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Gabapentin Enacarbil Improves Restless Legs Syndrome (RLS) Symptoms and Subjective Measures of Sleep in Subjects with Primary RLS with and without Severe Sleep Disturbance: Secondary Analyses from Two Studies

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Introduction

- Symptoms of Restless Legs Syndrome (RLS) negatively impact sleep, with more than 75% of patients with RLS reporting at least one sleep-related symptom. Many patients with RLS report performance-related effects, possibly resulting from sleep disruption (e.g. daytime sleepiness, difficulty concentrating).[1]
- Gabapentin enacarbil (GEn) is a transported prodrug of gabapentin under investigation for the treatment of moderate-to-severe primary RLS.[2,3]
- GEn is absorbed throughout the large and small intestine by high-capacity nutrient transporters and provides sustained, dose-proportional gabapentin exposure.[4–6]
- GEn 1200 mg significantly improved RLS symptoms compared with placebo (PBO) and was generally well tolerated in adults with moderate-to-severe primary RLS in two 12-week, multicenter, randomized, double-blind, PBO-controlled, parallel-group studies.[3,7] An integrated analysis of the subjective sleep outcomes in patients with severe/very severe or moderate-to-no baseline sleep disturbance is presented.

Methods

Study Design

- Data were integrated for the GEn 1200 mg and PBO treatment groups from two studies:
  - XenoPort, Inc. protocols XP052 and XP053 (ClinicalTrials.gov NCT00298623 and NCT00365352). Subjects were randomized to receive GEn 1200 mg (2 x 600 mg extended release tablets) or matching PBO once daily at 5 pm with food for 12 weeks.
- As GEn 600 mg was only assessed in study XP053, it was not included in this analysis.
- Subjects were divided into two subgroups based on the International Restless Legs Scale (IRLS) item 4 score at baseline: severe/very severe sleep disturbance or moderate-to-no sleep disturbance.

Assessments

- Coprimary endpoints at Week 12 LOCF:
  - mean change from baseline in IRLS total score[8]
  - proportion of responders (rated as 'much' or 'very much' improved) on the investigator-rated Clinical Global Impression–Improvement (CGI-I) scale.
- Secondary endpoints to assess sleep disturbance at Week 12 LOCF:
  - Medical Outcomes Study (MOS) Sleep Scale: mean change from baseline in the four domains of sleep disturbance, sleep quantity, sleep adequacy, and daytime somnolence
  - Post-Sleep Questionnaire (PSQ): responses on the three items specifically related to sleep disturbance were analyzed at baseline and Week 12 LOCF: overall quality of sleep over the past week, number of nighttime awakenings from RLS symptoms, and time awake due to RLS symptoms.
- Tolerability assessments included treatment-emergent adverse events (AEs) and serious AEs.

Statistical Analyses

- Safety data were summarized for the safety population, which comprised all subjects who received at least one dose (or portion of a dose) of study medication.
- Efficacy outcomes were performed on the modified intent-to-treat (mITT) population, which comprised all subjects in the safety population who also had a baseline and at least one post-baseline IRLS assessment.
- Efficacy outcomes were analyzed as:
  - change from baseline data using an ANCOVA model, adjusted for baseline IRLS score, pooled site, study, and treatment
  - CGI-I responders using a logistic regression model adjusted for pooled site, study, and treatment
  - PSQ responses at Week 12 LOCF; Cochran–Mantel–Haenszel mean score test with interval scoring, stratified by pooled site
  - No adjustment was made for multiple comparisons as these secondary analyses were considered exploratory.

Results

Subjects

- Overall, 432 subjects were randomized (GEn 1200 mg=227; PBO=205) and 367 subjects (GEn 1200 mg=198; PBO=169) completed the studies.
- The mITT population comprised 427 subjects (GEn 1200 mg=223; PBO=204).
- Subject demographics and baseline characteristics were similar across treatment groups (**Table 1**).
- At baseline, 187 (43.8%) subjects reported severe/very severe sleep disturbance and 240 (56.2%) subjects reported moderate-to-no sleep disturbance on item 4 of the IRLS (**Table 1**).

Coprimary Endpoints

- GEn 1200 mg significantly improved mean (SD) IRLS total score from baseline to Week 12 LOCF compared with PBO in both subgroups (severe/very severe, –16.6 [9.82] vs –11.5 [8.17] adjusted mean treatment difference [AMTD]: –3.9; 95% CI: –6.46, –1.42; *P*=0.0024; moderate-to-no, –10.5 [7.67] vs –7.4 [7.78]; AMTD: –3.3; 95% CI: –5.20, –1.30; *P*=0.0012).
- A significantly greater proportion of GEn 1200 mg-treated subjects were responders on the investigator-rated CGI-I scale compared with PBO in each subgroup at Week 12 LOCF (severe/very severe, 77.4% vs 47.8%; adjusted odds ratio [AOR]: 3.7; 95% CI: 1.93, 7.18; *P*<0.0001; moderate-to-no, 76.4% vs 36.6%; AOR: 5.4; 95% CI: 3.03, 9.53; *P*<0.0001).

Improvement in Sleep

- GEn 1200 mg significantly improved all MOS Sleep Scale domain scores from baseline to Weeks 4, 8, and 12 LOCF compared with PBO in both subgroups, with the exception of daytime somnolence from baseline to Week 8 for subjects with severe/very severe sleep disturbance (**Figure 1**).
- GEn 1200 mg-treated subjects with severe/very severe sleep disturbance reported significantly higher overall sleep quality (*P*=0.0004 for distribution of responses), fewer nighttime awakenings (*P*<0.0001 for distribution of responses), and fewer hours awake per night due to RLS symptoms (*P*=0.0004 for distribution of responses, **Figure 2**) at Week 12 LOCF compared with PBO on the PSQ.
- PSQ analysis was not performed for subjects with moderate-to-no sleep disturbance.

Table 1. Demographic and clinical characteristics at baseline (mITT population)

Characteristic	PBO (n=204)		GEn 1200 mg (n=223)	
Sleep disturbance at baseline	**Moderate-to-no n=112**	**Severe/very severe n=92**	**Moderate-to-no n=128**	**Severe/very severe n=95**
Age, years	49.0 (12.53)	50.4 (12.48)	49.1 (13.31)	53.0 (11.77)
Women, n (%)	66 (59)	56 (61)	68 (53)	63 (66)
Race, White or Caucasian, n (%)[a]	108 (96)	88 (96)	121 (95)	93 (98)
Previously treated for RLS, n (%)	30 (27)	47 (51)	32 (25)	40 (42)
Duration of RLS symptoms, years	15.6 (14.05)	13.1 (11.15)	12.2 (12.12)	16.2 (15.06)[d]
7-day RLS record, days with RLS[b]	6.1 (1.00)	6.2 (1.01)	6.0 (1.07)	6.2 (1.05)
Baseline IRLS total score	20.5 (3.44)	26.4 (4.18)	20.0 (3.14)	27.4 (3.95)
Baseline MOS Sleep Scale domain[c]				
Sleep disturbance (0–100)	43.4 (19.36)	60.8 (19.75)	42.4 (19.39)[e]	63.1 (20.96)
Sleep adequacy (0–100)	39.2 (23.64)	26.5 (21.30)	42.0 (23.06)[e]	22.7 (19.65)
Daytime somnolence (0–100)	30.4 (18.31)	41.0 (21.15)	33.1 (17.85)[e]	42.7 (22.16)
Sleep quantity (hours)	6.4 (1.00)	5.5 (1.31)	6.4 (1.26)[e]	5.5 (1.36)

All values are mean (SD) unless stated otherwise.
[a]Subjects could have been categorized to more than one race; [b]Number of days of RLS symptoms expressed during the week prior to baseline; [c]Comparator mean MOS domain scores based on a healthy cohort sample of US adults were: sleep disturbance=24.5, sleep adequacy=60.5, daytime somnolence=21.9, and sleep quantity=6.8 hours;[9] [d]n=94; [e]n=127.

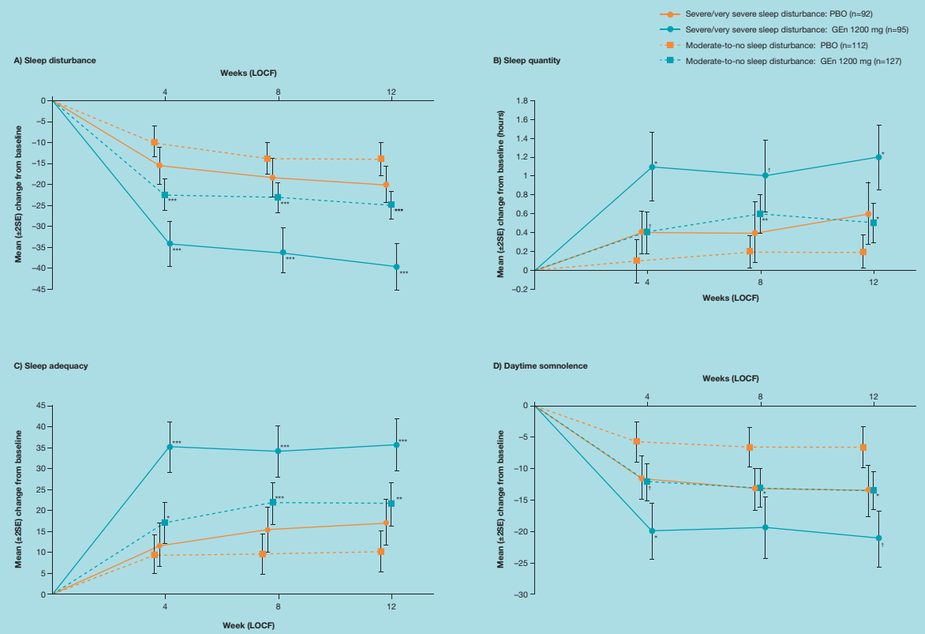
Tolerability

- The most commonly reported AEs were somnolence (GEn 1200 mg, 22%; PBO, 5%), dizziness (GEn 1200 mg, 22%; PBO, 5%), and headache (GEn 1200 mg, 14%; PBO, 10%).
- Twenty-six subjects withdrew due to an AE (GEn 1200 mg=17; PBO=9).
- The majority of AEs were rated as mild or moderate in intensity.
- Two subjects reported serious AEs: cholelithiasis (PBO) and appendicitis (PBO). Neither event was considered treatment-related, both resolved, and both subjects continued in the study.

Conclusions

- Integrated analyses from two PBO-controlled studies indicate that GEn 1200 mg once daily significantly improves RLS symptoms compared with PBO in subgroups of subjects with moderate-to-severe primary RLS with either severe/very severe or moderate-to-no sleep disturbance.
- Significant improvements in subjective sleep outcomes were observed with GEn 1200 mg compared with PBO for MOS scores in subjects with either severe/very severe or moderate-to-no sleep disturbance, and on the PSQ in subjects with severe/very severe sleep disturbance.
- GEn 1200 mg is generally well tolerated.

Figure 1. Mean (±2SE) change from baseline in domains of the MOS Sleep Scale by visit (mITT population)



[1]*P*<0.05, [2]*P*<0.01, [3]*P*<0.001, [4]*P*<0.0001.

References

1. Allen RP, *et al. Arch Intern Med* 2005;**165**:1286–92.
2. Kushida CA, *et al. Sleep* 2009;**32**:159–68.
3. Kushida CA, *et al. Neurology* 2009;**72**:439–46.
4. Cundy KC, *et al. J Pharmacol Exp Ther* 2004;**311**:315–23.
5. Cundy KC, *et al. J Clin Pharmacol* 2008;**48**:1378–88.
6. Lal R, *et al. Clin Ther* 2009;**31**:1776–86.
7. Lee DO, *et al. Mov Disord* 2009;**24**:S443–4.
8. The International Restless Legs Syndrome Study Group. *Sleep Med* 2003;**4**:121–32.
9. Hays RD and Stewart AL. Durham, NC: Duke University Press, 1992:235–59.

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Figure 2. Responses on the PSQ items 1, 4, and 5 at baseline and Week 12 LOCF (mITT population) for subjects with severe/very severe baseline sleep disturbance