P34

# Twenty-Seven Years of Continuous Treatment of Multiple Sclerosis With Glatiramer Acetate: Long-term Efficacy Results of the US Open-Label Extension Study

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## BACKGROUND

- Glatiramer acetate (GA) is the only treatment for relapsing-remitting multiple sclerosis (RRMS) that has been prospectively studied for up to 27 years in a continuously monitored, long-term study[1-6]
- In the pivotal trial (9001) of GA (20 mg subcutaneously [SC], once daily [QD]) in RRMS (n=251), the GA-treated group showed a 29% reduction in the relapse rate over 2 years (primary endpoint) compared to the placebo group ($P$=0.007)[3]
- This initial trial was extended for 11 months (9001E), under double-blind conditions, for a total of 35 months[7]
  - At 35 months, the relapse rate was reduced by 32% versus placebo ($P$=0.002)[7]
- After 35 months, most patients in the GA group entered a long-term, open-label extension (OLE) study (9004)
  - Follow-up data at 6, 10, and 15 years were published; they demonstrated the sustained clinical efficacy and safety of GA treatment[4-6,8]
  - Here we present the clinical efficacy results of the completed study (9004), spanning 27 years of GA treatment

## OBJECTIVE

- To assess the long-term efficacy of GA over a span of 27 years in patients with RRMS and to compare efficacy with early start (ES) of GA treatment to that of delayed start (DS) (i.e., delay of 35 months)

## METHODS

### Study Design

- At the end of the placebo-controlled 35-month US GA trial (9001E), patients could enter an OLE phase (9004) in which those receiving GA continued treatment (early start, ES), and those receiving placebo switched to GA (delayed start, DS)
- Patients were given the option to switch to GA 40 mg/mL SC three times weekly (TIW) in 2014, and the option to switch back to 20 mg/mL QD in 2017
- Any patient who stopped GA for any reason or who took another disease-modifying therapy was withdrawn from the study and further analyses
- Patients were required to provide informed consent for each study extension
- The 11 original US academic centers participated in the OLE study (9004), and their institutional review boards periodically reviewed and approved each site's ongoing participation in the study
- The study is now completed; the last patient visit date was March 29, 2018

### Endpoints

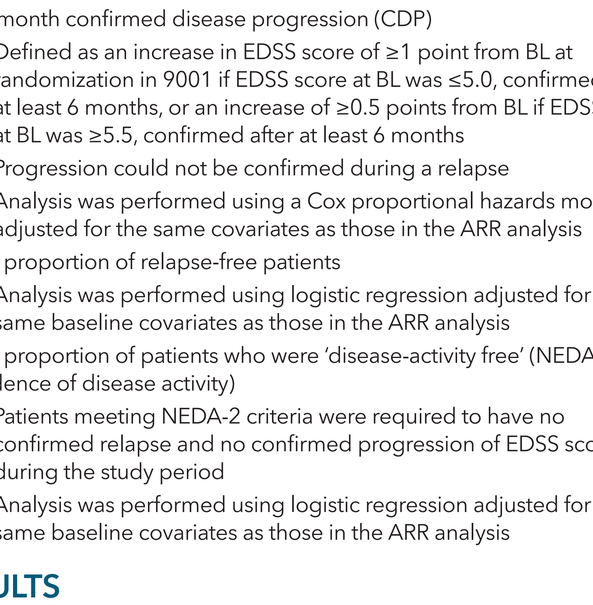
- Annualized relapse rate (ARR) (primary endpoint)
  - Obtained from a negative binomial log of exposure-weighted regression model adjusted for baseline (BL) Expanded Disability Status Scale (EDSS) score and number of relapses in the 2 years prior to the study
- Six-month confirmed disease progression (CDP)
  - Defined as an increase in EDSS score of ≥1 point from BL at randomization in 9001 if EDSS score at BL was ≤5.0, confirmed after at least 6 months, or an increase of ≥0.5 points from BL if EDSS score at BL was ≥5.5, confirmed after at least 6 months
  - Progression could not be confirmed during a relapse
  - Analysis was performed using a Cox proportional hazards model adjusted for the same covariates as those in the ARR analysis
- The proportion of relapse-free patients
  - Analysis was performed using logistic regression adjusted for the same baseline covariates as those in the ARR analysis
- The proportion of patients who were 'disease-activity free' (NEDA-2=no evidence of disease activity)
  - Patients meeting NEDA-2 criteria were required to have no confirmed relapse and no confirmed progression of EDSS score during the study period
  - Analysis was performed using logistic regression adjusted for the same baseline covariates as those in the ARR analysis

## RESULTS

### Patient Disposition

- Of 251 patients originally randomized to treatment with GA or placebo (9001/9001E), 208 entered the open-label study (9004), with 52 completing the study (**Figure 1**)
- In 2014, 39 patients (58.2%) switched to GA 40 mg/mL TIW; in 2017, one patient (2.6%) switched back to 20 mg/mL QD

**Figure 1. Patient Disposition**




GA, glatiramer acetate.

### Patient Demographics

- Mean age and duration of disease at randomization were 34.4 and 7.0 years, respectively
- At randomization, mean EDSS score was 2.6, and the mean number of relapses during the previous 2 years was 2.9 (**Table 1**)

**Table 1. Patient Demographics and Disease Characteristics at Randomization**

| Characteristic | ES (N=125) | DS (N=126) | All (N=251) |
|---|---|---|---|
| **Demographics** | | | |
| Age at randomization (y), mean (SD) | 34.6 (6.0) | 34.3 (6.5) | 34.4 (6.2) |
| Sex, female, n (%) | 88 (70) | 96 (76) | 184 (73) |
| **Baseline disease characteristics** | | | |
| Age at onset (y) of first MS symptoms, mean (SD) | 27.3 (5.9) | 27.6 (6.5) | 27.5 (6.2) |
| Duration of disease at randomization (y), mean (SD) | 7.3 (4.9) | 6.6 (5.1) | 7.0 (5.0) |
| EDSS score at randomization, mean (SD) | 2.8 (1.2) | 2.4 (1.3) | 2.6 (1.3) |
| No. of relapses during the last 2 years at randomization, mean (SD) | 2.9 (1.3) | 2.9 (1.1) | 2.9 (1.2) |

EDSS, Expanded Disability Status Scale; ES, early start; DS, delayed start; GA, glatiramer acetate; MS, multiple sclerosis; SD, standard deviation; y, year.

### Exposure to GA

- The mean (±SD) study duration was 13.6±9.0 years (ES: 13.5±9.0; DS: 13.7±9.1)
- The mean (±SD) duration of GA treatment was 12.3±9.3 years (ES: 12.4±9.6; DS: 12.1±9.1)
  - The median (min, max) duration of GA treatment was 9.8 (0.1, 26.3) years (ES: 9.4 [0.1, 26.3]; DS: 10.6 [0.1, 23.5])
- A total of 29.5% of patients had >20 years exposure to GA (**Table 2**)

**Table 2. Distribution of Patients by Duration of GA Exposure**

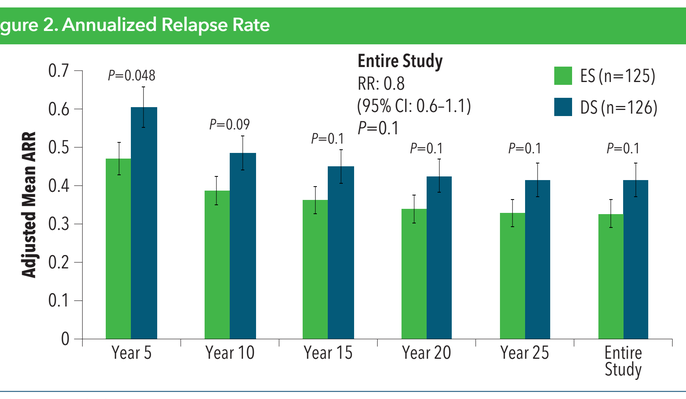
| Duration of GA Exposure | ES (n=125) | DS (n=126) | All (N=251) |
|---|---|---|---|
| None, n (%) | 0 (0) | 19 (15) | 19 (8) |
| >0 years to ≤1 year, n (%) | 9 (7) | 12 (10) | 21 (8) |
| >1 year to ≤2 years, n (%) | 7 (6) | 8 (6) | 15 (6) |
| >2 years to ≤5 years, n (%) | 26 (21) | 17 (13) | 43 (17) |
| >5 years to ≤10 years, n (%) | 24 (19) | 15 (12) | 39 (16) |
| >10 years to ≤15 years, n (%) | 9 (7) | 8 (6) | 17 (7) |
| >15 years to ≤20 years, n (%) | 8 (6) | 15 (12) | 23 (9) |
| >20 years to ≤25 years, n (%) | 16 (13) | 32 (25) | 48 (19) |
| >25 years to ≤30 years, n (%) | 26 (21) | 0 (0) | 26 (10) |

DS, delayed start; ES, early start; GA, glatiramer acetate.

### Mean Accumulated ARR

- Over the entire study period, the BL-adjusted ARR was 0.3 for ES and 0.4 for DS (RR: 0.8; 95% confidence interval [CI]: 0.6, 1.1; $P$=0.1) (**Figure 2**)

**Figure 2. Annualized Relapse Rate**

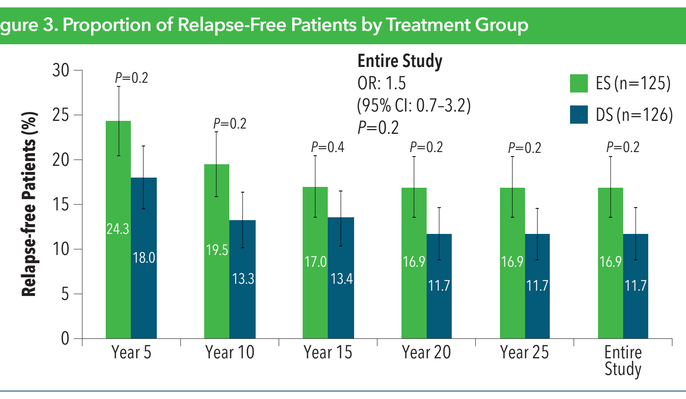



Error bars are standard error.
ARR, annualized relapse rate; CI, confidence interval; DS, delayed start; ES, early start; RR, risk ratio.

### Cumulative Proportion of Relapse-Free Patients

- BL-adjusted percent of patients without relapse over the entire study period was 16.9% for ES and 11.7% for DS (odds ratio [OR]: 1.5; 95% CI: 0.7, 3.2; $P$=0.2) (**Figure 3**)

**Figure 3. Proportion of Relapse-Free Patients by Treatment Group**

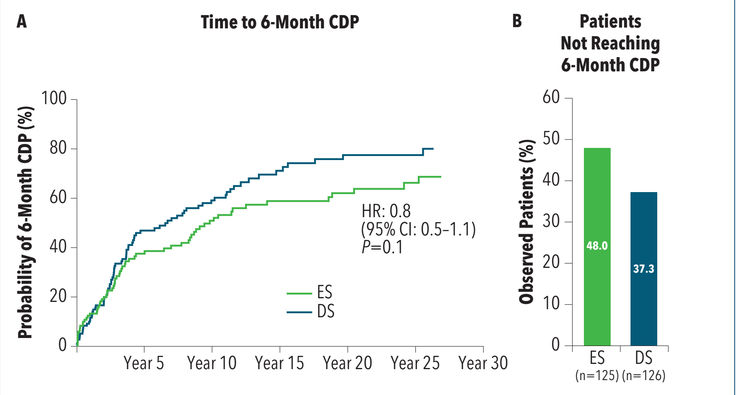



Error bars are standard error.
CI, confidence interval; DS, delayed start; ES, early start; OR, odds ratio.

### Years to 6-Month CDP

- ES treatment prolonged the time to 6-month CDP (median of 9.8 years) compared with DS treatment (median of 6.7 years) (hazard ratio: 0.8; 95% CI: 0.5, 1.1; $P$=0.1) (**Figure 4**)
- The observed proportion of patients who remained free of 6-month CDP was 48.0% for ES and 37.3% for DS treatment

**Figure 4. Years to 6-Month CDP by Treatment Group**




Population at risk

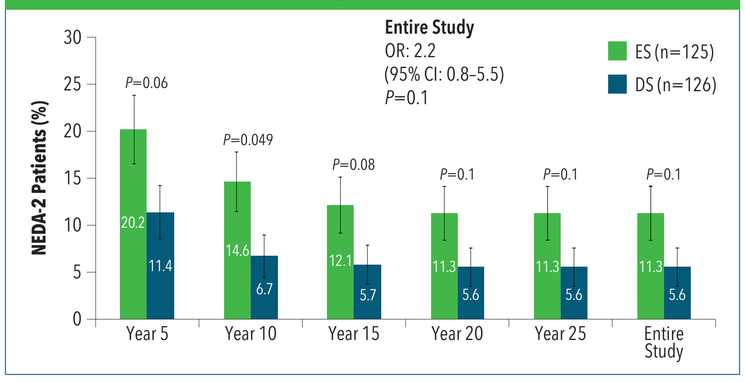
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ES (n) | 125 | 59 | 43 | 28 | 23 | 14 | 0 |
| DS (n) | 126 | 55 | 38 | 19 | 14 | 10 | 0 |

CDP, confirmed disease progression; CI, confidence interval; DS, delayed start; ES, early start; HR, hazard ratio.

### Cumulative Proportion of 'Disease Activity–Free' Patients

- BL-adjusted percentage of 'disease activity–free' patients (as defined by NEDA-2 criteria, i.e., no relapse, no 6-month CDP) over the entire study period was 11.3% for ES and 5.6% for DS (OR: 2.2; 95% CI: 0.8, 5.5; $P$=0.1) (**Figure 5**)

**Figure 5. Proportion of Patients Meeting NEDA-2 Criteria by Treatment Group**




Error bars are standard error.
CI, confidence interval; DS, delayed start; ES, early start; NEDA-2, no evidence of disease activity; OR, odds ratio.

## CONCLUSIONS

- Results from the 27-year open-label extended study reinforce the effective use of GA in patients with RRMS
  - ARR, proportion of relapse-free patients, and proportion of patients meeting NEDA-2 criteria remained relatively stable from year 10 to year 25
  - A high proportion of GA-treated patients remained free of 6-month CDP over the entire study period
- Early initiation of GA increased clinical benefit compared to delayed GA treatment
  - The mean ARR for the first 5 years of the study was significantly lower in the ES group versus the DS group
  - The proportion of patients meeting NEDA-2 criteria was significantly lower in the ES group versus the DS group at Year 10 of the study
  - All endpoints remained numerically lower in the ES group versus the DS group over the course of the study, suggesting the benefits of early GA treatment
- Limitations of the study include the lack of a continuous randomized placebo arm and possible selection bias caused by patient dropout
- With data from more than 25 years, this is the longest clinical study to routinely and continuously evaluate the efficacy of any monotherapy in patients with RRMS

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**Yafit Stark** is a former employee of Teva Pharmaceuticals, Netanya, Israel.

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