid use was similar between dose groups. The rates of patient self-reported relapses were slightly higher than those calculated for IV steroid use, a surrogate marker for severe relapses. This effect has also been observed in other studies. For example, in the PRISMS study,[6] the mean number of relapses per patient (evaluated according to the protocol definition) was higher than the mean number of courses of IV steroid treatment. This difference is to be expected because not all relapses are treated with steroids.

Based on the results of our study and those from multiple-dose studies with IFNβ-1b and IFNβ-1a SC, we hypothesize that there may be a dose-response effect below a certain threshold dose and a ceiling at higher doses of IFNβ products.[5-8] In the phase III trial of IFNβ-1b,[5] a dose effect was observed for the primary endpoint of relapse rate, with IFNβ-1b 250 μg more effective than 50 μg ($p = 0.0086$). In the

placebo-controlled part of the phase III trial of IFNβ-1a SC,[6] both 22 μg and 44 μg demonstrated significant effects on many primary and secondary endpoints vs placebo; however, a significant difference between doses was only observed on one MRI endpoint: the number of active lesions.[6] Table 6 presents comparative data on the progression of disability reported from all phase III studies of IFNβ products in which disability was included as an endpoint. Although on a microgram basis the weekly doses of the different products differ almost 30-fold, there is no obvious dose effect concerning this endpoint.

Both doses of IFNβ-1a were well tolerated, with a safety profile consistent with that observed in other clinical studies with the same product,[1,4] and from postmarketing surveillance. Previous multiple-dose studies with IFNβ-1b and IFNβ-1a SC have shown that higher doses produced higher incidences of selected adverse events.[5,6] In the current study, flulike symptoms and muscle weakness were significantly more frequent in the IFNβ-1a 60-μg group than the IFNβ-1a 30-μg group. The rates of discontinuation from study drug (32% vs 31%) and discontinuation from the study (23% vs 23%) over the study duration (time until all patients were followed for 36 months) were similar between the 30-μg and 60 μg-groups. The total sample size was chosen to allow for 25% of subjects to withdraw from the study prematurely, and hence, discontinuations from the study (23%) were within this predicted dropout rate. The number of patients on study dropped again after 36 months because a proportion of investigators and patients simply stopped follow-up after completing 3 years on study.

The current study was not designed to determine whether more frequent dosing of IFNβ-1a is better than once-weekly dosing. However, the optimal weekly dose of IFNβ-1a may be different for different dosing schedules (three times versus once weekly) and for different routes of administration (SC vs IM). Based on the recently published results of the 4-year PRISMS extension study,[9] it has been suggested that clinical benefit of higher IFNβ doses may be more prominent with long-term observation. However, in the current study, which is the largest study completed to date in relapsing MS, a 3-year period of observation under double-blind conditions did not reveal even a weak trend for superior clinical efficacy of the higher dose. The sustained efficacy of both doses in the current study may be related to the low incidence of NAB associated with IFNβ-1a or its different route of administration; NAB have been shown to reduce the clinical efficacy of IFNβ.[9,23] The incidence of NAB observed at any time during this 3-year study (2.3% to 5.8%) was substantially lower than those reported for IFNβ-1b (45.0% to 47.0% at any time during 24 months of treatment) and IFNβ-1a SC (12.5% to 23.8% at the end of 24 months of treatment),[5,6] although studies differ with regard to the technique used to measure NAB. The issue of IFNβ dose frequency and the long-term effects of NAB on clinical efficacy require further study.

Appendix

The European IFNβ-1a (Avonex) Dose-Comparison Study Investigators. *Investigators.* **Austria**: Primary W. Kristoferitsch, Examining Dr. Schrieber, Treating Dr. Schlederer (Vienna). **Belgium**: Primary P. Seeldrayers, Examining Dr. Piette (Brussels). **Cyprus**: Primary S. Papacostas, K. Kyriallis, Examining Dr. Pantzaris (Nicosia). **France**: Primary B. Brochet, Treating A. Gayou, Examining M. Rouanet, F. Rouant (Bordeaux); Primary C. Confavreux, Treating G. Riche, S. Blanc, Examining J. Achiti, C. Magnier, P. Aubertin (Lyon); Principal investigator M. Clanet, Treating C. Mekies, D. Brassat, C. Thalamas, C. Vuilleman, Examining A. Senard, G. Lau (Toulouse); Primary P. Cesaro, Treating F. Degos (Creteil); Primary G. Defer, Treating S. Schaeffer (Caen); Primary G. Edan, Treating Dr. de Marco, Examining V. Cahagne, S. Belliard (Rennes); Primary O. Lyon-Caen, Treating B. Stankoff, Examining C. Lubetzki, I. Arnulf, P. Damier (Paris); Primary J. Pelletier, Treating D. Tamman, Examining L. Suchet, A. Dalecky (Marseille); Primary L. Rumbach, Treating Dr. Moulin, Examining E. Berger (Besançon); Primary E. Roullet, Treating D. Pez, O. Heinzlef, Examining P. Lecanuet (Paris); Primary P. Vermersch, Examining A. Engles (Lille). **Germany**: Primary R. Dengler/F. Heidenreich, Examining Dr. Lindert, Dr. Koehler, Dr. Windhagen, Treating Dr. Steiner (Hannover), Primary R. Zschenderlein, Treating J. Luenemann, H. Gelderblom, N. Kassim (Berlin); Primary B. Storch-Hagenlocher, Examining Dr. Koerner, Treating Dr. Vogt-Schaden, Dr. Stingle, Dr. Storch-Hagenlocher (Heidelberg); Primary M. Sailer, Examining Dr. Matzke (Magdeburg); Primary R. Hohlfeld, Treating Dr. Dose (Munich); Primary C. Weiler, K. Kunze, C. Heesen (Hamburg); Primary P. Bamborschke, Examining H. Petereit, Treating Dr. Liu, Dr. Nolden (Cologne); Primary F. Grunwald, Co-investigators Dr. Menck, Dr. Grupe (Seesen); Primary H.-P. Hartung, P. Rieckmann, Examining Dr. Weilbach, Dr. Flachenecker, Treating Dr. Chan, Dr. Maurer (Würzburg). **Netherlands**: Primary J. De Keyser, Examining G. Zwanniken, Treating Dr. Azordrager (Groningen). **Spain**: Primary X. Montalban, Treating Dr. Nos (Barcelona); Primary O. Fernández, Treating J.A. Tamayo, Examining F. Romero (Malaga); Primary T. Arbizu, Treating Dr. Martínez-Yélamos, Examining Dr. Martin, Dr. Casado (Barcelona). **Sweden**: Primary M. Sandberg-Wollheim, Co-investigator R. Ekberg (Lund). **Switzerland**: Primary L. Kappos, Treating Dr. N. Achalbedaschwili, Dr. D. Schött, Examining Dr. C. Lienert, Study nurse E. Luthringer (Basel). **United Kingdom**: Primary D. Bates, Co-investigator M. Westwood (Newcastle); Primary M.J. Campbell, Examining Dr. Burrows (Bristol); Primary R. Capildeo, Examining Dr. Abbas, Dr. Riaz (Orsett); Primary A. Compston, Co-investigator I. Bjornson (Cambridge); Primary C.P. Hawkins, Co-investigators S. Wetherby, S. Ellis (Stoke-on-Trent); Primary S. Hawkins, Co-investigator M. Duddy (Belfast); Primary D.L. McLellan (Southampton); Primary S. Wroe, Co-investigator K. Powell (Ipswich); Primary C.A. Young, Co-investigator Dr. Lecky (Liverpool). *Liaison committee.* M. Clanet (Chair), H.-P. Hartung, R. Hohlfeld, L. Kappos, E.W. Radue (Basel), P. Rieckmann, M. Sandberg-Wollheim. *Data Monitoring Committee.* C. Polman (Chair; Amsterdam), J. Kesselring (Valens), A. Thompson (London), H. Wekerle (Planegg Martinsried), J. Whitehead (Reading). *Sponsor.* A. Bains, E. Butler, M. Kooijmans-Coutinho, E.C. Tsao, J. Alam, A.W. Sandrock, K. White (Biogen, Inc., Cambridge, MA). *Central MRI evaluation center.* E.W. Radue, L. Kappos, P. Freitag, E. DeBattista, C. Albrecht, D. Welti (Basel); G. Székely (Zurich). *Data coordinating center.* D. Anderson, S. Liddiard, R. Keane (Quintiles).

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