Phase III Dose-Comparison Study of Glatiramer Acetate for Multiple Sclerosis

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Objective: To evaluate the safety, tolerability, and efficacy of glatiramer acetate (GA) 40mg compared to a 20mg dose.
Methods: Patients with multiple sclerosis (MS) with $\geq$1 documented relapse in 12 months prior to screening, or $\geq$2 documented relapses in 24 months prior to screening, and Expanded Disability Status Scale (EDSS) score 0 to 5.5 were enrolled. Patients were evaluated at screening, baseline, and at months 1, 2, 3, 6, 9, and 12. Primary endpoint was rate of confirmed relapses observed during 12-month study. Analysis was by intent-to-treat.
Results: A total of 1,155 patients randomized to GA 20mg (n = 586) or 40mg (n = 569). The groups were well-matched at baseline on demographic, clinical, and magnetic resonance imaging (MRI) characteristics. The primary endpoint was similar in both groups (relative risk [RR] = 1.07; 95% confidence interval [CI], 0.88–1.31; $p = 0.486$) with mean annualized relapse rates (ARRs) of 0.33 for the 20mg group, 0.35 for the 40mg group, and 0.27 for patients from both groups who completed the entire 1-year treatment. A total of 77% of patients remained relapse-free in both groups. Both groups showed a reduction in mean number of gadolinium-enhancing and new T2 lesions over time with trend for faster reduction in the first trimester with the 40mg dose compared with 20mg dose. Both doses were well-tolerated with a safety profile similar to that observed in previous studies of 20mg GA.
Interpretation: In relapsing-remitting MS patients, both the currently-approved GA 20mg and 40mg doses were safe and well-tolerated, with no gain in efficacy for the higher dose.

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Glatiramer acetate (GA) is 1 of 7 disease modifying agents currently-approved to treat relapsing-remitting multiple sclerosis (RRMS). In 3 double-blind placebo-controlled trials, subcutaneous (sc) GA at a once-daily 20mg dose significantly reduced relapse frequency, magnetic resonance imaging (MRI) disease activity, and burden.[1–3] Additionally, it has been shown that GA 20mg is able to significantly reduce the rate of developing clinically definite multiple sclerosis (MS) and MRI activity in patients with a first demyelinating event suggestive of the disease.[4] The efficacy of GA in MS is thought to result from induction of immune tolerance; ie, reduced T cell proliferation and a shift to a T helper 2 (Th2) cytokine profile.[5] Reaching immune tolerance could depend on the dose and the frequency of administration of the mixture of polypeptides of GA, suggesting that higher doses of GA may be more efficacious in influencing disease course.

Studies of GA administered by sc injection in RRMS used a 20mg daily dose, the currently-approved regimen. Small early studies provided little data regarding doses other than 20mg daily.[6] A phase II dose-comparative study suggested 40mg given sc once daily was well tolerated and showed a trend for an increased effect on clinical and MRI activity in RRMS compared to the marketed dose.[7] Based on these initial results, a double-blind, placebo-controlled trial was undertaken to determine whether a dose of 40mg is more effective than the currently available dose of 20mg in reducing relapse rate, MRI activity, and the accumulation of white matter lesion burden in patients with RRMS.

Patients and Methods

Patients

Enrollment started in September 2006 and was completed in May 2007. Key inclusion criteria included: (1) age 18–55 years

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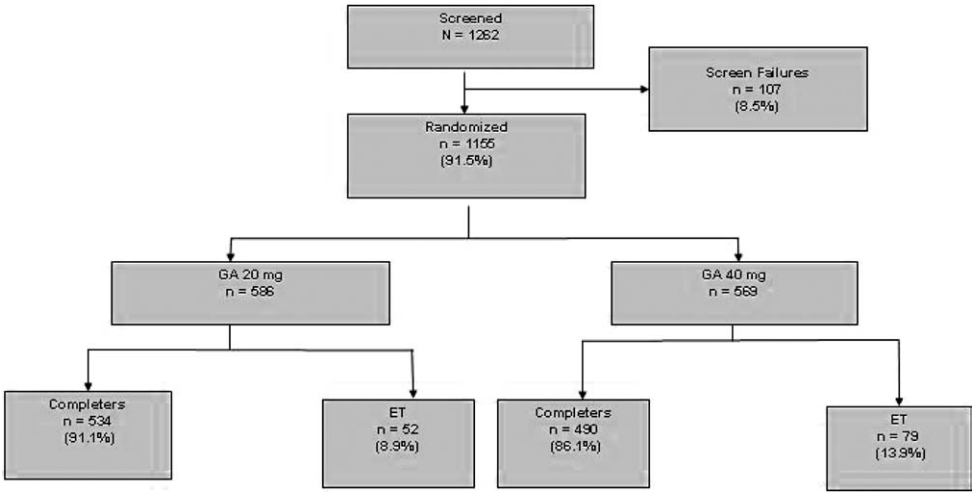

FIGURE: Patient disposition during the course of the study. Of patients on GA 20mg and on GA 40mg, 91% and 86% completed the study, respectively, while 9% and 14%, respectively, were ET. ET = terminated early from the study; GA = glatiramer acetate.

inclusive; (2) a diagnosis of RRMS[8,9]; (3) Expanded Disability Status Scale (EDSS) score 0–5.5; and (4) at least 1 documented relapse in the 12 months prior to screening, at least 2 documented relapses in the 24 months prior to screening, or 1 documented relapse between 12 and 24 months prior to screening with at least 1 documented gadolinium-enhancing (GdE) lesion on an MRI scan performed within 12 months prior to screening. Key exclusion criteria included: (1) a clinical relapse or steroid treatment within 30 days prior to screening; (2) previous treatment with immunomodulators within the last 2 months; or (3) immunosuppressive treatments within the last 6 months and previous use of GA or natalizumab. The protocol and consent documents were approved by the institutional review boards and ethics committees of the participating centers. Patients provided written informed consent prior to undergoing any study-related procedures. This study is registered, as number NCT00337779.

Treatment

Patients were treated with a daily sc dose of a single prefilled syringe of either GA 20mg or GA 40mg. Labeling and packaging for the doses were identical.

Design

The trial was a multicentre, randomized, double-blind, parallel-group, dose-comparison study lasting 12 months. The study was conducted in 20 countries worldwide, with a total of 136 sites. The randomization procedure employed a 1:1 assignment ratio, and a scheme using blocks stratified by center.

For trial purposes, a month was defined as 30 $\pm$ 4 days. At each study site, a treating neurologist was responsible for the overall medical management of patients including safety monitoring. An examining neurologist performed a standardized neurological examination, and assessed Timed 25-Foot Walk (T25FW), Functional System and EDSS scores (Neurostatus, L. Kappos, MD, Department of Neurology, University Hospital, Basel, Switzerland) at scheduled and unscheduled visits. All patients underwent evaluations including vital signs (blood pressure, pulse, and temperature), adverse events, and concomitant medications, at screening (month −1), baseline (month 0), months 1, 2, 3, and every 3 months thereafter; and safety laboratory assessments (hematology, serum biochemistry, and urinalysis) at screening, baseline, and months 1, 3, 6, 9, and 12. Neurological examinations were performed every 3 months and MRI scans at baseline and month 12. A "frequent MRI cohort" of patients from 38 sites performed additional scans at months 1, 2, 3, 6, and 9. After completion of 12 months of double-blind treatment, both treatment groups were assigned to open label treatment with GA 40mg for an additional 12 months.

A relapse was defined as the appearance of 1 or more new neurological abnormalities or the reappearance of 1 or more previously observed neurological abnormalities. An event was counted as a relapse only when the subject's symptoms were accompanied by objective changes in the examining neurologist's assessment corresponding to an increase of at least 0.5 points on the EDSS, 1 grade in 2 or more Functional System scores, or 2 grades in 1 Functional System score. Isolated changes in bowel, bladder, and cognitive function did not qualify as relapses. The treating neurologist determined whether the change in symptoms qualified as an on-study relapse, which could be treated at the discretion of the treating neurologist with a standard 1g dose of intravenous (iv) methylprednisolone for a maximum 5 consecutive days.

The Steering Committee supervised the conduct of the study. An independent Data Monitoring Committee met 3 times during the trial, in person or via teleconference, to review study conduct as well as blinded safety data. Unblinded safety data were provided to the Data Monitoring Committee upon their request by an unblinded statistician not directly involved in the trial. Serious adverse events were reported to the Data Monitoring Committee members on a monthly basis.

Outcome Measures

The primary efficacy outcome measure was the rate of confirmed relapses during the 12-month double-blind phase.

Secondary outcome measures included, in a hierarchical order for statistical analysis, the cumulative number of GdE lesions at months 3, 6, 9, and 12 (frequent MRI cohort), and the number of new T2 lesions at month 12 compared to baseline scan. Rate of brain volume changes defined as the percentage brain volume changes from baseline to month 12 was an exploratory endpoint.

MRI Scanning and Analysis

The Neuroimaging Research Unit in Milan, Italy, served as the MRI analysis centre (MRI-AC). Before a site could enroll study participants they were required to image a volunteer patient with definite MS twice with repositioning according to a strict study imaging protocol using imagers with minimum field strength of 1.0T. Conventional or fast spin echo (repetition time [TR] = 2200–3000ms, echo time [TE] = 15–50/80–120ms, echo train length = 4–6, slice thickness = 3mm, and contiguous axial slices = 44) sequences were used to obtain proton density and T2-weighted images. Conventional spin echo T1-weighted images (TR = 600–650ms, TE = 10–20ms) with the same scan geometry were obtained 5 minutes after injection of 0.1mmol/kg of gadolinium. A series of axial, coronal, and sagittal images was obtained to create an axial reference scan for subsequent careful repositioning of each patient at the follow-up session. Axial slices were positioned to run parallel to a line joining the most inferioanterior and inferioposterior parts of the corpus callosum.

Image quality was reviewed at the MRI-AC using predetermined criteria. The identification of GdE and T2-hyperintense lesions was done by consensus of 2 experienced observers. The number of total and new GdE lesions and new T2-hyperintense lesions were counted. The identified lesions were then outlined by trained technicians using a semiautomated segmentation technique based on local thresholding (Jim 4.0; Xinapse System, Leicester, UK) and lesion volumes were calculated automatically. Percentage brain volume changes and cross-sectional normalized brain volumes were measured on postcontrast T1-weighted images, with Structural Image Evaluation of Normalized Atrophy (SIENA) software and a cross-sectional method (SIENAX) (available from the FMRIB Software Library, Oxford University, Oxford, UK; http://www.fmrib.ox.ac.uk/analysis/research/siena/siena), as described elsewhere.[10]

Statistical Analysis

A total of 980 patients equally randomized to the 2 study arms was expected to provide 90% power to detect a 30% difference in relapse rate during the double-blind phase, based on the following assumptions: (1) expected 1-year relapse-rate of a virtual placebo arm equal to 0.7; (2) annual relapse rate reduction by treatment with GA 20mg = 30% compared with placebo to 0.49; and (3) annual relapse rate reduction by treatment with GA 40mg = 30% compared to GA 20mg to 0.343 relapses per year.

All efficacy and safety analyses were performed on the intent-to-treat cohort, defined as all randomized patients. For analysis of the primary efficacy endpoint, a baseline-adjusted, quasilikelihood (overdispersed) Poisson regression was employed. An offset based on the log of subject's exposure was employed to adjust the number of relapses to rates. Prior number of relapses, baseline EDSS, subject's exposure and centers were included in the model as covariates. Also, an alternative primary analysis was considered, the analysis of covariance (ANCOVA), utilizing normal approximation large sample theory, in case the randomization distribution simulation did not confirm the statistical significance of the quasilikelihood Poisson regression. Secondary efficacy end points were analyzed in a hierarchical order using a baseline-adjusted negative binomial regression. Baseline GdE lesion counts and center effect were used as covariates in the model in addition to the treatment effect. Brain volume changes were analyzed by applying an ANCOVA that compared the adjusted means of the percentage changes in brain volumes detected between groups. The number of patients withdrawing early due to adverse events, and patients who were free of relapses during study were compared for treatment effects using the chi square test, and time to withdrawal was analyzed by a log-rank test.

Results

Patients Disposition

A total of 1,262 patients were considered for this study, 107 (8.5%) of whom were screening failures. The vast majority of the screening failures (80.4%) occurred because the patients did not meet the inclusion/exclusion criteria. The others withdrew consent (14.0%), and 5.6% were not randomized due to other reasons, mainly related to scheduling issues. A total of 1,155 eligible patients were randomized either to GA 20mg (n = 586) or 40mg (n = 569). A total of 1,024 patients (88.7%) completed the double-blind phase. Premature termination from the double-blind phase was higher (p = 0.0071) in the GA 40mg arm (79 patients; 13.9%) compared to GA 20mg arm (52 patients; 8.9%) (Fig). The reasons for early termination are summarized in Table 1. The most common reason was adverse events (mainly injection site reactions), which was reported for 4.8% of the discontinued patients on GA 20mg vs 9.0% on GA 40mg.

Baseline Characteristics

The 2 groups were well-matched on demographic, clinical, and MRI baseline characteristics (Table 2).

Efficacy Results

PRIMARY ENDPOINT. No difference between the groups was observed in the mean number of confirmed relapses during the double-blind phase (0.28 ± 0.58 for patients on GA 20mg and 0.27 ± 0.54 for patients on GA 40mg); mean annualized number of confirmed relapses was 0.33 ± 0.81 for patients on GA 20mg,

TABLE 1: Reasons for Early Termination

Reasons	GA 20mg(n = 586)		GA 40mg(n = 569)		
	Number	%	Number	%	*p*
All	52	8.9	79	13.9	0.007
Adverse events	28	4.8	51	9.0	0.005
Subject withdrew consent	10	1.7	12	2.1	0.617
Failed to return/lost to follow-up	6	1.0	5	0.9	0.799
Request of investigator	3	0.5	6	1.1	0.290
Pregnancy	3	0.5	2	0.4	0.677
Sponsor's decision	1	0.2	1	0.2	0.983
Noncompliance	1	0.2	1	0.2	0.983
Death			1[a]	0.2	0.234

[a]Traffic accident. GA = glatiramer acetate.

compared to 0.35 ± 0.99 for patients on GA 40mg (risk ratio = 1.07; 95% CI, 0.88–1.31; $p = 0.486$). The alternative ANCOVA analysis, yielded similar results: $p = 0.872$ adjusted for center, and $p = 0.844$ adjusted for country (Table 3). Similar proportions of patients were free of relapses: 77.0% in the GA 40mg arm and 77.6% in the GA 20mg arm.

SECONDARY AND EXPLORATORY ENDPOINTS. The analysis of the cumulative number of GdE lesions was carried out for a subset of patients that included 126 patients on GA 20mg and 108 patients on GA 40mg (frequent MRI cohort). In this cohort, there were more GdE lesions at baseline in the 40mg arm (2.5 ± 5.8) compared to the low-dose group (1.5 ± 3.4, $p = 0.081$). On the scans performed at months 3, 6, 9, and 12, in patients of this cohort, the mean number of GdE lesions was similar in both arms (Table 4). The mean number of GdE lesions at month 3 decreased compared with baseline by 21.9% ($p = 0.172$) in the GA 20mg arm and by 37.6% ($p = 0.012$) in the GA 40mg arm, and further decreased significantly at month 6 compared to baseline (57.3%, $p = 0.0007$) in the GA 20mg arm and −69.2% ($p < 0.0001$) in the GA 40mg arm. These reductions of MRI activity were maintained with 70.8% reduction at the end of the 9 months in the GA 20mg group and a reduction by 72.2% in the GA 40mg group compared to baseline ($p < 0.0001$). The cumulative number of GdE lesions at months 3, 6, 9, and 12 was higher in the high dose group (3.49 vs 2.83), but this

TABLE 2: Baseline Characteristics of Enrolled Patients

Characteristics	GA 20mg(n = 586)[a]	GA 40mg(n = 569)[a]	*p*
Age (yr)	36.3 ± 9.0, 36.0	36.3 ± 9.0, 36.3	0.959
Gender (% F)	71.8	71.5	0.906
Time from first symptom (yr)	6.3 ± 6.5, 4.3	6.5 ± 6.7, 4.2	0.608
Time from diagnosis (yr)	3.0 ± 4.0, 1.0	3.3 ± 4.8, 1.0	0.258
Number of relapses in the previous year	1.5 ± 0.7, 1.0	1.4 ± 0.7, 1.0	0.022
Number of relapses in the previous 2 years	2.0 ± 1.0, 2.0	2.0 ± 1.0, 2.0	0.152
Number of GdE lesions	2.2 ± 6.9, 0	2.2 ± 4.8, 0	0.888
Volume of T2 lesions (ml)	9.7 ± 12.4, 5.8	9.8 ± 10.4, 6.5	0.880
EDSS score	2.2 ± 1.2, 2.0	2.1 ± 1.1, 2.0	0.773

All *p* values are derived from *t* test, except for gender *p* value which was derived from the log-likelihood chi-square test.
[a]Values are mean ± SD; median.EDSS = Expanded Disability Status Scale; F = female; GA = glatiramer acetate; GdE = gadolinium-enhancing; SD = standard deviation.

TABLE 3: Results of Primary and Secondary Endpoints

Analysis	GA 20 mg(n = 586)[3]	GA 40 mg(n = 569)[3]	*p*
Annualized relapse rate	0.33 ± 0.81; 0.0	0.35 ± 0.99; 0.0	0.486[b]
Relapse free patients (%)	77.6 ± 17.4	77.0 ± 17.7	1.000[c]
Number of GdE lesions at month 12	0.68 ± 2.30; 0	0.54 ± 1.77; 0	[d]
Number of new T2 lesions at month 12	2.87 ± 6.57; 1.0	2.72 ± 8.36; 0	[d]
Percent brain volume changes (%)	0.58	0.53	0.423

[3]Values are mean ± SD; median.
[b]Poisson regression.
[c]Log likelihood chi square.
[d]Negative binomial regression model did not converge.AG = glatiramer acetate; GdE = gadolinium-enhancing; SD = standard deviation.

difference was not significant $p = 0.091$), and was not supported by the results of the number of GdE lesions in the entire study population.

In the entire study population at month 12, the mean number of GdE lesions per patient was 0.68 in the 20mg group and 0.54 in the 40mg group (−21%). The mean number of new T2 lesions at month 12 was similar in the 2 treatment groups: 2.87 in the GA 20mg group and 2.72 in the GA 40mg group (see Table 3). Percent brain volume changes were similar in both groups with a mean of 0.58% in the GA 20mg arm and of 0.53% in the GA 40mg arm ($p = 0.423$).

Safety Results

The safety profile of both doses was similar to that observed in previous studies of GA 20mg. Both doses were well-tolerated with only 25 cases (4.3%) of severe adverse events in the GA 20mg arm and 24 (4.3%) in the GA 40mg arm. A similar incidence rate was also seen for injection site reactions: 336 patients (55.6%) in GA 20mg and 330 patients (58%) in GA 40mg, the majority of which were mild. Out of a total of 776 reports of injection site reactions in the GA 20mg arm, 615 (79.3%) were classified as mild by the investigators, 145 (18.7%) were moderate, and only 16 (2%) were classified as severe. Similarly, out of the total 824 reports of injection site reactions in the GA 40mg arm, 628 (76.2%) were mild, 175 (21.2%) were moderate, and 21 (2.6%) were severe. The incidence of immediate postinjection reactions was low: 36 patients (6.1%) in GA 20mg and 43 patients (7.6%) in GA 40mg. There were no safety concerns in either treatment group with regards to laboratory results, electrocardiogram (ECG) and vital signs.

Discussion

The safety and efficacy of GA at the currently-approved 20mg daily dose are supported by 3 placebo-controlled trials,[1–3] a meta-analysis of these studies,[11] 2 long-term follow-up studies,[12,13] and postmarketing experience. This first large, 12-month multicentre, randomized, double-blind, parallel-group dose-comparison trial of GA demonstrated that, over 12 months, there is no gain in efficacy with a double dose of GA compared to the

TABLE 4: Results of Number of GdE Lesions Over Time—Frequent MRI Cohort

GdE Lesions	GA 20mg(n = 126)[a]	GA 40mg(n = 108)[a]	*p*
Number of GdE lesions at baseline	1.48 ± 3.41	2.47 ± 5.83	0.082
Number of GdE lesions at mo 3	1.21 ± 2.61 (21.9, $p = 0.172$)	1.64 ± 3.91 (37.6, $p = 0.012$)	0.325
Number of GdE lesions at mo 6	0.65 ± 1.56 (57.3, $p = 0.0007$)	0.76 ± 2.19 (69.2, $p < 0.0001$)	0.666
Number of GdE lesions at mo 9	0.45 ± 1.27 (70.8, $p < 0.0001$)	0.72 ± 2.11 (72.2, $p < 0.0001$)	0.208
Number of GdE lesions at mo 12	0.75 ± 3.30 (48.9, $p = 0.103$)	0.79 ± 2.91 (69.0, $p = 0.004$)	0.904
Cumulative number of GdE lesions during 12 mo	2.83 ± 6.58	3.49 ± 8.19	0.091

[a]Values are mean ± SD (% change from baseline, p value). GA = glatiramer acetate; GdE = gadolinium-enhancing; MRI = magnetic resonance imaging; SD = standard deviation.

currently-approved 20mg dose. There were no differences between the 2 doses in relapse rate, proportion of patients free from relapses, various MRI markers of disease activity or rates of brain volume change. The clinical and MRI measures of disease activity during study were greatly reduced in both arms compared to the corresponding prestudy and baseline values.

The annualized relapse rate on study was 0.33 in the GA 20mg dose group and 0.35 in the GA 40mg dose group, values which are very low compared to those in the pivotal trial of GA,[2] but close to that observed for GA in the more recent "Rebif vs Glatiramer Acetate in Relapsing MS Disease" (REGARD) (0.29) and "Betaferon Efficacy Yielding Outcomes of a New Dose" (BEYOND) (0.34) studies.[14,15]

MRI analyses support the conclusion that both doses of GA were equally effective in this study. The mean number of GdE lesions decreased at the end of the study compared to baseline by about 70% in both treatment groups. The onset of the reduction of MRI activity appeared to occur earlier than expected based on the previous analysis of the European-Canadian MRI trial.[3] The analysis of new T2 lesions formation in the frequent MRI cohort confirmed that onset of action of GA on MRI activity started before 3 months from onset of treatment. The degree of progression of brain volume changes observed with both doses of GA is modestly lower than the values observed for GA in the BEYOND trial and in the European-Canadian MRI trial.[3,15] Although comparisons across studies should be always considered with great caution, the MRI protocol was the same and the analysis was performed by the same MRI analysis center. The lower increase in brain volume changes observed in this study could be explained by the potential neuroprotective effect of available immunomodulatory treatments in early MS.[10,15,16]

In recently completed clinical trials in RRMS patients, the on-study relapse rate has been lower than that observed in earlier clinical trials. This behavior has been explained by the concurrence of several factors, including: (1) changing patterns of diagnosis and the so-called Will Rogers phenomenon;[17] (2) the availability for recruitment of a less active population (because most patients are treated early, as reflected by the low EDSS and the short duration of disease (3 years) in the recruited population compared to earlier clinical trials; (3) lacking placebo group (added effect of drug and positive expectations); and (4) the fact that more active patients often are no longer considered candidates for clinical trials for ethical reasons. This change in the characteristics of the disease in a clinical trial setting, mirrored by the low relapse rate of the placebo arms in recent trials,[18] combined with the notion that early treatment with immunomodulatory drugs has better efficacy than delayed treatment,[4,19] may suggest that the efficacy in terms of reduction in clinical and MRI activity achieved in recent trials is more similar than different compared with the previous clinical trials.

Since patients in this trial tended to be more active than the patients treated with GA in the BEYOND and REGARD trials, as revealed by the higher mean number of GdE lesions at baseline (2.2 in this study vs 1.8 or 1.65 in the BEYOND and REGARD, respectively), one might have expected higher relapse rates during this study compared to those. However, this was not the case. The proportion of clinically active patients was low (22.4%) in the GA 20mg group compared to 38% in the GA arm of the REGARD and 41% in the GA arm of the BEYOND trials, even considering that the numbers relate to 1-year follow-up only.

Treatment with GA was safe and tolerable, consistent with the safety and tolerability profile already observed in previous studies. Less than 5% of the patients discontinued treatment in the 20mg group because of adverse effects. This almost doubled with the 40mg dose. Injection site reactions remained the most commonly reported adverse event, with similar incidence rate in both doses of GA. Also the immediate postinjection reactions incidence rate were similar in the 2 groups.

In conclusion, this study confirms that the double dose when administered daily showed no gains in efficacy (based on annualized relapse rate [ARR] and MRI measures over 1 year), indicating it has no role in treatment of early, mildly affected RRMS patients.

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Potential Conflicts of Interest

G.C. has received grants from Teva Pharmaceuticals; has received personal compensation for participating in advisory boards and acting as consultant from Teva Pharmaceuticals, Novartis, Sanofi-Aventis, Merck-Serono, and Bayer Schering; and has received honoraria for speaking activities from Teva Pharmaceuticals, Novartis, Serono Symposia International Foundation, Sanofi-Aventis, Merck-Serono, Biogen-Dompè, and Bayer Schering. J.A.C. received personal compensation for serving as a consultant or speaker from Biogen Idec, Eli Lilly,

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Appendix: FORTE Study Group

Study Committees

CORE CLINICAL STEERING COMMITTEE. Giancarlo Comi (PI), Jeffrey A. Cohen (PI), Massimo Filippi, Douglas L. Arnold, Daniel Wynn. The MRI Analysis Center, Neuroimaging Research Unit, San Raffaele Scientific Institute, Milan, Italy. Massimo Filippi; Maria A. Rocca, Elisabetta Stefania Perego, Martina Absinta, Sarlota Mesaros, Roberto Vuotto, Paolo Misci, Melissa Petrolini.

DATA SAFETY MONITORING COMMITTEE. Patricia Coyle (Chair), Jerry Wolinsky, Jack Antel, Scott Zamvil, Paul Feigin.

Study Sites

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