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ORIGINAL RESEARCH ARTICLE

Sleep and Quality of Life Under Prolonged Release Oxycodone/Naloxone for Severe Restless Legs Syndrome: An Analysis of Secondary Efficacy Variables of a Double-Blind, Randomized, Placebo-Controlled Study with an Open-Label Extension

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Abstract

Objective The aim was to assess the effects of prolonged release oxycodone/naloxone (OXN PR) on sleep and quality of life (QoL) in patients with severe restless legs syndrome (RLS) refractory to first-line dopaminergic RLS treatment.

Methods Sleep and QoL data from a 12-week, randomized, double-blind, placebo-controlled study with subsequent 40-week, open-label extension were analyzed. Instruments included the Medical Outcomes Study (MOS) sleep scale, RLS-6 rating scale, and RLS-QoL questionnaire.

Results The full analysis population included 132 OXN PR and 144 placebo patients. After 12 treatment weeks, improvements in the MOS domains 'sleep disturbance' [−18.6; 95 % confidence interval (CI) −24.4 to −12.9; $p < 0.0001$], 'sleep adequacy' (14.9; 95 % CI 7.9–21.9; $p < 0.0001$), and 'sleep quantity' (0.77 h; 95 % CI 0.43–1.11; $p < 0.0001$) were significantly greater under OXN PR than under placebo. OXN PR also reduced symptom severity (when falling asleep and during the night) and daytime tiredness, and increased sleep satisfaction to a significantly greater extent than placebo (all $p < 0.001$; RLS-6). QoL improved in both treatment arms, with a significant difference of −9.02 (95 % CI −12.85 to −5.19; $p < 0.001$) in the mean sum score in favor of OXN PR. All sleep and QoL aspects also improved under 40 weeks of open-label OXN PR treatment.

Conclusions OXN PR improved RLS symptom severity and sleep quantity and adequacy, resulting in greater sleep satisfaction, less daytime tiredness, and improved QoL. In appropriate patients, OXN PR should be considered as an alternative treatment option for severe RLS that cannot be controlled by first-line dopaminergic medications.

Trial Registration ClinicalTrials.gov (NCT01112644) and EudraCT (2009-011107-23).

Key Points

Opioid therapy has been recommended as a potentially effective treatment option in restless legs syndrome (RLS) patients inadequately controlled by first-line medications.

The reduction in symptom severity observed under treatment with the opioid prolonged release oxycodone/naloxone (OXN PR) also resulted in improved quality of life and fewer sleep complaints, with improved sleep quantity and adequacy, greater sleep satisfaction, and less daytime tiredness.

In appropriate patients, OXN PR should be considered as an alternative treatment option for severe RLS that cannot be controlled by first-line dopaminergic medications.

Members of the Study Group are listed in "Acknowledgments" (RELOXYN = **RE**stless **L**egs Syndrome and **OXY**codone/**N**aloxone).

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1 Introduction

Diagnostic criteria for the neurological disorder restless legs syndrome (RLS; formerly termed Willis-Ekbom disease) were revised in 2014 and include amendments relevant for the approach to treatment [1]. A fifth criterion (differential diagnosis) was added to the existing four essential criteria as well as specifiers to differentiate between chronic-persistent and intermittent RLS and to delineate clinically significant RLS [1]. Patients with severe RLS usually suffer from disturbed sleep with delayed sleep onset and frequent awakenings [2], and more than 40 % have daily daytime symptoms [3]. Physical functioning can be significantly impaired [4, 5], and mood disorders are a common comorbidity [6]. The negative impact on quality of life (QoL) is profound, and RLS is associated with a substantial economic burden [7].

Depending on symptom severity, medical history, and cognitive and comorbidity status, both dopamine agonists and alpha 2-delta ligands are currently recommended as first-line treatment options for clinically significant RLS [8, 9]. However, alternative treatment choices are required in case of loss of efficacy, tolerability issues, or augmentation (worsening of RLS symptoms after an initial response to treatment [10]). For these patients refractory to first-line dopaminergic medications, prolonged release oxycodone/naloxone (OXN PR) therapy is currently licensed in Europe [11]. We recently reported a significant and sustained treatment effect with the fixed-dose combination opioid OXN PR in patients with severe RLS inadequately controlled by first-line dopaminergic treatment [12]. Although there were differences in baseline RLS severity, the treatment effect was at least comparable to treatment effects previously reported for first-line dopaminergic medications in moderate to severe RLS [13, 14]. Here, we present further study findings focusing on sleep and QoL parameters.

2 Methods

2.1 Study Design

This 12-week, randomized, double-blind, placebo-controlled study with subsequent 40-week, open-label extension was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice at 55 hospitals/specialized private neurology practices in Austria, Germany, Spain, and Sweden from April 2010 to March 2012. The study is registered with ClinicalTrials.gov (no. NCT01112644) and with EudraCT (no. 2009-011107-23).

The study design has been described in detail elsewhere [12]. Using a validated interactive response technology system, patients were randomized 1:1 to OXN PR or placebo treatment following screening and a 7-day wash-out of previous RLS medications (Fig. 1). Initial doses of 5 mg oxycodone/2.5 mg naloxone twice daily (bid) (or placebo) were up-titrated to the patients' optimal dose (maximum 40 mg oxycodone/20 mg naloxone bid) in weekly, fixed, symmetrical increments during the first 6 treatment weeks. Treatment was maintained for a further 6 weeks. Doses were then down-titrated to 5 mg oxycodone/2.5 mg naloxone bid, which was the starting dose for participants of the open-label extension phase. Titration to optimum dose in the extension phase was permitted daily up to 40 mg oxycodone/20 mg naloxone bid. Records of study medication and doses administered were kept during the study. The Clinical Research Associates (CRAs) reviewed drug accountability during site visits and at the completion of the study. Patients were asked to return all unused medication and used medication containers at each visit to evaluate medication compliance.

The specifics associated with the symptoms of withdrawal reactions were not documented during the study. The term 'withdrawal symptom' is generally understood to be based on the typical symptoms associated with withdrawal of opioids. Those can be found in the Subjective Opioid Withdrawal Scale (SOWS) and Clinical Opiate Withdrawal Scale (COWS).

2.2 Study Participants

A total of 304 patients were randomized into the double-blind phase (OXN PR $n = 150$, placebo $n = 154$), 197 patients continued to participate in the open-label extension, and 157 participants completed the extension phase. Detailed inclusion and exclusion criteria for the study have been published [12]. The main inclusion criteria were a diagnosis of RLS according to the RLS-Diagnostic Index (score $\geq$11 [15]) with RLS symptoms for at least 6 months, an International RLS Study Group Severity Rating Scale (IRLS [16]) sum score of $\geq$15 at screening and $\geq$21 (severe RLS) after wash-out of previous RLS medication, daytime onset of RLS symptoms before 6 pm at least 4 days/week, and failed treatment of current RLS symptoms as a result of intolerable side effects or insufficient efficacy according to investigator or patient (but not acute augmentation). Patients with secondary RLS or RLS associated with previous/concomitant dopamine receptor blocking agents, or a history or presence of sleep disturbances caused by sleep apnea syndrome, narcolepsy, or myoclonus epilepsy were excluded from the study. Intake of medication likely to have influenced sleep architecture

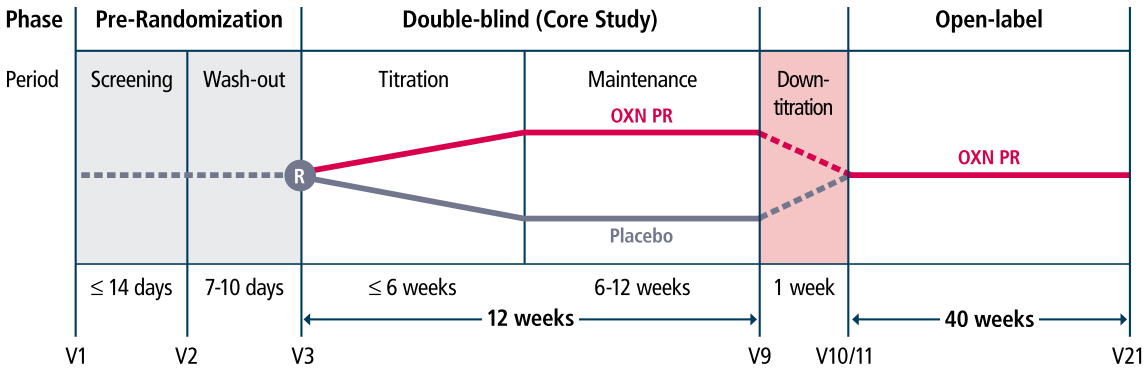

Fig. 1 Study design. *OXN PR* prolonged release oxycodone/naloxone, *V* visit

or motor manifestations during sleep, like antidepressant use, also led to exclusion. Antidepressant use was not permitted from the last week before the randomization visit (visit 3) onwards. Inclusion was possible if patients were on stable therapy for depression or anxiety disorders with antidepressants [selective serotonin reuptake inhibitor (SSRI) or noradrenaline reuptake inhibitor (NARI)] or anxiolytic drugs for at least 6 months.

Inclusion criteria for the open-label extension phase were completion of the double-blind study phase or treatment for more than 8 weeks in case of premature discontinuation due to loss of efficacy, and no clinically significant augmentation according to the Max Planck Institute diagnostic criteria [10] in the double-blind phase.

2.3 Assessments of Sleep and Quality of Life

Both sleep and QoL were secondary efficacy variables. During the double-blind study phase, sleep was assessed subjectively at baseline, week 4, and week 12 with the patient-reported Medical Outcomes Study (MOS) sleep scale [17, 18], which documents patients' perceptions of sleep over the previous 4 weeks. The 12-item questionnaire has been found a reliable and valid scale for assessing changes in sleep parameters in moderate to severe primary RLS [19]. It measures different aspects of sleep across the six domains: sleep disturbance, sleep adequacy, sleep quantity, snoring, waking up short of breath or with a headache, and somnolence. Ten of the items are rated using a 6-point rating scale (from 1 = all the time to 6 = never), onset of sleep is scored on a 5-point scale (from 1 = 0–15 min to 5 = more than 60 min), and sleep quantity is recorded as hours of sleep/night. Item scores except for sleep quantity were converted to scores on a 0–100 range, with scores representing the achieved percentage of the total possible score according to Spritzer and Hays [17].

Further sleep-related parameters (sleep satisfaction, symptom severity falling asleep, symptom severity during the night, and daytime tiredness) were rated by the patients at baseline, weekly for the first 4 treatment weeks, and then at weeks 8 and 12 using the validated 11-point RLS-6 rating scale [20]. Each item is graded from 0 = not present/completely satisfied to 10 = very severe/not at all satisfied. Patients and investigators also evaluated the severity of sleep disturbances due to RLS symptoms (IRLS item 4 [16]) on a 5-point scale from 4 = very severe to 0 = none. Additionally, the impact of RLS symptoms on sleep was assessed with the RLS-QoL item 1 (see scale description below).

QoL was evaluated at screening visit, week 4, and week 12 using the validated RLS-specific QoL questionnaire (RLS-QoL) [21]. The 12-item questionnaire rates the effects of RLS symptoms on daily activities, sleep, mood, social interactions, and coping behavior over the previous 4 weeks, and is answered by the patients using a 6-point scale (from 1 = not at all impaired to 6 = extremely impaired). Questions are grouped into five dimensions, with scores averaged over the relevant items: effects of RLS symptoms, disturbed sleep and its effects, effects of other features, coping with RLS symptoms, and overall QoL summary question. The QoL 12-item sum score ranges from 12 = no impairment to 72 = extreme impairment.

During the 40-week extension, sleep and QoL were assessed at the end of the study. Standard safety assessments were carried out at screening and throughout the study and included the occurrence of adverse events (AEs), premature study withdrawal due to AEs, physical examinations, changes in clinical laboratory parameters, vital signs, and 12-lead electrocardiogram, and Clinical Global Impression (CGI) tolerability scale (side effect assessment). AEs and vital signs were documented at each study visit.

Following ethics committee advice, a follow-up visit was conducted 4 weeks after the end of the open-label extension to document symptoms of physical and psychological dependence.

2.4 Statistical Analysis

All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA). Efficacy was evaluated using the full analysis set (FAS), a modified intent-to-treat population, which in accordance with the European Medicines Agency regulation ICH-E9 [22] included all randomized patients who received at least one dose of study medication during the double-blind phase and who had at least a 1-week, double-blind assessment for the primary efficacy variable. All secondary efficacy analyses were exploratory using the last observation carried forward (LOCF) approach for missing data. All end of double-blind phase data (week 12) included all early study discontinuers due to lack of therapeutic effect or augmentation. Differences between the treatment groups regarding sleep and QoL outcomes were evaluated by analysis of covariance (ANCOVA).

Correlations between the MOS domains 'sleep quantity,' 'sleep disturbance,' and 'sleep adequacy' and items of the RLS-6 [sleep satisfaction, symptom severity falling asleep, symptom severity during the night (questions 1–3)], and items of the RLS-QoL [impact of RLS symptoms on sleep, impact of disturbed sleep on daytime activities, impact of daytime sleepiness on mental health/mood (questions 1, 5, and 6)] were calculated using Pearson's correlation coefficient. The correlation analyses assessed the relationship between MOS sleep parameters and QoL parameters (at baseline and at final visit). High correlations between two parameters indicate that patients judged item scores to be similar.

Data analysis of the open-label extension phase was descriptive and 'as observed.' It included all patients who had received the study medication.

The descriptive safety analysis for both study phases included all enrolled patients who received study medication. AEs were encoded using the *Medical Dictionary for Regulatory Activities* (version 12.1).

3 Results

A total of 495 patients were screened; 150 patients were randomly assigned to OXN PR and 154 to placebo (Fig. 2). The OXN PR group received mean daily doses of 21.9 ± 15 mg oxycodone and 11 ± 7.5 mg naloxone for a median of 91 days; the placebo group received mean daily doses of 34.4 ± 19.4 mg oxycodone equivalent for a median of 68 days. The 12-week, double-blind treatment was completed by 67 % of the patients (71 % OXN PR, 63 % placebo patients). Of the 197 patients entering the open-label extension phase (101 OXN PR, 96 placebo patients), 157 participants (79.7 %) completed 40 weeks of open-label treatment (i.e., patients randomized to OXN PR completed 52 weeks of OXN PR treatment). Patients received mean daily doses of 18.1 ± 10.5 mg oxycodone and 9.1 ± 5.3 mg naloxone for a median of 281 days. Table 1 lists the demographic patient characteristics at double-blind and extension phase study entry. At enrolment, patients had suffered from RLS for a mean 10.3 ± 10 years and had received RLS treatment for a mean 5.0 ± 4.2 years. In the FAS, which included 132 OXN PR and 144 placebo patients, 221 patients reported receiving dopaminergic treatment at the start of the study, consisting of dopamine agonists (41.1 % monotherapy, 23.1 % in combination with other RLS treatments) or levodopa (32.6 % monotherapy, 3.2 % in combination with other RLS treatments except dopamine agonists).

Despite this, patients presented with severe RLS: mean IRLS sum scores were 28.6 ± 5.4 for the OXN PR group and 27.6 ± 5.5 for the placebo group, which increased further after wash-out of previous RLS medications (31.7 ± 4.4 for OXN PR, 31.6 ± 4.7 for placebo at randomization).

3.1 Efficacy Outcome

3.1.1 Sleep

Baseline ratings for the MOS sleep scale were comparable between the treatment groups (Table 2). Patients presented with marked sleep problems; on average, they needed 30–45 min to fall asleep, reported frequent awakenings, and only had 5 h of nighttime sleep. During the double-blind study phase, most aspects of sleep improved in both treatment arms, with significantly better outcomes under OXN PR compared with placebo for eight of the 12 MOS items (Table 2). This translates to significantly better improvements in the MOS domains 'sleep disturbance' [−18.6; 95 % confidence interval (CI) −24.4 to −12.9; $p < 0.0001$], 'sleep adequacy' (14.9; 95 % CI 7.9–21.9; $p < 0.0001$), and 'sleep quantity' (0.77 h; 95 % CI 0.43–1.11; $p < 0.0001$), but not in the domain 'daytime somnolence' ($p = 0.276$; Fig. 3). All sleep aspects also improved during the extension phase (Table 2).

Marked improvements under OXN PR were also observed in symptom severity (falling asleep and during the night), sleep satisfaction, and daytime tiredness during the 12-week, double-blind treatment phase, with significant differences to placebo (RLS-6 scale; Table 3). All parameters further improved during the extension phase (Table 3).

At baseline, patients rated sleep disturbance due to RLS symptoms (IRLS item 4) as 'very severe' (median IRLS item score of 4; mean scores 3.42 ± 0.82 for OXN PR, 3.45 ± 0.79 for placebo), which improved at the end of the

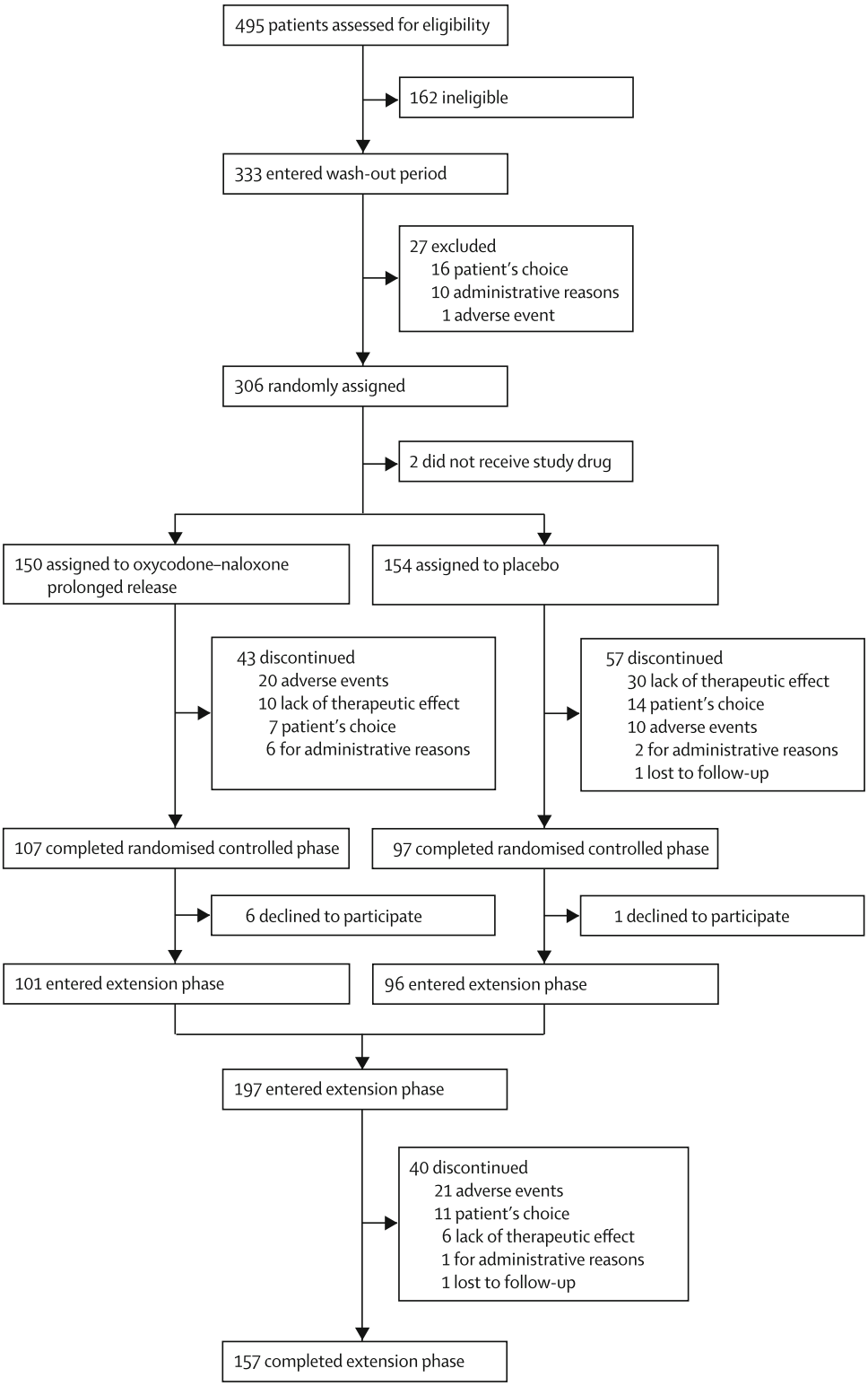

Fig. 2 Study profile. Reprinted from *The Lancet Neurology* [12], Trenkwalder et al., Prolonged release oxycodone-naloxone for treatment of severe restless legs syndrome after failure of previous treatment: a double-blind, randomised, placebo-controlled trial with an open-label extension. Pages 1141–50, copyright (2013), with permission from Elsevier

double-blind phase to a median score of 1 ('mild'; mean score 1.45 ± 1.37) for OXN PR and a median score of 3 ('severe'; mean score 2.34 ± 1.45) for placebo patients. At the end of the extension, a median score of 1 ('mild'; mean score 0.89 ± 0.89) was documented. The findings are supported by ratings for the RLS-QoL item 1. Under 12 weeks of OXN PR treatment, the mean impact of RLS symptoms on sleep was reduced from 4.6 ± 1.0 at baseline to 3.0 ± 1.5 (4.5 ± 1.1 to 4.0 ± 1.6 for placebo), with an estimated treatment difference of −1.07 (95 % CI −1.46 to

Table 1 Demographic patient characteristics for the double-blind and extension phase study populations

	Double-blind phase		Open-label extension phase
	OXN PR ($n = 150$)	Placebo ($n = 154$)	OXN PR ($n = 197$)
Age, years	63.1 ± 11.4	61.7 ± 11.0	61.2 ± 11.0
Female gender	97 (64.7 %)	105 (68.2 %)	131 (66.5 %)
Caucasian	149 (99.3 %)	154 (100 %)	196 (99.5 %)
Body mass index, kg/m^2	27.9 ± 4.3[a]	28.5 ± 5.4	28.5 ± 4.8

Data are mean ± standard deviation or number of patients (%)

OXN PR prolonged release oxycodone/naloxone

[a] Data missing for one patient

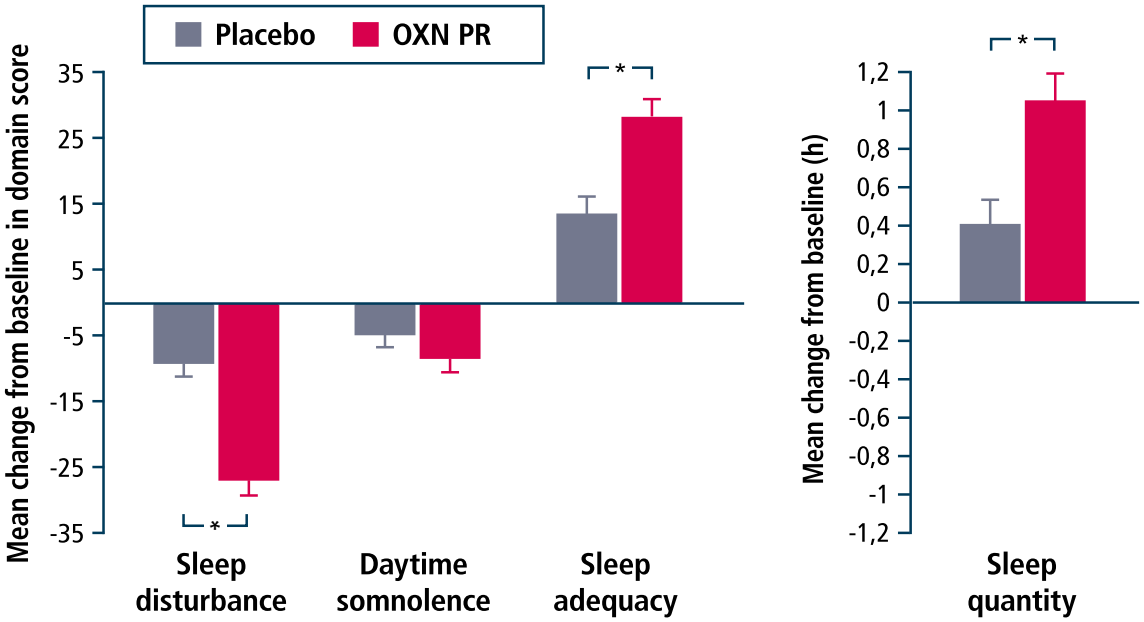

Fig. 3 Mean change (SE) from baseline to end of 12-week, double-blind study phase in Medical Outcomes Study sleep scale domains (full analysis set, OXN PR $n = 132$, placebo $n = 144$). *$p < 0.0001$ compared with placebo. Item scores were converted to a 0–100 scale, except for sleep quantity (h), according to Spritzer and Hays [17]. Decreases in sleep disturbance and daytime somnolence and increases in sleep adequacy and sleep quantity indicate improvements. *OXN PR* prolonged release oxycodone/naloxone, *SE* standard error

−0.69; $p < 0.001$) in favor of OXN PR. Further improvements were observed at the end of the extension (from 3.1 ± 1.6 to 2.3 ± 1.1).

3.1.2 *Quality of Life*

QoL was markedly impaired at start of study; a mean RLS-QoL sum score of 45.4 ± 10.0 was reported. Over the 12-week, double-blind phase, the score improved in both treatment arms (Fig. 4), with a significant treatment difference of −9.02 (95 % CI −12.85 to −5.19; $p < 0.001$) in favor of OXN PR. The impact of RLS symptoms on QoL was further reduced under 40 weeks of open-label OXN PR treatment.

OXN PR treatment ameliorated the RLS burden in all five RLS-QoL dimensions, with significant treatment differences to placebo in four dimensions (all $p < 0.001$; Fig. 5): −0.95 (95 % CI −1.31 to −0.6) for 'effects of RLS symptoms,' −0.71 (95 % CI −1.05 to −0.36) for 'disturbed sleep and its effect,' −0.79 (95 % CI −1.13 to −0.45) for 'coping with RLS symptoms,' and −0.8 (95 % CI −1.19 to −0.41) for 'overall quality of life.' The dimension 'effects of other features' was not statistically different between the groups (−0.24; 95 % CI −0.55 to 0.06; $p = 0.113$). At the end of the 40-week, open-label OXN PR treatment, impairments in RLS-specific QoL were considered 'mild,' with mean scores of 2.3 ± 1.2 for 'effects of RLS symptoms,' 2.6 ± 1.3 for 'disturbed sleep and its effect,' 2.3 ± 1.2 for 'effects of other features,' 2.1 ± 1.2 for 'coping with RLS symptoms,' and 2.4 ± 1.3 for 'overall quality of life.'

Table 2 Changes in MOS sleep scale domains

	Double-blind phase			Extension phase
	OXN PR ($n = 132$)	Placebo ($n = 144$)	P value[a]	Baseline $n = 197$ Week 40 $n = 157$
Sleep disturbances				
Time to fall asleep[b]				
Baseline	3.31 ± 1.17	3.35 ± 1.33		2.49 ± 1.29
End of study phase	2.30 ± 1.23	3.06 ± 1.37	<0.0001	2.10 ± 1.01
Trouble falling asleep[c]				
Baseline	2.52 ± 1.36	2.62 ± 1.49		3.83 ± 1.62
End of study phase	4.10 ± 1.43	3.01 ± 1.69	<0.0001	4.45 ± 1.34
Restlessness in sleep[c]				
Baseline	2.58 ± 1.38	2.42 ± 1.27		3.72 ± 1.49
End of study phase	3.94 ± 1.25	3.04 ± 1.58	<0.0001	4.24 ± 1.20
Awakening during sleep[c]				
Baseline	2.77 ± 1.30	2.56 ± 1.20		3.84 ± 1.48
End of study phase	4.06 ± 1.31	3.07 ± 1.53	<0.0001	4.42 ± 1.05
Sleep adequacy				
Rested when waking up[c]				
Baseline	4.65 ± 1.22	4.68 ± 1.27		3.47 ± 1.61
End of study phase	3.30 ± 1.47	4.06 ± 1.65	<0.0001	2.87 ± 1.39
Getting the amount of sleep needed[c]				
Baseline	4.80 ± 1.4	4.86 ± 1.4		3.31 ± 1.7
End of study phase	3.29 ± 1.7	4.03 ± 1.7	<0.0001	2.82 ± 1.5
Sleep quantity (h)				
Baseline	5.15 ± 1.5	4.97 ± 1.5		6.06 ± 1.6
End of study phase	6.25 ± 1.3	5.36 ± 1.8	<0.0001	6.58 ± 1.2
Daytime somnolence				
Drowsy/sleepy during the day[c]				
Baseline	3.05 ± 1.32	3.08 ± 1.32		3.84 ± 1.43
End of study phase	3.70 ± 1.35	3.49 ± 1.52	0.1274	4.15 ± 1.27
Trouble staying awake during the day[c]				
Baseline	3.89 ± 1.31	4.10 ± 1.21		4.61 ± 1.33
End of study phase	4.46 ± 1.32	4.33 ± 1.43	0.1118	4.73 ± 1.23
Naps during the day[c]				
Baseline	4.27 ± 1.55	4.28 ± 1.47		3.31 ± 1.74
End of study phase	4.34 ± 1.36	4.33 ± 1.47	0.6136	4.54 ± 1.36
Snoring during sleep[c]				
Baseline	4.14 ± 1.52	4.07 ± 1.59		4.15 ± 1.47
End of study phase	4.31 ± 1.44	4.06 ± 1.54	0.0448	4.32 ± 1.43
Short of breath/headache[c]				
Baseline	5.02 ± 1.19	4.88 ± 1.24		5.26 ± 1.01
End of study phase	5.23 ± 1.07	5.17 ± 1.02	0.7455	5.43 ± 0.98

Data are mean ± standard deviation. FAS for the double-blind phase (LOCF data); data as observed for the extension population. Baseline values for the double-blind phase are taken at randomization; baseline values for extension phase are taken at the end of double-blind phase and reflect the mean value of the patients under placebo and under OXN PR who participated in the open label extension

ANCOVA analysis of covariance, *FAS* full analysis set, *LOCF* last observation carried forward, *MOS* Medical Outcomes Study, *OXN PR* prolonged release oxycodone/naloxone

[a] OXN PR vs. placebo at end of double-blind phase (ANCOVA)

[b] From 1 = 0–15 min to 5 = more than 60 min

[c] From 1 = all the time to 6 = never

Table 3 Changes in sleep-related parameters rated with the RLS-6 scale[a]

	Double-blind phase			Extension phase
	OXN PR ($n = 132$)	Placebo ($n = 144$)	P value[b]	Baseline $n = 197$ Week 40 $n = 152$
Sleep satisfaction				
Baseline	8.2 ± 2.0	8.1 ± 2.0		4.1 ± 3.2
End of study phase	3.8 ± 3.1	5.9 ± 3.3	<0.0001	2.0 ± 2.0
Symptom severity falling asleep				
Baseline	7.2 ± 2.5	7.3 ± 2.7		3.3 ± 3.3
End of study phase	2.7 ± 2.9	5.1 ± 3.6	<0.0001	1.5 ± 1.7
Symptom severity during the night				
Baseline	7.6 ± 2.5	7.4 ± 2.4		3.2 ± 3.2
End of study phase	2.8 ± 3.0	5.2 ± 3.5	<0.0001	1.5 ± 1.7
Daytime tiredness				
Baseline	6.4 ± 2.6	6.5 ± 2.9		3.5 ± 3.1
End of study phase	3.7 ± 3.0	4.9 ± 3.5	0.0008	2.2 ± 2.3

Data are mean ± standard deviation. FAS for the double-blind phase (LOCF data); data as observed for the extension population. Baseline for the double-blind phase is randomization; baseline for extension phase is end of double-blind phase

ANCOVA analysis of covariance, *FAS* full analysis set, *LOCF* last observation carried forward, *OXN PR* prolonged release oxycodone/naloxone, *RLS* restless legs syndrome

[a] From 0 = not present to 10 = very severe

[b] OXN PR vs. placebo at end of double-blind phase (ANCOVA)

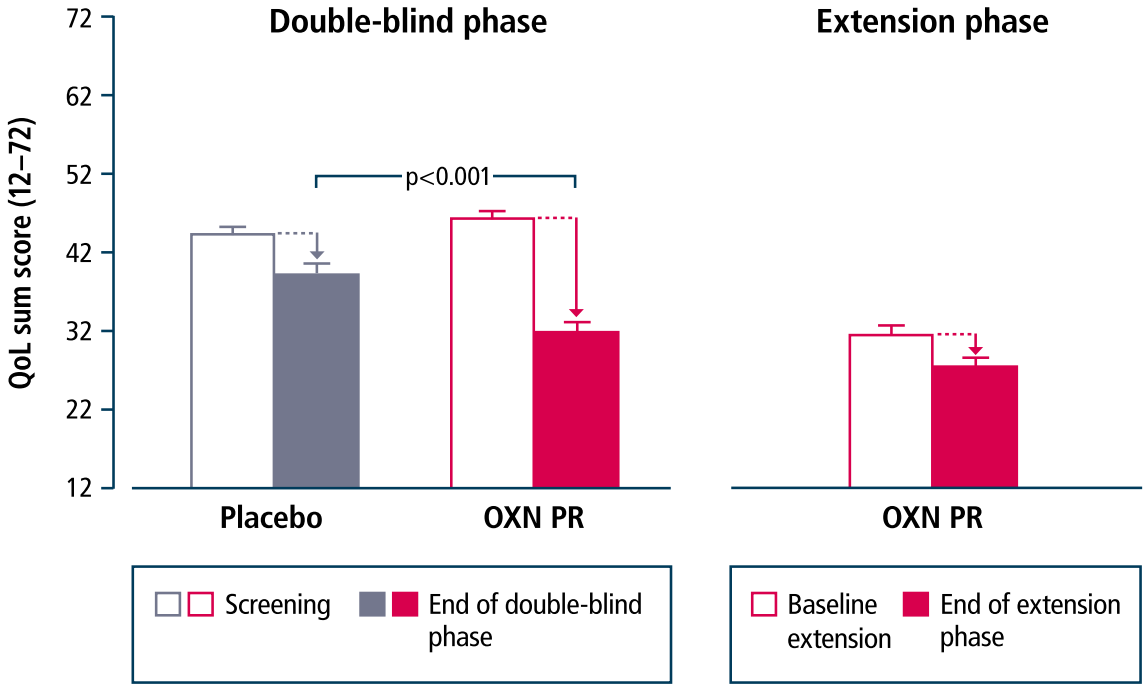

Fig. 4 Mean changes (+SE) in QoL (sum score) during the study. Full analysis set for the double-blind phase: OXN PR $n = 132$, placebo $n = 144$, LOCF data; baseline extension: $n = 197$; end of extension: $n = 190$. *LOCF* last observation carried forward, *OXN PR* prolonged release oxycodone/naloxone, *QoL* quality of life, *SE* standard error

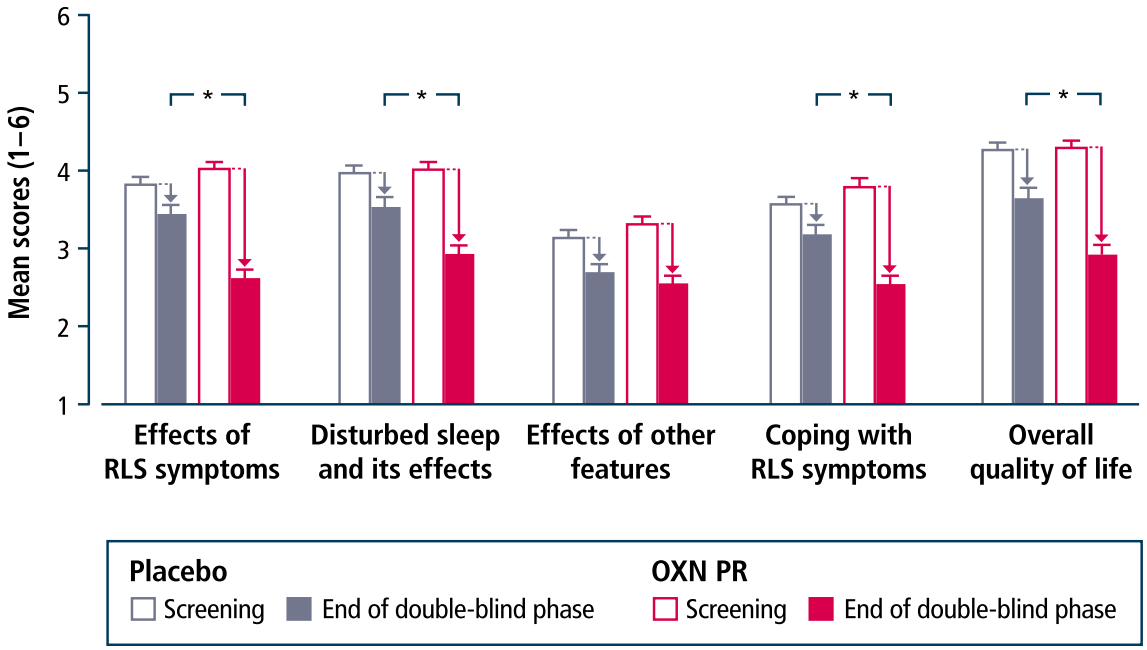

Fig. 5 Mean changes (+SE) in RLS-QoL dimensions at start of study and end of 12-week, double-blind phase. Full analysis set (LOCF data); *$p < 0.001$ compared with placebo. Dimensions: effects of RLS symptoms (items 1–4: impairment of sleep, general performance, mental health, and social activities); disturbed sleep and its effects (item 5 and 6: impairment of daily activities due to lack of sleep, impairment of well-being due to daytime tiredness); effects of other features (item 7 and 8: medication side effects, arm or leg pain); coping with RLS symptoms (items 9–11: strain of using coping strategies, avoidance of certain activities/situations, strain of lifestyle changes); and overall quality of life summary question (item 12). *LOCF* last observation carried forward, *QoL* quality of life, *RLS* restless legs syndrome, *SE* standard error

3.1.3 Correlation Analysis

Correlation coefficients have been calculated to investigate the relationship between the parameters of interest. At baseline, correlations between the MOS sleep scale domains and the RLS-6 and RLS-QoL items were mainly moderate (Table 4); low correlations were observed between the domain 'sleep quantity' and the three single RLS-QoL items and between the domain 'sleep disturbance' and 'impairment of daily activities due to a lack of sleep' and 'impairment of well-being due to daytime tiredness.' Following treatment with OXN PR or placebo, at the end of the study, all correlations were high (>0.6) between the MOS and RLS-6 sleep parameters, but also between the MOS domains and the QoL items. The correlation between the domain 'sleep adequacy' and the QoL items 'disturbed sleep,' 'impairment of daily activities due to lack of sleep,' and 'impairment of well-being due to daytime tiredness' was ≥0.7 for all three items.

3.2 Safety

During the double-blind phase, treatment-related AEs were documented for 73 % of the patients receiving OXN PR and 43 % of patients in the placebo group; for 3 % of the OXN PR patients, these AEs were serious. Most frequently reported (with an incidence of ≥5 %) were events consistent with the safety profile of opioids [23]: fatigue (29 vs. 13 % for placebo), constipation (19 vs. 5 %), nausea (17 vs. 9 %), headache (13 vs. 7 %), somnolence (11 vs. 5 %), dizziness (9 vs. 3 %), dry mouth (8 vs. 2 %), and pruritus (7 vs. 3 %). Only 12 OXN PR patients (8 %) had clinically meaningful constipation during the double-blind phase that was serious or severe or, independent of severity, required withdrawal/dose reduction or additional therapy. During extension, 57 % of the patients experienced treatment-related AEs, mainly constipation (15 %), fatigue (10 %), and nausea (10 %).

Thirteen percent of OXN PR patients and 7 % of placebo patients discontinued the double-blind phase prematurely because of AEs; during extension this was documented for 11 % of the patients.

Assessment of symptoms of physical and psychological dependence 4 weeks after the end of treatment in 176 patients showed withdrawal symptoms in one patient after 12 weeks and in two patients after 1 year of treatment. None of the patients required medical treatment for the event.

Table 4 Correlation of MOS sleep scale domains with items from the RLS-6 and RLS-QoL questionnaires (Pearson's correlation coefficient). Full analysis set of the double-blind study population ($n = 276$)

	MOS sleep scale domains		
	Sleep disturbance	Sleep adequacy	Sleep quantity
Sleep satisfaction (RLS-6 item 1)			
Baseline	0.47	−0.55	−0.40
12 weeks	0.78	−0.70	−0.66
Symptom severity falling asleep (RLS-6 item 2)			
Baseline	0.47	−0.36	−0.3
12 weeks	0.70	−0.61	−0.63
Symptom severity during the night (RLS-6 item 3)			
Baseline	0.45	−0.48	−0.43
12 weeks	0.71	−0.67	−0.69
Disturbed sleep (RLS-QoL item 1)			
Baseline	0.39	−0.38	−0.11
12 weeks	0.74	−0.70	−0.66
Impairment of daily activities due to lack of sleep (RLS-QoL item 5)			
Baseline	0.29	−0.33	−0.10
12 weeks	0.67	−0.70	−0.61
Impairment of well-being due to daytime tiredness (RLS-QoL item 6)			
Baseline	0.29	−0.35	−0.11
12 weeks	0.61	−0.72	−0.56

MOS Medical Outcomes Study, *QoL* quality of life, *RLS* restless legs syndrome

4 Discussion

The analysis of sleep and QoL data under OXN PR treatment for severe RLS shows that the reduction in symptom severity under OXN PR also resulted in improved QoL and fewer sleep complaints, with improved sleep quantity and adequacy, greater sleep satisfaction, and less daytime tiredness during the 12-week, double-blind treatment period. OXN PR was significantly more effective than placebo during this short-term period; improvements could be sustained over the following 40-week, open-label OXN PR treatment.

Sleep disturbance is the primary complaint for the majority of patients with clinically significant RLS and a hallmark of the disease itself [24, 25]. It is therefore not surprising that sleep has to be improved by all medications that improve RLS symptomatology. More than 80 % of RLS sufferers are also affected by periodic leg movements in sleep [26]. It is, however, surprising that the less frequent awakenings observed under dopaminergic treatment did not improve sleep efficacy [13]. The current data are therefore a promising pre-requisite to study sleep during OXN PR treatment using polysomnography to prove the reduced number of awakenings.

Our patient population presented with marked sleep complaints and most of the time felt that their sleep was not adequate; on average, they needed 30–45 min to fall asleep, reported frequent awakenings, and rated the sleep disturbances due to RLS symptoms as 'very severe.' The median sleep duration was only 5 h/night. The recommended appropriate sleep duration for healthy adults is 7–9 h; less than 6 h is not recommended [27] and may be associated with health risks when occurring chronically. Under OXN PR treatment, median sleep duration was prolonged by 1 h/night in the first 12 treatment weeks and had increased to a median of 7 h/night at the end of the 40-week extension. All aspects of sleep improved, with significantly better outcomes for the domains 'sleep disturbance,' 'sleep quantity,' and 'sleep adequacy' than under placebo. RLS-associated sleep disturbances were considered mild, whereas placebo patients still reported severe nocturnal disruptions after 12 weeks (IRLS item 4). The positive effect on sleep is important as RLS-related sleep deprivation can have daytime consequences and may substantially contribute to the development of depression [28]. Causal relationships between sleep-related problems (especially sleep fragmentation and sleep deprivation) and decreased daytime functioning and disability are, however, a matter for debate.

Despite only a medium 5 h nighttime sleep, patients reported only moderate daytime tiredness at baseline and only took daytime naps 'a little of the time.' Interestingly, RLS patients are less tired than other sleep-disturbed patients with a short sleep duration, and this may be part of the syndrome itself. But still, shorter latency, longer sleep duration, and fewer sleep disturbances with a better sleep quality under

OXN PR resulted in less tiredness during the day. No difference in daytime somnolence was evident (MOS sleep scale scores) between the OXN PR and the placebo treatment groups. This suggests that administration of OXN PR did not lead to sedation of the patients, and thus, improvement in quality of sleep was not due to opioid treatment-induced sedation but to a reduction in RLS symptom severity.

The QoL of our patient population was markedly impaired at the start of the study, with all five dimensions of the rating scale affected. Treatment with OXN PR improved all aspects of QoL over the 12-week, double-blind treatment period; improvements in four of the five dimensions were significantly greater than under placebo. Effects could be sustained during the 40-week, open-label extension. We noted that there were also strong correlations after treatment between the MOS domain 'sleep adequacy' and the three QoL items 'impact of RLS symptoms on sleep,' 'impact of disturbed sleep on daytime activities,' and 'impact of daytime sleepiness on mental health/mood' and between the MOS domain 'sleep disturbance' and 'impact of RLS symptoms on sleep.' The mean changes in sleep and QoL parameters as well as the high and increased correlations at study end between both aspects indicate that improvement of sleep due to improved RLS symptoms leads to a better QoL.

Our results show several limitations: the study was not designed as a sleep study and does not contain any objective data for sleep such as apnea screening or polysomnographic recordings. Polysomnographic recordings would have been useful to detect potential deleterious effects of OXN PR on breathing during sleep. It should also be noted that our study showed the efficacy of OXN PR as second-line treatment in patients after failure of a dopaminergic therapy; efficacy as first-line RLS medication cannot be presumed.

Scales that measure the patients' QoL and sleep are either numerical or ordinal. For ordinal scales, while it is commonly acknowledged that a difference of one category, for example, moderate to mild, is seen as relevant, a between-scale comparison brings a potential risk of interpretation error and should be carried out with care. The idea behind the presented work was to compare the different tools, to put the results into context with respect to QoL and sleep assessments, and to evaluate the consistency of the results.

Our large randomized, double-blind trial investigated the efficacy and safety of an opioid in RLS treatment; it is the second and by far largest ever published placebo-controlled opioid study. The first small, double-blind, polysomnographic study was carried out 20 years before, which showed the beneficial effects of oxycodone on RLS symptoms and sleep [29]. Other previous opioid studies were retrospective analyses and case series with a low level of evidence [8]. Although side effects were common in our study, incidence of drug withdrawal symptoms was low. Low physical dependence under OXN PR was already observed in chronic non-cancer pain treatment; stable, low, subjective Opiate Withdrawal Scale scores after 12 treatment months have been reported for mean daily oxycodone doses of 38 mg, a higher dosage than administered for RLS treatment in our study (mean 22 mg) [30]. This was also found for open-label, long-term RLS management with other opioids [31, 32].

5 Conclusions

Treatment of severe RLS with OXN PR was efficacious and could be sustained over the 1-year study period. Alleviation of symptoms improved subjectively rated sleep quantity and adequacy and resulted in greater sleep satisfaction, less daytime tiredness, and improved QoL. The safety profile was as expected for an opioid. In appropriate patients, OXN PR should be considered as an alternative treatment option for severe RLS that cannot be controlled by first-line medications.

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Compliance with Ethical Standards

Ethical approval Study protocol and amendments were approved by the national and local ethics committees of the participating study sites, and all participating patients gave written informed consent at enrolment.

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