

# An Examination of Mood, Quality of Life, and Functioning in Subjects with Primary Restless Legs Syndrome (RLS) Treated with Gabapentin Enacarbil Compared with Placebo

Ronald B. Ziman,<sup>1</sup> Daniel O. Lee,<sup>2</sup> A. Thomas Perkins,<sup>3</sup> J. Steven Poceta,<sup>4</sup> Arthur S. Walters,<sup>5</sup> Ronald W. Barrett<sup>6</sup>

<sup>1</sup>Northridge Neurological Center, Northridge, CA; <sup>2</sup>Sleep Disorders Center, East Carolina Neurology, Inc., Greenville, NC; <sup>3</sup>Raleigh Neurology Associates, Raleigh, NC; <sup>4</sup>Scripps Clinic, La Jolla, CA; <sup>5</sup>Vanderbilt University, Nashville, TN; <sup>6</sup>XenoPort, Inc., Santa Clara, CA

## Introduction

- Restless Legs Syndrome (RLS) is a neurologic disorder characterized by an urge to move the legs, usually accompanied or caused by unpleasant sensations in the legs.<sup>1</sup>
- Symptoms of RLS negatively impact patients' mood, quality of life (QoL), and daily functioning.<sup>1,2</sup>
- Gabapentin enacarbil (GEN) is a non-dopaminergic, actively transported prodrug of gabapentin that provides sustained, dose-proportional gabapentin exposure and has demonstrated efficacy in improving RLS symptoms.<sup>3-9</sup>
- PIVOT RLS II (XenoPort, Inc. protocol XP053; ClinicalTrials.gov identifier NCT00365352) was a multicenter, 12-week, randomized, double-blind, placebo (PBO)-controlled study that assessed the efficacy and tolerability of GEN 600 mg and 1200 mg once daily in subjects with moderate-to-severe primary RLS.<sup>10</sup> Secondary endpoints assessing the effects of GEN 600 mg and 1200 mg on mood, QoL, and functioning are presented.

## Methods

### Study Procedures

- Adult (≥18 years) male and female subjects with RLS and International Restless Legs Scale (IRLS) total score ≥15 at Visits 1 and 2, body mass index (BMI) ≤34 kg/m<sup>2</sup>, and estimated creatinine clearance of ≥60 mL/min were eligible to participate in this study.
- Subjects were randomized 1:1:1 to receive GEN 1200 mg (2 x 600 mg extended release tablets [600 mg on Days 1–3]), GEN 600 mg (1 x 600 mg extended release tablet), or matching PBO once daily at 5 pm with food.

### Assessments

- Copriary endpoints at Week 12 LOCF for GEN 1200 mg compared with PBO included:
  - mean change from baseline in International Restless Legs Scale (IRLS) total score
  - proportion of responders (rated as “much improved” or “very much improved”) on the investigator-rated Clinical Global Impression-Improvement (CGI-I) scale.
- Secondary endpoints:
  - Comparisons between GEN 600 mg and PBO for IRLS total score and CGI-I at Week 12 LOCF were assessed.
- Mood:
  - Profile of Mood State-Brief (POMS-B) total mood disturbance score: mean change from baseline to Weeks 4, 8, and 12 LOCF.
  - Mood Assessment Question (MAQ): at Week 12 LOCF. Overall change in mood from study start: “very much improved”, “much improved”, “minimally improved”, “no change”, “minimally worse”, “much worse”, or “very much worse”.
- QoL:
  - Johns Hopkins RLS QoL questionnaire: mean change from baseline to Weeks 4, 8, and 12 LOCF in overall impact score.

- Functioning:
  - Post-Sleep Questionnaire (PSQ): item 2 (ability to function in the past week) at Week 12 LOCF. Responses: Excellent, Good, Moderate and Poor.

### Tolerability

- Treatment-emergent adverse events (AEs), vital signs, clinical laboratory parameters (hematology, serum chemistry, and urinalysis), and electrocardiograms (ECGs) were evaluated.

### Statistical Analyses

- All 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.
- All 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 (LOCF) were analyzed as:
  - changes from baseline using an ANCOVA model, adjusted for baseline score, pooled site, and treatment group; a treatment by pooled site interaction term was also included in the model, if significant ( $P < 0.10$ )
  - IRLS QoL instrument scale scores (social function, daily function, sleep quality, and emotional well-being)
  - Mood Assessment (the domain scores of the POMS)
- CGI-I responder outcomes using a logistic regression model adjusted for pooled site and treatment group
- MAQ and PSQ item 2, using the Cochran-Mantel-Haenszel mean score test with interval scoring, stratified by pooled site.

## Results

### Subjects

- Overall, 325 subjects were randomized (GEN 1200 mg, n=113; GEN 600 mg, n=115; PBO, n=97) and 279 (GEN 1200 mg, n=98; GEN 600 mg, n=104; PBO, n=77) completed the study. The mITT population comprised 321 subjects (GEN 1200 mg, n=111; GEN 600 mg, n=114; PBO, n=96).
- Subject demographics and baseline characteristics were similar across treatment groups (Table 1).

### Copriary Endpoints

- GEN 1200 mg significantly improved mean (SD) IRLS total score from baseline to Week 12 LOCF compared with PBO (-13.0 [9.12] vs -9.8

Characteristic	PBO (n=96)	GEN 600 mg (n=115)	GEN 1200 mg (n=111)
Age, years	49.1 (12.19)	48.3 (12.83)	49.5 (12.67)
Women, n (%)	57 (59.4)	67 (58.3)	65 (58.6)
Race, White or Caucasian, n (%)	92 (94.8)	107 (96.4)	107 (96.4)
Duration of RLS symptoms, years	14.4 (12.85)	13.5 (13.07)	14.1 (12.36)
IRLS total score <sup>a,b</sup>	23.8 (4.58)	23.1 (4.93) <sup>c</sup>	23.2 (5.32)
POMS-B total mood disturbance score <sup>a</sup>	17.9 (16.45)	19.4 (18.12) <sup>c</sup>	19.1 (18.23)
RLS QoL overall life impact score <sup>b</sup>	66.8 (18.10)	68.3 (14.92) <sup>c</sup>	67.2 (17.70)

All values are mean (SD) unless otherwise stated.  
<sup>a</sup>Number of days RLS symptoms expressed; <sup>b</sup>mITT population; <sup>c</sup>n = 114.

[7.69]; adjusted mean treatment difference [AMTD]: -3.5; 95% CI: -5.6, -1.3;  $P = 0.0015$ ).

- Significantly more GEN 1200 mg-treated subjects were considered CGI-I responders compared with PBO at Week 12 LOCF (77.5% vs 44.8%; adjusted odds ratio [AOR]: 4.3; 95% CI: 2.34, 7.86;  $P < 0.0001$ ).

### Secondary Endpoints

- GEN 600 mg significantly improved mean (SD) IRLS total score from baseline compared with PBO at Week 12 LOCF (-13.8 [8.09] vs -9.8 [7.69]; AMTD: -4.3; 95% CI: -6.4, -2.3;  $P < 0.0001$ ).
- Significantly more GEN 600 mg-treated subjects were CGI-I responders compared with PBO at Week 12 LOCF (72.8% vs 44.8%; AOR: 3.3; 95% CI: 1.84, 5.99;  $P < 0.0001$ ).

### Mood

- POMS-B total mood disturbance score was reduced (improved) at Week 12 LOCF compared with baseline in all treatment groups (Figure 1).
  - The treatment differences between GEN 1200 mg and PBO (AMTD: -3.5; 95% CI: -7.6, 0.5;  $P = 0.0893$ ) and GEN 600 mg and PBO (AMTD: -2.8; 95% CI: -6.8, 1.3;  $P = 0.1795$ ) were not statistically significant at Week 12 LOCF. However, GEN 1200 mg significantly improved total mood disturbance score at Weeks 4 and 8 LOCF ( $P \leq 0.01$ ), with similar findings for GEN 600 mg at Week 8 LOCF ( $P \leq 0.5$ ) (Figure 1).
- GEN 1200 mg significantly improved overall mood (MAQ,  $P = 0.0168$  for distribution of responses) compared with PBO at Week 12 LOCF. More subjects reported their mood as “much improved” or “very much improved” (35.45%) compared with PBO (20.7%).
  - A higher proportion of GEN 600 mg subjects reported their mood as “much improved” or “very much improved” compared with PBO; however, the distributions of responses were not significantly different ( $P = 0.1190$ ).

### QoL

- GEN 1200 mg significantly increased the mean (SD) RLSQoL overall life-impact score from baseline to Week 12 LOCF compared with PBO (20.4 [17.14] vs 14.5 [15.74]; AMTD: 6.1;  $P = 0.0009$ ; Figure 2).

Figure 1. Mean change from baseline in the POMS-B total mood disturbance score by visit (mITT population)

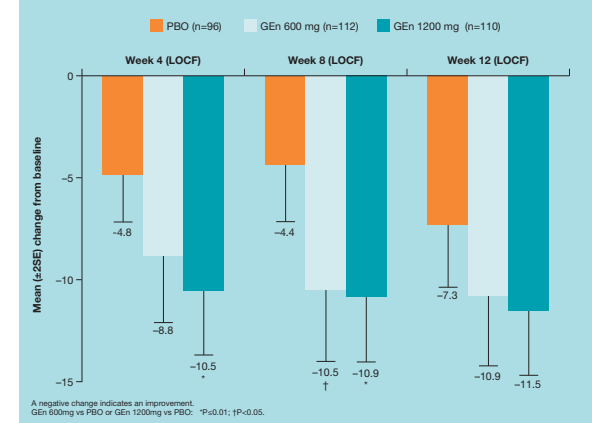
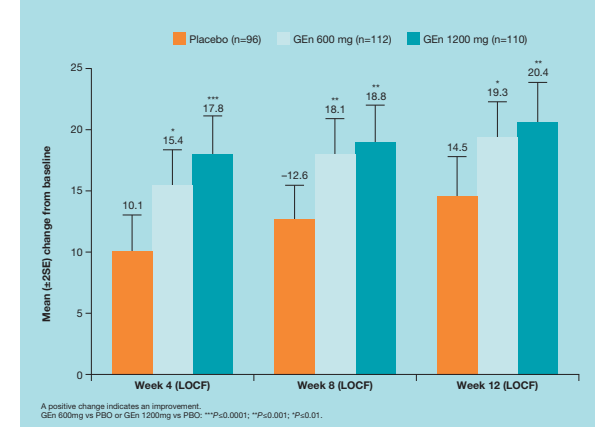


Figure 2. Mean change from baseline in the RLSQoL overall life impact score by visit (mITT population)



- A similar improvement was seen with GEN 600 mg compared with PBO at Week 12 LOCF (19.3 [15.57] vs 14.5 [15.74]; AMTD: 5.5;  $P = 0.0025$ ; Figure 2).

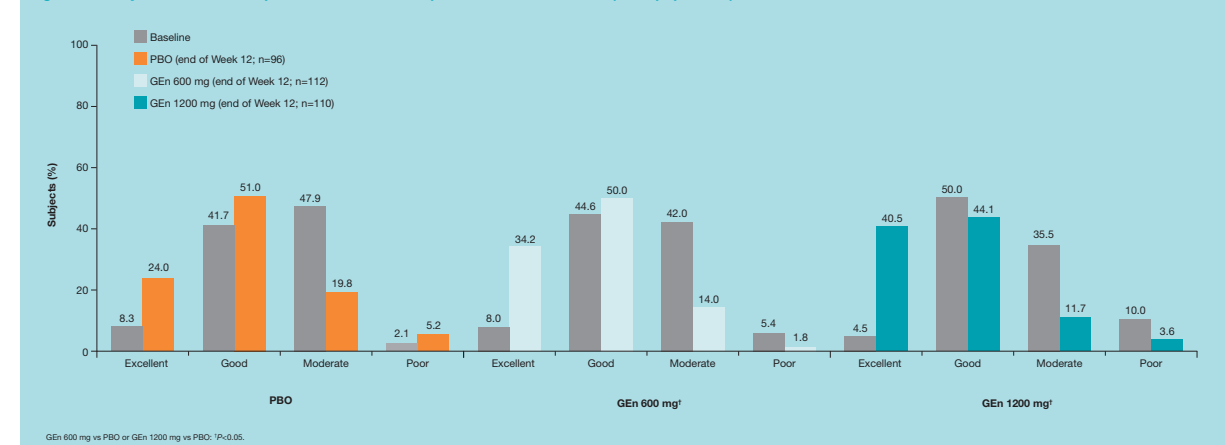
### Functioning

- GEN 1200 mg significantly improved ability to function in the past week compared with PBO at Week 12 LOCF (PSQ, item 2;  $P = 0.0152$  for distribution of responses [poor to excellent]; Figure 3).
- A similar response was seen with GEN 600 mg ( $P = 0.0366$  for distribution of responses; Figure 3).

### Tolerability

- A total of 94 (84.7%) subjects in the GEN 1200 mg group, 100 (87.0%) subjects in the GEN 600 mg group and 76 (79.2%) subjects in the PBO group reported at least one treatment-emergent AE.
- The two most commonly reported AEs (GEN 1200 mg, GEN 600 mg, PBO) were dizziness (24%, 10%, 5%) and somnolence (18%, 22%, 2%); the majority were mild or moderate in intensity.
- No clinically significant changes in vital signs, ECGs, or laboratory parameters were observed.

Figure 3. Ability to function in the past week based on responses to the PSQ item 2 (mITT population)



## Conclusions

- GEN 1200 mg and 600 mg significantly improves QoL and ability to function, in addition to improving RLS symptoms in subjects with moderate-to-severe primary RLS compared with PBO.
- In addition, GEN 1200 mg significantly improved overall mood compared with PBO.
- GEN 1200 mg and 600 mg are generally well tolerated.

## References

- Allen RP, et al. *Arch Intern Med* 2005;165:1286–92.
- Abetz L, et al. *Clin Ther* 2004;26:925–35.
- Gidal BE, et al. *Epilepsy Res* 1998;31:91–9.
- Gidal BE, et al. *Epilepsy Res* 2000;40:123–7.
- Kushida CA, et al. *Neurology* 2009;72:439–46.
- Kushida CA, et al. *Sleep* 2009;32:159–68.
- Cundy KC, et al. *J Clin Pharmacol* 2008;48:1378–88.
- Cundy KC, et al. *J Pharmacol Exp Ther* 2004;311:315–23.
- Cundy KC, et al. *J Pharmacol Exp Ther* 2004;311:324–33.
- Lee DO, et al. *Mov Disord* 2009;24:S443.

## Acknowledgments

This study was supported by XenoPort, Inc., Santa Clara, CA. The authors acknowledge Brian Hunter, PhD (GlaxoSmithKline) for coordination, critical review, and editorial assistance, and Nicola Williams, MSc (GlaxoSmithKline) for statistical support and interpretation of the data. Editorial support in the form of writing, drafting tables and figures, and collating author comments was provided by Nicola West, BSc (Hons) (Caudex Medical Ltd., Oxford, UK), and was funded by GlaxoSmithKline. The authors also acknowledge the contributions of the following investigators: Donald Ayres, MD; Eileen Brady, MD; David Chen, MD; John Cochran, MD; William Ellison, MD; Ramedevi Gourineni, MD; Dennis Hill, MD; John Hudson, MD; David Kudrow, MD; Antoinette Pragalos, MD; Marc Raphaelson, MD, PA; Albert Razzetti, MD; Paul Scheinberg, MD; Markus Schmidt, MD, PhD; Susan Steen, MD; Stephen Thein, PhD; Alberto Vasquez, MD; Jan Westerman, MD; David Winslow, MD.

## Disclosures

RBZ has received compensation for speaker services from GlaxoSmithKline, Novartis, Sanofi-Bristol Myers Squibb, Forest Pharmaceuticals, and UCB, and has received research funding from XenoPort, Inc., GlaxoSmithKline, Pfizer, UCB, and Sepracor. DOL has served on the RLS Scientific Advisory Board for GlaxoSmithKline. ATP has received compensation for speaker services from Cephalon, and has received research support from GlaxoSmithKline. JSP is on the speakers' bureau for Cephalon, and has received research support from GlaxoSmithKline and Alexza Pharmaceuticals. ASW has received compensation for speaker services from Boehringer Ingelheim. RWB is an employee of XenoPort, Inc.