Three Times Weekly Glatiramer Acetate in Relapsing–Remitting Multiple Sclerosis

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Objective: To assess the efficacy and safety of glatiramer acetate (GA) 40mg administered 3× weekly (tiw) compared with placebo in patients with relapsing–remitting multiple sclerosis (RRMS).
Methods: This randomized, double-blind study was conducted in 142 sites in 17 countries. Patients with RRMS with at least 1 documented relapse in the 12 months before screening, or at least 2 documented relapses in the 24 months before screening, and an Expanded Disability Status Scale score $\leq$ 5.5, were randomized 2:1 to receive either subcutaneous (sc) GA 40mg tiw (1ml) or placebo for 12 months.
Results: Of 1,524 patients screened, 1,404 were randomized to receive GA 40mg sc tiw (n = 943) or placebo (n = 461). Ninety-three percent and 91% of patients in the placebo and GA groups, respectively, completed the 12-month study. GA 40mg tiw was associated with a 34.0% reduction in risk of confirmed relapses compared with placebo (mean annualized relapse rate = 0.331 vs 0.505; $p < 0.0001$). Patients who received GA 40mg tiw experienced highly significant reduction ($p < 0.0001$) in the cumulative number of gadolinium-enhancing T1 (44.8%) and new or newly enlarging T2 lesions (34.7%) at months 6 and 12. GA 40mg tiw was safe and well tolerated. The most common adverse events in the GA group were injection site reactions (35.5% with GA vs 5.0% with placebo).
Interpretation: GA 40mg sc tiw is a safe and effective regimen for the treatment of RRMS, providing the convenience of fewer sc injections per week.

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Multiple sclerosis (MS) is a chronic relapsing disorder of the central nervous system characterized by inflammation, multifocal demyelination, astrocytic proliferation, and neuronal and axonal damage.[1,2] MS affects >2 million people worldwide, with about 85% of patients presenting with a relapsing–remitting (RR) course, defined by acute attacks and intervening periods of full or partial recovery without disease progression.[3,4] Although there is no cure for MS, current disease-modifying therapies aimed at reducing relapse rates and slowing disease progression have improved the prognosis for patients with MS.[3]

Glatiramer acetate (GA), a heterogeneous mixture of synthetic polypeptides composed of 4 amino acids, is approved for reducing relapse frequency in patients with RRMS, including patients who have experienced a first clinical episode and have magnetic resonance imaging (MRI) features consistent with MS (clinically isolated syndromes).[5] Although the precise mechanism by which GA mediates clinical benefit in MS has not been fully elucidated, it is known to have multiple coordinated immunomodulatory effects involving T cells and B cells of the adaptive immune system, and antigen-nonspecific

Members of the GALA Study Group are listed in the Appendix on page 8.

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alteration of the function of antigen-presenting cells of the innate immune system.[6,7]

GA is approved as a 20mg daily subcutaneous (sc) injection.[5] Three randomized, double-blind, placebo-controlled studies with this dosing regimen and a meta-analysis of those studies demonstrated reduced annualized relapse rates (ARRs) and disease activity on MRI in patients with RRMS.[8–11] In a subsequent phase 3 study, GA 20mg significantly delayed progression to clinically definite MS and reduced MRI disease activity in patients with clinically isolated syndromes.[12]

A recent phase 3 dose comparison study of GA 40mg once daily in patients with RRMS showed similar safety and efficacy profiles compared with the 20mg, once-daily approved dose.[13] Two randomized exploratory studies have compared GA 20mg sc daily to GA 20mg sc administered on alternate days or twice weekly for 2 years.[14,15] Both studies showed no significant difference in the ARR and brain MRI T2 lesion volume between the alternate GA dosing regimens compared to daily GA. However, less frequent weekly administration of GA showed significantly fewer localized injection reactions including lipoatrophy compared to daily GA.[14,15] The GALA (Glatiramer Acetate Low-frequency Administration) study was designed to investigate the efficacy and safety of GA 40mg administered 3× weekly (tiw) in patients with RRMS. This dosing regimen would provide the convenience of fewer weekly injections while maintaining a similar weekly dose as the approved 20mg regimen.

Patients and Methods

Study Design and Patients

The GALA study was a randomized, placebo-controlled (PC), parallel-group, phase 3 study. It was conducted at 142 sites in 17 countries, including the United States, Bulgaria, Croatia, Germany, Poland, Romania, and Ukraine.

Patient eligibility criteria were previously described.[13] Briefly, patients were eligible for study participation if they were 18 to 55 years of age, had a confirmed RRMS diagnosis (according to the revised McDonald criteria[16]), had an Expanded Disability Status Scale (EDSS) score of $\leq$5.5, and were relapse-free for $\geq$30 days. Patients also were required to have $\geq$1 documented relapse in the 12 months prior to screening, $\geq$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 T1 gadolinium (Gd)-enhancing lesion in an MRI performed within 12 months of screening. Women of childbearing potential were required to practice an acceptable method of birth control.

Patients with progressive forms of MS and previous treatment with GA or any other glatiramoid were excluded. Other exclusion criteria included treatment with immunomodulators, including interferon-β and intravenous immunoglobulin, within 2 months of screening; use of immunosuppressive agents, including mitoxantrone and fingolimod, cytotoxic agents, or chronic (>30 days) systemic corticosteroid treatment within 6 months of screening; treatment with cladribine, natalizumab, or any other monoclonal antibody treatment within 2 years of screening; known sensitivity to Gd or mannitol; and inability to successfully undergo MRI scanning.

All institutional review boards or ethics committees of the participating centers approved the protocol, and all patients gave written informed consent before any study-related procedures were performed. Study progress was overseen by an independent data-monitoring committee.

Randomization and Blinding

Patients were treated with a tiw sc injection of either a single-use, prefilled syringe containing GA 40mg (Teva Pharmaceutical Industries, Petah Tikva, Israel) in a 1ml suspension containing 40mg of mannitol dissolved in water, or matching placebo (40mg of mannitol dissolved in water). During the randomization period, eligible patients were assigned to treatment groups in a 2:1 ratio (GA 40mg tiw or placebo) according to the randomization scheme produced by the study sponsor (Teva Pharmaceuticals). The randomization scheme used constrained blocks stratified by center.

The investigators, the sponsor, and any personnel involved in patients' assessments, monitoring, analysis, and data management were blinded to treatment assignment. Study drugs were packaged and labeled in a way that maintained the masked nature of the study; the appearance, shape, color, and smell were identical. Patients' general medical assessments were performed separately from the neurological assessments by 2 neurologists or physicians. The examining neurologist/physician was responsible for all neurological assessments.

Seven scheduled site visits occurred during the 12-month PC phase: at screening, baseline, and months 1, 3, 6, 9, and 12. Patients who completed the PC phase were given the opportunity to participate in an open-label phase, during which they would continue treatment with GA 40mg tiw until either the dose formulation is commercially available for the treatment of RRMS or development is stopped by the sponsor. The open-label phase is ongoing.

Procedures

A complete neurological assessment, including Kurtzke's EDSS and functional system (FS) assessment, was performed at screening, baseline, and months 3, 6, 9, and 12. Patients were instructed to contact their local center within 48 hours of onset of any symptoms suggestive of relapse. Patients with suspected relapses were evaluated within 7 days of symptom onset.

Relapse was defined as the appearance of $\geq$1 new neurological abnormalities or the reappearance of $\geq$1 previously observed neurological abnormalities lasting at least 48 hours and preceded by an improving neurological state of at least 30 days from the onset of previous relapse. An event was counted as a relapse when the patient's symptoms were accompanied by

TABLE 1. Baseline Patient and Disease Characteristics[a]

ITT Population	GA 40mg tiw, n = 943	Placebo, n = 461
Age, mean yr (± SD)	37.4 (9.4)	38.1 (9.2)
Female gender, No. [%]	641 [68.0]	313 [67.9]
Race/ethnicity, No. [%]		
Caucasian	916 [97.1]	455 [98.7]
Black/African American	12 [1.3]	3 [0.7]
Asian	2 [0.2]	0 [0.0]
Native American/Alaskan Native	1 [0.1]	0 [0.0]
Body mass index, mean (± SD)	24.4 (4.7)	24.4 (4.8)
Prior DMT treatment, No. [%]	128 [13.6]	63 [13.7]
EDSS, mean (± SD)	2.8 (1.2)	2.7 (1.2)
Years from onset of first MS symptoms, mean (± SD)	7.7 (6.7)	7.6 (6.4)
Exacerbations over 1 year prior to study initiation, mean (± SD)	1.3 (0.6)	1.3 (0.6)
Exacerbations over 2 years prior to study initiation, mean (± SD)	1.9 (0.9)	1.9 (0.9)
Number of GdE T1 lesions, mean (± SD)	1.7 (4.7)	1.4 (3.7)
Patients with >0 GdE T1 lesions, No. [%]	336 [35.6]	154 [33.4]
Volume of T2 lesion, mean ml (± SD)	19.7 (20.7)	17.4 (17.4)

[a]No significant differences between the 2 groups at baseline.
DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; GdE = gadolinium-enhancing; ITT = intent-to-treat; MS = multiple sclerosis; SD = standard deviation; tiw = 3× weekly.

observed objective neurological changes consistent with an increase of ≥0.5 points in the EDSS score compared with previous evaluation, or an increase of 1 grade in the actual score of ≥2 or more of the 7 FSs; or an increase of 2 grades in the score of 1 FS, compared with the previous assessment. The patient must not have had any acute metabolic changes, and a change in bowel/bladder function or cognitive function must not have been entirely responsible for confirmation of a relapse.

The treatment of relapses was determined by the examining neurologist, and the per-protocol allowed treatment consisted of intravenous methylprednisolone, 1g/day for 5 days. In addition to neurological assessment at the next scheduled visit, follow-up visits to monitor the course of the relapse were made at the discretion of the treating neurologist. All follow-up neurological examinations were performed by the blinded examining neurologist.

Brain MRI assessments were performed at baseline, and months 6 and 12. Before scanning study participants, MRI facilities underwent a qualification procedure to ensure that image acquisition was optimized and standardized per protocol, for measuring the endpoints specified by the study protocol. The MRI protocol included dual echo T2-weighted image (WI), 3-dimensional inversion recovery spoiled-gradient recalled T1-WI, fluid attenuated inversion recovery, and spin-echo T1-WI with and without Gd contrast. Brain MRI scans were obtained according to a protocol provided by the MRI reading center (Buffalo Neuroimaging Analysis Center, Buffalo, NY) that also performed all MRI analysis. The details of the MRI procedures are provided in the Supplementary Material.

Safety assessments included adverse events (AEs), standard clinical laboratory tests, vital signs, and electrocardiographic (ECG) measurements.

Statistical Analysis

A sample size of 1,350 patients (900 patients in the GA treatment group and 450 in the placebo group) was considered necessary to provide 90% power to detect a statistically significant difference in the total number of confirmed relapses between the treatment groups. The calculation accounted for an expected ARR of 0.35 in an untreated population, an expected ARR of ≤0.245 in the GA-treated population, and a dropout rate of 15%.

The principal analysis for the primary endpoint of total number of confirmed relapses during the 12-month PC phase was performed on the intent-to-treat (ITT) cohort, defined as all randomized patients. The GA group was compared with the placebo group using a baseline-adjusted quasi-likelihood (over-dispersed) negative binomial regression analysis with an offset based on the log of the patient's exposure to treatment. In addition to treatment group, the negative binomial regression model included the following covariates: baseline EDSS score, log of

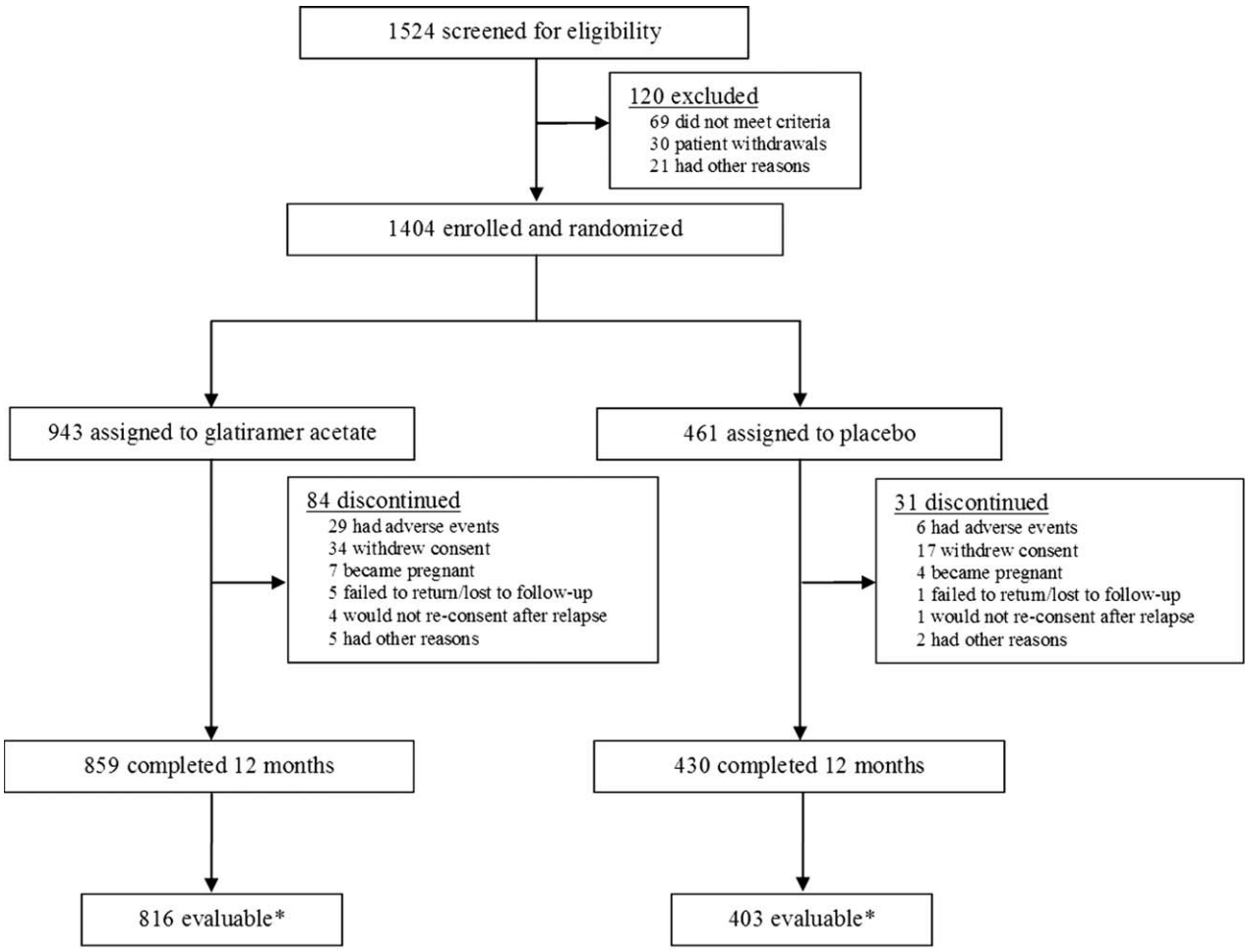


FIGURE 1: Patient disposition.

the number of relapses in the previous 2 years, volume of T2 lesions at baseline, status of Gd-enhancing T1 activity at baseline, and country or geographical region.

Significance testing of the prospectively defined secondary endpoints and their hierarchical order was predefined in the protocol. All secondary analyses were performed on the ITT population where data were available. The first 2 secondary endpoints, the cumulative number of new/newly enlarging T2 lesions at months 6 and 12 and the cumulative number of Gd-enhancing lesions on T1-WI taken at months 6 and 12, were analyzed using a baseline-adjusted negative binomial regression, with an offset employing the log of the proportion of the number of available postbaseline scans to adjust for missing scans. Patients who missed both 6- and 12-month scans were excluded from the analysis. The regression model included the number of Gd-enhancing lesions on T1-WI at baseline, and country or geographical region as covariates. The third endpoint, brain atrophy—defined as the percentage brain volume change from baseline to month 12—was analyzed using a baseline-adjusted analysis of covariance, with normalized brain volume at baseline, the number of Gd-enhancing lesions on T1-WI at baseline, and country or geographical region as covariates. Patients who missed brain volume measurements at 12 months were excluded from the analysis.

Exploratory endpoints included the time to the first confirmed relapse, the proportion of relapse-free patients, and the total number of severe confirmed relapses (defined as those requiring hospitalization or intravenous steroids). All exploratory analyses were performed on the ITT population during the PC phase. The time to the first confirmed relapse for the GA group versus the placebo group was compared using Cox's proportional hazards model. Censoring time was defined as the time from randomization until the PC phase termination date. In several cases, the PC phase termination date exceeded the study drug stop date. Baseline-adjusted logistic regression was used to analyze the proportion of relapse-free patients. Baseline-adjusted quasi-likelihood negative binomial regression with an offset based on the log of the patient's exposure to treatment was used to analyze the total number of severe relapses. Covariates included in all 3 exploratory models were baseline EDSS score, log of the number of relapses over the previous 2 years, volume of T2 lesions at baseline, status of Gd-enhancing T1 activity at baseline (0 if no lesions and 1 if lesions present), and country or geographical region.

TABLE 2. Annualized Relapse Rate/Severe Relapse Rate, Time to First Relapse, and Proportion of Relapse-Free Subjects

Endpoint	Analysis Estimate (95% CI)				
	GA 40mg tiw, n = 943	Placebo, n = 461	RR, GA vs placebo	*p*	RRR, GA vs placebo
Primary					
Annualized relapse rate	0.331 (0.280–0.392)	0.505 (0.418–0.609)	0.656 (0.539–0.799)	<0.0001	34.0%
Exploratory					
Annualized severe relapse rate	0.301 (0.252–0.359)	0.466 (0.383–0.568)	0.644 (0.526–0.790)	<0.0001	35.4%
Time to first relapse, days	393	377	0.606[a] (0.493–0.744)	<0.0001	NA
Relapse-free patients, %	77.0	65.5	1.928[b] (1.491–2.494)	<0.0001	NA

[a]Hazard ratio.
[b]Odds ratio.
CI = confidence interval; GA = glatiramer acetate; NA = not applicable; RR = risk ratio; RRR = relative risk reduction; tiw = 3× weekly.

Each of the exploratory endpoints was analyzed at a nominal significance level of 5%. As the exploratory endpoints were not part of the primary and secondary objectives, this did not affect the study's overall type I error.

Results

In total, 1,524 patients were screened for entry into the study (Fig). Of these patients, 1,404 were randomized to study treatment (GA 40mg tiw, n = 943; placebo, n = 461) and received at least 1 dose of treatment. Baseline demographics showed no significant differences between the 2 groups (Table 1). The majority of screening failures occurred because of study ineligibility (4.5%) and consent withdrawal (2.0%). The proportions of patients who discontinued were similar for the GA 40mg tiw (8.9%) and placebo (6.7%) groups. The

TABLE 3. Secondary Magnetic Resonance Imaging Endpoints

Endpoint	Analysis Estimate (95% CI)				
	GA 40mg tiw, n = 884[a]	Placebo, n = 441[a]	RR, GA vs placebo	*p*	RRR, GA vs placebo
Cumulative GdE T1 lesions at months 6 and 12	0.905 (0.750 to 1.093)	1.639 (1.300 to 2.066)	0.552 (0.436 to 0.699)	<0.0001	44.8%
Cumulative new or newly enlarging T2 lesions at months 6 and 12	3.650 (3.176 to 4.194)	5.592 (4.710 to 6.640)	0.653 (0.546 to 0.780)	<0.0001	34.7%
Percentage change in brain volume from baseline to month 12	−0.706 (−0.779 to −0.632)	−0.645 (−0.737 to −0.553)	−0.061 (−0.154 to 0.033)	0.2058	+9.4%

[a]For change in brain volume from baseline to month 12, n = 840 for GA 40mg tiw and n = 423 for placebo.
CI = confidence interval; GA = glatiramer acetate; GdE = gadolinium-enhancing; RR = risk ratio; RRR = relative risk reduction; tiw = 3× weekly.

TABLE 4. Frequency of Common AEs

AE	GA 40mg tiw, n = 943	Placebo, n = 461
Total	680 (72.1)	284 (61.6)
AEs occurring in ≥5% in either treatment group		
Injection site erythema	197 (20.9%)	7 (1.5%)
Nasopharyngitis	100 (10.6%)	39 (8.5%)
Injection site pain	98 (10.4%)	9 (2.0%)
Headache	95 (10.1%)	55 (11.9%)
Systemic immediate postinjection reactions	72 (7.6%)	8 (1.7%)
Injection site pruritus	56 (5.9%)	0 (0.0%)
Urinary tract infection	46 (4.9%)	23 (5.0%)
Upper respiratory tract infections	42 (4.5%)	25 (5.4%)

One patient death (cardiopulmonary failure) was reported in the placebo group.
AE = adverse event; GA = glatiramer acetate; tiw = 3× weekly.

main reasons for discontinuation were withdrawal of consent (3.6% for GA, 3.7% for placebo) followed by AEs (3.1% for GA, 1.3% for placebo).

Patients receiving GA 40mg tiw demonstrated a 34% reduction in the risk of confirmed relapse compared with placebo (mean ARR = 0.331 vs 0.505; risk ratio [RR] = 0.656, 95% confidence interval [CI] = 0.539–0.799, $p < 0.0001$; Table 2). EDSS progression was similar between treatment groups (Supplementary Table 1), and the time to first relapse was significantly longer in the GA 40mg tiw group compared with placebo (393 vs 377 days; hazard ratio = 0.606, 95% CI = 0.493–0.744, $p < 0.0001$). A greater proportion of patients were relapse-free during treatment with GA 40mg tiw compared with placebo (77.0% vs 65.5%). Relative to placebo, GA 40mg tiw was also associated with a significant 35% reduction in annualized rate of severe relapse (0.301 vs 0.466; RR = 0.644, 95% CI = 0.526–0.790, $p < 0.0001$).

Compared with patients receiving placebo, patients who received GA 40mg tiw experienced 45% reduction in the cumulative number of Gd-enhancing T1 lesions (RR = 0.552, 95% CI = 0.436–0.699, $p < 0.0001$) and 35% reduction in the cumulative number of new or newly enlarging T2 lesions (RR = 0.653; 95% CI = 0.546–0.780, $p < 0.0001$) at months 6 and 12 (Table 3). The percentage change in normalized brain volume at month 12 from baseline was not statistically different between treatment arms (−0.706 with GA vs −0.645 with placebo; $p = 0.2058$). Results of unadjusted and adjusted analyses for baseline characteristics, for primary and secondary endpoints, showed no significant differences (Supplementary Table 2).

AEs recorded in this study were consistent with the known safety profile of the approved 20mg formulation of GA. The most common AEs were injection site reactions (ISRs; 35.2% of GA 40mg tiw patients and 5.0% of placebo patients), 99.9% of which were mild or moderate in severity. The most common ISRs, with an incidence of >5% in the GA group, were erythema (20.9%), injection site pain (10.4%), and pruritis (5.9%; Table 4). At least 1 symptom related to systemic immediate postinjection reactions occurred in 7.6% of patients

TABLE 5. Immediate Postinjection Reactions

Adverse Event	GA 40mg tiw, n = 943	Placebo, n = 461
Total	72 (7.6%)	8 (1.7%)
Dyspnea	29 (3.1%)	2 (0.4%)
Feeling hot	12 (1.3%)	0 (0.0%)
Tachycardia	10 (1.1%)	1 (0.2%)
Flushing	9 (1.0%)	1 (0.2%)
Palpitations	9 (1.0%)	0 (0.0%)
Chest pain	8 (0.8%)	3 (0.7%)
Hyperemia	6 (0.6%)	0 (0.0%)
Chest discomfort	5 (0.5%)	1 (0.2%)
Musculoskeletal chest pain	4 (0.4%)	0 (0.0%)
Hot flush	3 (0.3%)	0 (0.0%)
Heart rate increased	2 (0.2%)	0 (0.0%)

GA = glatiramer acetate; tiw = 3× weekly.

who received GA 40mg tiw and 1.7% of patients who received placebo (see Tables 4 and 5).

Serious AEs occurred in approximately 4.5% of patients in each treatment group (see Table 4, Supplementary Table 3). During the PC phase, 1 patient in the placebo group died of cardiopulmonary failure during the study. AEs leading to discontinuation of treatment occurred in 3.1% of patients in the GA group and 1.3% of patients in the placebo group. The highest rate of discontinuation was attributed to ISRs, which led to discontinuation of GA 40mg tiw in 1.0% of patients. There was no increase in the incidence of infections or malignant diseases, or clinically significant changes or safety concerns, in either treatment group with regard to laboratory values, ECG readings, and vital signs.

Discussion

This study demonstrated that, compared with placebo, treatment with GA 40mg sc tiw was associated with a significant reduction in the total number of confirmed relapses in patients with RRMS over a 12-month period. The efficacy of GA 40mg tiw was also supported by secondary endpoints that demonstrated reduction of MRI-measured disease activity. The safety profile of GA 40mg tiw in this study was consistent with that of the approved 20mg once-daily dose.

The 40mg tiw schedule of GA was selected for the study because it provided a cumulative weekly dose of 120mg, similar to the 140mg cumulative weekly dose provided with the approved 20mg daily regimen. This alternative dosing regimen of GA provides the convenience of 4 fewer sc injections per week while maintaining a similar weekly dose. In the absence of adequate data regarding the efficacy of reduced injection frequency of GA 20mg in large, well-controlled studies, the conservative 40mg approach adopted by the GALA study was deemed most appropriate, in that a reduction in injection frequency would be offset by the use of a higher dose that had already been shown to be effective and safe when administered on a daily basis.[13,17]

The efficacy and safety of a 40mg dose of GA is supported by previous phase 2 and 3 dose comparison studies in which patients with RRMS were randomized to daily treatment with GA 40mg or 20mg.[12,17] The phase 2 study showed a trend toward an increased effect on clinical and MRI activity of the 40mg dose compared with the approved 20mg dose.[17] However, these findings were not supported by the phase 3 study, in which both doses of GA were equally effective in terms of ARR and MRI activity.[12]

In addition to the significant reduction of ARR observed with GA 40mg tiw versus placebo in the current study, secondary MRI analyses also support the conclusion that GA 40mg tiw was significantly more effective than placebo as demonstrated by significant reductions in cumulative numbers of Gd-enhancing lesions and new or enlarging T2 lesions at 6 and 12 months. These findings are consistent with previously reported reductions in ARR values (28–33% reduction) and improved MRI outcomes in patients treated with GA 20mg and 40mg once daily.[8,10,11,13] However, the differences between the designs of the previous studies with daily GA and the GALA study limit meaningful comparisons. Exploratory endpoints provided additional insight into the therapeutic effect of GA 40mg tiw, revealing significant advantages over placebo in the rate of severe relapse, time to first relapse, and the incidence of relapse-free patients.

Treatment with GA 40mg tiw was safe and well tolerated. The safety profile was comparable with that of GA 20mg once daily, which has been well established in patients with RRMS in previous clinical trials and postmarketing clinical experience.[5] Fewer than 5% of patients in either study group discontinued treatment because of AEs. Similar to this and other previous studies of GA 20mg once daily, ISRs remained the most commonly reported AE with GA 40mg tiw.[5,8,10,13] These reactions, which were predominantly mild, led to the discontinuation in the GA 40mg tiw arm in a small proportion of patients (1.0%). Notably, the incidence of ISRs in patients treated with GA 40mg tiw was approximately 20 to 50% less compared with previous studies of patients treated with GA 20mg and 40mg once daily.[8,10,13] The incidence of systemic immediate postinjection reactions in this study (7.6%) was lower than the approximately15% reported in other placebo-controlled studies with GA 20mg.[8,10]

In conclusion, this study has established GA 40mg tiw as a safe and effective alternative regimen for the treatment of RRMS. The use of GA 40mg tiw offers a treatment alternative for RRMS patients who prefer a less-frequent injection schedule.

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Authorship

All authors were members of the steering committee and site investigators. All authors reviewed the study report and contributed to its preparation.

Potential Conflicts of Interest

O.K.: consultancy, Teva, Biogen Idec, Genzyme, Novartis; grants/grants pending, NIH, NINDS, NMSS (USA), Teva, Novartis, Biogen Idec, Genzyme, Roche, Genentech, Sanofi-Aventis, Acorda Therapeutics; speaking fees, Teva, Novartis, Biogen Idec. P.R.: speaking fees, Bayer, Biogen Idec, Boehringer Ingelheim, Novartis, Merck Serono, Teva, Genzyme; clinical trial steering committees, Novartis, Merck Serono, Teva. A.B.: advisory boards, Bayer Schering, Merck Serono, Teva, Novartis, Biogen Idec, Nycomed, Genzyme. K.S.: board membership, Biogen Idec, Novartis, Genzyme, ONO Pharma, Roche, Synthon; consultancy, Bayer, Hoffman-La Roche, Biogen Idec, Merck Serono; speaking fees, Biogen Idec, Novartis, Merck Serono. R.Z.: consultancy, Teva, Biogen Idec, EMD Serono, Genzyme-Sanofi, Bayer, Questcor Pharmaceuticals, Novartis; grants/grants pending, Biogen Idec, Teva, Novartis, Genzyme-Sanofi, Bracco, Questcor Pharmaceuticals, EMD Serono; speaking fees, Teva, Biogen Idec, EMD Serono, Genzyme-Sanofi, Bayer, Questcor Pharmaceuticals, Novartis.

APPENDIX

GALA Study Group

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