ORIGINAL ARTICLE

Placebo-Controlled Trial of an Oral BTK Inhibitor in Multiple Sclerosis

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ABSTRACT

BACKGROUND

Bruton's tyrosine kinase (BTK) regulates the functions of B cells and myeloid cells that are implicated in the pathogenesis of multiple sclerosis. Evobrutinib is a selective oral BTK inhibitor that has been shown to inhibit B-cell activation both in vitro and in vivo.

METHODS

In this double-blind, randomized, phase 2 trial, we assigned patients with relapsing multiple sclerosis to one of five groups: placebo, evobrutinib (at a dose of 25 mg once daily, 75 mg once daily, or 75 mg twice daily), or open-label dimethyl fumarate (DMF) as a reference. The primary end point was the total (cumulative) number of gadolinium-enhancing lesions identified on T_1-weighted magnetic resonance imaging at weeks 12, 16, 20, and 24. Key secondary end points included the annualized relapse rate and change from baseline in the score on the Expanded Disability Status Scale (EDSS).

RESULTS

A total of 267 patients were randomly assigned to a trial group. The mean (±SD) total number of gadolinium-enhancing lesions during weeks 12 through 24 was 3.85±5.44 in the placebo group, 4.06±8.02 in the evobrutinib 25-mg group, 1.69±4.69 in the evobrutinib 75-mg once-daily group, 1.15±3.70 in the evobrutinib 75-mg twice-daily group, and 4.78±22.05 in the DMF group. The baseline adjusted rate ratios for the total number of lesions over time as compared with placebo were 1.45 in the evobrutinib 25-mg group (P=0.32), 0.30 in the evobrutinib 75-mg once-daily group (P=0.005), and 0.44 in the evobrutinib 75-mg twice-daily group (P=0.06). The unadjusted annualized relapse rate at week 24 was 0.37 in the placebo group, 0.57 in the evobrutinib 25-mg group, 0.13 in the evobrutinib 75-mg once-daily group, 0.08 in the evobrutinib 75-mg twice-daily group, and 0.20 in the DMF group. There was no significant effect of trial group on the change from baseline in the EDSS score. Elevations in liver aminotransferase values were observed with evobrutinib.

CONCLUSIONS

Patients with relapsing multiple sclerosis who received 75 mg of evobrutinib once daily had significantly fewer enhancing lesions during weeks 12 through 24 than those who received placebo. There was no significant difference with placebo for either the 25-mg once-daily or 75-mg twice-daily dose of evobrutinib, nor in the annualized relapse rate or disability progression at any dose. Longer and larger trials are required to determine the effect and risks of evobrutinib in patients with multiple sclerosis. (Funded by EMD Serono; ClinicalTrials.gov number, NCT02975349.)

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Multiple sclerosis is a progressive demyelinating, inflammatory, and neurodegenerative autoimmune disease that results in the formation of lesions in the protective layer around nerves in the brain and spinal cord.[1] Goals in the treatment of patients' disabling symptoms include reducing the frequency of relapses and slowing disability progression. A change in measures of disease activity on magnetic resonance imaging (MRI) may be used as a surrogate marker of treatment response.[2]

The activity and interactions of B cells, T cells, and myeloid cells are involved in the immunopathological features of multiple sclerosis.[1,3,4] Antigen-activated B cells exert effector functions through antigen presentation and the production of cytokines and antibodies. Macrophages and microglia that are abundant in multiple sclerosis lesions contribute to tissue damage and repair.[5,6]

Bruton's tyrosine kinase (BTK), a member of the Tec family of kinases, transmits signals through a variety of receptors in B cells and myeloid cells, so it presents a rational target in multiple sclerosis.[7-9] BTK inhibitors are currently under investigation in several types of autoimmune disease, including systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis.[10] Evobrutinib is a selective, covalent, oral inhibitor of BTK that blocks B-cell activation and cytokine release[11] and has been shown to inhibit the activation, differentiation, and polarization of proinflammatory M1 macrophages and their release of cytokines in vitro.[12] Evobrutinib has shown in vivo efficacy against experimental autoimmune encephalomyelitis (an animal model of brain inflammation) regardless of B-cell activity.[13,14]

We selected the doses of evobrutinib that were used in this trial to cover a range of BTK-receptor binding that was anticipated to be effective on the basis of animal models. The irreversible binding of evobrutinib to BTK results in a pharmacodynamic effect that is longer than the pharmacokinetic plasma half-life of evobrutinib. The drug has greater selectivity than first-generation BTK inhibitors[15] and was designed with the expectation of having fewer off-target side effects. We report the results of a phase 2 trial comparing evobrutinib with placebo and using dimethyl fumarate (DMF) as a reference in patients with clinical and imaging evidence of active relapsing–remitting multiple sclerosis and in those with secondary progressive multiple sclerosis with superimposed relapses.[16-18]

Methods

Trial Design

From March 2017 through July 2018, we conducted this randomized, placebo-controlled, phase 2 trial at 56 centers in Europe and Russia (see the Supplementary Appendix, available with the full text of this article at NEJM.org). After a 4-week screening period, patients were randomly assigned to one of five groups, in a 1:1:1:1:1 ratio, by an interactive Web-response system to receive oral evobrutinib (at a dose of 25 mg once daily, 75 mg once daily, or 75 mg twice daily), placebo, or open-label DMF (at a dose of 120 mg twice daily for the first week and 240 mg twice daily thereafter) (Fig. S1 in the Supplementary Appendix). After 24 weeks of the placebo-controlled phase of the trial, patients in the placebo group were switched to receive 25 mg of evobrutinib once daily for a further 24-week blinded extension phase; patients who were receiving evobrutinib or DMF continued to be given the same dose. There was a 4-week safety follow-up period after the end of trial. A temporary interruption or discontinuation of treatment was required in patients who had any of several prespecified laboratory abnormalities. (Details are provided in the Supplementary Appendix.)

Trial visits were scheduled every 4 weeks (±3 days) after screening to assess MRI results, starting at week 12; clinical disease activity, including relapse assessment, which was also evaluated at unscheduled visits for suspected new or worsening neurologic symptoms including relapse; the score on the Expanded Disability Status Scale (EDSS) at weeks 12, 24, 36, and 48 only; and safety during the 52-week period. The treating investigator at each trial site was unaware of trial-group assignments with the exception of open-label DMF. The assessing neurologists and independent central MRI readers were unaware of all trial-group assignments.

Trial Oversight

The trial was conducted in accordance with the principles of the Declaration of Helsinki, the guidelines for Good Clinical Practice of the International Conference on Harmonisation, and additional local regulations. The trial was designed by the sponsor (EMD Serono) with input

from a steering committee. The sponsor was also involved in the collection, analysis, and interpretation of the data and the writing of the manuscript. The sponsor provided the evobrutinib, DMF, and placebo that were used in the trial; it paid for data collection and analysis by IQVIA (a clinical research organization) and for professional writing assistance. An independent data monitoring committee monitored safety. All the authors vouch for adherence of the trial to the protocol (available at NEJM.org), the accuracy and completeness of data reporting, and complete reporting of adverse events. All the authors approved the final version of the manuscript and were involved in the decision to submit the manuscript for publication. Confidentiality agreements were in place between the authors and the sponsor.

PATIENTS

Patients were eligible for treatment if they were between the ages of 18 and 65 years, had relapsing–remitting multiple sclerosis or secondary progressive multiple sclerosis with superimposed relapses,[17,18] and had a score of no more than 6 on the EDSS (which ranges from 0 [no disability] to 10 [death]); all the patients provided written informed consent (Fig. S1 in the Supplementary Appendix). Patients were offered and encouraged to undertake treatment with available therapies for multiple sclerosis, and they consented to participate in the trial with full awareness of alternative treatment options.

The diagnosis of secondary progressive multiple sclerosis was based on investigator judgment; requirements for the determination of relapse were stipulated in the inclusion criteria. Key exclusion criteria were progressive multiple sclerosis, either primary or secondary with no superimposed relapses; a disease duration of more than 15 years with an EDSS score of 2 or less; and exposure to DMF within 6 months before randomization. (Details regarding inclusion and exclusion criteria are provided in the Supplementary Appendix.)

END POINTS

The primary end point was the total (cumulative) number of gadolinium-enhancing lesions identified on T_1-weighted MRI at weeks 12, 16, 20, and 24.[19] Key secondary end points were the annualized relapse rate, based on qualified relapses; qualified relapse-free status; change from baseline in the EDSS score at week 24; and safety. A qualified relapse was defined as new, worsening, or recurrent neurologic symptoms attributed to multiple sclerosis that lasted for at least 24 hours without fever, infection, or adverse reaction to a prescribed medication and that was preceded by a stable or improving neurologic status of at least 30 days. A qualified relapse was accompanied by new clinical signs, such as changes in the neurologic examination or an increase in the EDSS score.

All outcome measures that were based on relapse data used qualified relapses. The 13 additional secondary end points related to the active treatment groups in the trial are listed in the Supplementary Appendix. Investigation of the effects of evobrutinib, as compared with placebo, on health-related quality of life was an exploratory end point. Serious adverse events were defined as described in the Supplementary Appendix and did not include relapse as an adverse event.

STATISTICAL ANALYSIS

We estimated that the enrollment of 44 patients in each group would provide a power of 85% to detect a 90% lower total number of gadolinium-enhancing lesions in each evobrutinib group than in the placebo group, using the Wilcoxon rank-sum test at a two-sided significance level of 5% and assuming a negative binomial distribution for the total number of lesions in each group. We based our assumptions regarding the mean total number of lesions (estimated to be 5.5 lesions in the placebo group) on four MRI evaluations and the negative binomial distribution on results from recent phase 2 studies involving patients with multiple sclerosis.[19,20] On the basis of an assumed annual dropout rate of 12%, we set a target enrollment of 50 patients per group.

The primary efficacy analysis at week 24 was based on the modified intention-to-treat analysis population, which consisted of the patients who had undergone randomization and who had undergone MRI at baseline and at least once after baseline. We analyzed the total number of gadolinium-enhancing lesions using negative binomial regression, with offset given by the log number of available scans and adjustment for lesion activity at baseline. This analysis resulted

in a comparison of each evobrutinib group with placebo on the basis of the estimated lesion rate ratio. In the lesion analyses, data regarding scans that had been performed within 3 weeks after the receipt of high-dose glucocorticoids were considered to be missing, but the total lesion count was not imputed unless all available scans were affected. Other lesion-count end points were analyzed similarly.

The relative change in the annualized relapse rate was evaluated with a negative binomial model for the number of relapses, with offset given by the log years on trial and adjustment for baseline relapse activity. This analysis resulted in a comparison of each evobrutinib group with placebo on the basis of the estimated relapse rate ratio. Data for patients who discontinued a trial agent early were considered in the total number of relapse events, and these patients were followed until discontinuation.

Relapse-free status was analyzed by means of logistic regression, after adjustment for baseline values; patients who withdrew from the trial without relapse before week 24 were not considered to be free of relapse. The change from baseline in the EDSS score was analyzed by means of the stratified Wilcoxon rank-sum test, with adjustment for the baseline EDSS score. Missing values for the change from baseline in the EDSS score at week 24 were imputed with the use of the median value among patients in the same trial group and baseline covariates. We used a multistage testing algorithm to handle multiple comparisons of the three evobrutinib dose groups on the basis of the evaluation of four efficacy end points (primary and key secondary end points). The family-wise error rate for the null hypotheses associated with dose-group comparisons for a given end point was controlled by the truncated Hochberg procedure for the primary end point and the first two key secondary end points (annualized relapse rate and relapse-free status) and by the standard Hochberg procedure for the third key secondary end point (change from baseline in the EDSS score). The analysis of additional secondary end points was not adjusted for multiple comparisons, so these outcomes are reported as point estimates and 95% confidence intervals without P values. The statistical analysis plan, including the handling of missing data, is provided in the Supplementary Appendix.

Within-group analyses of 48-week data were based on a subgroup of patients in the modified intention-to-treat population, including all the patients who entered the extension portion of the trial and underwent at least one MRI assessment after week 24. Efficacy end points were compared between the two time points (week 24 and 48) or trial phases (weeks 0 to 24 and weeks 25 to 48) with the use of the Hodges–Lehmann estimate of shift in location and the Wilcoxon signed-rank test. There were no statistical comparisons between evobrutinib and placebo at week 48, since the placebo group was switched to active treatment for the extension period at 24 weeks.

The safety analysis population consisted of all the patients who had received at least one dose of evobrutinib, placebo, or DMF. Descriptive statistics were used to evaluate safety and secondary end points, including all end points related to the DMF reference group. No statistical comparisons of DMF with evobrutinib or placebo were prespecified or conducted.

RESULTS

PATIENTS

Of the 267 patients who underwent randomization, 261 were included in the modified intention-to-treat analysis, after the exclusion of 6 patients owing to a lack of post-baseline MRI assessments. Of the 244 patients (91%) who completed 24 weeks of the trial, 229 were included in the extension analysis after the exclusion of 15 patients who had not undergone MRI assessment after week 24; of the 267 patients who had undergone randomization, 227 (85%) completed 48 weeks of treatment (Fig. 1).

All the patients were white, with a mean age of 42 years; 69% were women. A total of 87% had relapsing–remitting multiple sclerosis; the remainder had secondary progressive multiple sclerosis with superimposed relapses (Table 1). The mean (±SD) number of gadolinium-enhancing lesions at baseline was 1.54±4.37, and the mean EDSS score at baseline was 3.3±1.6. The patients' disease characteristics at baseline were similar across the trial groups.

EFFICACY OUTCOMES

The mean total number of gadolinium-enhancing lesions at weeks 12 through 24 (the primary

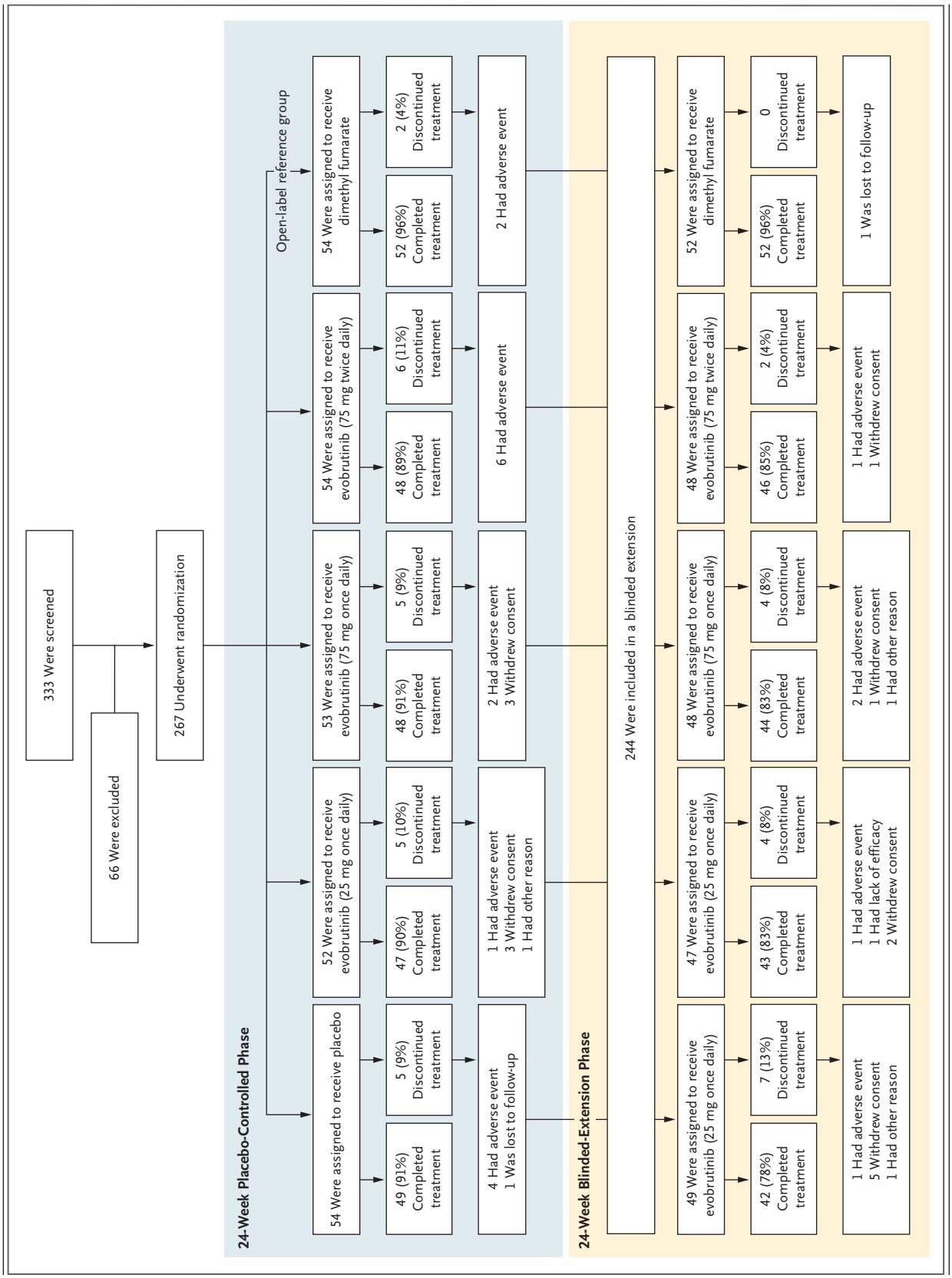


Figure 1 (facing page). Enrollment in Placebo-Controlled Phase and Extension Phase.

After 24 weeks of receiving the assigned trial agent, patients in the placebo group were switched to receive 25 mg of evobrutinib once daily (QD) for a further 24-week blinded extension phase; patients who were receiving evobrutinib and dimethyl fumarate continued to be given the same dose. The percentages of patients who completed or discontinued the extension phase are based on the original number of patients who underwent randomization to each trial group.

end point) was 3.85±5.44 in the placebo group, 4.06±8.02 in the evobrutinib 25-mg group, 1.69±4.69 in the evobrutinib 75-mg once-daily group, 1.15±3.70 in the evobrutinib 75-mg twice-daily group, and 4.78±22.05 in the DMF group (Table 2). The baseline adjusted rate ratios for the total number of lesions over time, as compared with placebo, were 1.45 in the evobrutinib 25-mg group (95% confidence interval [CI], 0.72 to 2.91; P=0.32 after adjustment for multiple comparisons), 0.30 in the evobrutinib 75-mg once-daily group (95% CI, 0.14 to 0.63; P=0.005), and 0.44 in the evobrutinib 75-mg twice-daily group (95% CI, 0.21 to 0.93; P=0.06). (P values that were adjusted for multiple comparisons and those that were not adjusted are provided in Table 2 and Fig. 2A, and in Table S1 in the Supplementary Appendix.)

The distribution of the gadolinium-enhancing lesions at week 24 in the DMF group was influenced by a patient with 46 lesions at baseline and a total of 160 lesions over three post-baseline MRI evaluations. For within-group comparisons at all doses, there was no evidence of difference in effect of evobrutinib on the number of gadolinium-enhancing lesions between weeks 24 and 48 (Table S2 in the Supplementary Appendix).

At 24 weeks, 9 relapses had occurred in the placebo group, 13 in the evobrutinib 25-mg group, 3 in the evobrutinib 75-mg once-daily group, 2 in the evobrutinib 75-mg twice-daily group, and 5 in the DMF group. As compared with placebo at week 24, there was no significant effect on the annualized relapse rate in the evobrutinib groups, with an unadjusted annualized relapse rate of 0.37 (95% CI, 0.17 to 0.70) in the placebo group, 0.57 (95% CI, 0.30 to 0.97) in the evobrutinib 25-mg group, 0.13 (95% CI, 0.03 to 0.38) in the evobrutinib 75-mg once-daily group, and 0.08 (95% CI, 0.01 to 0.30) in the evobrutinib 75-mg twice-daily group (Table 2 and Fig. 2B). The unadjusted annualized relapse rate over 48 weeks was 0.37 (95% CI, 0.21 to 0.59) in the placebo–evobrutinib 25-mg group, 0.52 (95% CI, 0.33 to 0.78) in the evobrutinib 25-mg group, 0.25 (95% CI, 0.12 to 0.44) in the evobrutinib 75-mg once-daily group, 0.11 (95% CI, 0.04 to 0.25) in the evobrutinib 75-mg twice-daily group, and 0.14 (95% CI, 0.06 to 0.29) in the DMF group (Fig. 2C).

The percentage of patients who were relapse-free at week 24 was 77% in the placebo group, 74% in the evobrutinib 25-mg group, 88% in the evobrutinib 75-mg once-daily group, 87% in the evobrutinib 75-mg twice-daily group, and 89% in the DMF group (Table 2); the percentages were similar at 48 weeks (Fig. S2 in the Supplementary Appendix). The median change from baseline in the EDSS score at weeks 24 and 48 was zero in all five groups (Table 2, and Table S2 in the Supplementary Appendix).

At 24 weeks, the secondary outcome of the lesion rate ratio for new or enlarging lesions on T_2-weighted MRI was 0.42 (95% CI, 0.20 to 0.87) in the evobrutinib 75-mg twice-daily group, indicating a better response than in the other evobrutinib dose groups. The results of this and other imaging and clinical secondary end points are provided in Table S2 and the results of quality-of-life analyses are provided in Table S3 in the Supplementary Appendix.

SAFETY OUTCOMES

Adverse events that occurred during the 52-week safety period are listed in Table 3, and Table S4 in the Supplementary Appendix. The highest rate of serious adverse events (7%) occurred in patients treated with evobrutinib 75 mg twice daily. Grade 3 or 4 adverse events were most frequent among patients in the evobrutinib 75-mg once-daily group (13%), the evobrutinib 75-mg twice-daily group (15%), and the DMF group (13%). The most commonly observed adverse events of any grade that were associated with evobrutinib were nasopharyngitis and increases in levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lipase. Patients with elevations in aminotransferase levels were asymptomatic, the elevations were reversible, and no cases fell within the criteria of Hy's law for drug-induced liver injury, as defined by the Food

Table 1. Demographic and Disease Characteristics of the Patients at Baseline (Modified Intention-to-Treat Population).*

Characteristic	Placebo (N=53)	Evobrutinib, 25 mg QD (N=50)	Evobrutinib, 75 mg QD (N=51)	Evobrutinib, 75 mg BID (N=53)	Dimethyl Fumarate (N=54)	All Patients (N=261)
Age — yr	41.6±10.8	42.4 ±9.4	42.9±10.1	42.2±11.5	42.8±11.7	42.4±10.7
Female sex — no. (%)	39 (74)	32 (64)	35 (69)	36 (68)	39 (72)	181 (69)
Type of multiple sclerosis — no. (%)						
Relapsing–remitting disease	47 (89)	42 (84)	43 (84)	47 (89)	49 (91)	228 (87)
Secondary progressive disease	6 (11)	8 (16)	8 (16)	6 (11)	5 (9)	33 (13)
Median time since disease onset (range) — yr	7.5 (0.1–39.4)	8.4 (0.2–26.4)	11.4 (0.4–24.6)	10.1 (0.2–39.4)	7.3 (0.3–32.5)	8.4 (0.1–39.4)
Relapse in the previous 2 yr — no. (%)						
1 relapse	26 (49)	27 (54)	18 (35)	25 (47)	20 (37)	116 (44)
≥2 relapses	27 (51)	23 (46)	33 (65)	28 (53)	34 (63)	145 (56)
Score on Expanded Disability Status Scale†						
Mean	3.2±1.7	3.3±1.5	3.5±1.4	3.4±1.6	3.0±1.7	3.3±1.6
Median (range)	3.0 (0.0–6.0)	3.0 (0.0–6.0)	3.5 (1.5–6.0)	3.0 (1.0–6.0)	2.5 (0.0–6.0)	3.0 (0.0–6.0)
Gadolinium-enhancing lesions on T_1-weighted MRI						
Patients with lesions — no. (%)	24 (45)	19 (38)	18 (35)	23 (43)	19 (35)	103 (39)
Mean no.	1.19±1.91	0.92±2.02	1.65±5.44	1.72±3.40	2.20±6.79	1.54±4.37
Median no. (range)	0 (0–9)	0 (0–10)	0 (0–38)	0 (0–19)	0 (0–46)	0 (0–46)
Mean volume of lesions on T_2-weighted MRI — cm^3	15.89±12.63	13.79±11.67	14.03±12.23	19.02±13.54	18.84±17.67	16.37±13.85

* Plus–minus values are means ±SD. Patients were included in the modified intention-to-treat analysis if they had undergone randomization and MRI assessment at baseline and at least once after baseline. All the patients in this trial were white (98% were non-Hispanic or Latino; 99% of the patients were from Eastern Europe and 1% from Western Europe), as recorded by the investigators. BID denotes twice daily, MRI magnetic resonance imaging, and QD once daily.

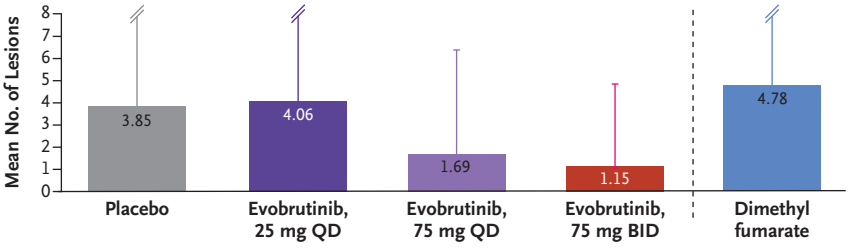
† Scores on the Expanded Disability Status Scale (EDSS) range from 0 (no disability) to 10 (death).

Table 2. MRI and Clinical Outcomes at 24 Weeks (Modified Intention-to-Treat Population).*

Outcome	Placebo (N=53)	Evobrutinib, 25 mg QD (N=50)	Evobrutinib, 75 mg QD (N=51)	Evobrutinib, 75 mg BID (N=53)	Dimethyl Fumarate (N=54)
Cumulative no. of gadolinium-enhancing lesions on T_1-weighted MRI at 12, 16, 20, and 24 wk†					
Mean	3.85±5.44	4.06±8.02	1.69±4.69	1.15±3.70	4.78±22.05
Median	1	1	0	0	0
Range	0–20	0–38	0–27	0–25	0–160‡
Interquartile range	0–6	0–2	0–1	0–1	0–1
Lesion rate ratio (95% CI)§	NA	1.45 (0.72 to 2.91)	0.30 (0.14 to 0.63)	0.44 (0.21 to 0.93)	NA
Adjusted P value vs. placebo	NA	0.32	0.005	0.06	NA
Unadjusted P value vs. placebo	NA	0.29	0.002	0.03	NA
Relapse at 24 wk¶					
No. of relapses	9	13	3	2	5
Unadjusted annualized relapse rate (95% CI)‖	0.37 (0.17 to 0.70)	0.57 (0.30 to 0.97)	0.13 (0.03 to 0.38)	0.08 (0.01 to 0.30)	0.20 (0.06 to 0.47)
Relapse rate ratio (95% CI)**	NA	1.66 (0.67 to 4.09)	0.31 (0.08 to 1.20)	0.23 (0.05 to 1.09)	NA
Relapse-free status at wk 24¶					
Patients with no relapse (95% CI) — %	77 (64 to 88)	74 (60 to 85)	88 (76 to 96)	87 (75 to 95)	89 (77 to 96)
Odds ratio for no relapse (95% CI)††	NA	0.75 (0.29 to 1.95)	2.79 (0.92 to 8.41)	2.08 (0.72 to 5.99)	NA
Change from baseline in EDSS score at 24 wk¶‡‡					
Median	0.0	0.0	0.0	0.0	0.0
Range	–1.0 to 1.0	–2.5 to 2.5	–4.5 to 0.5	–0.5 to 1.0	–1.0 to 1.0

* Plus–minus values are means ±SD. CI denotes confidence interval, and NA not applicable.
† This outcome is the primary end point.
‡ The distribution of the total number of gadolinium-enhancing lesions on T_1-weighted MRI at week 24 in the dimethyl fumarate group was influenced by one patient who had 46 lesions at baseline and a total of 160 lesions over three post-baseline scans. In a post hoc analysis that excluded data for this patient, the dimethyl fumarate group had improved outcomes.
§ The lesion rate ratio was estimated on the basis of a negative binomial model for the total number of gadolinium-enhancing lesions on T_1-weighted MRI summed over the available scans through week 24. The model includes factors for trial group and a covariate for the presence or absence of gadolinium-enhancing lesions at baseline, with offset equal to the log number of available scans. The lesion rate ratio, which compares the number of lesions per scan (i.e., lesion rate) between groups, equals one minus the relative reduction in lesion rate. Data regarding scans that were performed within 3 weeks after the receipt of high-dose glucocorticoids were considered to be missing.
¶ This outcome was one of the key secondary end points.
‖ The unadjusted annualized relapse rate was defined as the number of relapses among patients divided by the number of patient-years of follow-up. For patients who discontinued the trial early, all relapses and follow-up through the safety follow-up visit were included.
** The relapse rate ratio was estimated on the basis of a negative binomial model for relapse count over 24 weeks. The model includes factors for trial group and a covariate for baseline relapse activity (≤1 or >1 relapse in 2 years before trial entry), with offset equal to the log years of follow-up. The relapse rate ratio equals one minus the relative reduction in the annualized relapse rate.
†† The relapse-free odds ratio was estimated on the basis of a logistic model that included factors for trial group and a covariate for baseline relapse activity. Patients who discontinued the trial before week 24 without relapse were not considered to be relapse-free. The calculation of the 95% confidence interval for the proportion of patients is based on the Clopper–Pearson exact method, and the calculation of the odds ratio is based on the Thomas algorithm.
‡‡ The EDSS score ranges from 0 (no disability) to 10 (death). Missing values for the change from baseline in the EDSS score at week 24 were imputed by the median value among patients in the same trial group and baseline covariate stratum.

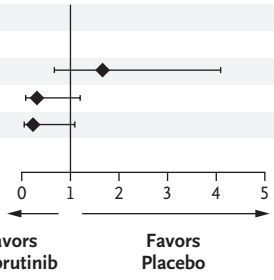
A Total No. of Lesions at Wk 12 through 24



Lesion rate ratio (95% CI)	1.45 (0.72–2.91)	0.30 (0.14–0.63)	0.44 (0.21–0.93)
Adjusted P value vs. placebo	0.32	0.005	0.06
Unadjusted P value vs. placebo	0.29	0.002	0.03

B Relapse Rate Ratio and Annualized Relapse Rate at Wk 24

Trial Group	Relapse Rate Ratio (95% CI)	Annualized Relapse Rate (95% CI)
Placebo		0.37 (0.17–0.70)
Evobrutinib		
25 mg QD	1.66 (0.67–4.09)	0.57 (0.30–0.97)
75 mg QD	0.31 (0.08–1.20)	0.13 (0.03–0.38)
75 mg BID	0.23 (0.05–1.09)	0.08 (0.01–0.30)
Dimethyl fumarate		0.20 (0.06–0.47)



C Annualized Relapse Rate at Wk 24 and 48

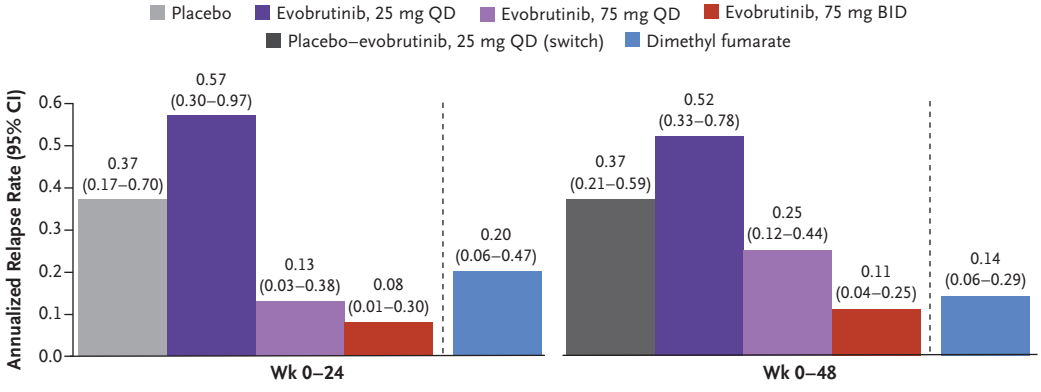


Figure 2. Total Number of Lesions at Weeks 12 through 24, Relapse Measures at 24 Weeks, and Annualized Relapse Rate at 24 Weeks and 48 Weeks.

Panel A shows the total number of gadolinium-enhancing lesions identified on T_1-weighted magnetic resonance imaging at weeks 12, 16, 20, and 24 (primary end point) in the five trial groups. The T bars denote the standard deviation. The vertical dashed line separates the open-label dimethyl fumarate group from the groups in the placebo-controlled analysis. Panel B shows the relapse rate ratio and annualized relapse rate at 24 weeks (a key secondary end point). The relapse rate ratio is based on a negative binomial model for the relapse count that was adjusted for patients' relapse activity at baseline. The annualized relapse rate was not adjusted for baseline relapse activity. The relapse rate ratio for the three evobrutinib groups was calculated as a comparison with placebo and did not include the dimethyl fumarate reference group. Panel C shows the annualized relapse rate at weeks 24 and 48. All the analyses were performed in the modified intention-to-treat population. BID denotes twice daily, and QD once daily.

Table 3. Adverse Events at 52 Weeks (Safety Population).

Adverse Event	Placebo–Evobrutinib, 25 mg QD* (N=54)	Evobrutinib, 25 mg QD (N=52)	Evobrutinib, 75 mg QD (N=53)	Evobrutinib, 75 mg BID (N=54)	Dimethyl Fumarate (N=54)
	number of patients (percent)				
Any adverse event	30 (56)	28 (54)	35 (66)	34 (63)	35 (65)
Any grade 3 or 4 adverse event†	6 (11)	1 (2)	7 (13)	8 (15)	7 (13)
Serious adverse event‡	2 (4)	2 (4)	2 (4)	4 (7)	2 (4)
Adverse event leading to discontinuation	5 (9)	3 (6)	6 (11)	7 (13)	2 (4)
Adverse event deemed by investigator to be related to trial agent	14 (26)	10 (19)	15 (28)	18 (33)	26 (48)
Infection	16 (30)	17 (33)	10 (19)	12 (22)	12 (22)
Neoplasm§	2 (4)	0	0	0	1 (2)
Most common adverse events¶					
Nausea	0	2 (4)	0	1 (2)	3 (6)
Diarrhea	2 (4)	1 (2)	0	0	4 (7)
Nasopharyngitis	5 (9)	9 (17)	3 (6)	7 (13)	2 (4)
Upper respiratory tract infection	2 (4)	1 (2)	1 (2)	1 (2)	3 (6)
Urinary tract infection	5 (9)	2 (4)	1 (2)	0	2 (4)
Increase in alanine aminotransferase	4 (7)	3 (6)	6 (11)	5 (9)	3 (6)
Increase in aspartate aminotransferase	1 (2)	1 (2)	2 (4)	4 (7)	2 (4)
Increase in lipase	5 (9)	2 (4)	5 (9)	5 (9)	3 (6)
Increase in creatinine	1 (2)	0	3 (6)	3 (6)	1 (2)
Low lymphocyte count	0	0	0	1 (2)	5 (9)
Arthralgia	1 (2)	2 (4)	3 (6)	0	4 (7)
Headache	2 (4)	3 (6)	2 (4)	1 (2)	1 (2)
Flushing	0	0	0	0	12 (22)

* After 24 weeks, patients in the placebo group were switched to receive 25 mg of evobrutinib once daily for a further 24-week blinded extension period. There was a 4-week safety follow-up period after the end of trial.
† No deaths occurred during the trial.
‡ Serious adverse events (each of which occurred in 1 patient) included pneumonia, lung neoplasm, and peripheral embolism in the placebo–evobrutinib 25-mg group; toxic hepatitis (asymptomatic elevation in aminotransferase levels and no elevation in bilirubin level) and overdose of the trial agent in the evobrutinib 25-mg group; traffic accident and spontaneous abortion in the evobrutinib 75-mg once-daily group; toxic hepatitis (as previously defined), elevation in aminotransferase levels, epilepsy, and restless leg syndrome in the evobrutinib 75-mg twice-daily group; and Lyme disease and gastric cancer in the dimethyl fumarate group.
§ In the placebo–evobrutinib 25-mg group, 1 patient had a lung neoplasm before switching to evobrutinib after week 24, and 1 had a skin papilloma after switching to evobrutinib; in the dimethyl fumarate group, gastric cancer was diagnosed in 1 patient.
¶ This list includes the most common adverse events that were reported in at least 5% of the patients in any group. A list of additional adverse events is provided in Table S4 in the Supplementary Appendix.

and Drug Administration.[21] Shifts in laboratory values from normal (grade 0) at baseline to elevated ALT levels and from any baseline grade to highest grade over 52 weeks in all the trial groups (including patients who switched from placebo to evobrutinib) are shown in Table S5 in the Supplementary Appendix. All elevations occurred within the first 24 weeks of the trial.

The percentage of patients who had infections was higher in the evobrutinib 25-mg group and the placebo–evobrutinib 25-mg group (30 to 33%) than in other groups (Table 3). Single

cases of infection occurred in the evobrutinib 25-mg group (viral infection, 2%) and the evobrutinib 75-mg once-daily group (oral herpes and viral respiratory tract infection, 2% each).

Over the 24-week placebo-controlled phase of the trial, the percentage of patients who had a shift from a normal lymphocyte count to a decreased count (grade 1 lymphopenia) was similar in the placebo group (6%) and the evobrutinib groups (4% in the evobrutinib 25-mg group, 4% in the evobrutinib 75-mg once-daily group, and 6% in the evobrutinib 75-mg twice-daily group); 2% of the patients in the evobrutinib 75-mg twice-daily group had a shift from normal to grade 2 lymphopenia. The percentage of patients with a shift from normal to a decreased lymphocyte count in the DMF group was 19.6% to grade 1 and 13.7% to grade 2. Findings over 52 weeks were similar. Data regarding shifts in the lymphocyte count from normal and from baseline are provided in Table S6 in the Supplementary Appendix.

Trial discontinuation owing to an adverse event associated with a trial agent was most frequent in the evobrutinib 75-mg once-daily and twice-daily groups (11% and 13%, respectively) (Fig. 1). Most of the discontinuations were due to protocol-mandated withdrawals for elevations in levels of ALT, AST, and lipase in evobrutinib-treated patients (Table S7 in the Supplementary Appendix). There were no deaths during the trial.

DISCUSSION

Biologic pathways involving activated B cells and myeloid cells play a role in multiple sclerosis,[1,3-6] and BTK inhibition may alter these pathways. After 24 weeks of treatment, the primary end point of the total number of gadolinium-enhancing lesions on T_1-weighted MRI, measured at weeks 12 through 24, was significantly lower among patients in the evobrutinib 75-mg once-daily group than in the placebo group. However, the difference with placebo was not significant in the groups that received either a lower dose or a higher dose of evobrutinib, as assessed by the lesion rate ratio adjusted for baseline lesion activity. Also, there was no significant between-group difference with placebo in the annualized relapse rate (a secondary outcome) at any evobrutinib dose. The trial was not designed to compare evobrutinib with DMF, but the percentage of patients in the DMF group who had not had a relapse at 24 weeks was 89%, as compared with 74%, 88%, and 87% in the three evobrutinib dose groups.

Evobrutinib 75-mg once-daily and twice-daily doses were associated with higher rates of adverse events, including grade 3 events, than the evobrutinib 25-mg dose or placebo. Higher evobrutinib doses were associated with a higher frequency of elevations in ALT, AST, or lipase levels than in the other trial groups at 52 weeks. Since most discontinuations from evobrutinib were caused by hepatobiliary disorders and changes in liver aminotransferase levels, the adoption of hepatic risk-mitigation strategies and stopping rules in future clinical trials may be appropriate.

This trial has several limitations. As compared with other trials involving patients with multiple sclerosis,[19,20,22-32] the population was older, the disease duration was longer, and fewer patients had had relapses within 2 years before baseline. These observations may have been related to the inclusion of patients with secondary progressive multiple sclerosis with superimposed relapses and a relatively high baseline EDSS score at trial entry. In addition, only white patients were enrolled, which may limit the generalizability of the findings to other populations. One patient in the DMF group had very large numbers of gadolinium-enhancing lesions at baseline and over 24 weeks, which may have influenced the results for the number of lesions in that group. In addition, this phase 2 trial was powered for MRI disease activity as an outcome measure; nevertheless, the confidence intervals for differences between evobrutinib and placebo in secondary end points did not support a significant effect for evobrutinib on other outcomes.

In conclusion, in patients with relapsing multiple sclerosis, the inhibition of BTK with evobrutinib at a dose of 75 mg once daily, but not at doses of 75 mg twice daily or 25 mg once daily, reduced the total number of enhancing MRI lesions, as compared with placebo, at weeks 12 through 24. Treatment with evobrutinib at any dose had no effect on the annualized relapse rate or disability progression and was associated with elevations in liver aminotransferase levels.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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