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Long-Term Efficacy Including Clinical NEDA and Safety of Three-Times-Weekly Dosing Regimen of Glatiramer Acetate: 7-Year Results of the Glatiramer Acetate Low-Frequency Administration (GALA) Open-Label Extension Study

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BACKGROUND

- Glatiramer acetate (GA) is a first-line therapy approved for the treatment of relapsing forms of multiple sclerosis (MS), including clinically isolated syndrome (CIS)[1,2]
- GA has a well-characterized long-term safety profile and established efficacy, with more than 2 million patient-years of overall exposure to GA, administered daily via subcutaneous injection[2]
- Earlier initiation of GA 20 mg/mL once-daily subcutaneous injections (GA20) treatment is associated with greater reduction in number of relapses and reduced conversion of CIS to MS[3,4]
- The GALA study was an international phase 3 trial conducted at 142 sites to investigate the efficacy and safety of a GA 40 mg/mL subcutaneous injection administered 3 times weekly (GA40) over 12 months to patients with relapsing-remitting MS (RRMS)[5]
  - The less-frequent GA40 dosing regimen was shown to have an efficacy and safety profile similar to that of the established GA20 regimen[5]
  - The GALA study showed that GA40 dosing significantly reduced the number of confirmed relapses and the number of cumulative gadolinium-enhancing (GdE) T1 and new or enlarging T2 lesions in patients with RRMS[5]
- Patients who completed the 12-month placebo-controlled (PC) phase of the GALA study were eligible to receive GA40 treatment in an ongoing open-label extension (OLE) study[6]
- Three-year interim results of the OLE study have been published and show comparable relapse and magnetic resonance imaging activity between early start (ES) and delayed start (DS) patients in Years 2 and 3, suggesting that DS patients experience benefit on initiation of GA40[6]
  - Adverse events (AEs) in the OLE study were consistent with those of the PC phase[6]

OBJECTIVE

- To describe the long-term effects of ES and DS GA40 treatment for up to 7 years in the GALA study

METHODS

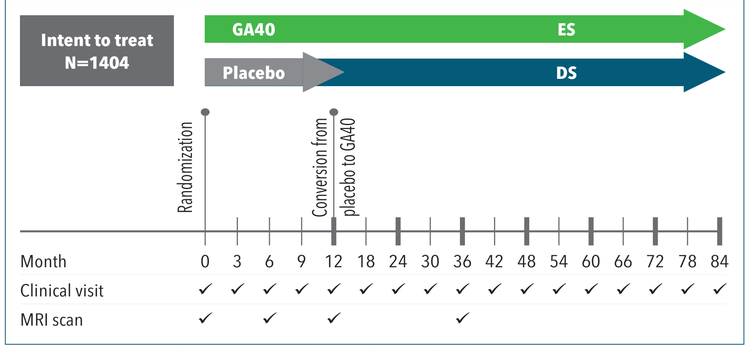
Study Design

- The patient eligibility criteria have been described previously[5]
- Of the 1404 patients originally randomized to the study, 1289 (92%) patients completed the PC phase; 1253 (97%) patients who completed the PC phase continued into the OLE phase
  - ES patients (n=834) received GA40 for the duration of the study (i.e. the PC and OLE phases)
  - DS patients (n=419) converted from placebo to GA40 at Month 12 (i.e. the end of the PC phase and beginning of the OLE phase)

Procedures

- Procedures and evaluations performed during the PC phase have been described previously[5] (**Figure 1**)
- The OLE phase included scheduled visits every 3 months for the first 12 months, then every 6 months thereafter
  - Each visit: vital signs, concomitant medications, AEs, and evaluation of relapse[6]
  - Every 6 months: a neurological and physical examination[6]
  - Every 12 months: electrocardiograms, safety laboratory tests, and serum pregnancy tests[6]

Figure 1. Study Design



DS, delayed start; ES, early start; GA40, glatiramer acetate 40 mg/mL 3 times weekly; MRI, magnetic resonance imaging.

Endpoints

- Primary endpoint: annualized relapse rate (ARR)
- Additional endpoints were exploratory or *post hoc* analyses
- Safety endpoints included frequencies of total AEs, serious AEs, and common AEs

Statistical Analyses

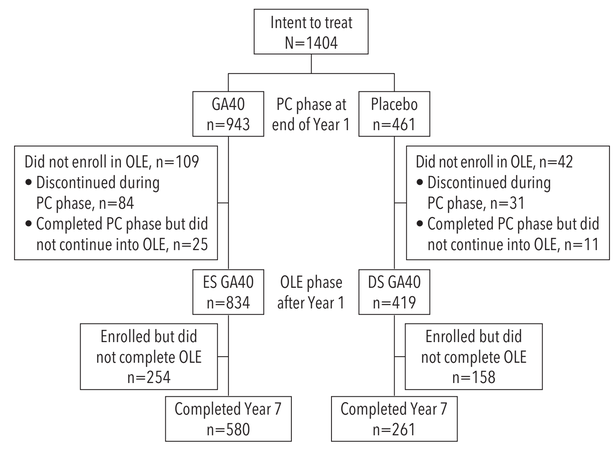
- For efficacy, all analyses were based on data from the intent-to-treat (ITT) population, including all randomized patients (N=1404), regardless of continuation status to the OLE phase
- For safety, exposure only under GA40 was considered
- All time-to-event analyses were measured from the PC baseline throughout the OLE phase and are presented in Kaplan–Meier curves
- ARR estimates were derived from a baseline (BL)-adjusted exposure-weighted negative binomial regression modeling the number of confirmed relapses observed during the entire study period
  - Covariates included baseline Expanded Disability Status Scale score, log of the number of relapses in the previous 2 years, BL volume of T2 lesions, BL status of GdE T1 activity, and country/geographic region (CGR)
- Time-to-event endpoints were analyzed using the BL-adjusted Cox proportional hazards model. The analysis model was adjusted for the same covariates as those in the ARR analysis
- Proportions were derived from unadjusted (no evidence of disease activity [NEDA-2]) or BL-adjusted logistic regression models (relapse free and free from 6-month confirmed disease progression [CDP]). Covariates were the same as those in the ARR analysis, except for CGR, which was excluded from part of the non-cumulative by-year analyses due to model convergence issues

RESULTS

Patient Disposition

- A total of 1404 patients (ITT analysis set) were randomized to GA (n=943) or placebo (n=461)
- After completion of the 1-year PC phase, 834 (88%) ES patients and 419 (91%) DS patients continued into the 6-year OLE study. 580/834 (70%) ES patients and 261/419 (62%) DS patients completed the GALA OLE study (**Figure 2**)
- The most common reasons for discontinuation were withdrawal of consent (21%, n=299) and AEs (7%, n=93)
- The median follow-up for the ITT population was 5.5 years

Figure 2. Patient Disposition



DS, delayed start; ES, early start; GA40, glatiramer acetate 40 mg/mL 3 times weekly; OLE, open-label extension; PC, placebo-controlled.

Duration of GA Exposure

- The overall ITT median GA exposure was 4.9 years
- 10% of patients were exposed to GA for more than 6 years (**Table 1**)

Table 1. Duration of GA Exposure by Treatment Category

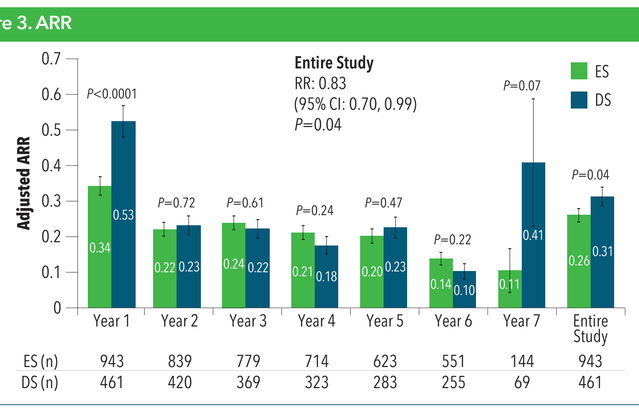
	ES (n=943)	DS (n=461)	All (N=1404)
All, n (%)	943 (100)	461 (100)	1404 (100)
Exposure to GA treatment category			
>0 years to ≤1 year, n (%)	107 (11)	45 (10)	152 (11)
>1 year to ≤2 years, n (%)	58 (6)	48 (10)	106 (8)
>2 years to ≤3 years, n (%)	68 (7)	43 (9)	111 (8)
>3 years to ≤4 years, n (%)	86 (9)	26 (6)	112 (8)
>4 years to ≤5 years, n (%)	70 (7)	180 (39)	250 (18)
>5 years to ≤6 years, n (%)	419 (44)	77 (17)	496 (35)
>6 years, n (%)	135 (14)	0 (0)	135 (10)

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

Annualized Relapse Rate

- During the entire study period, the ARR was 0.26 for ES patients and 0.31 for DS patients (risk ratio: 0.83; 95% confidence interval [CI]: 0.70, 0.99; *P*=0.04) (**Figure 3**)

Figure 3. ARR

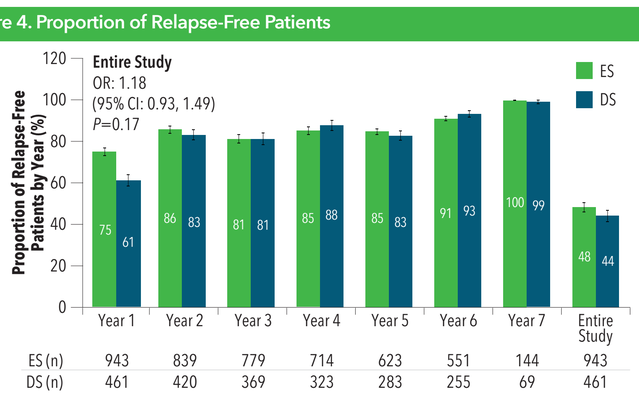


Error bars show standard error.
ARR, annualized relapse rate; CI, confidence interval; DS, delayed start; ES, early start; RR, risk ratio.

Proportion of Relapse-Free Patients

- The percentage of patients without relapse over the entire study period was 48% for ES patients and 44% for DS patients (odds ratio [OR]: 1.18; 95% CI: 0.93, 1.49; *P*=0.17) (**Figure 4**)

Figure 4. Proportion of Relapse-Free Patients

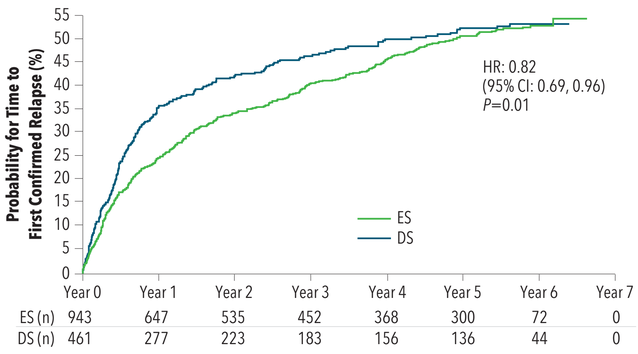


Error bars show standard error.
CI, confidence interval; DS, delayed start; ES, early start; OR, odds ratio.

Time to First Confirmed Relapse

- ES treatment prolonged the median time from randomization to first relapse (4.91 years) by 6 months (4.32 years) compared with DS treatment. Analysis significantly favored ES treatment (hazard ratio [HR]: 0.82; 95% CI: 0.69, 0.96; *P*=0.01) (**Figure 5**)

Figure 5. Time to First Confirmed Relapse

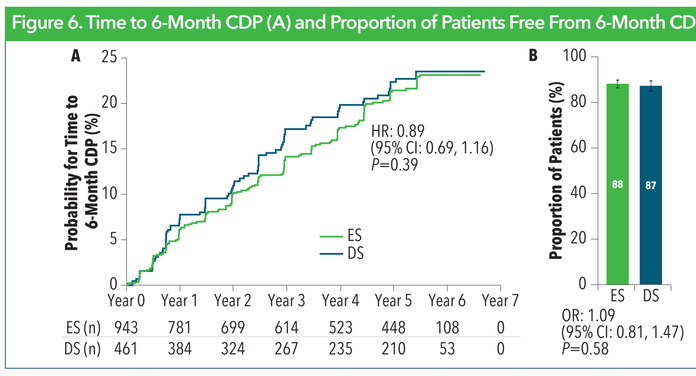


CI, confidence interval; DS, delayed start; ES, early start; HR, hazard ratio.

Time to 6-Month CDP and Proportion of Patients Free From 6-Month CDP

- Over the entire study, the HR for time to 6-month CDP of ES treatment compared with DS treatment was 0.89; 95% CI: 0.69, 1.16; *P*=0.39 (**Figure 6A**)
- The BL-adjusted percentage of patients without 6-month CDP was 88% for ES treatment and 87% for DS treatment (**Figure 6B**)

Figure 6. Time to 6-Month CDP (A) and Proportion of Patients Free From 6-Month CDP (B)

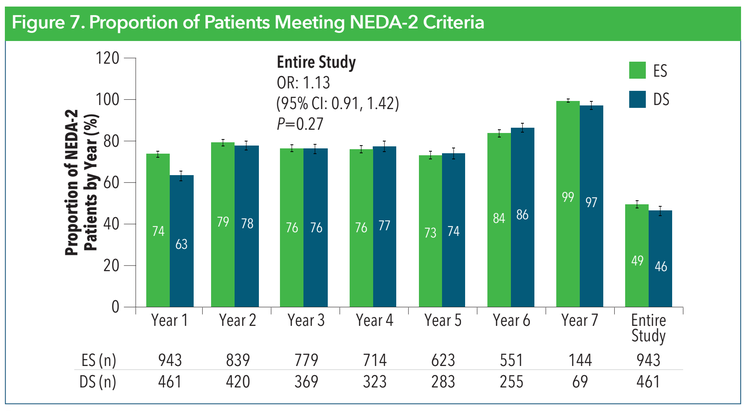


CI, confidence interval; CDP, confirmed disease progression; DS, delayed start; ES, early start; HR, hazard ratio; OR, odds ratio.

Proportion of Patients Meeting NEDA-2 Criteria

- During the entire study period, the unadjusted proportions of patients meeting NEDA-2 criteria (defined as no relapse and no 6-month CDP) were 49% for ES patients and 46% for DS patients (OR: 1.13; 95% CI: 0.91, 1.42; *P*=0.27) (**Figure 7**)

Figure 7. Proportion of Patients Meeting NEDA-2 Criteria



Error bars show standard error.
CI, confidence interval; DS, delayed start; ES, early start; NEDA-2, no evidence of disease activity (no relapse and no 6-month confirmed disease progression); OR, odds ratio.

Safety Profile

- The most common AEs – injection-site reactions (40%) and immediate post-injection reactions (12%) – were generally mild and consistent with the well-established GA safety profile (**Table 2**)

Table 2: Frequency of Common AEs in All Patients Exposed to GA40

	PC Phase	OLE Phase		
	GA40 (n=943, PY=884.4)	ES (n=943, PY=4169.7)	DS (n=419, PY=1549.2)	All (N=1362, PY=5718.8)
Patients with serious AEs, total, n (%)	42 (5)	117 (12)	36 (9)	153 (11)
Patients with AEs, total, n (%)	680 (72)	777 (82)	322 (77)	1099 (81)
Influenza	36 (4)	68 (7)	25 (6)	93 (7)
Nasopharyngitis	100 (11)	167 (18)	56 (13)	223 (16)
Upper respiratory tract infection	46 (5)	98 (10)	32 (8)	130 (10)
Urinary tract infection	46 (5)	105 (11)	36 (9)	141 (10)
Back pain	30 (3)	99 (10)	33 (8)	132 (10)
Headache	95 (10)	132 (14)	39 (9)	171 (13)
Injection-site reaction	332 (35)	378 (40)	162 (39)	540 (40)
Immediate post-injection reaction	14 (2)	119 (13)	41 (10)	160 (12)

AE, adverse event; DS, delayed start; ES, early start; GA40, glatiramer acetate 40 mg/mL subcutaneous injection administered 3 times weekly; OLE, open-label extension; PC, placebo-controlled; PY, patient-years.

CONCLUSIONS

- Treatment with GA40 over 7 years showed sustained efficacy at levels comparable to those in the OLE study with GA20 and the phase 3 trials with GA20 and GA40[4,5,7,8]
- At the end of the OLE study, 60% of patients remained on GA40 treatment for up to 7 years
- 48% and 44% of patients in the ES and DS groups, respectively, were free of relapse over 7 years
- 88% and 87% of patients in the ES and DS groups, respectively, did not experience 6-month CDP over 7 years
- The annual unadjusted proportion of patients remaining free of clinical disease activity (NEDA-2) was high in GA40-treated patients and was maintained over 7 years
- After converting from placebo to GA40, DS patients experienced similar efficacy (e.g. ARR, percentage of relapse-free patients, percentage of patients meeting NEDA criteria) compared with ES patients
- No new or unexpected AEs emerged in patients receiving GA40 for up to 7 years

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Disclosures

Peter Rieckmann was the co-PI international for the GALA study.

Jessica Alexander reports personal fees as an employee of Teva Pharmaceuticals.

Shaul Kadosh is a former employee of Teva Pharmaceuticals, Netanya, Israel, and reports personal fees for consulting for Teva Pharmaceuticals.

Svetlana Rubinchick reports personal fees as an employee of Teva Pharmaceuticals, Netanya, Israel.

Emily Bernstein-Hanlon reports personal fees as an employee of Teva Pharmaceuticals, Netanya, Israel.

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

Robert Zivadinov has no relevant conflicts.

References

1. Copaxone [prescribing information]. Overland Park, KS: Teva Neuroscience, Inc.; 2019.
2. Boster AL *et al. Expert Rev Neurother* 2015;15:575–586.
3. Comi G *et al. Lancet* 2009;374:1503–1511.
4. Johnson KP *et al. Mult Scler* 2003;9:585–591.
5. Khan O *et al. Ann Neurol* 2013;73:705–713.
6. Khan O *et al. Mult Scler* 2017;23:818–829.
7. Johnson KP *et al. Neurology* 1995;45:1268–1276.
8. Johnson KP *et al. Neurology* 1998;50:701–708.

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