

Gabapentin Enacarbil Improves Pain Associated with Restless Legs Syndrome

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Introduction

- Pain associated with Restless Legs Syndrome (RLS) is reported by approximately 60% of subjects, with 19% reporting pain as their most troublesome symptom.¹
- Gabapentin enacarbil (GEN) is a transported prodrug of gabapentin, absorbed throughout the large and small intestine,^{2,3} that provides sustained, dose-proportional gabapentin exposure.^{4,5}
- GEN, a non-dopaminergic treatment, has demonstrated efficacy in improving RLS symptoms.^{6,7}
- PIVOT RLS II (XenoPort, Inc. protocol XP053; ClinicalTrials.gov identifier NCT00365352) was a parallel group, 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.⁸ Secondary endpoints assessing the efficacy of GEN 600 mg and 1200 mg in relieving pain associated with RLS are presented.

Methods

Study Design

- Men and women (≥18 years) with RLS and International Restless Legs Scale (IRLS) total score ≥15 at Visits 1 (baseline) and 2 (Day 1), body mass index ≤34 kg/m², and estimated creatinine clearance of ≥60 mL/min were eligible.
- Subjects were randomized 1:1:1 to receive GEN 1200 mg (2 × 600 mg extended release tablets [600 mg on Days 1–3]), GEN 600 mg (1 × 600 mg extended release tablet), or matching PBO once daily at 5 pm with food.

Assessments

- Subjects recorded "pain associated with RLS symptoms" in the past 24 hours on an 11-point scale (0=no pain, 10=most intense pain imaginable) for 7 days prior to baseline and at each study visit at Weeks 2, 4, 8, and 12 (or the early termination visit). Average daily pain scores were calculated for each 7-day period.
- Coprimary efficacy endpoints (GEN 1200 mg compared with PBO at Week 12 LOCF):
 - mean change from baseline in 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:
 - GEN 600 mg compared with PBO at Week 12 LOCF:
 - mean change from baseline in IRLS total score
 - proportion of responders on the investigator-rated CGI-I scale.
 - GEN 1200 mg and GEN 600 mg compared with PBO at Week 12 LOCF (for subgroups of subjects with average daily pain score >0 and average daily pain score ≥4 baseline):
 - mean change from baseline in average daily RLS pain score
 - proportion of responders with ≥30% or ≥50% improvement in average daily pain score from baseline (subjects who withdrew from the study within 2 weeks of randomization and those who had no pain [average daily pain score of 0] at both baseline and Week 12 LOCF were counted as non-responders).

Tolerability and Safety

- Treatment-emergent adverse events (AEs), clinical laboratory parameters (hematology, serum chemistry, and urinalysis), vital signs, 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 were analyzed as change from baseline data 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 ($P < 0.10$), or responder outcomes using a logistic regression model adjusted for pooled site and treatment group.
- Subgroup analyses of the proportion of responders with ≥30% or ≥50% improvement in average daily pain score from baseline were performed *post hoc* on those subjects with average daily pain scores ≥4 at baseline.

Results

Subjects

- Overall, 325 subjects were randomized (GEN 1200 mg, n=113; GEN 600 mg, n=115; PBO, n=97) and 279 subjects (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 reflected a population with moderate-to-severe primary RLS (Table 1).
- A total of 285/314 (91%) subjects reported RLS pain scores >0 at baseline or Week 12 LOCF, and 178/314 (57%) had average daily pain scores ≥4 at baseline.

Coprimary 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 [7.69]; AMTD: −4.3; 95% CI: −6.4, −2.3; $P < 0.0001$).
- 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; $P < 0.0001$).

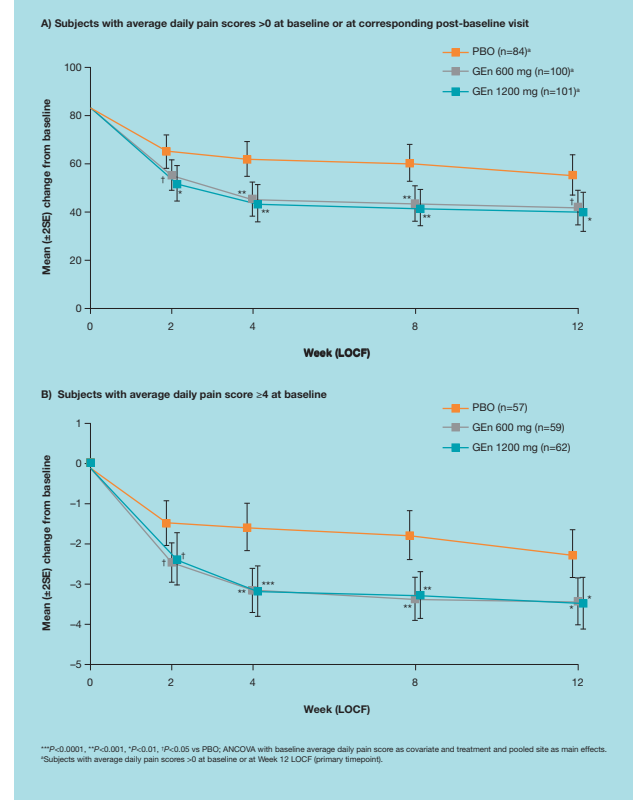
Secondary Endpoints

- 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; $P < 0.0001$).

Reduction in Average Daily Pain Scores

- GEN 1200 mg significantly reduced mean (SD) average daily pain scores at Week 12 LOCF compared with PBO for subjects with average daily pain scores >0 at baseline or Week 12 LOCF (−2.6 [2.43] vs −1.7 [2.28]; AMTD: −0.9; 95% CI: −1.5, −0.4; $P = 0.0015$; Figure 1A) and subjects with baseline scores ≥4 (−3.5 [2.51] vs −2.3 [2.34]; AMTD: −1.1; 95% CI: −1.9, −0.3; $P = 0.0054$; Figure 1B).
- GEN 600 mg significantly reduced mean (SD) average daily pain scores at Week 12 LOCF compared with PBO for subjects with average daily

Figure 1. Mean (±2SE) change from baseline in average daily pain score (mITT population)



pain scores >0 at baseline or Week 12 LOCF (−2.5 [2.20] vs −1.7 [2.28]; AMTD: −0.9; 95% CI: −1.4, −0.3; $P = 0.0029$; Figure 1A) and subjects with baseline scores ≥4 (−3.5 [2.19] vs −2.3 [2.34]; AMTD: −1.1; 95% CI: −1.9, −0.3; $P = 0.0084$; Figure 1B).

Response of ≥30% Improvement in Average Daily Pain Scores

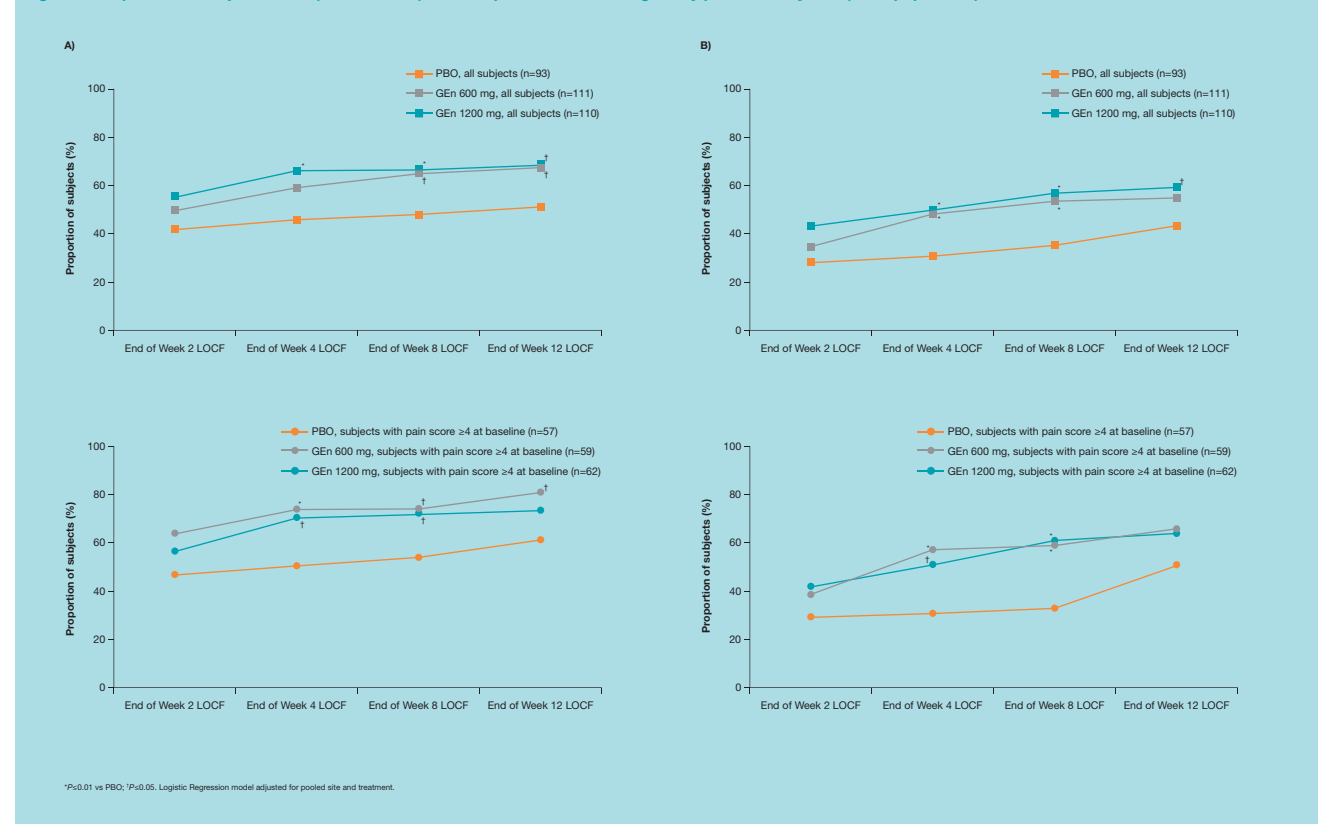
- Significantly more GEN 1200 mg-treated subjects reported a ≥30% reduction from baseline in pain compared with PBO at Week 12 LOCF (all subjects, 69.1% vs 51.6%; $P = 0.0117$); there was no significant treatment difference among subjects with average daily pain scores ≥4 at baseline (74.2% vs 61.4%; AOR: 1.8; 95% CI: 0.83, 4.02; $P = 0.1330$; Figure 2A).
- Significantly more GEN 600 mg-treated subjects reported a ≥30% reduction from baseline in pain compared with PBO at Week 12 LOCF (all subjects, 67.6% vs 51.6%; $P = 0.0235$ and; subjects with average daily pain scores ≥4 at baseline, 81.4% vs 61.4%; AOR: 2.8; 95% CI: 1.20, 6.69; $P = 0.0178$; Figure 2A).

Table 1. Subject demographic and clinical characteristics at baseline (mITT population), by average daily pain score at baseline

	Baseline average daily pain score >0			Baseline average daily pain score ≥4		
	PBO (n=83)	GEN 600 mg (n=100)	GEN 1200 mg (n=100)	PBO (n=57)	GEN 600 mg (n=59)	GEN 1200 mg (n=62)
Age, years	49.8 (12.24)	48.3 (12.75)	49.5 (12.51)	48.8 (11.70)	47.3 (12.35)	50.4 (12.91)
Proportion of women, n (%)	46 (55)	55 (55)	58 (58)	31 (54)	32 (54)	36 (58)
Race, White or Caucasian, n (%)	78 (94)	93 (93)	96 (96)	55 (96)	53 (90)	60 (97)
Number of days with RLS in the past week	6.3 (0.90)	6.3 (0.91)	6.3 (1.02)	6.4 (0.92)	6.5 (0.77)	6.4 (1.00)
Duration of RLS symptoms, years	15.2 (13.45)	12.4 (12.23)	14.1 (12.13)	13.9 (12.55)	12.3 (12.55)	12.7 (11.86)
Previously treated for RLS, n (%)	33 (40)	33 (33)	37 (37)	27 (47)	18 (31)	27 (44)
IRLS total score	23.8 (4.42)	23.3 (4.86)	23.4 (5.27)	24.6 (4.32)	24.0 (4.50)	23.8 (5.46)
Average daily RLS pain score	4.6 (2.02)	4.4 (2.14)	4.6 (2.14)	5.7 (1.29)	5.9 (1.26)	5.8 (1.52)

All values are mean (SD) unless otherwise stated.

Figure 2. Proportion of subjects with A) ≥30% and B) ≥50% improvement in average daily pain score by visit (mITT population).



Response of ≥50% Improvement in Average Daily Pain Scores

- Significantly more GEN 1200 mg-treated subjects reported a ≥50% reduction from baseline in pain compared with PBO at Week 12 LOCF (60.0% vs 44.1%; $P = 0.0253$); there was no significant treatment difference among subjects with average daily pain scores ≥4 at baseline (64.5% vs 50.9%; AOR: 1.8; 95% CI: 0.84, 3.72; $P = 0.1347$; Figure 2B).
- A greater proportion of GEN 600 mg-treated subjects reported a ≥50% reduction from baseline in pain compared with PBO for all subjects (55.9% vs 44.1%; $P = 0.0997$) and subjects with average daily pain scores ≥4 at baseline (66.1% vs 50.9%; AOR: 1.9; 95% CI: 0.88, 4.07; $P = 0.1023$; Figure 2B), although these differences were not statistically significant.

Tolerability and Safety

- The two most commonly reported treatment-emergent AEs (GEN 1200 mg, 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.

Conclusions

- GEN 600 mg and 1200 mg significantly improved RLS symptoms (IRLS total score and CGI-I) and pain (mean reduction and response of at least 30% improvement in average daily pain scores) associated with RLS compared with PBO, in subjects with moderate-to-severe primary RLS.
- GEN 600 mg and 1200 mg are generally well tolerated.

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Disclosures

DOL has served on the RLS Scientific Advisory Board for GlaxoSmithKline. 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. 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 for Boehringer Ingelheim. RWB is an employee of XenoPort, Inc.