

Introduction: Gabapentin enacarbil (GEN) delivers improved and sustained, dose-proportional exposure compared with gabapentin. The extended release formulation allows once-daily dosing in Restless Legs Syndrome (RLS). GEN is under investigation for the treatment of moderate-to-severe primary RLS. PIVOT RLS I (XP052) and PIVOT RLS II (XP053) demonstrated that GEN 1200 mg significantly improved RLS symptoms compared with placebo (PBO) and was generally well tolerated in adults with moderate-to-severe primary RLS. PIVOT RLS II also demonstrated the efficacy and tolerability of GEN 600 mg compared with PBO. Data are presented from an integrated analysis of these two randomized trials for GEN 1200 mg vs PBO.

Methods: Data from two 12-week, multicenter, double-blind, randomized, PBO-controlled studies (XP052 and XP053) were integrated for the 1200-mg dose groups. As GEN 600 mg was only assessed in XP053, it was not included in this integrated analysis. Subjects received GEN 1200 mg or PBO once daily at 5 pm with food. Coprimary endpoints were mean change from baseline in International Restless Legs Scale (IRLS) total score, and proportion of responders (rated 'very much' or 'much improved') on the investigator-rated Clinical Global Impression-Improvement (CGI-I) scale at Week 12 last observation carried forward (LOCF) for GEN 1200 mg vs PBO. **Results:** The integrated modified intent-to-treat population included 427 subjects: GEN 1200 mg = 223, PBO = 204. GEN 1200 mg improved mean (SD) IRLS total score vs PBO from baseline to Week 12 LOCF (-13.1 [9.15] vs -9.3 [8.20]; adjusted mean treatment difference [AMTD]: -3.8; 95% CI: -5.36, -2.32; $P < 0.001$). More subjects receiving 1200 mg GEN were CGI-I responders vs PBO (77% vs 42%; adjusted odds ratio: 4.7; 95% CI: 3.07, 7.15; $P < 0.001$). The two most commonly reported adverse events (GEN 1200 mg, PBO) in the integrated data were somnolence (22%, 5%) and dizziness (22%, 5%).

Conclusions: Integrated analyses from two studies demonstrate that GEN 1200 mg once daily significantly improves RLS symptoms compared with PBO and is generally well tolerated.

Introduction

- Restless Legs Syndrome (RLS) is a neurological disorder characterized by an urge to move the legs, accompanied or caused by unpleasant sensations in the legs. Symptoms generally begin or worsen during periods of rest or inactivity, are relieved by movement, and are worse during the evening or night than during the day.¹
- Absorption of gabapentin is mediated by low-capacity nutrient transporters located in a narrow region of the small intestine, which saturate at normal therapeutic doses.² As a result, gabapentin displays dose-dependent bioavailability and highly variable exposure that may limit its clinical utility.^{3,4}
- Gabapentin enacarbil (GEN) is an actively transported prodrug of gabapentin under investigation for the treatment of moderate-to-severe primary RLS.^{5,6}
- GEN is absorbed throughout the large and small intestine by high-capacity nutrient transporters and is rapidly and extensively hydrolyzed to gabapentin.⁷⁻⁹
- GEN provides sustained, dose-proportional gabapentin exposure up to GEN 6000 mg, with low intersubject variability.⁷⁻⁹
- GEN 1200 mg and 600 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 studies, PIVOT RLS I² and PIVOT RLS II.¹⁰ Analyses of integrated data for GEN 1200 mg compared with PBO from PIVOT RLS I and II are presented here.

Methods

Study design

- PIVOT RLS I (XenoPort, Inc., protocol XP052) and PIVOT RLS II (XenoPort, Inc., protocol XP053) were multicenter, 12-week, randomized, double-blind, PBO-controlled, parallel-group studies that assessed the efficacy and tolerability of GEN in subjects with moderate-to-severe primary RLS.
 - PIVOT RLS I: Subjects were randomized 1:1 to receive GEN 1200 mg (2 x 600 mg extended release tablets) or PBO once daily at 5 pm with food.
 - PIVOT RLS II: Subjects were randomized 1:1:1 to receive GEN 1200 mg (2 x 600 mg extended release tablets), GEN 600 mg (1 x 600 mg extended release tablet) or PBO once daily at 5 pm with food.
- Data were integrated for the PBO and GEN 1200 mg treatment groups. The GEN 600 mg treatment group from PIVOT RLS II was not included in these analyses because there was no GEN 600 mg treatment group in PIVOT RLS I.

Subjects

- Key inclusion criteria:
 - adults 18 years or older, diagnosis of primary RLS based on International RLS Study Group diagnostic criteria¹¹

Efficacy and Tolerability of Gabapentin Enacarbil in Primary Restless Legs Syndrome: Results of Two Randomized Studies

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- RLS symptoms for ≥ 15 nights during the month prior to screening and ≥ 4 evenings/nights during the 7-day baseline period
- International Restless Legs Scale (IRLS) total score¹¹ ≥ 15
- estimated creatinine clearance of ≥ 60 mL/min.
- Key exclusion criteria:
 - sleep disorders affecting RLS assessment
 - history of RLS symptom augmentation or end-of-dose rebound with dopamine agonists
 - moderate-to-severe depression, neurological disease or movement disorders.

Assessments

- Coprimary efficacy endpoints:
 - mean change from baseline to Week 12 LOCF in IRLS total score (assessed using subject responses on the IRLS).
 - proportion of responders (rated as 'much improved' or 'very much improved') on the investigator-rated Clinical Global Impression-Improvement (CGI-I) scale¹² at Week 12 LOCF.
- Secondary endpoints included mean change from baseline in IRLS total score at Week 1 LOCF and the proportion of responders on the investigator-rated CGI-I scale at Week 1.

Tolerability

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

Statistical analyses

- The safety population comprised all subjects who received at least one dose (or portion of a dose) of study medication.
- The modified intent-to-treat (mITT) population 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, study, and treatment
 - responder data using a logistic regression model adjusted for pooled site, study, and treatment.

Results

Subjects

- Subject disposition is shown in **Figure 1**. The mITT population comprised 112 GEN 1200 mg-treated subjects and 108 PBO-treated subjects from PIVOT RLS I, and 111 GEN 1200 mg-treated subjects and 96 PBO-treated subjects from PIVOT RLS II. Completion rates were similar in both studies.
- Subject demographics and baseline characteristics were similar across treatment groups (**Table 1**).

Coprimary endpoints

- GEN 1200 mg significantly improved mean (SD) IRLS total score from baseline compared with PBO at Week 12 LOCF (-13.0 [9.15] vs -9.2 [8.20]; adjusted mean treatment difference [AMTD] for change from baseline: -3.8; 95% CI: -5.36, -2.32; $P < 0.001$; **Figure 2**).
- Significantly more GEN 1200 mg-treated subjects were rated as responders on the investigator-rated CGI-I scale compared with PBO at Week 12 LOCF (77% vs 42%; adjusted odds ratio [AOR]: 4.7; 95% CI: 3.07, 7.15; $P < 0.0001$; **Figure 3**).

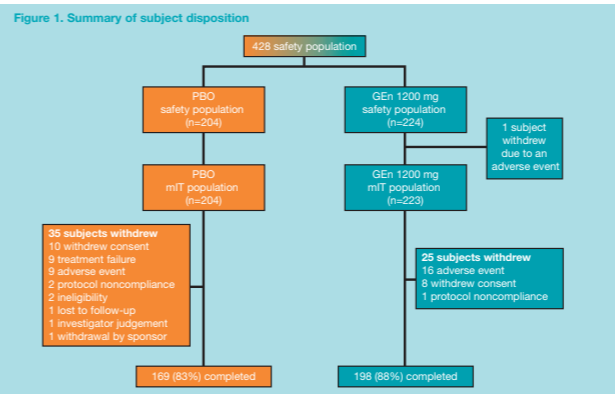


Table 1. Demographic and clinical characteristics at baseline (mITT population)

Characteristic	PBO (n=204)	GEN 1200 mg (n=223)
Age, years	49.7 (12.50)	50.8 (12.80)
Proportion of women, n (%)	122 (60)	131 (59)
Race: White or Caucasian, n (%) ^a	196 (96)	214 (96)
Previously treated for RLS, n (%)	77 (38)	72 (32)
Duration of RLS symptoms, years	14.5 (12.85)	13.9 (13.55)
7-day RLS record, days with RLS ^b	6.2 (1.00)	6.1 (1.06)
Baseline IRLS scores	23.2 (4.78)	23.1 (5.08)

All values are mean (SD) unless otherwise stated.
^aSubjects could have been categorized to more than 1 race; ^bNumber of days RLS symptoms expressed during week prior to baseline.

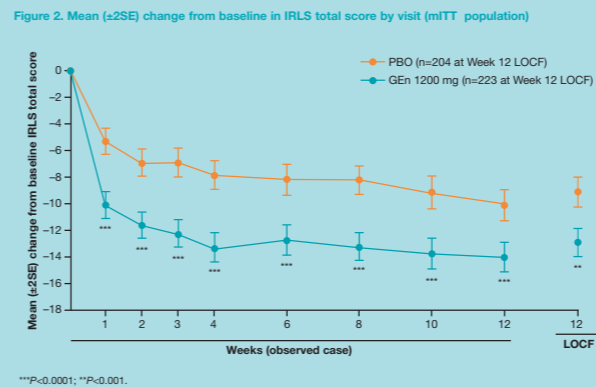
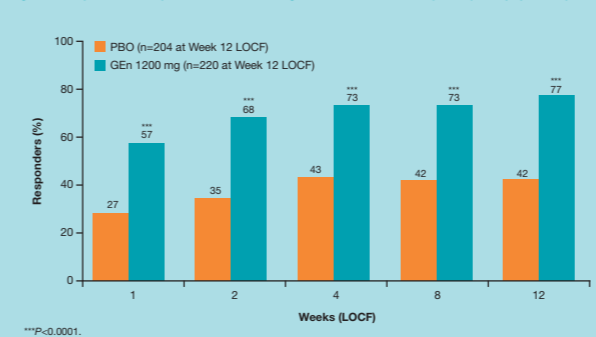


Figure 3. Proportion of responders on the investigator-rated CGI-I scale by visit (mITT population)



Secondary endpoints

- Significant improvement in IRLS total score was seen as early as Week 1 OC (the first assessment) in GEN 1200 mg-treated subjects compared with PBO (mean [SD] change from baseline: -10.2 [7.96] vs -5.4 [6.60]; AMTD: -4.8; 95% CI: -6.12, -3.40; $P < 0.0001$; **Figure 2**).
- A significantly higher proportion of responders was seen on the investigator-rated CGI-I scale as early as Week 1 in GEN 1200 mg-treated subjects compared with PBO (57% vs 27%; AOR: 3.6; 95% CI: 2.36, 5.50; $P < 0.0001$; **Figure 3**).

Tolerability

- Treatment-emergent AEs reported in $\geq 5\%$ of subjects in any treatment group are shown in **Table 2**.
 - 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%).
 - 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 the two subjects continued in the studies.
- No clinically significant changes in vital signs, ECGs or laboratory parameters were observed in the individual studies.

Table 2. Treatment-emergent AEs occurring in $\geq 5\%$ of subjects in any treatment group (safety population)

Characteristic	PBO (n=204)	GEN 1200 mg (n=224)
All AEs, n (%)	156 (76)	187 (83)
Somnolence	10 (5)	50 (22)
Dizziness	10 (5)	49 (22)
Headache	21 (10)	32 (14)
Nasopharyngitis	14 (7)	18 (8)
Fatigue	7 (3)	14 (6)
Nausea	7 (3)	15 (7)
Sedation	2 (<1)	11 (5)

Conclusion

- Integrated analyses from two PBO-controlled studies indicate that GEN 1200 mg once daily significantly improves RLS symptoms and is generally well tolerated in subjects with moderate-to-severe primary RLS.
- Improvements in RLS symptoms were noted as early as one week after beginning treatment.

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