The Effect of Gabapentin Enacarbil on Individual Items of the International Restless Legs Scale and Post-Sleep Questionnaire in Adult Patients With Severe Primary Restless Legs Syndrome: Pooled Analyses From 3 Randomized Trials

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Introduction

- Gabapentin enacarbil (GEn) is an actively transported prodrug of gabapentin that has been approved at a dose of 600 mg once daily for the treatment of moderate-to-severe primary restless legs syndrome (RLS) in adults by the United States Food and Drug Administration.[1]
- In three double-blind, placebo-controlled, randomized studies (XP052/XP053/XP081) in adult patients with moderate-to-severe primary RLS, GEn 600 mg and 1200 mg significantly improved RLS symptoms compared with placebo with regard to the mean change from baseline in the International Restless Legs Syndrome (IRLS) rating scale total score and the proportion of responders on the investigator-rated Clinical Global Impression–Improvement scale at week 12.[2–4]
  - GEn was well tolerated; in all three studies, the most frequently reported treatment-emergent adverse events (TEAEs) were somnolence and dizziness.[2–4]
- The effect of GEn on efficacy and sleep-related outcomes has not yet been analyzed exclusively in patients with severe primary RLS, defined as those having a baseline total score ≥24 on the IRLS rating scale. Therefore, pooled data from the XP052, XP053, and XP081 studies were analyzed to further investigate the effect of GEn on individual questions of the IRLS rating scale scores and PSQ items in this population.

Methods

Study design

- The study designs of the three 12-week, double-blind, placebo-controlled, randomized trials XP052, XP053, and XP081 in adult patients with moderate-to-severe primary RLS have been published previously.[2–4]
- In all three studies, patients were diagnosed with RLS using the IRLS Study Group criteria,[5] RLS symptoms with a duration ≥15 days during the month before screening (or, if on treatment, similar symptom frequency before the start of treatment), documented RLS symptoms for ≥4 of the 7 consecutive evenings/days during the baseline period, and IRLS rating scale total score ≥15. Patients discontinued prior RLS treatment ≥2 weeks prior to baseline.

Pooled analysis

- Patient-level data were pooled across GEn 600 mg, GEn 1200 mg, and placebo treatment groups, for all patients from the XP052, XP053, and XP081 trials with severe primary RLS (defined as having baseline IRLS rating scale total score ≥24).
- The safety population included all patients who received at least one dose (or portion of a dose) of study medication, and efficacy analyses were conducted for the modified intent-to-treat (MITT) population, which included patients in the safety population with a baseline and at least one postbaseline IRLS rating scale total score.
- Least squares (LS) mean treatment differences for IRLS rating scale items and PSQ responses were used to compare treatment groups and were calculated as the differences in LS mean change from baseline to week 12 between treatment groups.
- Treatment effects were also analyzed using a mixed model for repeated measures (MMRM) for the 10 IRLS rating scale items and Cochran–Mantel–Haenszel row mean scores testing for the five PSQ items at all time points. The MMRM model included terms for treatment, visit, and treatment by visit. Baseline values were used as covariates, and an unstructured covariance matrix was used.
- Safety and tolerability, including evaluations of all TEAEs, were analyzed according to multiple clinical and laboratory measurements.

Results

Patients

- In this pooled analysis, 45% (110/244) of patients in the placebo group, 50% (80/161) in the GEn 600-mg group, and 45% (119/266) in the GEn 1200-mg group had severe RLS (IRLS rating scale total score ≥24) at baseline. Demographic and baseline characteristics were generally similar across treatment groups for this patient cohort (Table 1).

Table 1. Baseline characteristics of adult patients with severe RLS at baseline (MITT population)[a]

Characteristic	Placebo (n=110)	GEn 600 mg (n=80)	GEn 1200 mg (n=119)
Mean (SD) age, years	49.2 (11.68)	46.8 (12.15)	51.6 (10.40)
Female sex, n (%)	72 (65)	50 (63)	78 (66)
White race, n (%)	104 (95)	74 (93)	115 (97)
Mean (SD) IRLS rating scale total score, points	27.5 (2.96)	27.6 (3.00)	28.0 (3.32)
Mean (SD) duration of RLS symptoms, years	14.1 (13.48)	14.3 (13.53)	14.4 (13.10)
Yes, prior RLS treatment, n (%)[b]	53 (48)	26[c] (33)	46 (39)

[a]Severe RLS population (baseline IRLS rating scale total score ≥24) includes 45%, 50%, and 45% of the placebo, GEn 600 mg, and GEn 1200 mg treatment groups, respectively; [b]Includes patients whose treatment terminated prior to the month before the start of study drug, who received treatment within the month of the start of study drug or within the previous month; [c]Two patients had missing data; percentage is calculated out of a total of 78 patients.

GEn = gabapentin enacarbil; IRLS = International Restless Legs Syndrome; MITT = modified intent-to-treat; RLS = restless legs syndrome; SD = standard deviation.

Efficacy

- GEn 600 mg significantly improved LS mean treatment differences compared with placebo for most IRLS rating scale items at week 12, except RLS severity as a whole. GEn 1200 mg significantly improved LS mean treatment differences compared with placebo for all IRLS rating scale items at week 12 (Table 2). There were no significant LS mean treatment differences between GEn 600 mg and GEn 1200 mg for any IRLS rating scale item at week 12.

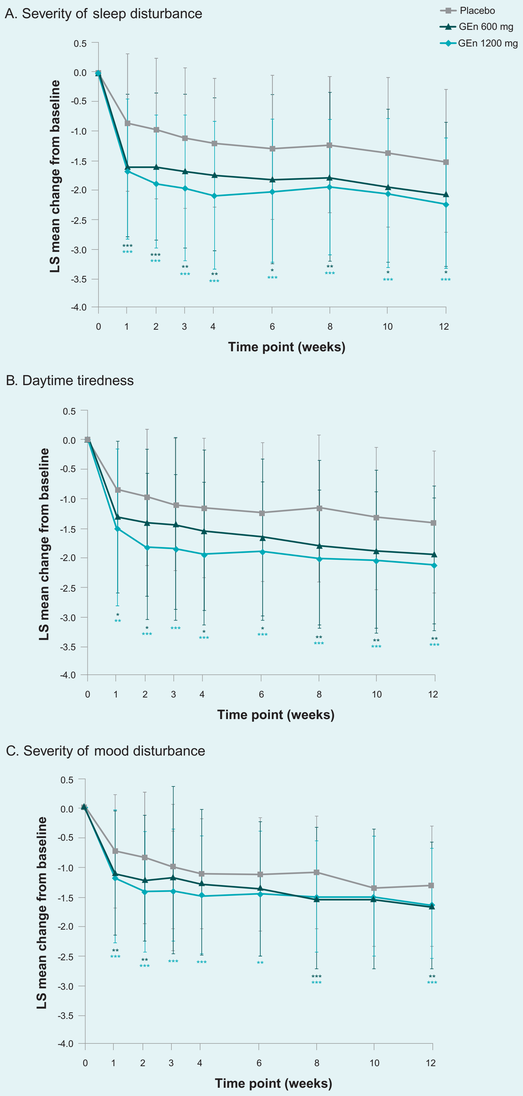
Table 2. IRLS rating scale treatment differences in the change from baseline to week 12 (MITT population)

Questionnaire item	Treatment comparison LS mean treatment difference (SE) *P* value		
	GEn 600 mg vs placebo	GEn 1200 mg vs placebo	GEn 600 mg vs 1200 mg
1. Overall RLS discomfort in legs or arms	0.4 (0.15) .026	0.5 (0.14) <.001	0.1 (0.15) .399
2. Overall need to move	0.4 (0.17) .041	0.5 (0.15) .003	0.1 (0.16) .506
3. Overall relief from moving	0.4 (0.16) .021	0.5 (0.15) <.001	0.1 (0.16) .484
4. Severity of sleep disturbance	0.4 (0.17) .010	0.6 (0.15) <.001	0.2 (0.16) .279
5. Tiredness during the day	0.5 (0.15) .002	0.6 (0.14) <.001	0.1 (0.15) .479
6. Severity of RLS as a whole	0.2 (0.16) .197	0.5 (0.14) <.001	0.3 (0.15) .056
7. How often were symptoms experienced	0.5 (0.22) .016	0.9 (0.19) <.001	0.3 (0.21) .131
8. Severity, on average, of symptoms	0.6 (0.17) <.001	0.7 (0.15) <.001	0.1 (0.16) .427
9. Severity of impact on daily affairs	0.4 (0.13) .006	0.5 (0.12) <.001	0.1 (0.13) .431
10. Severity of mood disturbance due to RLS symptoms	0.3 (0.12) .006	0.4 (0.11) <.001	0.04 (0.12) .747

GEn = gabapentin enacarbil; RLS = restless legs syndrome; IRLS = International Restless Legs Syndrome.

- GEn 600 mg and GEn 1200 mg significantly improved LS mean changes from baseline to each week for the majority of IRLS rating scale items, including severity of sleep disturbance, daytime tiredness, and severity of mood disturbance (Figure 1).

Figure 1. LS mean changes from baseline per week for IRLS rating scale items



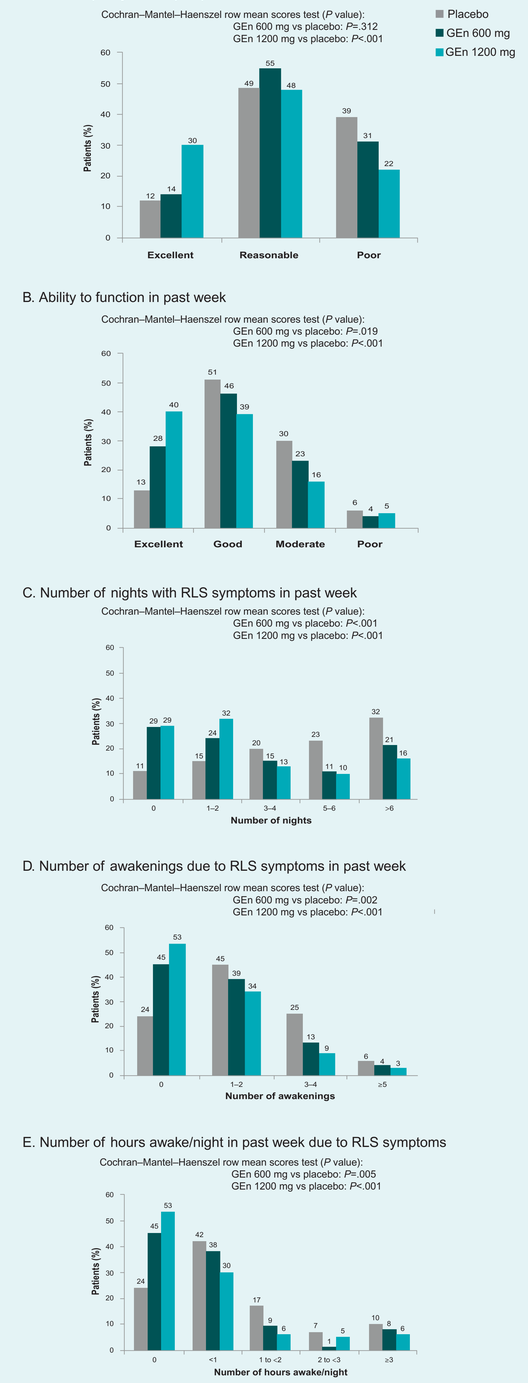
GEn = gabapentin enacarbil; IRLS = International Restless Legs Syndrome; LS = least squares.
*P<.05, **P<.01, ***P<.001

Conclusions

- In this pooled analysis, GEn 600 mg improved the majority of individual questions of the IRLS rating scale and PSQ items compared with placebo, except the severity of RLS as a whole in the IRLS rating scale and overall quality of sleep from the PSQ, for patients with severe RLS.
- GEn 1200 mg significantly improved all individual questions of the IRLS rating scale and PSQ items compared with placebo, including clinically relevant sleep-related scores, for patients with severe RLS.
- GEn was well tolerated, and in all three studies, somnolence and dizziness were the most commonly reported TEAEs.[2–4]
- Significant differences between GEn 600 mg and 1200 mg did not emerge for many of these analyses, although GEn 1200 mg demonstrated a greater degree of statistical significance compared with placebo for the PSQ measurements. However, none of these studies were powered to detect significant treatment effects between these two doses. It remains unknown whether patients with severe RLS who initially do not respond to the GEn 600 mg regimen may subsequently benefit from treatment with GEn 1200 mg; this question warrants further research.

- GEn 600 mg significantly improved all PSQ items compared with placebo, except overall quality of sleep, from baseline to week 12, and GEn 1200 mg significantly improved all PSQ items compared with placebo from baseline to week 12 (Figure 2).

Figure 2. Distribution of post-sleep questionnaire responses at week 12.



GEn = gabapentin enacarbil; RLS = restless legs syndrome.

Tolerability

- The most common TEAEs reported in ≥5% of the safety population with GEn 600 mg and 1200 mg were somnolence and dizziness.
- Other common TEAEs reported in ≥5% of the safety population across placebo and GEn treatment groups included headache, nausea, fatigue, nasopharyngitis, diarrhea, constipation, insomnia, irritability, paresthesia, and sinusitis.

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Disclosures

DGB served as a consultant for UCB, XenoPort, Inc., Impax Pharmaceuticals, and Otsuka. MJ is a consultant to XenoPort, Inc. RK and GS are employees of and own stock in XenoPort, Inc.

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