**Introduction**

- Gabapentin enacarbil (GEN) is an orally administered prodrug of gabapentin that has been approved by the United States FDA at a dose of 600 mg once daily for the treatment of moderate-to-severe primary RLS in adults.\(^1\)

- In 3 randomized, double-blind, placebo-controlled trials (XP052/XP053/XP081) in patients with moderate-to-severe primary RLS, GEN 1200 mg improved RLS symptoms compared with placebo with regard to the mean change from baseline in International Restless Legs Scale (IRLS) total score (primary outcome) in the investigator-rated Clinical Global Impression-Improvement (CGI-I) scale at week 12.\(^2\)

- In studies XP052 and XP011, similar results were obtained with GEN 600 mg.\(^3\)

- GEN was well tolerated in all 3 studies; the most commonly reported adverse events (AEs) were somnolence and dizziness.\(^4\)

- The primary analyses focused on the overall study population of patients with moderate-to-severe RLS, but did not investigate efficacy in the subset of patients with severe primary RLS.

**Objective**

- To further investigate the efficacy and safety of GEN in the subset of patients with severe primary RLS using pooled data from the XP052, XP053, and XP081 studies from the GEN 600 mg, GEN 1200 mg, and placebo treatment groups.

**Methods**

**Study design**

- The design of the 3-week, 12-randomized, double-blind, placebo-controlled trials (XP052, XP053, and XP081) have previously been published.\(^1\)

- In XP052, GEN 1200 mg once daily was compared with placebo.

- In XP053, GEN 600 mg and 1200 mg once daily were compared with placebo.

- In XP081, the pharmacokinetics, efficacy, and safety of GEN 600 mg, 1200 mg, 1800 mg, 2400 mg, and placebo were examined.

- In all 3 studies, patients had a diagnosis of RLS using the IRLS Study Group criteria.\(^5\)

- At week 12, change from baseline RLS total score was statistically significantly greater with GEN 600 mg and 1200 mg compared with placebo. Statistically significant differences emerged as early as week 1 and were maintained throughout the treatment phase.

**Results**

**Patients**

- Demographic and baseline characteristics are shown in Table 1.

- In the pooled analysis, 45.1% (1120/2484) of patients in the placebo group, 45.7% (851/1854) in the GEN 600 mg group, and 44.7% (916/2046) in the GEN 1200 mg group had severe RLS (RLS total score ≥28 at baseline).

- Of the patients with severe RLS, 73.3% (851/1160) in the placebo group, 80.2% (916/1140) in the GEN 600 mg group, and 86.0% (919/1079) in the GEN 1200 mg group completed their respective study.

**Table 1. Baseline characteristics of the safety population of patients with moderate-to-severe primary restless legs syndrome (MITT population)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=2484)</th>
<th>GEN 600 mg (n=2440)</th>
<th>GEN 1200 mg (n=2142)</th>
<th>p value – .003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, Mean (SD)</td>
<td>54.7 (12.8)</td>
<td>54.9 (12.3)</td>
<td>52.6 (12.4)</td>
<td>* **</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>* **</td>
</tr>
<tr>
<td>Male</td>
<td>1246 (50.4)</td>
<td>1267 (51.9)</td>
<td>1073 (50.2)</td>
<td>* **</td>
</tr>
<tr>
<td>Female</td>
<td>1238 (49.6)</td>
<td>1173 (48.1)</td>
<td>1069 (49.8)</td>
<td>* **</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>* **</td>
</tr>
<tr>
<td>White/European</td>
<td>1934 (78.0)</td>
<td>1926 (79.0)</td>
<td>1655 (77.1)</td>
<td>* **</td>
</tr>
<tr>
<td>Black/African American</td>
<td>191 (7.8)</td>
<td>171 (7.0)</td>
<td>136 (6.4)</td>
<td>* **</td>
</tr>
<tr>
<td>Asian</td>
<td>45 (1.8)</td>
<td>46 (1.9)</td>
<td>36 (1.7)</td>
<td>* **</td>
</tr>
<tr>
<td>Total RLS total score, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>* **</td>
</tr>
<tr>
<td>&lt;24 at baseline</td>
<td>580 (23.5)</td>
<td>565 (23.3)</td>
<td>506 (23.7)</td>
<td>* **</td>
</tr>
<tr>
<td>≥28 at baseline</td>
<td>1904 (76.5)</td>
<td>1875 (76.7)</td>
<td>1636 (76.3)</td>
<td>* **</td>
</tr>
<tr>
<td>Total RLS score change from baseline, Mean (SD)</td>
<td>27.5 (33.3)</td>
<td>27.6 (33.3)</td>
<td>28.8 (33.3)</td>
<td>* **</td>
</tr>
<tr>
<td>Duration of RLS symptoms, years, Median (Q1-Q3)</td>
<td>14 (6-31)</td>
<td>14 (6-31)</td>
<td>14 (6-31)</td>
<td>* **</td>
</tr>
<tr>
<td>Prior treatment, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>**</td>
</tr>
<tr>
<td>In the past 12 months</td>
<td>371 (14.8)</td>
<td>369 (15.1)</td>
<td>374 (17.5)</td>
<td>**</td>
</tr>
</tbody>
</table>

**Figure 1. LS mean changes (SE) and treatment differences in RLS total score from baseline at week 12**

- Compared with placebo, GEN 600 mg and GEN 1200 mg significantly improved RLS total score from baseline at each time point, starting as early as week 1 (Figure 2).

- Although this analysis was not powered to detect differences between GEN doses, statistically significant changes from baseline in RLS total score were observed with GEN 1200 mg at week 12 (16.8), 4 weeks (14.3), and 12 weeks (13.3) of therapy. The changes from baseline were numerically greater with GEN 1200 mg without statistical significance.

**Table 2. Percentage of responders ("much" or "very much" improved) on the investigator-rated CGI-I by visit**

- Compared with placebo, significantly more patients were responders according to the investigator-rated CGI-I at week 1 in the GEN 600 mg and 1200 mg groups (Figure 3).

- At week 12, patients treated with GEN 600 mg or 1200 mg were significantly more likely than placebo-treated patients to be responders on the CGI-I (Table 2).

**Conclusions**

- This is the first analysis of GEN efficacy in the subset of patients with severe primary RLS and provides evidence that even patients with severe cases of RLS can benefit from treatment with GEN.

- In the pooled analysis of patients with severe primary RLS from 3 randomized trials, treatment with GEN was associated with statistically significant improvements in response compared with placebo.

- At week 12, change from baseline in RLS total score was statistically significantly greater with GEN 600 mg and 1200 mg compared with placebo. Statistically significant treatment differences emerged as early as week 1 and were maintained throughout the treatment phase.

- At week 12, there was a significantly greater proportion of responders according to the investigator-rated CGI-I than placebo in the GEN 1200 mg group (55.3% vs 21.0% in placebo; p < 0.001).

- Similar to the AEs seen for the overall study population,\(^6\) the most common treatment-related AEs were moderate-to-severe primary RLS to GEN once daily. A daily dose greater than 1200 mg provided no additional benefit, but caused an increase in adverse reactions.

- There were no statistically significant treatment effects for patients with severe primary RLS, carefull consideration should be given to the benefits and risks of dose selection for these patients.

- Conclusions with published data in the overall moderate-to-severe RLS patient population, GEN 600 mg and 1200 mg demonstrated consistent and significant efficacy compared with placebo in these patients with severe RLS.

**References**


**Disclosures**

- XenoPort, Inc., a wholly owned subsidiary of Servier SA, receives research grants and services from Biogen Idec, Eisai, Inc., Theravance, Inc., and United Therapeutics. XenoPort is committed to increasing access to its oral Gabapentin Enacarbil (GEN) by implementing a抄写 and transparency of research. This document was co-authored by Servier SA, XenoPort, Inc., and Summit Analytical, LLC. The authors declare no conflicts of interest relevant to this work.