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ORIGINAL RESEARCH

Gabapentin enacarbil in subjects with moderate to severe primary restless legs syndrome with and without severe sleep disturbance: an integrated analysis of subjective and novel sleep endpoints from two studies

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Purpose: The aim of the study reported here was assessment of subjective and novel sleep endpoints, according to sleep disturbance severity at baseline, in adult subjects with moderate to severe primary restless legs syndrome (RLS) treated with gabapentin enacarbil (GEn) 1200 mg or placebo.

Methods: Integrated analysis of two 12-week randomized trials in subjects with RLS was undertaken. Sleep outcomes from the Medical Outcomes Study (MOS) Sleep Scale and the Post Sleep Questionnaire were evaluated. Novel sleep endpoints derived from the 24-Hour RLS Symptom Diary were compared with similar endpoints derived from the Pittsburgh Sleep Diary (PghSD). Subjects were divided into two subgroups based on their level of sleep disturbance (responses to item 4 of the International Restless Legs Scale) at baseline. Data were analyzed using a last observation carried forward approach.

Results: The modified intent-to-treat population comprised 427 subjects (GEn 1200 mg, n = 223; placebo, n = 204). GEn significantly improved all MOS Sleep Scale domain scores from baseline compared with placebo ($P < 0.05$) in both subgroups. Compared with placebo, GEn-treated subjects with very severe to severe sleep disturbance reported higher overall sleep quality, fewer nighttime awakenings, and fewer hours awake per night due to RLS symptoms at Week 12 on the Post Sleep Questionnaire (all $P < 0.001$, distribution of responses); sleep quality was the only significant item in those with moderate to no sleep disturbance ($P < 0.0001$). Evaluation of sleep endpoints derived from the 24-Hour RLS Symptom Diary and PghSD yielded similar results.

Conclusion: Once-daily GEn 1200 mg significantly improves subjective sleep outcomes compared with placebo in subjects with RLS, regardless of the severity of sleep disturbance at baseline, although a greater improvement in sleep assessments may be observed in subjects with very severe to severe sleep disturbance than in those with moderate to no disturbance. Similar patterns were observed between treatment groups when comparing sleep endpoints derived from the PghSD and the novel sleep endpoints derived from the 24-Hour RLS Symptom Diary.

Keywords: 24-Hour RLS Symptom Diary, Pittsburgh Sleep Diary, Medical Outcomes Study Sleep Scale, Post Sleep Questionnaire

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Introduction

Restless legs syndrome (RLS) is a common neurologic disorder characterized by an urge to move the legs, often accompanied by unpleasant or painful leg sensations

that are partially or totally relieved by movement.[1] Owing to the occurrence or worsening of RLS in the evening or night, more than 75% of subjects report at least one sleep-related impairment.[2] RLS symptoms may delay sleep onset, decrease total sleep time, and cause multiple awakenings, resulting in significant sleep disturbance.[3,4] This in turn may lead to a subsequent increase in daytime fatigue and sleepiness.[2,5] Comparative studies have shown that subjects with RLS suffer reduced sleep compared with both healthy controls[6] and those with major depressive disorders.[7] Further, poor sleep patterns at RLS diagnosis appear to be predictive of poor psychological functioning about 3.5 years later.[8]

Gabapentin enacarbil (GEn) is an actively transported prodrug of gabapentin that is indicated for the treatment of moderate to severe primary RLS in adults.[9] It is absorbed throughout the large and small intestine by high-capacity nutrient transporters and is rapidly and extensively hydrolyzed to gabapentin, providing sustained, dose-proportional gabapentin exposure.[10–12] GEn conversion to gabapentin following absorption is efficient and provides more predictable gabapentin exposure and increased bioavailability than milligram-equivalent doses of oral gabapentin.[12] As GEn is a prodrug of gabapentin, its therapeutic effects in RLS are attributable to gabapentin; however, the precise mechanism by which gabapentin treats RLS is unknown.[9]

The efficacy and tolerability of GEn in adults with moderate to severe primary RLS have been demonstrated in two Phase III, 12-week, multicenter, placebo-controlled, randomized clinical trials.[13,14] These showed that, compared with placebo, treatment with GEn 600 mg (Study XP053)[14] and 1200 mg (Studies XP052 and XP053)[13,14] is associated with significant improvements in both restlessness and sleep disturbance, as measured using established tools such as the International Restless Legs Scale (IRLS), which measures specific RLS-related symptoms and symptom impact; the Clinical Global Impression – Improvement (CGI-I) scale, which assesses global change in condition; the Medical Outcomes Study (MOS) Sleep Scale, which provides a general measure of several sleep domains; the Post Sleep Questionnaire (PSQ), which evaluates sleep disturbance in RLS; and the Pittsburgh Sleep Diary (PghSD), which quantifies sleep and waking behaviors. GEn 600 mg is the daily dose approved by the US Food and Drug Administration for the treatment of moderate to severe primary RLS in adults.

In addition to such established tools, both studies also used a novel instrument to monitor RLS symptoms: the 24-Hour RLS Symptom Diary. This patient diary, developed by XenoPort (Santa Clara, CA, USA) for use in clinical trials, assesses whether a subject experiences RLS symptoms over a 24-hour period. Patients have to indicate whether symptoms are present and, if so, their severity, and also record when they are asleep and symptoms cannot be measured. In both Studies XP052 and XP053, GEn-treated groups showed a delayed time of onset of RLS symptoms within the 24-hour period compared with placebo groups, as well as a higher percentage of symptom-free subjects.[13,14]

Here, we present a retrospective integrated analysis of Studies XP052 and XP053, assessing subjective sleep outcomes and the tolerability of once-daily GEn 1200 mg using pooled data from the two trials. The objective of such analysis was two fold: first to evaluate – using data pooled according to severity of sleep disturbance at study entry – whether baseline sleep disturbance could have an effect on sleep outcomes, as the interaction between treatment effect and baseline sleep disturbance was not assessed in the original studies; second, to assess how informative two novel sleep endpoints derived from the 24-Hour RLS Symptom Diary were. These were analyzed alongside well-established subjective sleep outcomes from the MOS Sleep Scale and the PSQ for exploration and concurrence, and then compared with similar endpoints derived from the PghSD.

Subjects and methods

Study design

Data from two 12-week, randomized, double-blind, parallel-group, placebo-controlled Phase III trials of GEn versus placebo were integrated. In Study XP052 (XenoPort protocol number; clinical trials.gov identifier NCT00298623[15]), which was conducted at 22 centers in the USA, subjects were randomized to receive GEn 1200 mg or placebo.[13] In Study XP053 (XenoPort protocol number; clinical trials.gov identifier NCT00365352),[16] conducted at 28 centers in the USA, subjects were randomized to receive GEn 600 mg, 1200 mg, or placebo.[14] In both studies, GEn or placebo was administered once daily at 5 pm with food; GEn was initiated at a dose of 600 mg with subsequent titration to 1200 mg after 3 days. At the end of the study or at early termination (ET), subjects receiving GEn 1200 mg had their dose tapered over 7 days.

Subjects

Key inclusion and exclusion criteria were similar for each study and have been described previously.[13,14] Briefly, the studies included adults with moderate to severe primary RLS as per International Restless Legs Syndrome Study Group diagnostic criteria, with RLS symptoms for ≥15 days during

the month prior to screening and for ≥4 nights during the 7-day baseline period, and with a total IRLS score of ≥15 at baseline. Exclusion criteria included secondary RLS, a history of RLS symptom augmentation, or rebound with previous dopamine agonist treatment, and neurologic, sleep, or movement disorders other than RLS.

For this analysis, subjects were divided into two sleep disturbance subgroups (very severe to severe sleep disturbance or moderate to no sleep disturbance) based on their response to IRLS item 4 at baseline.[17] Subjects were asked, "Overall, how severe is your sleep disturbance from your RLS symptoms?" and were allocated to one of the two subgroups according to the following responses: "very severe" and "severe" versus "moderate," "mild," or "none."

All subjects provided institutional review board-approved written informed consent prior to study participation. The study was conducted in accordance with Good Clinical Practice and the guiding principles of the Declaration of Helsinki.

Study assessments

Subjective sleep endpoints

Subjective sleep endpoints from the MOS Sleep Scale, the PSQ, and the PghSD were assessed by baseline sleep disturbance subgroup and by treatment group. For the MOS Sleep Scale, change from baseline in the four domains of sleep disturbance, sleep adequacy, sleep quality, and daytime somnolence was evaluated at Weeks 4, 8, and 12. For the PSQ, responses to item 1, "overall quality of sleep in the last week"; item 4, "number of awakenings during the night in the past week due to RLS symptoms"; and item 5, "number of hours awake per night in the past week due to RLS symptoms," were assessed at Week 12. Regarding the PghSD, two endpoints were considered and assessed at Weeks 2, 4, 8, and 12: wake time after onset (WASO) and total sleep time (TST). WASO was expressed in minutes and calculated as the mean of available "time awake during the night" values recorded over the 7 days prior to each visit. TST was expressed in hours and calculated using the following formula: (wake-up time – lights out time) – time (minutes) to fall asleep – time awake during the night (minutes); it was analyzed for each of the 7 days prior to each visit and then averaged over that period.

Novel sleep endpoints

On the 24-Hour RLS Symptom Diary, participants indicated whether symptoms were "not present," "mild," "moderate," or "severe" at 30-minute intervals while awake, and had to record when they were asleep and symptoms could not be measured. The 24-Hour RLS Symptom Diary was completed the day before visits at Weeks 2 and 12/ET.

Two novel sleep endpoints were derived using the 24-Hour RLS Symptom Diary: sleep time (ST) and time awake during the night (TAN). ST was expressed in hours and calculated using the formula: (wake-up time – time asleep) – TAN. In this formula, "time asleep" is the first (earliest) time point occurring after 5.59 pm when the subject indicated they were asleep; "wake-up time" is the first (earliest) time point occurring after "time asleep" when the subject indicated they were awake and stayed awake at all subsequent time points; and "TAN" is the number of intervals occurring after initial "time asleep" during the night and before "wake-up time" in which the subject indicated they were awake, multiplied by 30 minutes.

Sleep-related tolerability endpoints

Somnolence and sedation, reported as treatment-emergent adverse events (AEs), were summarized (as number of patients [%]) for both subgroups, including those leading to withdrawal from the studies. The change from baseline in Epworth Sleepiness Scale (ESS) total score was assessed for the overall group of subjects and for each subgroup.

Statistical analyses

Changes from baseline for the MOS Sleep Scale, ST, TST, and WASO were analyzed using a parametric analysis of covariance (ANCOVA) model adjusted for baseline value, study, pooled site, and treatment. Changes from baseline in TAN were analyzed using non-parametric methods (rank ANCOVA model), adjusted for baseline TAN, pooled site, and study, as the assumption of normality was not met for these data. Categorical PSQ responses were analyzed using a Cochran–Haenszel mean score test with interval scoring, stratified by pooled site. Clinical Global Impression of Improvement responders were analyzed using a logistic regression model adjusted for pooled site, study, and treatment.

All statistical tests were considered exploratory. For the PSQ, all *P* values presented are for distribution of responses. No multiplicity adjustments were made for treatment group comparisons, and missing values were imputed using the last observation carried forward (LOCF) technique for the MOS Sleep Scale, PSQ, and PghSD endpoints. The analysis of ST and TAN from the 24-Hour RLS Symptom Diary used observed case data, as no imputation was applied between visits, which was consistent with the original data-handling in the individual studies. If sleep status was missing for a

particular 30-minute interval within a visit, it was assumed that the subject was awake during that interval.

The safety population comprised all subjects who were enrolled into either study and received at least one dose (or part of a dose) of study medication. The modified intent-to-treat population included all subjects in the safety population who completed an IRLS score assessment at baseline and at least one IRLS rating during the treatment period.

Results

Study population

The modified intent-to-treat population comprised 427 subjects, 223 of whom received GEn 1200 mg and 204 of whom received placebo. At baseline, 187 (44%) subjects reported very severe to severe sleep disturbance, and 240 (56%) reported moderate to no sleep disturbance (Table 1). The number of subjects who completed the studies was similar in each subgroup: 83% in the very severe to severe subgroup and 88% in the moderate to no sleep disturbance group. Subject demographics were similar across treatment groups and between sleep disturbance subgroups. Baseline characteristics were similar across treatment groups, but baseline IRLS total score and sleep outcomes indicated a greater severity of symptoms in subjects with very severe to severe sleep disturbance (Table 1).

Efficacy

Subjective sleep endpoints

GEn 1200 mg significantly improved all MOS Sleep Scale domain scores from baseline to Week 12 LOCF compared with placebo in both subgroups (Figure 1).

On the PSQ, compared with placebo-treated subjects with very severe to severe sleep disturbance, GEn 1200 mg-treated subjects with very severe to severe sleep disturbance reported significantly better overall sleep quality (GEn vs placebo: excellent, 32% vs 11%; reasonable, 47% vs 51%; poor, 21% vs 38%; $P = 0.0004$ for distribution of responses), fewer nighttime awakenings (GEn vs placebo: none, 47% vs 21%; 1–2, 42% vs 55%; 3–4, 8% vs 19%; ≥5 times, 2% vs 5%; $P < 0.0001$ for distribution of responses), and fewer hours awake per night due to RLS symptoms (GEn vs placebo: none, 47% vs 21%; <1 hour, 35% vs 46%; 1 to <2 hours, 8% vs 15%; 2 to <3 hours, 5% vs 7%; ≥3 hours, 4% vs 12%; $P = 0.0004$ for distribution of responses) at Week 12 LOCF (Figure 2). Subjects with moderate to no sleep disturbance also reported significantly higher overall sleep quality compared with those on placebo (GEn 1200 mg vs placebo: excellent, 23% vs 9%; reasonable, 70% vs 69%; poor, 8% vs 22%; $P < 0.0001$ for distribution of responses) at Week 12 LOCF, but no significant difference in nighttime awakenings (GEn

Table 1 Demographic and baseline characteristics (modified intent-to-treat population)

	Placebo (n = 204)		GEn 1200 mg (n = 223)	
	Moderate to no sleep disturbance (n = 112)	Very severe to severe sleep disturbance (n = 92)	Moderate to no sleep disturbance (n = 128)	Very severe to severe sleep disturbance (n = 95)
Age, years	49.0 (12.53)	50.4 (12.48)	49.1 (13.31)	53.0 (11.77)
Women, n (%)	66 (59.00)	56 (61.00)	68 (53.00)	63 (66.00)
Treated previously for RLS, n (%)	30 (27.00)	47 (51.00)	32 (25.00)	40 (42.00)
Duration of RLS symptoms, years	15.6 (14.05)	13.1 (11.15)	12.2 (12.12)	16.2 (15.06)[a]
7-day RLS record, days with RLS[b]	6.1 (1.00)	6.2 (1.01)	6.0 (1.07)	6.2 (1.05)
IRLS total score	20.5 (3.44)	26.4 (4.18)	20.0 (3.14)	27.4 (3.95)
Sleep disturbance at baseline				
Baseline MOS sleep scale domain[c]				
Sleep disturbance (0–100)	43.4 (19.36)	60.8 (19.75)	42.4 (19.39)[d]	63.1 (20.96)
Sleep adequacy (0–100)	39.2 (23.64)	26.5 (21.30)	42.0 (23.06)[d]	22.7 (19.65)
Daytime somnolence (0–100)	30.4 (18.31)	41.0 (21.15)	33.1 (17.85)[d]	42.7 (22.16)
Sleep quantity (hours)	6.4 (1.00)	5.5 (1.31)	6.4 (1.26)[d]	5.5 (1.36)
24-Hour RLS symptom diary				
TAN, minutes	65.8 (105.79)[e]	101.4 (124.28)	69.4 (107.88)[f]	111.2 (153.21)
ST, hours	5.7 (2.12)[e]	5.2 (2.20)	5.9 (2.05)[f]	4.5 (2.35)
PghSD				
WASO, minutes	24.9 (26.80)	45.5 (42.12)	23.7 (21.57)	39.0 (34.29)
TST, hours	6.8 (1.10)	6.5 (1.40)	6.8 (1.24)	6.1 (1.50)

Notes: All values are means (standard deviations) unless stated otherwise. [a]n = 94; [b]number of days of RLS symptoms experienced 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, sleep quantity = 6.8 hours[20]; [d]n = 127; [e]n = 109; [f]n = 127.

Abbreviations: GEn, gabapentin enacarbil; IRLS, International Restless Legs Scale; MOS, Medical Outcomes Study; PghSD, Pittsburgh Sleep Diary; RLS, restless legs syndrome; ST, sleep time; TAN, time awake during the night; TST, total sleep time; WASO, wake time after sleep onset.

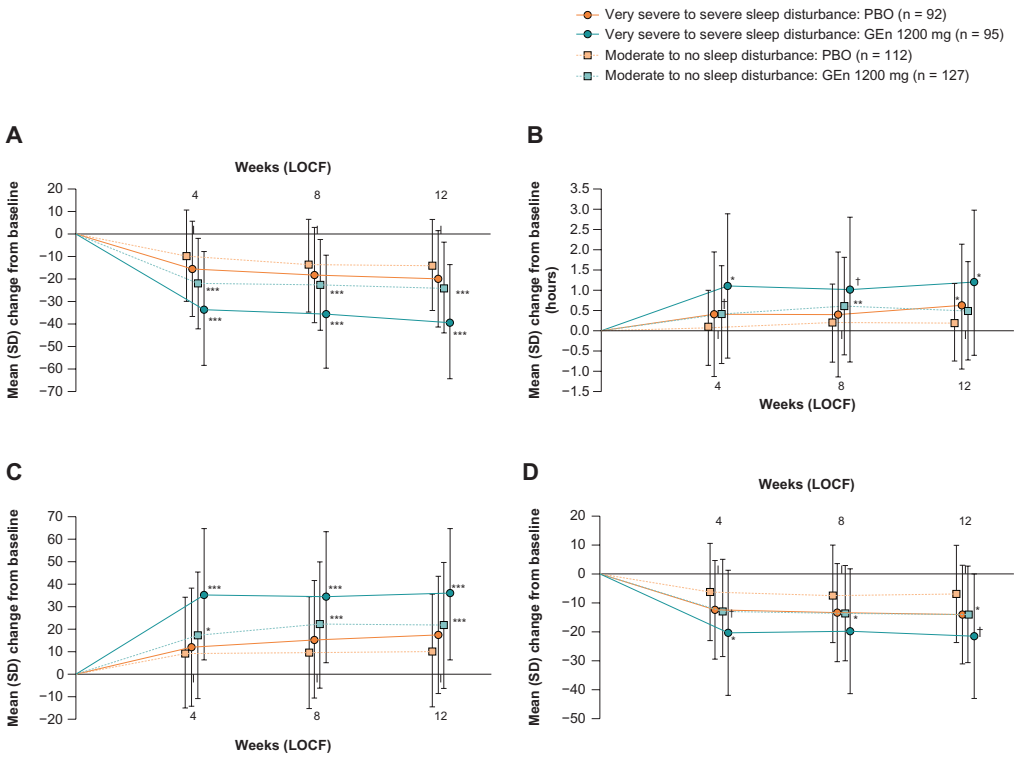

Figure 1 Mean (SD) change from baseline in domains of the Medical Outcomes Study Sleep Scale by visit (modified intent-to-treat population): (**A**) sleep disturbance, (**B**) sleep quantity, (**C**) sleep adequacy, and (**D**) daytime somnolence.
Notes: †$P < 0.05$; *$P < 0.01$; **$P < 0.001$; ***$P < 0.0001$.
Abbreviations: GEn, gabapentin enacarbil; LOCF, last observation carried forward; PBO, placebo; SD, standard deviation.

1200 mg vs placebo: none, 58% vs 48%; 1–2, 36% vs 42%; 3–4, 6% vs 7%; ≥5 times, 0% vs 3%; $P = 0.0694$ for distribution of responses), or hours awake per night due to RLS symptoms (GEn 1200 mg vs placebo: none, 58% vs 48%; <1 hour, 31% vs 38%; 1 to <2, 7% vs 9%; 2 to <3, 2% vs 3%; ≥3, 2% vs 2%; $P = 0.2719$ for distribution of responses) were observed.

Novel sleep endpoints

On the 24-Hour RLS Symptom Diary, GEn 1200 mg decreased TAN compared with placebo at Week 12/ET in the very severe to severe sleep disturbance subgroup (Figure 3A). The unadjusted mean (standard deviation [SD]) change from baseline was −17.2 (175.36) minutes for placebo and –83.1 (177.11) minutes for GEn 1200 mg; the adjusted mean treatment difference (AMTD) was −58.4. As the normality assumptions were not met in this case, the Chi-squared value for AMTD using non-parametric ANCOVA was calculated to be 10.9 ($P = 0.0010$). No significant treatment difference was observed for TAN at Week 12/ET in the moderate to no sleep disturbance subgroup. GEn 1200 mg increased ST compared with placebo at Week 12 in both subgroups (Figure 3B), but no significant treatment difference was observed.

PghSD sleep endpoints

GEn 1200 mg decreased WASO compared with placebo at Week 12 in both subgroups (Figure 4A). For the very severe to severe sleep disturbance subgroup, the AMTD was −12.7 minutes (95% confidence interval [CI]: –20.35, –5.15; $P = 0.0011$) and for the moderate to no sleep disturbance subgroup it was –4.8 minutes (95% CI: –8.36, –1.15; $P = 0.0100$). GEn 1200 mg increased TST compared with placebo at Week 12 in both subgroups (Figure 4B), but no significant treatment difference was observed.

Comparison of novel sleep endpoints and the PghSD

Subjects with very severe to severe sleep disturbance at baseline reported less ST and longer TAN compared with subjects with moderate to no sleep disturbance on the 24-Hour RLS Symptom Diary. Likewise, subjects with very severe to severe sleep disturbance at baseline reported less TST and greater WASO compared with subjects with moderate to no sleep disturbance on the PghSD (Table 1). However, there were differences in actual values recorded by the two assessment tools. At baseline, mean TST values taken from the PghSD were between 0.9 and 1.6 hours longer than the ST calculated using the 24-Hour RLS Symptom Diary (Table 1).

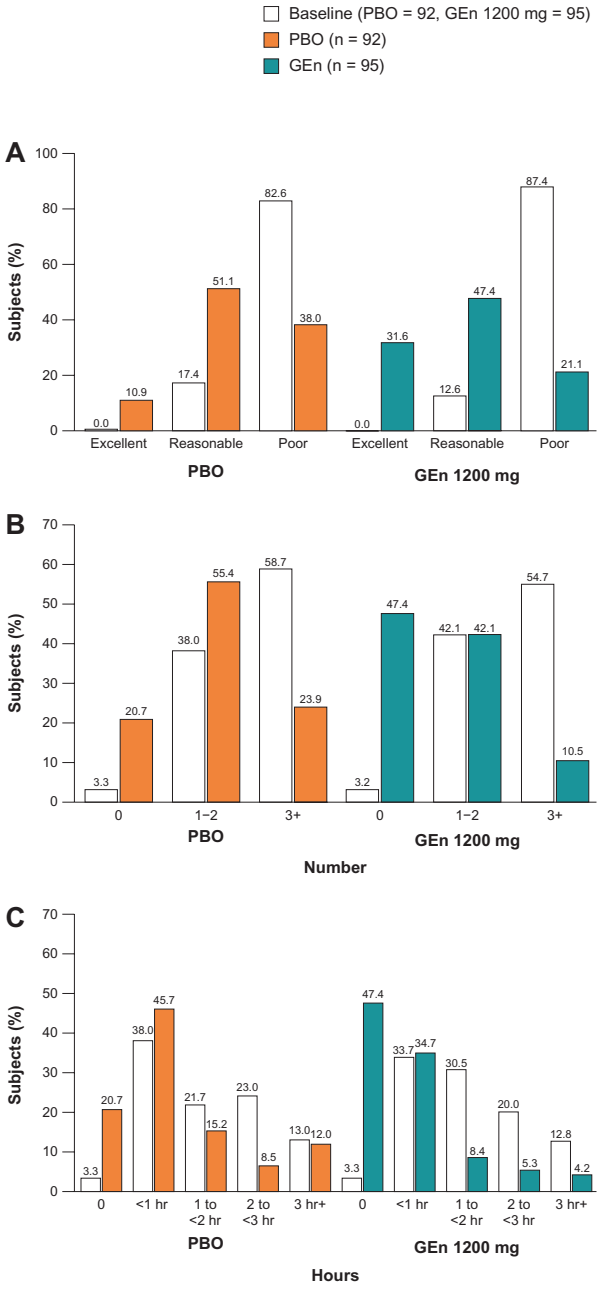

Figure 2 Responses on the Post Sleep Questionnaire items 1, 4, and 5 at baseline and Week 12, last observation carried forward for subjects with very severe to severe sleep disturbance at baseline (modified intent-to-treat population): (**A**) overall quality of sleep in the past week, (**B**) number of awakenings per night in the past week due to RLS symptoms, and (**C**) number of hours awake per night in the past week due to RLS symptoms.

Notes: A: $P = 0.0004$ for distribution of response. B: $P < 0.0001$ for distribution of response. C: $P = 0.0004$ for distribution of response.

Abbreviations: GEn, gabapentin enacarbil; PBO, placebo; RLS, restless legs syndrome.

The change from baseline in PghSD TST values were between 0.0 and 0.6 hours shorter than the change from baseline in ST as calculated from the 24-Hour RLS Symptom Diary for GEn subjects with moderate to no and very severe to severe sleep disturbance, respectively (Figure 5A).

Similarly, at baseline, mean WASO values taken from the PghSD were between 41 and 72 minutes shorter than TAN calculated using the 24-Hour RLS Symptom Diary (Table 1). Baseline mean WASO for all subjects was 34.2 minutes for placebo and 30.2 minutes for GEn 1200 mg. The change from baseline in WASO values was between 1 and 57 minutes shorter than the change from baseline in TAN, as calculated from the 24-Hour RLS Symptom Diary (Figure 5B).

Safety and tolerability

The proportion of subjects experiencing AEs of somnolence and/or sedation was similar between the subgroups (very severe to severe sleep disturbance: GEn, 25% and placebo, 7%; moderate to no sleep disturbance: GEn, 29% and placebo, 5%). Of these, the majority of GEn-treated subjects reported only one occurrence of these events, both in the very severe to severe (83%) and in the moderate to no sleep disturbance subgroups (89%). Most AEs were rated as mild or moderate in intensity. The mean (SD) maximum duration of the somnolence/sedation event in the GEn 1200 mg group was 17.5 (19.22) days for subjects with very severe to severe sleep disturbance and 14.3 (12.34) days for those with moderate to no sleep disturbance. The mean (SD) time to first occurrence of somnolence/sedation AEs was 7.8 (15.46) days in subjects with very severe to severe sleep disturbance and 9.2 (16.84) days for those with moderate to no sleep disturbance.

Baseline mean ESS total score was similar between subgroups: 9.6 for subjects with very severe to severe sleep disturbance (both in the GEn 1200 mg and in the placebo group) and 9.1–9.2 for subjects with moderate to no sleep disturbance. For subjects with very severe to severe sleep disturbance at baseline, there was a treatment benefit for GEn 1200 mg relative to placebo for the change in ESS total score at Week 12/ET (AMTD: –1.3; 95% CI: –2.57, –0.10; $P = 0.0349$). For subjects with moderate to no sleep disturbance at baseline, the change in ESS total score was not significant at any time point. Placebo response was similar between subgroups. There was a trend for a larger decrease (improvement) in ESS total score in subjects receiving GEn with very severe to severe sleep disturbance at baseline compared with those with moderate to no sleep disturbance.

Discussion

This integrated analysis indicates that, compared with placebo, once-daily GEn 1200 mg significantly improves subjective sleep outcomes in subjects with moderate to severe primary RLS suffering from varying degrees of

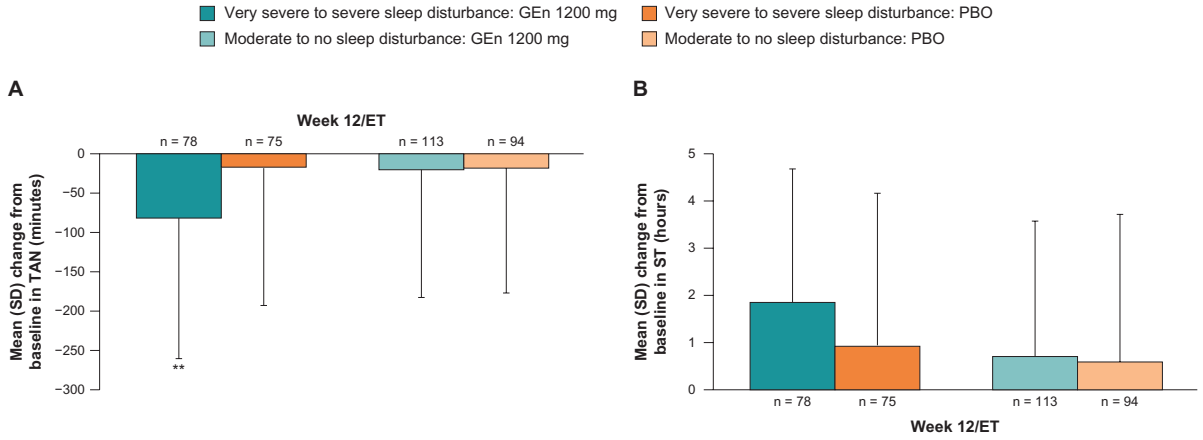

Figure 3 Change from baseline in novel sleep endpoints at Week 12/ET (modified intent-to-treat population): (**A**) mean (SD) change from baseline in TAN (minutes), OC and (**B**) mean change from baseline (SD) in ST (hours), OC.
Note: $^{**}P \leq 0.001$.
Abbreviations: ET, early termination; GEn, gabapentin enacarbil; OC, observed case; PBO, placebo; SD, standard deviation; ST, sleep time; TAN, time awake during the night.

sleep disturbance. This was demonstrated by results from the MOS Sleep Scale, with a significant improvement in all domains; the PSQ, with significant improvement in sleep quality (both the moderate to no sleep disturbance and the very severe to severe sleep disturbance groups), as well as nighttime awakenings and hours awake per night (very severe to severe sleep disturbance group only); and the PghSD, with significant improvement in WASO. The MOS Sleep Scale and PghSD results confirm those already reported in the individual studies;[13,14] for the PSQ, the individual studies reported significant improvements for GEn 1200 mg and 600 mg compared with placebo on all items.[13,14]

It is unsurprising that subjects with very severe to severe sleep disturbance at baseline reported less ST and TST and longer TAN and WASO on the 24-Hour RLS Symptom Diary and PghSD at baseline compared with subjects with moderate to no sleep disturbance. However, with the PghSD, more analyses yielded a significant treatment difference in favor of GEn versus placebo, regardless of sleep disturbance at baseline compared with results from the 24-Hour RLS Symptom Diary. Moreover, there were differences in reported values between the two assessment tools. The PghSD allows for greater fidelity of estimated sleep endpoints compared with the 24-Hour RLS Symptom Diary because it uses open text fields to collect data (subjects indicated an exact number of minutes they were awake during the night), and more frequent collection intervals were used in these two studies. In contrast, the 24-Hour RLS Symptom Diary collected data

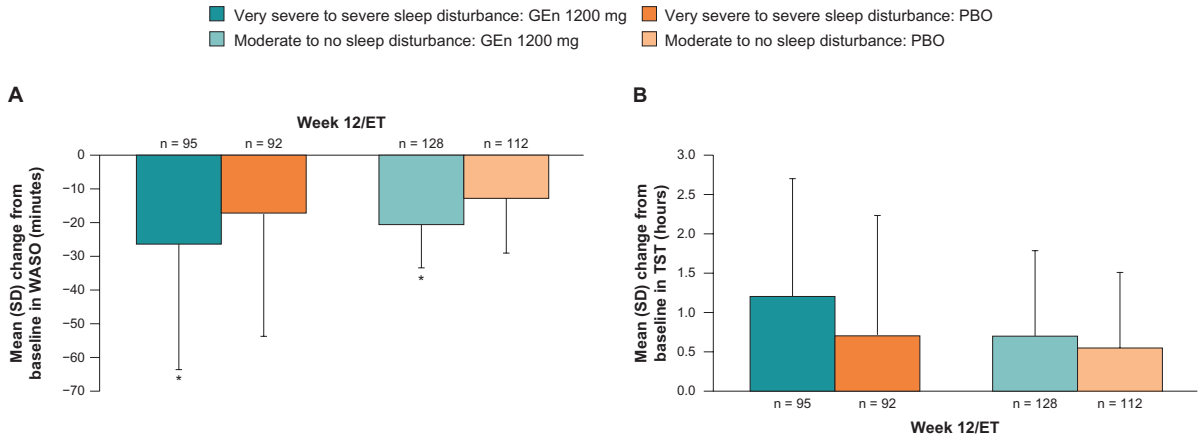

Figure 4 Change from baseline in Pittsburgh Sleep Diary sleep endpoints at Week 12/ET (modified intent-to-treat population): (**A**) mean (SD) change from baseline in WASO (minutes), LOCF and (**B**) mean (SD) change from baseline in TST (hours), LOCF.
Note: $^{*}P \leq 0.01$.
Abbreviations: ET, early termination; GEn, gabapentin enacarbil; LOCF, last observation carried forward; PBO, placebo; SD, standard deviation; TST, total sleep time; WASO, wake time after sleep onset.

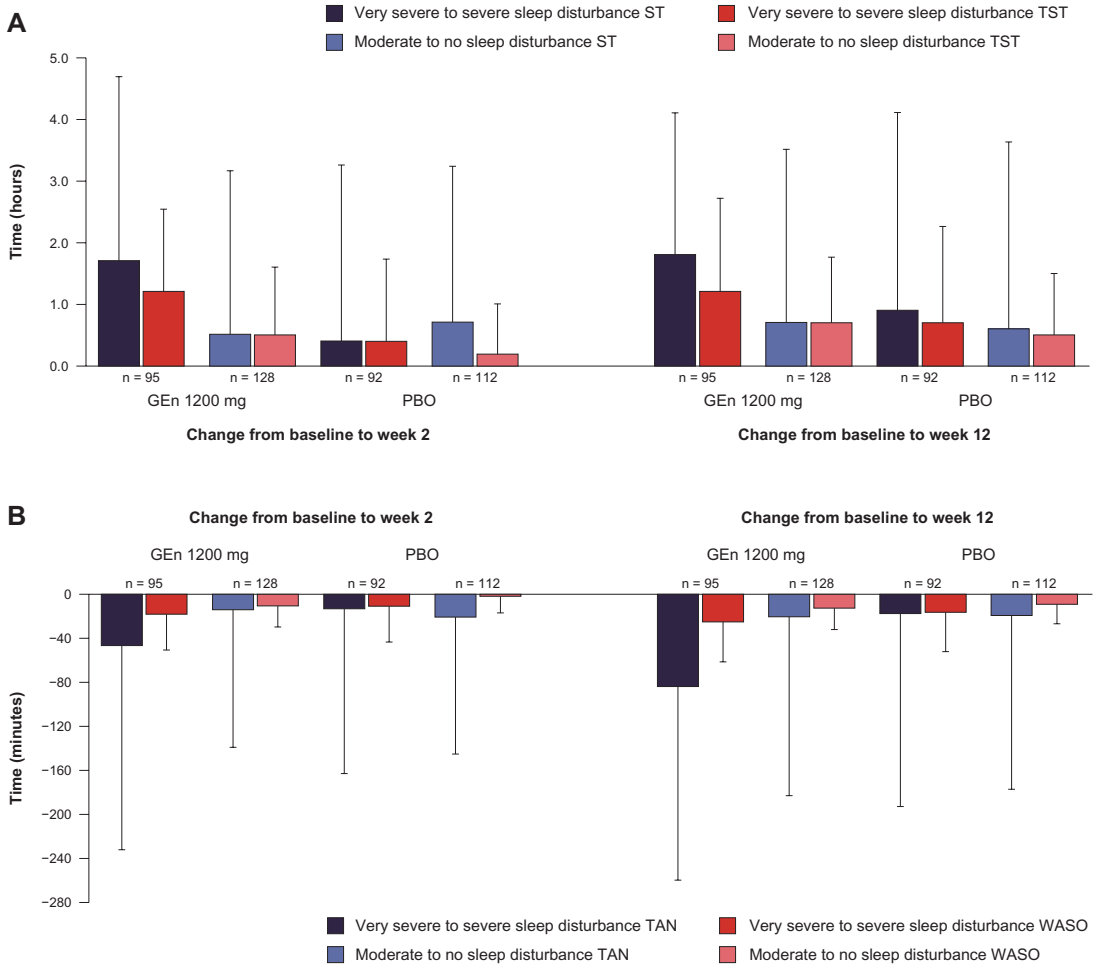

Figure 5 Comparison of novel sleep endpoints derived from the 24-Hour RLS Symptom Diary and the PghSD by sleep disturbance subgroup (modified intent-to-treat population): (**A**) mean (SD) change from baseline in ST (24-Hour RLS Symptom Diary) versus TST (PghSD) and (**B**) mean (SD) change from baseline in TAN (24-Hour RLS Symptom Diary) versus WASO (PghSD).
Abbreviations: GEn, gabapentin enacarbil; PBO, placebo; ST, sleep time; TAN, time awake during the night; TST, total sleep time; WASO, wake time after sleep onset.

in 30-minute intervals over a single 24-hour period prior to a visit (if a subject indicated they were awake at a particular interval, they were counted as being awake for the entire 30-minute period, even if in reality they were only awake for a portion of it). In addition, in the absence of a diary entry, it was assumed the subject was awake. This could have resulted in the subject's awake time being overestimated when using this tool. Although the PghSD is a well-established, validated tool for quantifying sleep behavior that has been shown to correlate well with other measures,[18,19] it is generally agreed that patients underestimate ST, and diaries may be a more accurate measure. While the 24-Hour RLS Symptom Diary allows assessment of onset and severity of RLS symptoms, the sleep measure component, as currently constructed, offers no clear advantage over traditional measures. However, with modifications to allow higher resolution of ST and enhanced patient compliance, use of the diary may be more intuitive to patients because it reflects a continuum of RLS symptoms and ultimately translate into a clinical tool for patient management.

The number of subjects reporting somnolence and/or sedation AEs was similar in both baseline sleep disturbance subgroups, although there was a greater improvement in ESS total score in subjects with very severe to severe sleep disturbance than in those with moderate to no sleep disturbance. Few subjects withdrew due to somnolence/sedation AEs: one in the very severe to severe sleep disturbance group and three in the moderate to no sleep disturbance subgroup. No subjects in either subgroup of the placebo group withdrew because of somnolence/sedation.

Limitations

Although this analysis of integrated data allows an evaluation of sleep outcomes in a large group of subjects by degree of

sleep disturbance at baseline, there are several limitations to the analysis and to the conclusions that may be drawn from it. First, this analysis used data only from subjects receiving GEn 1200 mg, although the daily dose of GEn approved by the US Food and Drug Administration for the treatment of moderate to severe primary RLS in adults is 600 mg. The 600 mg dose was evaluated in Study XP053 but not in Study XP052, so it could not be included in the integrated analysis with pooled data from the two trials. Another limitation is that the PghSD was assessed at Weeks 2, 4, 8, and 12, whereas the 24-Hour RLS Symptom Diary was assessed only at Weeks 2 and 12; therefore, these two instruments could be compared only at Weeks 2 and 12. Further, the recall periods differ between the PghSD and the 24-Hour RLS Symptom Diary, preventing a direct comparison at a given time. Although the study population has been categorized into subjects with very severe to severe and moderate to no sleep disturbance, this classification is based on one item of the IRLS relating to the severity of sleep disturbance. Subgroups could have been created based on the response to other items of the IRLS or on other scales.

Conclusion

GEn significantly improves subjective sleep outcomes compared with placebo in subjects with moderate to severe primary RLS, regardless of the severity of sleep disturbance at baseline. A greater treatment benefit is seen in subjects with very severe to severe sleep disturbance than in those with moderate to no sleep disturbance on the IRLS total score. Although similar patterns were observed between treatment groups when comparing sleep endpoints derived from the PghSD and the 24-Hour RLS Symptom Diary, the PghSD reported more ST than the 24-Hour RLS Symptom Diary. It is probable that the PghSD allows for a more sensitive evaluation of sleep in subjects with moderate to severe primary RLS – to confirm this, both measures would need to be studied further, with correlation to an objective measure such as actigraphy or polysomnography.

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