Background

- Glatiramer acetate (GA), the acetate salt of synthetic polypeptides, is composed of four amino acids: L-glutamic acid, L-alanine, L-tyrosine, and L-lysine
- GA 40 mg/1 mL subcutaneous (s.c.) three-times weekly (tiw) injection:
  - Is approved for the reduction of relapses in patients with relapsing-remitting multiple sclerosis (RRMS)
  - Requires fewer s.c. injections
  - Has an efficacy and safety profile consistent with the established GA 20 mg/1 mL once-daily (qd) regimen (Copaxone)
- Reducing the number of s.c. injections should improve patients’ treatment experience

Study Purpose and Objectives

- Rationale
  - To provide information about the safety, tolerability, and patient experience after converting from GA 20 mg qd to GA 40 mg tiw in order to demonstrate the clinical value of the new formulation
- Objectives
  - To assess injection reactions with GA 40 mg tiw compared with GA 20 mg qd
  - To assess patient perceptions of treatment convenience and satisfaction with GA 40 mg tiw and GA 20 mg qd

Author Disclosures

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Scott Kolodny: Employee of Teva Pharmaceuticals

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**Study Design**

<table>
<thead>
<tr>
<th>Screening (up to 1 month)</th>
<th>Core phase* (4 months)</th>
<th>Extension phase**</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA 20 mgqd</td>
<td>GA 20 mgqd</td>
<td>GA 40 mg tiw</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Months</td>
<td>Months</td>
<td>Months</td>
</tr>
</tbody>
</table>

Eligible patients

GA 20 mgqd

- Complete neurometric assessment (EDSS, FS)
- Subject reported outcomes questionnaires
- ECG and safety/laboratory tests (hematology, biochemistry)
- Vital signs measurement and physical examination

Inclusion 18 years of age or older

Confirmed and documented RRMS diagnosis (revised McDonald criteria)

Ambulatory with an Expanded Disability Status Scale (EDSS) score of 0–5.5

Stable neurological condition and relapse-free for 60 days prior to randomization

Treated with GA 20 mgqd for 26 months prior to screening

Exclusion

Subjects with progressive forms of MS or neuromyelitis optica

Use of other disease-modifying drugs for MS, investigational drugs, or participation in drug clinical trial studies within the 6 months prior to screening

Clinically significant or unstable medical or surgical condition that would preclude safe and complete study participation

**Baseline Disease Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>GA 20 mgqd (n=101)</th>
<th>GA 40 mg tiw (n=108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean (SD)</td>
<td>50.4 (9.3)</td>
<td>50.9 (11.0)</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>83 (82.2)</td>
<td>89 (82.4)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>96 (95.0)</td>
<td>100 (92.6)</td>
</tr>
<tr>
<td>Black/African American</td>
<td>5 (5.0)</td>
<td>5 (4.6)</td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Body mass index, mean (SD)</td>
<td>29.3 (6.4)</td>
<td>27.9 (6.2)</td>
</tr>
<tr>
<td>Years from onset of symptoms, mean (SD)</td>
<td>16.2 (11.0)</td>
<td>15.7 (11.1)</td>
</tr>
<tr>
<td>Years from MS diagnosis, mean (SD)</td>
<td>12.1 (10.0)</td>
<td>10.8 (8.6)</td>
</tr>
<tr>
<td>Exacerbations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>During 1 year before study, mean (SD)</td>
<td>0.2 (0.4)</td>
<td>0.2 (0.5)</td>
</tr>
<tr>
<td>During 2 years before study, mean (SD)</td>
<td>0.4 (0.7)</td>
<td>0.4 (0.6)</td>
</tr>
<tr>
<td>EDSS baseline score, median (range)</td>
<td>2.5 (0.0–5.5)</td>
<td>2.0 (0.0–5.5)</td>
</tr>
</tbody>
</table>

**SD, standard deviation**
Study Endpoints and Methodology

- **Primary endpoint**
  - The rate of injection-related adverse events (IRAEs) in subjects treated with GA 40 mg tiw versus GA 20 mg qd
    - Injection site reactions (ISRs): e.g. pain, swelling, erythema and/or symptoms/events related to immediate post-injection reactions (PIRs): e.g. flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction, urticaria
  - **Secondary endpoints**
    - The rate of ISRs in each study group
    - The impact on (1) physical well-being and (2) psychological well-being using the Multiple Sclerosis Impact Scale-29 (MSIS-29)
    - Subjects’ perceptions of (1) convenience and (2) overall satisfaction using the Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9)

- Per the open-label design, raters and subjects were not blinded; conclusions should be interpreted accordingly

Primary Endpoint: Reduction in the Annualized Rate of IRAEs With GA 40 mg tiw Compared With GA 20 mg qd

Secondary Endpoint Result: MSIS-29 Physical Score

In cases where ISR started on the same date for the same patient, they are counted as one ISR event for that patient
*RR (95% CI) and adjusted means (SE) are derived from a baseline-adjusted, quasi-likelihood (over-dispersed) Poisson regression with natural log of treatment duration (years) as an offset variable, adjusted for baseline EDSS score, treatment group, age, sex, and number of relapses in the 2 years prior to screening.
*The reported secondary endpoints were hierarchically organized for multiplicity adjustment using Bonferroni approach. Since the second secondary endpoint (MSIS-29 physical score) failed to show statistically significant difference, all further analyses of secondary endpoints could not be checked for significance difference.

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Secondary Endpoint Result: MSIS-29 Psychological Score

Unadjusted mean score over time

Adjusted mean score change (baseline to Month 4)

Treatment effect = -0.721
95% CI: -3.181 to 0.738

No difference between treatment arms

*Treatment effect (95% CI) and adjusted means (95% CI) derived from mixed model repeated measures analysis, adjusted for MSIS-29 score at baseline, treatment group, month, and treatment by month interaction.

Secondary Endpoint Result: TSQM-9 Convenience Score (Items 4, 5 and 6)

Unadjusted mean score over time

Adjusted mean score change (baseline to Month 4)

Treatment effect = 7.005
95% CI: 3.021–10.989

GA 40 mg tiw is perceived as more convenient than GA 20 mg qd

*Treatment effect (95% CI) and adjusted means (95% CI) derived from mixed model repeated measures analysis, adjusted for TSQM-9 score at baseline, treatment group, month, and treatment by month interaction.

Secondary Endpoint Result: TSQM-9 Satisfaction Score (Items 7, 8 and 9)

Unadjusted mean score over time

Adjusted mean score change (baseline to Month 4)

Treatment effect = -0.852
95% CI: -4.928 to 3.224

No difference between treatment arms

*Treatment effect (95% CI) and adjusted means (95% CI) derived from mixed model repeated measures analysis, adjusted for TSQM-9 score at baseline, treatment group, month, and treatment by month interaction.

Safety Endpoint: AEs – Event Rate per Year

Event rate per year

Event rate per year in patients with injection-site AE

*Event rate per year = total number of events/exposure to study drug (in years)
Conclusions

• The new dose regimen for Copaxone, GA 40 mg tiw, is shown to have a 50% lower rate of IRAEs compared with GA 20 mg qd
• Similarly, the rate of ISRs was significantly reduced by 50% in the GA 40 mg tiw group compared with the GA 20 mg qd group
• The MSIS-29 and TSQM-9 questionnaires demonstrated that patient-reported outcomes were comparable between the GA 40 mg tiw and GA 20 mg qd groups
• The most common AE was ISR
• No new safety signals for Copaxone were reported, and both doses of Copaxone were well-tolerated

The GA 40 mg tiw dosing regimen is a more favorable treatment option for patients who want Copaxone treatment but prefer fewer weekly s.c. injections

Acknowledgments