

# Ropinirole Prolonged Release In Advanced Parkinson's Disease

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## Abstract

- ▲ Ropinirole prolonged release is a non-ergoline dopamine receptor agonist that is indicated for the treatment of Parkinson's disease.
- ▲ Once-daily ropinirole prolonged release and three-times-daily ropinirole immediate release have similar exposure over 24 hours. The prolonged-release formulation is associated with fewer fluctuations in plasma ropinirole concentrations.
- ▲ Two well designed, placebo- or active comparator-controlled trials examined the efficacy of ropinirole prolonged release in patients with advanced Parkinson's disease suboptimally controlled by levodopa. In the placebo-controlled trial, 24 weeks' therapy with ropinirole prolonged release 6–24 mg once daily reduced hours of 'off' time (primary endpoint) to a significantly greater extent than placebo. In the active comparator-controlled trial, significantly more ropinirole prolonged-release recipients than ropinirole immediate-release recipients maintained a  $\geq 20\%$  reduction from baseline in 'off' time at week 24 (primary endpoint).
- ▲ Ropinirole prolonged release 6–24 mg once daily was generally well tolerated in patients with advanced Parkinson's disease; adverse events were generally typical of non-ergoline dopamine receptor agonists.

### Features and properties of ropinirole prolonged release

#### Featured indication

Advanced Parkinson's disease

#### Mechanism of action

Non-ergoline dopamine D<sub>2</sub>/D<sub>3</sub> receptor agonist

#### Dose and administration

Starting dose	2 mg
Recommended dose	4–24 mg
Route of administration	Oral
Frequency of administration	Once daily

#### Pharmacokinetic profile (dose-normalized steady-state pharmacokinetics of ropinirole prolonged release in patients with Parkinson's disease)

Geometric mean maximum plasma concentration (C <sub>max</sub> )	0.92 ng/mL/mg
Median time to C <sub>max</sub>	6 h
Geometric mean minimum plasma concentration	0.44 ng/mL/mg
Geometric mean area under the plasma concentration-time curve from time 0–24 h	16.3 ng • h/mL/mg

#### Adverse events

Dyskinesia, nausea, dizziness, somnolence, hallucinations, orthostatic hypotension

Parkinson's disease is a progressive age-related neurodegenerative disorder associated with the loss of dopaminergic cells in the substantia nigra.<sup>[1,2]</sup> The condition, which has an average age of onset of 60 years, is estimated to affect approximately 0.3% of the general population and 1% of adults aged >60 years.<sup>[2,3]</sup> The cardinal symptoms of Parkinson's disease include bradykinesia, rest tremor and rigidity.<sup>[1]</sup>

The introduction of levodopa revolutionized the treatment of Parkinson's disease,<sup>[2]</sup> but the effectiveness of dopaminergic therapy is eventually limited by motor fluctuations and dyskinesia.<sup>[4]</sup> Non-ergoline dopamine receptor agonists recommended to reduce motor fluctuations in patients with advanced Parkinson's disease include ropinirole, pramipexole and rotigotine.<sup>[5]</sup>

Although ropinirole immediate release is effective in the treatment of Parkinson's disease, the need for multiple drug doses per day and an extended titration phase may affect patient compliance and hinder the achievement of optimal patient function.<sup>[6]</sup> Thus, to further improve the management of Parkinson's disease, a prolonged-release formulation of ropinirole has been developed. Ropinirole prolonged release<sup>1</sup> is a once-daily formulation that provides controlled delivery of ropinirole over 24 hours, which may translate into efficacy and tolerability benefits.<sup>[6-8]</sup> In addition, while the immediate-release formulation is usually administered three times daily,<sup>[9]</sup> the prolonged-release formulation is administered once daily,<sup>[10]</sup> potentially improving patient compliance. Ropinirole prolonged release also has a simpler and faster titration schedule than ropinirole immediate release.<sup>[6]</sup>

Ropinirole prolonged release is approved in a number of EU countries for use in Parkinson's disease as both initial monotherapy and as an adjunct to levodopa,<sup>[10]</sup> and is approved in the US for the treatment of the signs and symptoms of idiopathic Parkinson's disease.<sup>[11]</sup> This article focuses solely on the use of ropinirole prolonged release as an adjunct to levodopa in patients with advanced

Parkinson's disease, and reviews the pharmacological properties of the drug as well as its clinical efficacy and tolerability. Medical literature on the use of ropinirole prolonged release in the treatment of advanced Parkinson's disease was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles.

## 1. Pharmacological Properties

### Mechanism of Action

- Ropinirole is a non-ergoline dopamine D<sub>2</sub>/D<sub>3</sub> receptor agonist that stimulates striatal dopamine receptors, thereby alleviating the dopamine deficiency that characterizes Parkinson's disease.<sup>[10,12]</sup>
- Ropinirole binds to central and peripheral dopamine receptors with an order of receptor affinity similar to that of dopamine.<sup>[13]</sup> It is ≈20-fold more selective for D<sub>3</sub> than D<sub>2</sub> receptors and ≈50-fold more selective for D<sub>3</sub> than D<sub>4</sub> receptors, with negligible affinity for D<sub>1</sub> receptors.<sup>[12]</sup> Ropinirole has little or no affinity for β-adrenoceptors or adrenergic, serotonergic, GABA or benzodiazepine receptors.<sup>[12]</sup> Ropinirole exerts its antiparkinsonian effects by acting on postsynaptic dopamine receptors in the CNS.<sup>[12,13]</sup>

### Pharmacokinetic Profile

The pharmacokinetic properties of ropinirole and its immediate-release formulation have been reviewed previously<sup>[14]</sup> and will be discussed briefly in this section. In addition, data concerning the pharmacokinetics of ropinirole prolonged release are available from two randomized, open-label studies in patients with early-stage Parkinson's disease (Hoehn and Yahr stage I–III) [23 and 28 randomized patients],<sup>[7]</sup> supplemented by data from the manufacturer's prescribing information.<sup>[10]</sup> The relative bioavailability of the prolonged- and immediate-release ropinirole formulations was examined at

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steady state in patients with early-stage Parkinson's disease who received ropinirole prolonged release 8 mg once daily or ropinirole immediate release 2.5 mg three times daily.<sup>[7]</sup> Ninety percent confidence intervals (CIs) for the ratio (ropinirole prolonged release : ropinirole immediate release) of the dose-normalized area under the plasma concentration-time curve from 0–24 hours (AUC<sub>24</sub>), the dose-normalized maximum plasma concentration (C<sub>max</sub>) and the dose-normalized minimum plasma concentration (C<sub>min</sub>) were calculated and assessed in relation to the limits normally associated with bioequivalence (0.80–1.25).<sup>[7]</sup>

- Ropinirole has a bioavailability of ≈50%.<sup>[10]</sup> Due to the controlled delivery of ropinirole from the prolonged-release formulation, the time to ropinirole C<sub>max</sub> (t<sub>max</sub>) was slower with the prolonged-release formulation than with the immediate-release formulation, with a median t<sub>max</sub> of 6 hours for ropinirole prolonged release 8 mg and 2 hours for ropinirole immediate release 2.5 mg.<sup>[7]</sup>

- At steady state, dose-normalized geometric mean AUC<sub>24</sub> (16.3 vs 16.0 ng • h/mL/mg) [ratio 1.02; 90% CI 0.96, 1.09] and dose-normalized geometric mean C<sub>min</sub> (0.44 vs 0.45 ng/mL/mg) [ratio 0.98; 90% CI 0.90, 1.06] were similar for prolonged- and immediate-release ropinirole formulations.<sup>[7]</sup> CIs for these two parameters were within the limits associated with bioequivalence. Dose-normalized geometric mean C<sub>max</sub> was ≈12% lower with prolonged-release ropinirole than with immediate-release ropinirole (0.92 vs 1.05 ng/mL/mg) [ratio 0.88; 90% CI 0.78, 0.99]. The degree of fluctuation in ropinirole plasma concentrations was 0.66 with ropinirole prolonged release and 0.85 with ropinirole immediate release.<sup>[7]</sup>

- C<sub>max</sub>, C<sub>min</sub> and AUC<sub>24</sub> values increased in a dose-proportional manner with ropinirole prolonged release 2–8 mg.<sup>[7]</sup> Ropinirole pharmacokinetics are associated with wide inter-individual variability; at steady state, inter-individual variability was 30–55% for C<sub>max</sub> and 40–70% for AUC with ropinirole prolonged release.<sup>[10]</sup>

- T<sub>max</sub> was delayed by ≈2 hours when ropinirole prolonged release 8 mg was administered with a

high-fat meal, compared with in the fasted state.<sup>[7]</sup> AUC<sub>24</sub> and C<sub>min</sub> values were similar in the fed and fasted states with ratios (fed : fasted) of 1.06 (90% CI 0.95, 1.19) and 0.96 (90% CI 0.85, 1.08); CIs for these parameters were within the limits associated with bioequivalence. C<sub>max</sub> was 15% higher in the fed than the fasted state (ratio 1.15; 90% CI 1.01, 1.31), although this was not deemed clinically significant.<sup>[7]</sup>

- The volume of distribution of ropinirole is ≈7 L/kg, with plasma protein binding of 10–40%.<sup>[10]</sup>

- Ropinirole is metabolized primarily by the cytochrome P450 (CYP) isozyme CYP1A2, with a minor contribution from CYP3A.<sup>[14]</sup> Only 10% of a ropinirole dose is excreted in its unchanged form,<sup>[14]</sup> with metabolites mainly excreted in urine.<sup>[10]</sup> Ropinirole has an average elimination half-life of ≈6 hours.<sup>[10]</sup>

- Dosage adjustment is not necessary in individuals with mild to moderate renal impairment (creatinine clearance 30–50 mL/min [1.8–3.0 L/h]), as ropinirole clearance is not altered in these patients.<sup>[10]</sup> However, ropinirole prolonged release is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min [<1.8 L/h]) and in those with hepatic impairment.<sup>[10]</sup>

- Ropinirole clearance is decreased by 15% in patients aged ≥65 years;<sup>[14]</sup> ropinirole dosages should be increased gradually and titrated to therapeutic response in this population, with slower titration during treatment initiation considered in very elderly patients.<sup>[10]</sup>

- In terms of potential drug interactions, the CYP1A2 inhibitor ciprofloxacin increased the ropinirole C<sub>max</sub> by 60% and the ropinirole AUC by 84%; ropinirole dosage adjustments may be needed when CYP1A2 inhibitors (e.g. ciprofloxacin, enoxacin, fluvoxamine) are introduced or withdrawn in patients already receiving ropinirole.<sup>[10]</sup> Ropinirole dosage adjustment may be necessary in patients who start or stop smoking during ropinirole therapy (smoking induces CYP1A2) or if hormone replacement therapy is started or stopped during ropinirole therapy (high-dose estrogens may increase ropinirole plasma concentrations).<sup>[10]</sup> Centrally active dop-

amine antagonists (e.g. sulpiride, metoclopramide) may reduce the efficacy of ropinirole.<sup>[10]</sup>

- No clinically significant pharmacokinetic interactions occurred between ropinirole and levodopa, domperidone, digoxin or the CYP1A2 substrate theophylline.<sup>[10,14]</sup>

#### Pharmacokinetic-Pharmacodynamic Relationship

The pharmacokinetic-pharmacodynamic relationship between ropinirole systemic exposure and efficacy was examined in an analysis<sup>[8]</sup> of the EASE-PD (Efficacy and Safety Evaluation in Parkinson's Disease) Adjunct study (see section 2 for study design details and results of the primary efficacy analysis).<sup>[6]</sup> The analysis, involving 294 evaluable patients, assessed the relationship between ropinirole systemic exposure (AUC<sub>24</sub>) and the probability of a patient having a  $\geq 20\%$  reduction from baseline in awake time spent 'off'.<sup>[8]</sup> Patients were randomized to receive ropinirole prolonged release (titrated to 6–24 mg once daily) or placebo.

- A response (defined as a decrease from baseline of  $\geq 20\%$  in awake time spent 'off') occurred in  $\approx 60\text{--}80\%$  of ropinirole prolonged-release recipients and  $\approx 40\%$  of placebo recipients.<sup>[8]</sup> The pharmacokinetic-pharmacodynamic analysis demonstrated that the probability of a response increased with increasing ropinirole exposure and was  $\approx 0.9$  at higher systemic exposures of ropinirole prolonged release versus  $\approx 0.4$  with placebo.

## 2. Therapeutic Efficacy

#### Comparison with Placebo

The efficacy of ropinirole prolonged release in advanced Parkinson's disease has been assessed in the EASE-PD Adjunct study, a randomized, double-blind, placebo-controlled, multinational, 24-week trial.<sup>[6]</sup> Additional analyses of the EASE-PD Adjunct trial are available as abstracts.<sup>[15–18]</sup>

The EASE-PD Adjunct study included 393 patients aged  $\geq 30$  years who had idiopathic Parkinson's disease (modified Hoehn and Yahr stage

II–IV) that was suboptimally controlled by levodopa.<sup>[6]</sup> Patients were eligible if they had been receiving a stable dosage of levodopa for at least 4 weeks and if they reported a minimum of 3 hours per day in the 'off' state.

After a 14-day placebo run-in period, patients were randomized to receive once-daily ropinirole prolonged release (n = 202) or placebo (n = 191) for 24 weeks, in addition to their current levodopa therapy.<sup>[6]</sup> Ropinirole prolonged release was initiated at a starting dosage of 2 mg/day and titrated until the occurrence of an optimal therapeutic response or adverse effects, with a minimum dosage of 6 mg/day and a maximum dosage of 24 mg/day. Ropinirole prolonged-release dosages  $> 8$  mg/day were accompanied by decreases in the levodopa dosage, which could be adjusted throughout the study according to the level of symptom control achieved (the mean levodopa dosage decreased by 278 and 164 mg/day in ropinirole prolonged-release and placebo recipients during the study). After 24 weeks' therapy, the mean ropinirole prolonged-release dosage was 18.8 mg/day (median 20 mg/day), with 50% of patients receiving the maximum dosage of 24 mg/day. At the end of the trial, patients entered a 7-day down-titration phase. Patients were permitted to receive selegiline, amantadine, anticholinergics and catechol-O-methyltransferase inhibitors during the trial, as long as the dosages of these agents had been stable for at least 4 weeks prior to screening.

At baseline, the mean patient age was 66.3 years in ropinirole prolonged-release recipients and 66.0 years in placebo recipients, with a mean duration of Parkinson's disease of 8.6 years.<sup>[6]</sup>

The primary endpoint was the mean change from baseline in hours 'off' after 24 weeks, as assessed by patient diaries.<sup>[6]</sup>

Secondary endpoints included the mean change from baseline in hours 'on'; the percentage of 'on' or 'off' time; the hours and percentage of 'on' time without troublesome dyskinesia; and mean changes from baseline in the Unified Parkinson's Disease Rating Scale (UPDRS) motor score (assessed  $\geq 2$  hours after the previous levodopa dose) [score ranges from 0 to 108, where 0 = normal/no symp-

toms]; the UPDRS activities of daily living (ADL) score (score ranges from 0 to 52, where 0 = normal/no symptoms; average of 'on' and 'off' scores); the Beck Depression Inventory (BDI)-II total score (score ranges from 0 to 63, with a lower score indicating less severe symptoms); the Parkinson's Disease Quality-of-Life questionnaire (PDQ-39) subscale scores (scores range from 0 to 100, where 0 = no problems); the Epworth Sleepiness Scale (ESS) total score (score ranges from 0 to 24, with a lower score indicating less chance of dozing); and the Parkinson's Disease Sleep Scale (PDSS) total score (score ranges from 0 to 150, with a lower score indicating more severe symptoms).<sup>[6]</sup>

Additional outcome measures included the proportion of patients 'very much improved' or 'much improved', as assessed by the Clinical Global Impression-Improvement (CGI-I) scale; the proportion of patients requiring levodopa reinstatement following a reduction in levodopa dosage; the time to levodopa reinstatement; and the response rate (i.e. proportion of patients with a  $\geq 20\%$  reduction from baseline in both 'off' time and levodopa dosage).<sup>[6]</sup>

One *post hoc* analysis examined the effect of ropinirole prolonged release on 'off' time according to whether patients had BDI-II scores at baseline of  $\leq 19$  (indicating minimal/mild depression) or  $> 19$  (indicating moderate/severe depression),<sup>[15]</sup> and another *post hoc* analysis examined the effect of ropinirole prolonged release on UPDRS tremor, rigidity and bradykinesia scores.<sup>[17]</sup> A third *post hoc* analysis examined the link between the baseline UPDRS motor score and the change in daily 'off' time.<sup>[18]</sup>

Efficacy was assessed in the modified intent-to-treat (ITT) population (comprising 201 ropinirole prolonged-release recipients and 190 placebo recipients) using last observation carried forward (LOCF) analysis.<sup>[6]</sup>

#### Primary Endpoint

- Once-daily administration of ropinirole prolonged release was effective in the treatment of patients with advanced Parkinson's disease who experienced suboptimal control with levodopa.<sup>[6]</sup> After 24 weeks, the mean reduction from baseline in total daily 'off' time was significantly greater in patients

receiving ropinirole prolonged-release than in placebo recipients ( $-2.1$  vs  $-0.3$  hours). The adjusted mean treatment difference (AMTD) was  $-1.7$  hours (95% CI  $-2.34$ ,  $-1.09$ ;  $p < 0.0001$ ), which was considered clinically significant. Mean total daily 'off' time at baseline was 7.0 hours in both treatment groups.

- A significant between-group difference in the mean change from baseline in daily 'off' time was observed as early as 2 weeks after the start of therapy (AMTD for ropinirole prolonged release vs placebo of  $-0.7$  [95% CI  $-1.09$ ,  $-0.23$ ];  $p = 0.0029$ ), and was maintained throughout the rest of the trial.<sup>[6]</sup>

#### Secondary Endpoints

- Ropinirole prolonged release resulted in a significantly greater mean reduction in percentage 'off' time than placebo ( $-12.1\%$  vs  $-0.9\%$ ; AMTD  $-11.2\%$  [95% CI  $-15.13$ ,  $-7.21$ ];  $p < 0.0001$ ) at 24 weeks.<sup>[6]</sup>

- Ropinirole prolonged release improved 'on' time to a significantly greater extent than placebo.<sup>[6]</sup> After 24 weeks' therapy, significantly greater mean increases in daily 'on' time ( $1.6$  vs  $-0.1$  hours; AMTD 1.7 hours [95% CI 1.06, 2.33];  $p < 0.0001$ ), daily 'on' time without troublesome dyskinesias ( $1.6$  vs  $0.1$  hours; AMTD 1.5 [95% CI 0.85, 2.13];  $p < 0.0001$ ), the percentage of 'on' time ( $12.1\%$  vs  $1.0\%$ ; AMTD 11.1% [95% CI 7.17, 15.08],  $p < 0.0001$ ) and the percentage of 'on' time without troublesome dyskinesias ( $12.3\%$  vs  $2.7\%$ ; AMTD 9.7% [95% CI 5.67, 13.69];  $p < 0.0001$ ) occurred with ropinirole prolonged release versus placebo.

- A significant difference between ropinirole prolonged release and placebo in the hours of daily 'on' time without troublesome dyskinesias was seen as early as week 2, with an AMTD of 0.4 hours (95% CI 0.01, 0.88;  $p = 0.0444$ ).<sup>[16]</sup>

- The mean UPDRS motor score improved to a significantly greater extent with ropinirole prolonged release than with placebo after 24 weeks' therapy ( $-6.5$  vs  $-1.7$ ; AMTD  $-4.8$  [95% CI  $-6.56$ ,  $-2.98$ ];  $p < 0.0001$ ), as did the mean UPDRS ADL score ( $-3.5$  vs  $-0.9$ ; AMTD  $-2.6$  [95% CI  $-3.36$ ,  $-1.83$ ];  $p < 0.0001$ ).<sup>[6]</sup> A *post hoc* analysis revealed a significant ( $p = 0.0444$ ) interaction between the

baseline UPDRS motor score and treatment effect (daily 'off' time).<sup>[18]</sup> The magnitude of the difference between ropinirole prolonged-release and placebo recipients increased as the baseline UPDRS motor score increased.<sup>[18]</sup>

- On the PDQ-39, a significantly greater mean improvement with ropinirole prolonged release than with placebo was observed for scores on the mobility (-4.9 vs 1.9; AMTD -6.8 [95% CI -10.07, -3.53];  $p < 0.0001$ ), ADL (-5.4 vs 1.1; AMTD -6.5 [95% CI -9.71, -3.25];  $p < 0.0001$ ), emotional well-being (-4.3 vs -0.6; AMTD -3.7 [95% CI -6.68, -0.82];  $p = 0.0124$ ), stigma (-3.3 vs 1.2; AMTD -4.5 [95% CI -8.06, 0.87];  $p = 0.015$ ) and communication (-1.4 vs 2.4; AMTD -3.7 [95% CI -6.88, -0.61];  $p = 0.0193$ ) subscales, but not on the social support (-1.5 vs -0.3; AMTD -1.2 [95% CI -4.07, 1.77]), cognition (3.4 vs 2.9; AMTD 0.5 [95% CI -2.13, 3.09]) or bodily discomfort (-3.6 vs -1.5; AMTD -2.1 [95% CI -5.40, -1.26]) subscales.<sup>[6]</sup>

- Compared with placebo, ropinirole prolonged release significantly improved the mean BDI-II total score (-2.1 vs -0.5; AMTD -1.6 [95% CI -2.86, -0.34];  $p = 0.013$ ).<sup>[6]</sup> A *post hoc* analysis revealed that 'off' time was reduced to a significantly greater extent with ropinirole prolonged release than with placebo in patients with a BDI-II baseline score of  $\leq 19$  (AMTD -1.6;  $p = 0.0001$ ) and those with a baseline BDI-II score of  $> 19$  (AMTD -2.0;  $p < 0.0001$ ).<sup>[15]</sup>

- The mean PDSS total score improved from baseline to a significantly greater extent with ropinirole prolonged release than with placebo after 24 weeks' therapy (1.3 vs -3.3; AMTD 4.7 [95% CI 0.75, 8.57];  $p = 0.0196$ ), although there was no significant between-group difference in the mean change from baseline in the ESS total score (0.5 vs 0.2; AMTD 0.3 [95% CI -0.41, 1.09]).<sup>[6]</sup>

#### Additional Outcomes

- After 24 weeks' therapy, significantly more ropinirole prolonged-release than placebo recipients were 'very much improved' or 'much improved' on the CGI-I scale (42% vs 14%; odds ratio [OR] 4.4 [95% CI 2.63, 7.20];  $p < 0.001$ ).<sup>[6]</sup>

- In a *post hoc* analysis, significantly greater improvement with ropinirole prolonged release than with placebo was observed for the UPDRS tremor score (AMTD -0.9 [95% CI -1.3, -0.4];  $p = 0.0001$ ), the UPDRS rigidity score (AMTD -0.9 [95% CI -1.4, -0.4];  $p = 0.0003$ ) and the UPDRS bradykinesia score (AMTD -1.8 [95% CI -2.5, -1.0];  $p < 0.0001$ ).<sup>[17]</sup>

- During the study, the mean levodopa dosage decreased by 278 mg/day in ropinirole prolonged-release recipients and 164 mg/day in placebo recipients.<sup>[6]</sup> Levodopa dose reduction occurred in 95% of patients receiving ropinirole prolonged release and 92% of patients receiving placebo; reinstatement of levodopa following dose reduction was necessary in 7% and 28% of patients in the corresponding treatment groups (adjusted OR 0.2 [95% CI 0.09, 0.34];  $p < 0.0001$ ).

- Time to reinstatement analyses revealed that ropinirole prolonged-release recipients were approximately 5-fold less likely than placebo recipients to require levodopa reinstatement following dose reduction at any timepoint (adjusted hazard ratio 0.2; [95% CI 0.11, 0.37];  $p < 0.001$ ).<sup>[6]</sup>

- The response rate was significantly higher in patients receiving ropinirole prolonged release than in patients receiving placebo (52% vs 20%; OR 4.3 [95% CI 2.73, 6.78];  $p < 0.001$ ).<sup>[6]</sup>

#### Comparison with Ropinirole Immediate Release

The efficacy of ropinirole prolonged release was compared with that of ropinirole immediate release in patients with advanced Parkinson's disease in the randomized, double-blind, multicentre PREPARED trial. Results from the PREPARED trial are available as abstracts.<sup>[19-21]</sup>

Patients in the PREPARED trial had advanced Parkinson's disease that was not optimally controlled with levodopa.<sup>[19]</sup> They received ropinirole prolonged release 2-24 mg once daily ( $n = 177$ ) or ropinirole immediate release 0.75-24 mg/day ( $n = 173$ ) for 24 weeks; the immediate-release formulation was administered three times daily.<sup>[19]</sup> At week 24,

mean dosages of ropinirole prolonged release and immediate release were 18.6 and 10.4 mg/day.<sup>[19]</sup>

The primary endpoint was the proportion of patients who maintained a  $\geq 20\%$  reduction from baseline in 'off' time over two consecutive visits at week 24, assessed in the ITT population using LOCF analysis.<sup>[19]</sup> Secondary endpoints included the proportion of patients who were 'very much improved' or 'much improved' on the CGI-I scale, the mean change from baseline in UPDRS motor and ADL scores (assessed in the 'on' state) and the mean change from baseline in the levodopa dosage.<sup>[19,20]</sup> Additional outcomes included the proportion of patients who maintained a  $\geq 20\%$  reduction from baseline in 'off' time and the mean change from baseline in the levodopa dosage assessed in the per-protocol population in *post hoc* analyses.<sup>[21]</sup>

#### Primary Endpoint

- The prolonged-release formulation of ropinirole was more effective than the immediate-release formulation in patients with advanced Parkinson's disease that was suboptimally controlled by levodopa.<sup>[19]</sup> Significantly more ropinirole prolonged-release recipients than ropinirole immediate-release recipients maintained a  $\geq 20\%$  reduction from baseline in 'off' time at week 24 (64% [110 of 172 patients] vs 51% [85 of 168];  $p = 0.009$ ), with an adjusted OR of 1.8.<sup>[19]</sup>

#### Secondary Endpoints

- At week 24, significantly more ropinirole prolonged-release recipients than ropinirole immediate-release recipients were 'very much improved' or 'much improved' on the CGI-I scale (55% [95 of 173 patients] vs 43% [73 of 168]).<sup>[20]</sup>
- The UPDRS motor score improved to a significantly greater extent in patients receiving ropinirole prolonged release than in those receiving ropinirole immediate release at week 24 (AMTD  $-2.3$ ;  $p = 0.022$ ), with no significant between-group difference in the change in UPDRS ADL score.<sup>[19]</sup>
- At week 24, the levodopa dosage was reduced from baseline by a mean 162 mg in ropinirole prolonged-release recipients and 113 mg in ropinirole immediate-release recipients.<sup>[19]</sup>

#### Additional Outcomes

- *Post hoc* analysis in the per-protocol population revealed that significantly more ropinirole prolonged-release recipients than ropinirole immediate-release recipients maintained a  $\geq 20\%$  reduction from baseline in 'off' time at week 24 (60% [48 of 80 patients] vs 40% [35 of 87];  $p = 0.004$ ), with an adjusted OR of 2.8.<sup>[21]</sup> In the per-protocol population, the mean reduction in the levodopa dosage was 216 mg in ropinirole prolonged-release recipients and 118 mg in ropinirole immediate-release recipients, according to *post hoc* analysis.<sup>[21]</sup> Mean dosages of ropinirole prolonged release and immediate release were 20.4 and 10.8 mg/day in the per-protocol population.<sup>[21]</sup>

### 3. Tolerability

Most of the data concerning the tolerability of ropinirole prolonged release in patients with advanced Parkinson's disease suboptimally controlled by levodopa were obtained from the well designed, placebo-controlled, 24-week EASE-PD Adjunct trial (see section 2 for study details).<sup>[6]</sup> Only descriptive analyses were reported. Long-term, open-label tolerability studies are ongoing.

Additional data were obtained from a 2-year study in patients with Parkinson's disease (Hoehn and Yahr stage I–III) whose symptoms were not optimally controlled with a levodopa dosage of up to 600 mg/day.<sup>[22]</sup> In this randomized, double-blind, flexible-dose study, patients received ropinirole prolonged release 2–24 mg once daily ( $n = 105$ ) or levodopa/carbidopa 50–1000 mg/day ( $n = 104$ ); reduction of the baseline levodopa dosage was not permitted. The primary endpoint was the time to onset of dyskinesia. The study was terminated prematurely because of difficulty in recruiting sufficient patients who had been initially treated with levodopa rather than dopamine agonists<sup>[23]</sup> and is only available as an abstract.<sup>[22]</sup>

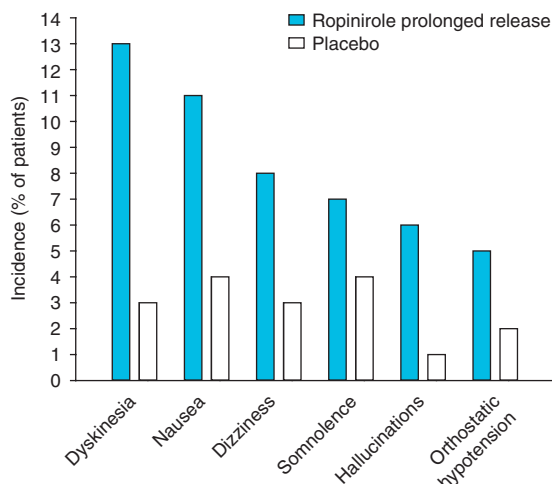
#### Comparison with Placebo

- Ropinirole prolonged release 6–24 mg once daily was generally well tolerated in patients with advanced Parkinson's disease suboptimally controlled

by levodopa.<sup>[6]</sup> Most adverse events were of mild or moderate severity and adverse events were generally typical of non-ergoline dopamine agonists.

- Adverse events occurred in 64% of patients receiving ropinirole prolonged release and in 55% of patients receiving placebo.<sup>[6]</sup> The most commonly occurring adverse events (reported by  $\geq 5\%$  of ropinirole prolonged-release recipients) included dyskinesia, nausea, dizziness, somnolence, hallucinations and orthostatic hypotension (figure 1). Dyskinesia and nausea tended to be reported during the first 4 weeks of the study (i.e. during the titration phase).

- Serious adverse events occurred in 4% of patients receiving ropinirole prolonged release and in 4% of patients receiving placebo.<sup>[6]</sup> Three ropinirole prolonged-release recipients experienced serious adverse events that were considered to be study-drug related (syncope in one patient and hallucinations in two patients). Study withdrawal because of adverse events occurred in 5% of ropinirole prolonged-release recipients and 5% of placebo recipients.



**Fig. 1.** Tolerability of ropinirole prolonged release in patients with advanced Parkinson's disease suboptimally controlled by levodopa. In the randomized, double-blind, placebo-controlled, multinational EASE-PD Adjunct trial, patients received once-daily ropinirole prolonged release (titrated to 6–24 mg/day) [n = 202] or placebo (n = 191) for 24 weeks.<sup>[6]</sup>

#### Comparison with Levodopa/Carbidopa

- Ropinirole prolonged release significantly ( $p < 0.001$ ) delayed the onset of dyskinesia compared with levodopa/carbidopa in patients with Parkinson's disease not optimally controlled with levodopa.<sup>[22]</sup> In the 2-year trial, dyskinesia occurred in 3% of patients receiving ropinirole prolonged release versus 17% of patients receiving levodopa/carbidopa.

#### 4. Dosage and Administration

EU prescribing information states that in patients with Parkinson's disease, oral ropinirole prolonged-release tablets should be initiated at a dosage of 2 mg once daily for 1 week, followed by 4 mg once daily from the second week.<sup>[10]</sup> If symptomatic control is not achieved, the daily dosage may be increased in 2 mg increments at intervals of at least 1 week up to a dosage of 8 mg once daily. If symptomatic control is still not achieved, the daily dosage may be increased in 2–4 mg increments at intervals of at least 2 weeks to a maximum daily dosage of 24 mg.<sup>[10]</sup>

US prescribing information states that in patients with Parkinson's disease, oral ropinirole prolonged-release tablets should be initiated at a dosage of 2 mg once daily for 1–2 weeks, followed by increases in 2 mg increments at intervals of at least 1 week up to a maximum daily dosage of 24 mg.<sup>[11]</sup>

Patients already receiving the immediate-release formulation of ropinirole can be switched to the prolonged-release formulation.<sup>[10,11]</sup> Patients previously receiving a total daily dosage of ropinirole immediate release 0.75–2.25, 3–4.5, 6, 7.5–9, 12, 15–18, 21 or 24 mg should be switched to a total daily dosage of ropinirole prolonged release 2, 4, 6, 8, 12, 16, 20 and 24 mg, respectively.<sup>[10,11]</sup>

In patients receiving ropinirole prolonged release as an adjunct to levodopa, it may be possible to gradually reduce the levodopa dosage.<sup>[10,11]</sup>

Local prescribing information should be consulted for detailed information concerning contraindications, warnings, precautions, drug interactions and use in special patient populations.

## 5. Ropinirole Prolonged Release: Current Status

Ropinirole prolonged release is approved in a number of EU countries for the treatment of Parkinson's disease as both initial monotherapy and in combination with levodopa when the effect of levodopa wears off or becomes inconsistent and fluctuations in the therapeutic effect occur, and in the US for the treatment of the signs and symptoms of idiopathic Parkinson's disease.

Ropinirole prolonged release is effective in the treatment of patients with advanced Parkinson's disease suboptimally controlled by levodopa, according to the results of two well designed, placebo- or active comparator-controlled, 24-week trials. In the placebo-controlled trial, ropinirole prolonged release 6–24 mg once daily reduced 'off' time to a significantly greater extent than placebo. In the active comparator-controlled trial, significantly more ropinirole prolonged-release recipients than ropinirole immediate-release recipients maintained a  $\geq 20\%$  reduction from baseline in 'off' time. Ropinirole prolonged release was generally well tolerated in patients with advanced Parkinson's disease.

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