

# Ropinirole 24-hour prolonged release

## Randomized, controlled study in advanced Parkinson disease

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on behalf of the EASE-PD Adjunct Study Investigators\*

**Abstract—Objective:** To evaluate the efficacy of ropinirole 24-hour prolonged release (ropinirole 24-hour) as an adjunct to levodopa in patients with Parkinson disease (PD) and motor fluctuations. **Methods:** In a double-blind, placebo-controlled, 24-week study, 393 subjects with PD were randomized to ropinirole 24-hour (n = 202) or placebo (n = 191). The primary outcome measure was reduction in hours of daily “off” time. **Results:** At week 24, the mean dose of ropinirole 24-hour was 18.8 mg/day with a mean reduction in daily levodopa of 278 mg. There was a mean reduction in daily “off” time of 2.1 hours in the ropinirole 24-hour group and 0.3 hours with placebo. Secondary outcome measures including change in hours and percent of daily “on” time and “on” time without troublesome dyskinesia, Unified PD Rating Scale motor and activities of daily living subscales, Beck Depression Inventory-II, PDQ-39 subscales of mobility, activities of daily living, emotional well-being, stigma and communication, and PD Sleep Scale were significantly improved at week 24 with ropinirole 24-hour. The most common adverse events (AE) with ropinirole 24-hour were dyskinesia, nausea, dizziness, somnolence, hallucinations, and orthostatic hypotension and AEs led to study withdrawal in 5% of both the active and placebo groups. **Conclusion:** Ropinirole 24-hour was effective and well tolerated as adjunct therapy in patients with Parkinson disease (PD) not optimally controlled with levodopa. Ropinirole 24-hour demonstrated an improvement in both motor and non-motor PD symptoms, while permitting a reduction in adjunctive levodopa dose.

NEUROLOGY 2007;68:1108–1115

Ropinirole is a non-ergot dopamine agonist that has demonstrated efficacy in early and advanced Parkinson disease (PD), when used as monotherapy or as an adjunctive therapy to levodopa.<sup>1-5</sup> Although ropinirole is well tolerated and effective, an extended titration phase and a need for multiple dosages per day may decrease patient compliance and provide a barrier to optimizing patient function.<sup>4,6</sup> Therefore, a simple and rapid titration schedule and a reduction in the number of daily doses may improve patient compliance and ultimately improve outcomes. In an effort to address these needs, a prolonged-release ropinirole formulation has been developed as a once-a-day formulation with a simple and faster dose-titration regimen. A prolonged-release formulation that allows a steady rate of absorption and reduces plasma-level fluctuations should produce a smoother pharmacokinetic profile and therefore may improve tolerability and efficacy and may lead to reduction in levodopa dose and motor fluctuations.

To assess the efficacy of prolonged release ropinirole, a Phase III, multicenter, multinational, randomized, double-blind, placebo-controlled study of ropinirole 24-hour prolonged release (ropinirole 24-hour) in patients with PD not optimally controlled by levodopa, the Efficacy And Safety Evaluation in PD-Adjunct (EASE-PD Adjunct) study was conducted. The primary objective of the study was to evaluate the efficacy of ropinirole 24-hour as adjunctive therapy in patients with PD not optimally controlled with levodopa.

**Methods. Patients.** A total of 393 patients with PD and suboptimal control from levodopa were enrolled in this trial between July 2003 and December 2004 at 67 centers in Belgium, the Czech Republic, France, Hungary, Italy, Poland, Spain, and the United States. Men and women at least 30 years of age with a diagnosis of idiopathic PD and a modified Hoehn & Yahr stage of II to IV with suboptimal control with levodopa therapy (e.g., end-of-dose akinesia, motor fluctuations) were eligible for the study. A stable dose of levodopa for at least 4 weeks prior to screening and a minimum of 3 hours in the “off” state as measured by each of four

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Disclosures: This study was sponsored by GlaxoSmithKline (GSK) and Skye Pharma. R. Pahwa, S.A. Factor, K.E. Lyons, F. Stocchi, B.P. Hersh, L.W. Elmer, and D. Truong have received research grant support from GSK for research studies not reported in this article. This research support exceeded \$10,000 for R. Pahwa, B.P. Hersh, and D. Truong. R. Pahwa, M.A. Stacy, S.A. Factor, K.E. Lyons, F. Stocchi, B.P. Hersh, and L.W. Elmer have received personal compensation from GSK. This compensation has exceeded \$10,000/year for R. Pahwa, F. Stocchi, and B.P. Hersh. N.L. Earl is an employee of GSK.

Received May 22, 2006. Accepted in final form December 5, 2006.

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patient diaries completed during the placebo run-in period were required. Selegiline, amantadine, anticholinergics, and catechol-O-methyl-transferase (COMT) inhibitors were permitted, provided the dose was stable for at least 4 weeks prior to screening. Neuroleptics and antiemetics were not permitted during the study. Patients with incapacitating peak dose or biphasic dyskinesia; any dopamine agonist use within 4 weeks of screening; significant or uncontrolled psychiatric, neurologic, or other medical disorders; clinically significant laboratory abnormalities at screening; a recent history of severe dizziness or fainting due to postural hypotension; clinical dementia precluding assessment; a recent history or current evidence of drug abuse or alcoholism; or withdrawal, introduction, or dose change of hormone replacement therapy or any drug known to substantially inhibit or induce cytochrome P450 1A2 were not eligible for the study. All patients provided written, informed consent approved by their respective ethics committee or institutional review board and the study was conducted in accordance with good clinical practice, subject privacy requirements, and the guiding principles of the Declaration of Helsinki.

**Study design/procedures.** This was a multicenter, multinational, randomized, double-blind, parallel-group, placebo-controlled study (EASE-PD Adjunct Study). Eligible subjects entered a 14-day placebo run-in period. Subjects who completed the run-in period and continued to meet the inclusion criteria were randomized 1:1 to receive once-daily, adjunctive treatment with ropinirole 24-hour or placebo for 24 weeks. A computer-generated randomization schedule using the Registration and Medication Ordering System (RAMOS) was used. Investigators or coordinators phoned into this system to register and randomize subjects. To ensure balance in the number of subjects allocated to each group within each center, the allocation schedule was generated in blocks. In order to achieve blinding, dosages were referred to as Levels 1 through 8, placebo subjects were dosed similarly to the ropinirole 24-hour group, and ropinirole 24-hour and placebo tablets were identical in appearance and packaging. Only in the event of an emergency affecting the clinical management or welfare of the subject could the investigator break the blind. In North American sites, the medication bottles were labeled with a two-panel label. The second panel tear-off contained a blackened disclosure panel that, when swabbed with alcohol, revealed the contents of the bottle. For all other centers, emergency unblinding was available via RAMOS.

Subjects were evaluated at baseline and weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24. At the end of the study, or at withdrawal, subjects entered a 7-day down-titration phase. A follow-up safety visit was performed 4 to 14 days after last dose of study medication. Study drug was titrated at a starting dose (Level 1) of 2 mg/day ropinirole 24-hour or matching placebo. Subjects were instructed to take the medication once daily at the same time each day. The following dose titration was used with levels increasing each visit as necessary: Level 1: 2 mg/day; Level 2: 4 mg/day; Level 3: 6 mg/day; Level 4: 8 mg/day; Level 5: 12 mg/day; Level 6: 16 mg/day; Level 7: 20 mg/day; Level 8: 24 mg/day. The dose was titrated until an optimal therapeutic response was achieved or adverse effects occurred. All subjects were titrated to a minimum dose of 6 mg/day ropinirole 24-hour or matching placebo (Level 3). Once an optimal therapeutic dose was achieved, the subject was maintained on that dose for the remainder of the treatment phase unless further titration was required up to a maximum of 24 mg/day.

Once subjects reached Level 4 (ropinirole 24-hour 8 mg/day or placebo), with each subsequent increase in study medication level, the total daily dose of levodopa was reduced by one half or one full tablet or possibly more if the subject was taking more than six tablets per day. If the subject was taking entacapone and a full dose of levodopa was removed the accompanying entacapone was also eliminated. If loss of symptom control occurred with the reduction in levodopa dose, the dose of study medication was increased to the next dose level, with no adjustment in levodopa dose. If loss of symptom control persisted, the dose of study medication was increased again to the next dose level with no adjustment in levodopa dose. Subjects could return to the clinic at weekly intervals, if necessary, for dose adjustments. Subjects who did not experience improvement in symptoms following up-titration of study medication by two dose levels could have their levodopa dose increased to, but not in excess of, baseline levels.

Subjects were not permitted to switch between controlled-release and immediate-release levodopa formulations.

**Outcome measures.** The primary outcome measure was mean change from baseline in hours "off" at week 24 as measured by patient diaries. Subjects completed 24-hour diaries at 30-minute intervals indicating if they were in the "off" state, "on" state, "on" state with troublesome dyskinesia, or asleep. "Off" state was when PD medication was not improving PD symptoms resulting in a lack of mobility; "on" state was when PD medication was working and providing benefit; and troublesome dyskinesia were involuntary movements during the "on" state that interfered with function or caused discomfort. Prior to completing any diaries, the investigator or coordinator reviewed the definitions for each motor state with the subject. The subject was required to accurately describe each state to the investigator or coordinator until they were comfortable that the subject could differentiate between motor states. Definitions for each state were also written on each diary form. Each subject completed two 24-hour diaries prior to each study visit and the mean of the two 24-hour periods was used for all analyses. For baseline values, the mean from all four diaries during the 2-week placebo run-in period was used.

Secondary outcome measures included the mean change from baseline in the hours of "on" time; percentage of "on" time; percentage of "off" time; hours of "on" time without troublesome dyskinesia; and percentage of "on" time without troublesome dyskinesia as measured by subject diaries. Mean changes from baseline were also examined for the Unified PD Rating Scale (UPDRS) Motor (Part III) score obtained at least 2 hours after the previous levodopa dose; UPDRS Activities of Daily Living (ADL; Part II) average of "on" and "off" scores; Beck Depression Inventory-II (BDI-II); PD Quality of Life questionnaire (PDQ-39) subscores; Epworth Sleepiness Scale (ESS); and PD Sleep Scale (PDSS). Additional measures included the proportion of subjects "very much improved" or "much improved" according to the Clinical Global Impression-Improvement (CGI-I) scale; the proportion of subjects requiring reinstatement of levodopa following dose reduction; the time to reinstatement of levodopa following dose reduction; and the proportion of responders, defined as those who had at least a 20% reduction from baseline in "off" time and at least a 20% reduction from baseline in levodopa dose.

Safety endpoints included adverse events (AEs), clinical laboratory data, vital signs (blood pressure and heart rate, orthostatic blood pressure, and heart rate), and EKG.

**Statistical analyses.** Sample size was based on the mean change from baseline to endpoint in hours "off." A difference of 1.2 hours between ropinirole 24-hour and placebo in the reduction in hours "off" was considered clinically relevant based on previous studies.<sup>7-9</sup> A total of 133 subjects per treatment group evaluable for the primary analysis (266 overall) were required to detect a difference of 1.2 hours with a SD of 3 hours, for a two-sided test with 90% power and a 5% level of significance. The total number of subjects to be randomized was 368, assuming an attrition rate of 27%.

The primary efficacy measure (change from baseline in hours "off") was analyzed using parametric analysis of covariance. Among the secondary efficacy measures normal, linear models were fitted to each of the continuous variables. Dichotomous variables were analyzed using logistic regression models and time to event data were analyzed using Cox's regression model. For all efficacy measures analyzed at week 24, missing data were imputed using the last observation carried forward (LOCF) method.

**Study populations.** The safety population consisted of all subjects who received at least one dose of randomized study medication. The primary inferences concerning the safety of ropinirole 24-hour were made using the safety population. The intention-to-treat (ITT) population consisted of all randomized subjects who received at least one dose of study medication and for whom at least one post-baseline efficacy assessment was available. The primary inferences concerning the efficacy of ropinirole 24-hour were made using the ITT population. The per protocol (PP) population consisted of all subjects in the ITT population who had no major protocol deviation with regard to inclusion or exclusion criteria; no major protocol deviation between randomization and completion of the active treatment phase of the study (weeks 1 to 24); and no more than 3 consecutive days of study medication missed throughout active treatment.

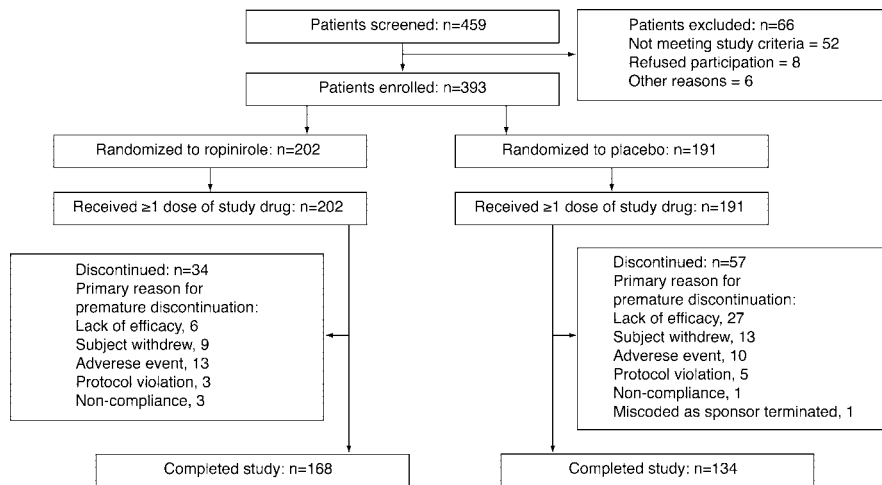


Figure 1. Subject flowchart.

**Results. Patients.** A total of 393 subjects were randomized and received at least one dose of study medication (safety population): ropinirole 24-hour ( $n = 202$ ), placebo ( $n = 191$ ) (figure 1). The ITT population comprised a total of 391 subjects: ropinirole 24-hour ( $n = 201$ ), placebo ( $n = 190$ ). The PP population comprised 82% (324/393) of all randomized subjects: ropinirole 24-hour ( $n = 168$ ), placebo ( $n = 156$ ). The most common reason for discontinuation was lack of efficacy (ropinirole 24-hour: 6/202 [3%]; placebo 27/191 [14%]).

Baseline demographics are shown in table 1. In the safety population, 189/202 (94%) of the ropinirole 24-hour group and 181/191 (95%) of the placebo group met the definition for overall compliance which required a tablet compliance of  $\geq 80\%$  and  $\leq 120\%$  and no more than 3 consecutive days of missed study medication. At week 24 the mean dose of ropinirole 24-hour was  $18.8 \pm 6.26$  mg/day and the median dose was 20 mg/day with a range from 2 to 24 mg/day. The mean placebo dose level at week 24 corresponded to  $20.0 \pm 5.62$  mg/day and the median dose level corresponded to 24 mg/day with a range from 2 to 24 mg/day. At week 24, 100/202 (50%) ropinirole 24-hour subjects were receiving the maximum 24 mg/day, compared with 107/191 (56%) subjects in the placebo group receiving the equivalent dose level (Level 8) of matching placebo.

**Primary outcome measure.** At baseline, mean “off” time was approximately 7 hours in each treatment group (table 1). Mean changes from baseline in “off” time by visit are shown in figure 2. At week 24, mean reduction from baseline in total “off” time was 2.1 hours in the ropinirole 24-hour group and 0.3 hours in the placebo group. The mean treatment difference between ropinirole 24-hour and placebo at week 24 was 1.7 hours (95% CI:  $-2.34, -1.09$ ;  $p < 0.0001$ ) indicating both a clinically relevant and significant benefit of ropinirole 24-hour over placebo. At all visits from week 2 to 24 there was a significant treatment difference for ropinirole 24-hour compared with placebo in change from baseline in “off” time (figure 2). The reduction in “off” time was also significantly reduced in the PP population at week 24 with ropinirole 24-hour compared to placebo.

**Secondary outcome measures.** Several secondary outcome measures resulted in significant improvement with ropinirole 24-hour compared to placebo including hours of “on” time and “on” time without troublesome dyskinesia;

percent of “off” time, “on” time, and “on” time without troublesome dyskinesia (figure 3); UPDRS motor and ADL scores; BDI-II total score; PDQ-39 subscores of mobility, ADLs, emotional well-being, stigma, and communication; and PDSS total score (table 2). There were no significant differences between ropinirole 24-hour and placebo in PDQ-39 subscores of social support, cognition, or bodily discomfort and ESS total scores (table 2).

More subjects in the ropinirole 24-hour group (83/200, 42%) were classified as responders (“much improved” or “very much improved”) on the CGI-I scale at week 24 vs the placebo group (27/189, 14%; OR: 4.4; 95% CI: 2.63, 7.20;  $p < 0.001$ ).

Mean levodopa dose at week 24 was  $546 \pm 378$  mg/day in the ropinirole 24-hour group and  $613 \pm 349$  mg/day in the placebo group. Over the course of the study there was a larger decrease in daily levodopa dose in the ropinirole 24-hour group vs placebo. Mean change from baseline was  $-278 \pm 193$  mg/day in the ropinirole 24-hour group and  $-164 \pm 164$  mg/day in the placebo group.

Among subjects who had levodopa dose reduction (ropinirole 24-hour: 191/201 subjects [95%]; placebo: 174/190 subjects [92%]), reinstatement of levodopa following dose reduction was required for 7% (14/191) of the ropinirole 24-hour group and 28% (49/174) of the placebo group. The odds of a subject receiving placebo requiring reinstatement with levodopa were five times those of a subject receiving the active drug (adjusted OR: 0.2; 95% CI: 0.09, 0.34;  $p < 0.001$ ). There was also a benefit for ropinirole 24-hour over placebo for time to reinstatement of levodopa following a reduction in dose (adjusted hazard ratio: 0.2; 95% CI: 0.11, 0.37;  $p < 0.0001$ ).

More subjects in the ropinirole 24-hour group (103/200, 52%) were classified as responders based on change in “off” time and levodopa dose (at least a 20% reduction in both from baseline) at week 24 vs the placebo group (38/190, 20%; OR: 4.3; 95% CI: 2.73, 6.78;  $p < 0.001$ ). Thus, the odds of a subject receiving ropinirole 24-hour and achieving a 20% reduction in “off” time and a 20% reduction in levodopa dose was more than four times that of a subject receiving placebo.

**Adverse events.** AEs were reported by 64% (129/202) of ropinirole 24-hour subjects vs 55% (106/191) of those receiving placebo. The most common AEs (reported by  $\geq 5\%$  of the ropinirole 24-hour group) were dyskinesia, nausea,

**Table 1** Demographics and baseline characteristics (intention-to-treat population)\*

	Ropinirole 24-hour (n = 201)	Placebo (n = 190)
Age, y	66.3 (9.2)	66.0 (9.7)
Women, n (%)	84 (42)	61 (32)
Age at onset of PD, y	57.6 (10.5); 200	57.3 (10.7); 188
Duration of PD, y	8.6 (4.8); 200	8.6 (5.2); 188
Hoehn & Yahr stage	2.7 (0.5); 201	2.7 (0.6); 190
Duration of levodopa, y	6.5 (4.4); 199	6.6 (4.3); 187
Baseline levodopa dose, mg/d	824 (424.4); 199	776 (357.3); 190
Total "off," h	7.0 (2.8)	7.0 (2.6)
Total "on," h	9.0 (2.8)	9.1 (2.7)
Total "on" without dyskinesia, h	8.5 (2.9); 200	8.4 (2.9); 188
UPDRS motor score†	29.8 (12.9); 197	30.7 (14.4); 188
UPDRS ADL score‡	13.9 (6.2); 200	14.2 (6.8); 189
BDI-II total score§	15.9 (9.0); 197	16.1 (8.8); 188
PDQ-39 domain score¶		
Mobility	42.2 (25.6); 194	43.4 (23.6); 183
ADL	42.3 (24.4); 193	45.1 (22.9); 185
Emotional well-being	32.5 (21.7); 190	31.9 (19.4); 181
Stigma	31.2 (23.9); 195	30.3 (24.2); 188
Social support	14.1 (19.9); 194	14.1 (18.3); 187
Cognitive impairment	25.0 (18.0); 197	24.7 (17.3); 188
Communication	24.7 (20.7); 195	25.7 (21.0); 187
Bodily discomfort	37.7 (20.8); 197	39.6 (21.4); 187
ESS total score	7.8 (4.5); 196	7.7 (4.4); 186
PDSS total score**	99.2 (24.6); 198	98.0 (25.9); 189

\* Unless noted otherwise, values are expressed as mean (SD); number.

† Range 0–108, where 0 = normal/no symptoms; assessed at least 2 hours after levodopa dose.

‡ Range 0–52, where 0 = normal/no symptoms; average of "on" and "off" scores.

§ Range 0–63 (least–most severe).

¶ Range 0–100 for all domains (no problem–maximum level of problem).

|| Range 0–24 (least–most chance of dozing).

\*\* Range 0–150 (most severe–free from all symptoms).

PD = Parkinson disease; UPDRS = Unified Parkinson's Disease Rating Scale; ADL = activities of daily living; BDI-II = Beck Depression Inventory II; PDQ-39 = Parkinson's Disease Quality of Life questionnaire; ESS = Epworth Sleepiness Scale; PDSS = Parkinson's Disease Sleep Scale.

dizziness, somnolence, hallucinations, and orthostatic hypotension (table 3). AEs during the down-titration phase did not suggest any rebound or withdrawal symptoms.

The number of subjects reporting AEs leading to withdrawal was low and similar in both treatment groups: 11 subjects (5%) in the ropinirole 24-hour group and 10 subjects (5%) in the placebo group. AEs that led to the withdrawal of at least two subjects within a treatment group were hallucinations (ropinirole 24-hour: 4 subjects, 2%;

placebo: 2 subjects, 1%), nausea (ropinirole 24-hour: 2 subjects, <1%; placebo: 1 subject, <1%), and worsening of parkinsonism (ropinirole 24-hour: 0 subjects; placebo: 2 subjects, 1%).

Serious AEs were reported by 4% of subjects in each treatment group (ropinirole 24-hour: 8/202; placebo: 7/191). Only three ropinirole 24-hour subjects reported serious AEs that were considered by the investigator to be related to the study drug (syncope: 1 subject; hallucinations: 2 subjects), and for two of these subjects (syncope and hallucinations) concomitant medications were also considered a possible cause. None of the subjects in the placebo group who reported a serious AE reported an event that was considered by the investigator to be related to the study drug.

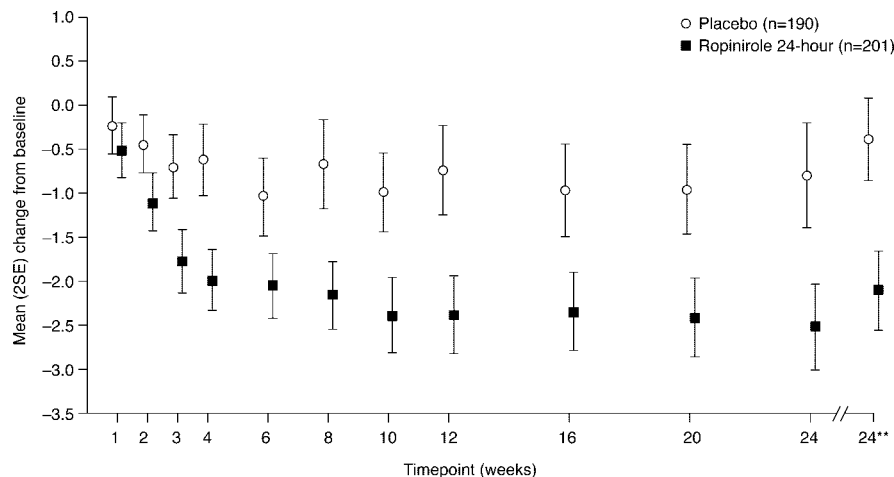
Three deaths were reported during the study: one in the ropinirole 24-hour group and two in the placebo group. None was considered related to study drug. In the ropinirole 24-hour group, the serious AE leading to death was pneumonia and in the placebo group, the serious AEs leading to death were hip fracture and pneumonia.

**Discussion.** We found that ropinirole 24-hour is effective in reducing "off" time compared to placebo in patients with PD not optimally controlled with levodopa. Patients receiving ropinirole 24-hour experienced a reduction in "off" time an average of 2.1 hours (adjusted treatment difference of 1.7 hours), which was both significant and clinically relevant. These benefits for ropinirole 24-hour were observed from week 2 through week 24.

The decrease in "off" time in the ropinirole 24-hour group was accompanied by an average increase in "on" time of 1.6 hours (treatment difference of 1.7 hours). At study end (week 24), there was a significant treatment difference in favor of ropinirole 24-hour for "on" time without troublesome dyskinesia. In contrast, the mean "on" time with troublesome dyskinesia decreased by 0.04 hours in the ropinirole 24-hour group and by 0.23 hours in the placebo group. Thus, the decrease in "off" time and increase in "on" time seen in the ropinirole 24-hour group did not result in an increase in troublesome dyskinesia. The reduction in troublesome dyskinesia is likely secondary to the reduction in levodopa dose in both groups.

The efficacy of ropinirole 24-hour in improving symptom control was supported by several other secondary outcome measures. Significant benefits in favor of ropinirole 24-hour were observed for the change in UPDRS motor score (indicating improvements in motor impairments and disability), UPDRS ADL score (indicating improvements in daily functioning), and in the proportion of patients classified as responders on the CGI-I scale (indicating global improvement).

Ropinirole 24-hour was also associated with significant treatment benefits compared with placebo in terms of mood (change in BDI-II total score) and various aspects of quality of life including PDQ-39 subscores for mobility, ADLs, emotional well-being, stigma, and communication. Furthermore, the lack



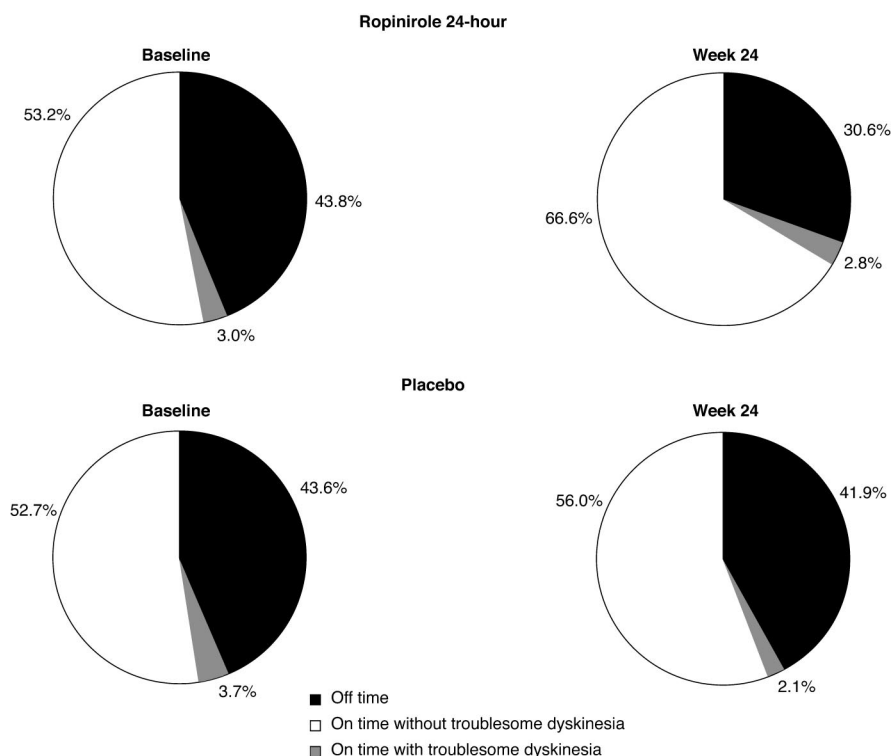
**Figure 2.** Mean (2 SE) change from baseline in total hours “off” at each visit for ropinirole 24-hour prolonged release and placebo. Adjusted treatment difference (95% CI), ropinirole 24-hour prolonged release vs placebo, for change from baseline in “off” time at each visit: week 1 =  $-0.3$  ( $-0.73, 0.13$ ;  $p = 0.1741$ ); week 2 =  $-0.7$  ( $-1.09, -0.23$ ;  $p = 0.0029$ ); week 3 =  $-1.1$  ( $-1.52, -0.59$ ;  $p < 0.0001$ ); week 4 =  $-1.3$  ( $-1.80, -0.79$ ;  $p < 0.0001$ ); week 6 =  $-0.9$  ( $-1.47, -0.39$ ;  $p = 0.0008$ ); week 8 =  $-1.5$  ( $-2.05, -0.87$ ;  $p < 0.0001$ ); week 10 =  $-1.4$  ( $-1.93, -0.78$ ;  $p < 0.0001$ ); week 12 =  $-1.6$  ( $-2.21, -0.96$ ;  $p < 0.0001$ ); week 16 =  $-1.3$  ( $-1.88,$

$-0.63$ ;  $p = 0.0001$ ); week 20 =  $-1.3$  ( $-1.99, -0.69$ ;  $p < 0.0001$ ); week 24 =  $-1.6$  ( $-2.30, -0.85$ ;  $p < 0.0001$ ); \*\* last observation carried forward.

of a significant treatment difference for the cognition subscore of the PDQ-39 suggests that treatment with ropinirole 24-hour was not associated with an adverse effect on mental function. Although the study dose was administered in the morning, subjects in the ropinirole 24-hour group experienced significant improvements in sleep compared with those receiving placebo as assessed by the PDSS.

The efficacy of ropinirole 24-hour was demonstrated alongside a levodopa-sparing effect. The study design mandated reductions in concomitant levodopa dose for increases in study medication and the decrease in levodopa dose was greater in the ropinirole 24-hour compared to the placebo group ( $-278$  mg/day vs  $-164$  mg/day). Among patients who underwent levodopa dose

reduction, the odds of requiring reinstatement of levodopa after such a reduction were five times greater in the placebo group than in the ropinirole 24-hour group. Furthermore, based on time to reinstatement analyses, at any time point subjects receiving placebo were approximately five times more likely to require levodopa rescue. This study therefore provides evidence that ropinirole 24-hour is effective as an adjunct therapy to levodopa, permitting a substantial reduction in the concomitant dose of levodopa while offering an improvement in motor fluctuations. Indeed, the proportion of subjects achieving both a  $\geq 20\%$  reduction in levodopa dose and a  $\geq 20\%$  reduction in “off” time was significantly greater in the ropinirole 24-hour group (52%) vs placebo (20%).



**Figure 3.** Percentage of “off” time, “on” time, and “on” time with troublesome dyskinesia at baseline and week 24 for ropinirole 24-hour prolonged release and placebo.

**Table 2** Mean change from baseline in diary measures, UPDRS motor and ADL scores, BDI-II total score, PDQ-39 domain scores, ESS total score, and PDSS total score at week 24 last observation carried forward for ropinirole 24-hour prolonged release and placebo

	Mean (2 SE); n change from baseline			p Value
	Ropinirole 24-hour prolonged release (n = 201)	Placebo (n = 190)	Adjusted treatment difference (95% CI)	
“Off” time (diary)	-2.1 (0.64); 201	-0.3 (0.64); 190	-1.7 (-2.34, -1.09)	<0.0001
“On” time (diary)	1.6 (0.64); 201	-0.1 (0.64); 190	1.7 (1.06, 2.33)	<0.0001
On without troublesome dyskinesia (diary)	1.6 (0.64); 200	0.1 (0.65); 188	1.5 (0.85, 2.13)	<0.0001
% “Off” time (diary)	-12.1 (4.01); 201	-0.9 (4.05); 190	-11.2 (-15.13, -7.21)	<0.0001
% “On” time (diary)	12.1(4.00); 201	1.0 (4.04); 190	11.1 (7.17, 15.08)	<0.0001
% “On” without troublesome dyskinesia (diary)	12.3 (4.04); 200	2.7 (4.08); 188	9.7 (5.67, 13.69)	<0.0001
UPDRS Motor	-6.5 (1.81);194	-1.7 (1.83); 183	-4.8 (-6.56, -2.98)	<0.0001
UPDRS ADL	-3.5 (0.78); 197	-0.9 (0.79); 184	-2.6 (-3.36, -1.83)	<0.0001
BDI-II total score	-2.1 (1.3); 188	-0.5 (1.3); 179	-1.6 (-2.86, -0.34)	0.0130
PDQ-39 Subscales				
Mobility	-4.9 (3.36); 186	1.9 (3.42); 172	-6.8 (-10.07, -3.53)	<0.0001
Activities of daily living	-5.4 (3.30); 185	1.1 (3.76); 176	-6.5 (-9.71, -3.25)	<0.0001
Emotional well-being	-4.3 (3.06); 182	-0.6 (3.06); 172	-3.7 (-6.68, -0.82)	0.0124
Stigma	-3.3 (3.68); 187	1.2 (3.70); 178	-4.5 (-8.06, -0.87)	0.0150
Social support	-1.5 (2.98); 185	-0.3 (3.0); 177	-1.2 (-4.07, 1.77)	0.4385
Cognition	3.4 (2.68); 188	2.9 (2.68); 178	0.5 (-2.13, 3.09)	0.7176
Communication	-1.4 (3.26); 187	2.4 (3.34); 176	-3.7 (-6.88, -0.61)	0.0193
Bodily discomfort	-3.6 (3.42); 189	-1.5 (3.50); 176	-2.1 (-5.40, 1.26)	0.2224
ESS total score	0.5 (0.78); 188	0.2 (0.82); 173	0.3 (-0.41, 1.09)	0.3692
PDSS total score	1.3 (4.18); 191	-3.3 (4.22); 178	4.7 (0.75, 8.57)	0.0196

UPDRS motor 0–108, 0 = normal/no symptoms, assessed at least 2 hours after levodopa dose; UPDRS ADL 0–52, 0 = normal/no symptoms, average of “on” and “off” scores; BDI-II total score = 0–63; PDQ-39 = 0–100 for each domain; ESS total score = 0–24; PDSS = range 0–150.

UPDRS = Unified Parkinson’s Disease Rating Scale; ADL = activities of daily living; BDI-II = Beck Depression Inventory II; PDQ-39 = Parkinson’s Disease Quality of Life questionnaire; ESS = Epworth Sleepiness Scale; PDSS = Parkinson’s Disease Sleep Scale.

AEs were typical of non-ergot dopamine agonists. The proportion of patients withdrawn due to AEs or reporting serious AEs was no greater in the ropinirole 24-hour group than in the placebo group. Most

**Table 3** Number (%) of subjects reporting any adverse event (AE) and the number (%) of subjects reporting the most common on-treatment AEs: reported by ≥5% of the ropinirole 24-hour prolonged release group

	Ropinirole 24-hour prolonged release (n = 202)	Placebo (n = 191)
Subjects with at least one AE	129 (64)	106 (55)
Dyskinesia	27 (13)	5 (3)
Nausea	23 (11)	7 (4)
Dizziness	16 (8)	6 (3)
Somnolence	14 (7)	7 (4)
Hallucinations	12 (6)	2 (1)
Orthostatic hypotension	11 (5)	3 (2)

patients reported AEs that were mild or moderate. In general, the most common AEs occurring in ≥10% of the ropinirole 24-hour group, dyskinesia (13%) and nausea (11%), were reported during the first 4 weeks of the study. This was during the up-titration phase before the planned reduction in levodopa dose occurred.

Although dyskinesia was the AE reported by the greatest proportion of subjects receiving ropinirole 24-hour, the amount of time spent “on” with troublesome dyskinesia was similar in each treatment group at study end and had decreased slightly over the course of the study. More specifically, 48% of the 27 ropinirole 24-hour subjects reporting dyskinesia as an AE during the study reported dyskinesia at baseline according to the UPDRS Part IV (item 32). The dyskinesia was mildly disabling in 23%, moderately disabling in 31%, and not disabling in 46%. Of the 27 subjects reporting dyskinesia throughout the study, 81% (22/27) reported dyskinesia at week 24. In these subjects, the dyskinesia was mildly disabling in 15%, moderately disabling in 19%, and not

disabling in 65%. The baseline daily dose of levodopa was greater in the ropinirole 24-hour group (824 mg/day) compared to the placebo group (776 mg/day) and the subjects in the ropinirole 24-hour group who reported dyskinesia as an AE had a higher baseline dose of levodopa (975 mg/day) compared to those who did not report dyskinesia as an AE (800 mg/day). The increased dyskinesia in the ropinirole 24-hour group compared to placebo may largely be due to the design of the study. During the titration phase of the study, the study drug was increased by 2 mg/week; however, reductions in levodopa did not occur until a daily dose of 8 mg was achieved. Therefore, the increase in dyskinesia could be due to an increased dopaminergic load in the ropinirole 24-hour group during the first several weeks of the study, which would not have been present in the placebo group. This hypothesis is further supported by the fact that 85% (23/27) of the subjects in the ropinirole 24-hour group who reported dyskinesia did so prior to week 12 of the study.

The proportion of subjects reporting AEs of special interest in terms of dopamine agonists (e.g., hallucinations, unintended sleep episodes) was low. Of the 16 subjects (8%) in the ropinirole 24-hour group who reported AEs of hallucinations, only 4 were discontinued from the study, compared with 2 of the 4 subjects (2%) reporting hallucinations in the placebo group. Only one ropinirole 24-hour subject reported an AE of an unintended sleep episode which was of moderate intensity on the first day of the study and resolved after 1 day. Ropinirole 24-hour was not discontinued as a result of this AE and the subject completed the study. One subject receiving placebo also reported an AE of an unintended sleep episode of moderate intensity 145 days after the first dose, which was resolved on the day of onset. Again, no action was taken with regard to study medication, and the subject completed the study. The proportion of subjects reporting AEs of orthostatic hypotension, hypotension, or blood pressure decreases was also low in both treatment groups and none of these subjects was withdrawn from the study as result of the AE. Syncope was reported for two ropinirole 24-hour recipients (<1%), and for one of these subjects led to withdrawal from the study. Both AEs of syncope were reported as resolved the day after onset. There were no AEs suggestive of fibrosis. Overall, the ropinirole 24-hour regimen was well tolerated in the population studied.

The adjusted mean treatment difference in the reduction in "off" time with ropinirole 24-hour and placebo of 1.7 hours was either comparable or superior to the reduction in hours of "off" time measured by subject diaries reported for other similar studies of adjunctive treatments in PD. A study of pergolide compared to placebo as an adjunct therapy to levodopa reported a treatment difference in the reduction of "off" time of 1.6 hours.<sup>10</sup> Similarly, a study of pramipexole dosed three times daily compared to placebo reported a treatment difference in the reduc-

tion of "off" time of 2.0 hours.<sup>11</sup> A study examining both rasagiline 1 mg and entacapone (200 mg per levodopa dose) compared to placebo demonstrated a treatment difference in reduction of "off" time for both drugs of 0.8 hours.<sup>12</sup> Similarly, a study of rasagiline 0.5 mg and rasagiline 1.0 mg compared to placebo reported treatment differences in the reduction in "off" time of 0.49 hours (0.5 mg) and 0.94 hours (1.0 mg).<sup>13</sup>

The results of this study suggest that ropinirole 24-hour is as efficacious but better tolerated when compared to the results of a similar study with immediate release ropinirole.<sup>4</sup> The percentage of responders ( $\geq 20\%$  reduction in levodopa dose and daily "off" time) on active drug in the immediate release ropinirole study was 35% compared to 52% in the current study. AEs with immediate release ropinirole were dyskinesia (34%), worsening of PD (21%), nausea (20%), ataxia (20%), dizziness (20%), somnolence (19%), postural hypotension (17%), and insomnia (14%). The percentages were higher than those for the same AEs in this current ropinirole 24-hour study. Furthermore, 16% of the subjects in the immediate release ropinirole study discontinued the study due to AEs compared with 5% in the present study despite a faster dose titration to 24 mg/day (8 weeks) of ropinirole 24-hour compared to immediate release (13 weeks).

Ropinirole 24-hour was effective and well tolerated as adjunct therapy in patients with PD not optimally controlled with levodopa. Ropinirole 24-hour demonstrated an ability to improve both motor and non-motor PD symptoms, while permitting a reduction in adjunctive levodopa dose.

## Appendix

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