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A randomized, fixed-dose, dose–response study of ropinirole prolonged release in advanced Parkinson’s disease

Theresa A Zesiewicz^{*,1}, Stephen Chriscoe^{†,2}, Theresa Jimenez^{‡,2}, James Upward³, Maria Davy³ & Susan VanMeter^{§,2}

Summary points

- Ropinirole prolonged release (PR) is approved for the treatment of Parkinson’s disease (PD) in the USA, the EU and many other countries, and allows once-daily dosing, simple dose titration and potentially earlier onset of efficacy in PD.
- This Phase IV, double-blind, placebo-controlled, dose-ranging, parallel-group, multi-center study characterized the dose–response and tolerability of fixed doses of ropinirole PR.
- Subjects with advanced PD were randomized to placebo or ropinirole PR 4, 8, 12, 16 or 24 mg once daily up-titrated for 13 weeks and maintained for 4 weeks.
- Of the 391 screened subjects, 352 were randomized and 294 (84%) completed the study.
- At maintenance period week 4, ropinirole PR 16 mg significantly reduced total awake ‘Off-time’ ($p = 0.027$) and ropinirole PR 8 mg demonstrated a trend for efficacy with a least squares mean difference from placebo similar to that of the ropinirole PR 16 mg group.
- At maintenance period week 4, ropinirole PR 8 mg increased absolute awake time spent ‘On’ without troublesome dyskinesia from baseline versus placebo ($p = 0.036$) and Unified Parkinson’s Disease Rating Scale motor scores were improved by all ropinirole PR doses versus placebo ($p = 0.005–0.016$).
- These results are consistent with previous studies in advanced PD, which demonstrated similar approximately 2-h improvements in ‘Off-time’ with flexible dose regimens of ropinirole.
- The safety profile of ropinirole PR in the current study is broadly consistent with the prescribing information and previous studies using flexible dose regimens, with no dose-related trends in adverse events observed and no new safety signals identified.

Aim: This Phase IV, double-blind, randomized, parallel-group study characterized the dose–response and tolerability of fixed doses of ropinirole prolonged release (PR) in subjects with advanced Parkinson’s disease. **Patients & methods:** Subjects receiving concomitant L-dopa received once-daily ropinirole PR 4, 8, 12, 16 or 24 mg, or placebo, up-titrated for 13 weeks, maintained for 4 weeks. **Results:** At maintenance period week 4, ropinirole PR significantly reduced total awake ‘Off-time’ (16 mg; $p = 0.027$); increased absolute awake time spent ‘On’ without troublesome dyskinesia from baseline versus placebo (8 mg; $p = 0.036$); improved Unified Parkinson’s Disease Rating Scale motor scores versus placebo (all doses; $p = 0.005–0.016$). Incidence of adverse events was similar between treatment groups; no dose-related trends were observed. **Conclusion:** Ropinirole PR (16 mg) reduced ‘Off-time’ with 8 mg the likely lowest maximally effective dose, and the safety profile was consistent with previous studies.

¹University of South Florida, Tampa, FL, USA

²GlaxoSmithKline, Research Triangle Park, Raleigh-Durham, NC, USA

³GlaxoSmithKline, Stevenage, Hertfordshire, UK

*Author for correspondence: Tel.: +1 813 974 5909; Fax: +1 813 974 8032; zesiewi@health.usf.edu

[†]Current affiliation, Chiltern International, Cary, NC, USA

[‡]Current affiliation, PAREXEL, Research Triangle Park, Raleigh-Durham, NC, USA

[§]Current affiliation, Mallinckrodt Pharmaceuticals, Ellicott City, MD, USA

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KEYWORDS

• advanced Parkinson's disease • dose–response • ropinirole • ropinirole prolonged release • total awake time 'Off'

Advanced Parkinson's disease (PD) is primarily treated with dopaminergic therapies, each requiring dose optimization to achieve an optimal balance between treatment responses and side effects [1]. Ropinirole, a nonergoline dopamine agonist, is used as a monotherapy in early PD and as an adjunct to levodopa (L-dopa) in advanced PD [2–5], and has been demonstrated to improve clinical symptoms [6,7]. In the long term, ropinirole has been demonstrated to delay the development of dyskinesia for up to 5 years compared with L-dopa [8,9].

The immediate release formulation of ropinirole is administered three-times daily and may require ≥ 13 up-titration steps to reach a maximum daily dose of 24 mg. Ropinirole prolonged release (PR) tablets are approved for the treatment of PD in the USA, the EU and many other countries [4,5]. The PR formulation has a dose range of 2–24 mg [4,5], allows once-daily dosing, has fewer titration steps and a potentially earlier onset of efficacy compared with the immediate release formulation [10,11].

Previous clinical trials with ropinirole in advanced PD have used flexible dosing regimens, which reflect clinical practice. In response to a regulatory agency request, this fixed-dose study was conducted to characterize the dose–response and tolerability of fixed doses of ropinirole PR as an adjunctive therapy to L-dopa in subjects with advanced PD.

Patients & methods

• Study design

This was a double-blind, fixed-dose, parallel-group study (NCT01494532; GSK identifier: ROP111569) of subjects from 41 centers across Argentina, Chile, Estonia, the Russian Federation, Slovakia, the Republic of Korea and the USA. Subjects were screened for 1–2 weeks and eligible subjects randomized 1:3:3:3:1:3 via an interactive voice recognition system to receive once-daily ropinirole PR 4, 8, 12, 16 or 24 mg, or placebo, respectively. This randomization ratio was chosen to provide 80% power for the primary end point comparisons between ropinirole PR 8, 12 and 16 mg, and placebo. The 4 and 24 mg ropinirole PR groups were not powered for statistical significance, but provided further information to determine the shape of the dose–response relationship. Ropinirole PR and placebo tablets were identical

in appearance. Following randomization, subjects entered a 13-week up-titration period (1–8 titration stages) to reach their target dose, followed by a 4-week maintenance period at this dose level. However, if poor tolerability was experienced, a reduction in L-dopa dose was permitted and was followed by ropinirole re-challenge or, if required, by ropinirole down-titration. Only one L-dopa adjustment and ropinirole re-challenge was permitted during each of the up-titration steps and maintenance period, extending these periods to a maximum of 21 and 7 weeks, respectively. A maximum of three L-dopa dose reductions was permitted. For each subject, the dose taken on the greatest number of days during the maintenance period was termed as the actual modal dose. Following the maintenance period, subjects entered a 1-week down-titration period, followed by a 1- to 2-week follow-up period. A stable L-dopa dose was maintained throughout the study unless tolerability issues required a dose reduction.

This study was conducted in accordance with the Declaration of Helsinki 2008 [12] and the International Conference on Harmonisation and Good Clinical Practice guidelines, and received approval from local ethics committees. Written informed consent was obtained from each subject prior to study participation.

• Subjects

Inclusion criteria were: male and nonpregnant/nonbreastfeeding women ≥ 30 years of age at screening; a diagnosis of idiopathic PD (modified Hoehn and Yahr criteria stages 2–4) demonstrating a lack of control with L-dopa (e.g., end-of-dose akinesia, simple 'On/Off' fluctuations); receiving a stable dose of L-dopa for ≥ 4 weeks prior to screening and ≥ 3 h awake 'Off' time per diary day at baseline. Exclusion criteria included an incapacitating peak dose or diphasic dyskinesia on their stable L-dopa dose; dopamine agonist treatment within 4 weeks of study randomization, physical or mental conditions that would preclude accurate assessment of safety or efficacy (including prior or current major psychosis, severe clinical dementia, severe dizziness or fainting, diagnosed impulse control disorder, suicidal thoughts or active suicidal plan or intent, current alcohol or drug dependence); clinically significant ECG or laboratory test abnormalities

at screening; a definite or suspected personal or family history of adverse reactions or hypersensitivity to ropinirole; any withdrawal, introduction or dose change of hormone replacement therapy and/or drugs known to inhibit or induce CYP450 CYP1A2 activity; use of investigational drugs from 30 days or five half-lives prior to enrollment or a personal history of melanoma.

• Prior & concomitant medications

Permitted medications included rasagiline, selegiline, amantadine, anticholinergics and catechol-*O*-methyltransferase inhibitors with stable doses for at least 4 weeks before screening; metoclopramide, domperidone and other peripherally acting anti-nausea medications were permitted during the up-titration period to treat peripheral dopaminergic symptoms, prophylactic use was not permitted. The following were not permitted during the study: monoamine oxidase A inhibitors and apomorphine within 2 weeks of study screening or deep brain stimulation.

• Outcomes & assessments

The primary efficacy end point was the change from baseline in total awake time spent ‘Off’ (defined as bradykinesia with/without tremor or rigidity) at week 4 of the maintenance period. Secondary efficacy end points, all assessed at week 4 of the maintenance period, included the seven-point Clinical Global Impression–Global Improvement (CGI-I) scale responder rate (defined as a score of 2 = ‘much improved’ or 1 = ‘very much improved’), the percentage of subjects with a ≥ 1 - or ≥ 2 -h reduction in baseline ‘Off-time’, and the change from baseline in percent awake time spent ‘On’ without troublesome dyskinesia, Unified PD Rating Scale (UPDRS) motor score in an ‘On’ state and total sleep time during the night hours of sleep (defined as 10 pm to 8 am). Safety assessments included adverse event (AE) monitoring, clinical laboratory tests, ECG, neurological and dermatological examinations, vital sign assessments and pregnancy tests. AEs of special interest

Figure 1. Subject disposition during the screening, allocation, follow-up and analysis periods.

ROP PR: Ropinirole prolonged release.

were monitored by the Questionnaire for Sudden Onset of Sleep (SOOS), Columbia Suicide Severity Rating Scale (C-SSRS) and Minnesota Impulse Disorders Interview (MIDI).

• Statistical analyses

The study was powered to detect a difference in the change from baseline in awake time 'Off' with ropinirole 8, 12 or 16 mg versus placebo. A sample size of 59 subjects per treatment group was required to detect a difference of 1.7 h (80% power, two-sided significance level of 5%, assuming a standard deviation of 3.25 h). The ropinirole PR 4 and 24 mg doses provided further information on the shape of the dose–response relationship but were not powered for the assessment of statistical significance.

The primary analysis was conducted on all subjects in the intent-to-treat (ITT) population (all randomized subjects who received at least one dose of study medication and had a baseline efficacy assessment and at least one respective postbaseline efficacy assessment) who had a nonmissing efficacy measurement during the maintenance period, using the observed cases (OC) data set. Data were analyzed according to randomized treatment and actual modal dose. A mixed-effect model repeated measures (MMRM) model was used, including terms for baseline total awake time 'Off', treatment, visit and treatment-by-visit interaction as fixed effects, regardless of their statistical significance. A hierarchical testing procedure was used to compare ropinirole doses with placebo for the primary end point. The step-down testing began with the 16 mg group, followed by 12, 8 and 4 mg. Inferential testing was stopped if a dose failed to reach statistical significance. The 24 mg dose was not included in the step-down testing since it was not powered for assessment of statistical significance.

If the data violated normality assumptions, prespecified nonparametric ranked analysis of covariance (ANCOVA) of the primary end point was conducted on all subjects from the ITT population who had a nonmissing efficacy observation during the maintenance period, using maintenance last observation carried forward (MLOCF) imputation for subjects entering but not completing the maintenance period, with data analyzed according to randomized treatment and actual modal dose.

Continuous secondary end points were analyzed as per the primary analysis. Dichotomous secondary efficacy variables were analyzed using

generalized estimating equations (GEE) on the OC data set for subjects with a nonmissing efficacy observation during the maintenance period. Analyses of secondary efficacy end points were not controlled for multiplicity.

The ITT population was used for all primary and secondary efficacy analyses. The safety population (all subjects who received at least one dose of study medication) was used for all safety analyses unless otherwise stated.

Results

• Study population & subject disposition

Of the 391 screened subjects, 352 were randomized and 294 (84%) completed the study (**Figure 1**). In total, 297 subjects had a nonmissing efficacy measurement during the maintenance period, 71–87% and 91% of those who received ropinirole PR and placebo, respectively, maintained a stable L-dopa dose. The most common reason for withdrawal in all groups was AEs and the majority of withdrawals were during the up-titration period. Overall, subject demographics and baseline characteristics were similar between treatment groups, although a higher proportion of subjects in the ropinirole 12 mg group had Hoehn and Yahr stages 3 and 4 (69%) compared with other ropinirole doses (40–56%) (**Table 1**). In the safety population, 80–100% of subjects in any ropinirole treatment group received the ropinirole PR actual modal dose to which they had been randomly assigned.

• Efficacy

Efficacy results are presented by randomized dose during the maintenance period unless otherwise stated.

Total awake 'Off-time' at week 4

Ropinirole PR 16 mg demonstrated a significant improvement from baseline in awake 'Off-time' at week 4 versus placebo ($p = 0.027$) in the primary analysis (MMRM model) (**Figure 2**). The ropinirole PR 12 mg ($p = 0.287$) dose was not significantly different compared with placebo and so inferential testing was stopped, and lower doses were not formally tested. However, there was a trend for efficacy observed in the ropinirole PR 8 mg group, which had a least squares (LS) mean difference from placebo similar to that of the ropinirole PR 16 mg group (**Table 2**).

As data were not normally distributed, planned nonparametric ANCOVA analysis was performed. Results from this analysis were consistent with the primary analysis (**Table 2**). Analysis of the primary

Table 1. Summary of subject demographics and baseline characteristics.

Characteristics	Placebo	ROP PR 4 mg	ROP PR 8 mg	ROP PR 12 mg	ROP PR 16 mg	ROP PR 24 mg	Total
Safety population							
n	74	25	76	75	75	25	350
Age (years):							
– Mean (SD)	63.8 (10.02)	66.5 (7.45)	65.6 (9.19)	65.2 (9.62)	63.8 (9.15)	66.9 (7.94)	64.9 (9.26)
– Min, max	35, 85	49, 80	43, 83	41, 84	44, 82	51, 80	35, 85
Gender, n (%):							
– Female	41 (55)	12 (48)	33 (43)	33 (44)	37 (49)	10 (40)	166 (47)
Race, n (%):							
– African–American/African heritage	2 (3)	0	0	0	0	0	2 (<1)
– American–Indian or Alaskan native	0	0	0	1 (1)	0	0	1 (<1)
– Asian	3 (4)	4 (16)	3 (4)	6 (8)	7 (9)	1 (4)	24 (7)
– White	69 (93)	21 (84)	73 (96)	68 (91)	68 (91)	24 (96)	323 (92)
Ethnicity, n (%):							
– Hispanic/Latino	25 (34)	9 (36)	24 (32)	22 (29)	16 (21)	9 (36)	105 (30)
Modified Hoehn and Yahr stage (during ‘Off’ time), n (%):							
– 1	0	0	0	0	0	0	–
– 1.5	0	0	1 (1)	0	0	0	–
– 2	6 (8)	2 (8)	8 (11)	4 (5)	11 (15)	1 (4)	–
– 2.5	33 (45)	13 (52)	26 (34)	19 (25)	22 (29)	13 (52)	–
– 3	25 (34)	8 (32)	36 (47)	45 (60)	36 (48)	8 (32)	–
– 4	10 (14)	2 (8)	5 (7)	7 (9)	6 (8)	3 (12)	–
Prior PD medication (used in ≥5% of patients), n (%):							
– L-dopa	74 (100)	25 (100)	76 (100)	75 (100)	75 (100)	25 (100)	–
– Carbidopa	52 (70)	16 (64)	53 (70)	48 (64)	54 (72)	12 (48)	–
– Benserazide	0	2 (8)	1 (1)	4 (5)	2 (3)	3 (12)	–
– Benserazide hydrochloride	25 (34)	8 (32)	25 (33)	31 (41)	26 (35)	12 (48)	–
– Piribedil	7 (9)	8 (32)	17 (22)	17 (23)	10 (13)	9 (36)	–
– Pramipexole	7 (9)	0	5 (7)	6 (8)	3 (4)	0	–
– Pramipexole dihydrochloride	10 (14)	2 (8)	14 (18)	14 (19)	14 (19)	5 (20)	–
– Amantidine	10 (14)	2 (8)	6 (8)	6 (8)	6 (8)	0	–
– Amantidine hydrochloride	1 (1)	0	1 (1)	1 (1)	2 (3)	0	–
– Amantidine sulfate	8 (11)	3 (12)	6 (8)	8 (11)	15 (20)	1 (4)	–
– Entacapone	6 (8)	3 (12)	7 (9)	5 (7)	9 (12)	2 (8)	–
– Rasagiline	3 (4)	2 (8)	4 (5)	2 (3)	2 (3)	0	–
– Rasagiline mesilate	7 (9)	1 (4)	9 (12)	5 (7)	4 (5)	0	–
– Trihexyphenidyl	2 (3)	0	2 (3)	5 (7)	3 (4)	2 (8)	–
– Trihexyphenidyl hydrochloride	0	1 (4)	0	1 (1)	2 (3)	0	–
– Biperiden	1 (1)	0	0	0	4 (5)	0	–
ITT population							
n	73	25	76	73	75	25	
Baseline total awake time ‘Off’ (h):							
– n	65	21	60	61	65	25	–
– Mean (SD)	6.46 (2.11)	5.84 (1.96)	5.98 (2.24)	6.47 (2.37)	5.60 (1.80)	6.29 (2.29)	–
Baseline percentage awake time spent ‘Off’ (%):							
– n	65	21	60	61	65	25	–
– Mean (SD)	41.7 (13.80)	36.9 (11.39)	38.5 (13.01)	41.3 (14.53)	36.5 (11.74)	40.1 (14.21)	–

ITT: Intent-to-treat; PD: Parkinson's disease; ROP PR: Ropinirole prolonged release; SD: Standard deviation; UPDRS: Unified Parkinson's Disease Rating Scale.

Table 1. Summary of subject demographics and baseline characteristics (cont.).

Characteristics	Placebo	ROP PR 4 mg	ROP PR 8 mg	ROP PR 12 mg	ROP PR 16 mg	ROP PR 24 mg	Total
<i>ITT population (cont.)</i>							
Baseline absolute awake time 'On' without troublesome dyskinesia (h):							
– n	65	21	60	61	65	25	–
– Mean (SD)	8.9 (2.60)	9.8 (1.98)	9.4 (2.35)	9.1 (2.53)	9.4 (2.61)	9.4 (2.48)	–
Baseline UPDRS motor score with subjects in an 'On' state:							
– n	64	21	59	60	65	24	–
– Mean (SD)	31.7 (12.30)	28.9 (10.74)	29.4 (11.36)	30.0 (12.71)	28.9 (11.58)	27.2 (12.03)	–
Baseline total sleep time during the nighttime hours of sleep (h):							
– n	65	21	60	61	65	25	–
– Mean (SD)	7.8 (1.27)	7.7 (1.17)	7.9 (1.24)	7.7 (1.23)	8.0 (1.14)	7.8 (1.4)	–

ITT: Intent-to-treat; PD: Parkinson's disease; ROP PR: Ropinirole prolonged release; SD: Standard deviation; UPDRS: Unified Parkinson's Disease Rating Scale.

end point by actual modal dose showed significant reductions from baseline in total awake 'Off-time' observed with ropinirole PR 16 mg ($p = 0.039$) and 6–8 mg doses ($p = 0.014$) (Table 2).

At week 4 of the maintenance period, there was no significant difference between any ropinirole dose and placebo in the proportion of responders on the CGI-I scale (subjects with scores of 'much improved' and 'very much improved') using the GEE model (Table 3). However, the proportion of responders (LS mean rate) increased with increasing dose from 28% in the ropinirole PR 4 mg group to 56% for the ropinirole 24 mg group, compared with 36% in the placebo group (Table 3).

At week 4 of the maintenance period, the decrease from baseline in the percentage of awake time spent 'Off' was significantly greater with ropinirole PR 8 mg ($p = 0.025$) and 16 mg ($p = 0.039$) versus placebo (MMRM model) (Table 3). However, the proportion of subjects with a ≥ 1 - or ≥ 2 -h reduction in baseline 'Off-time' was not statistically significantly different between any ropinirole PR dose and placebo (GEE model) (Table 3). Ropinirole PR 8 mg treatment resulted in significantly greater LS mean changes from baseline in absolute awake time spent 'On' without troublesome dyskinesia at week 4 versus placebo ($p = 0.036$) (Table 3). The 16 mg dose did not reach significance ($p = 0.089$) (Table 3).

UPDRS motor scores for subjects in an 'On' state were significantly changed from baseline at week 4 by all ropinirole PR doses (p -value = 0.005–0.016) versus placebo (Table 3). There was no statistically significant difference in total sleep time during the night hours of sleep

(defined as 10 pm to 8 am) with any dose of ropinirole PR versus placebo at week 4 of the maintenance period (Table 3).

• Safety

During the study, 53% of subjects receiving ropinirole PR compared with 46% receiving placebo reported one or more AE (Table 4). The most frequently reported AEs among subjects randomized to any dose of ropinirole PR were somnolence (8%), nausea (8%), dyskinesia (7%) and dizziness (6%). The frequency of AEs was highest in the up-titration period with 46% of subjects receiving ropinirole PR reporting AEs, compared with 13% during the maintenance phase and 10% during down-titration. Similarly, the frequency of AEs in the placebo group was highest in the up-titration period (39%) (Table 4). The majority of AEs were judged to be of mild or moderate intensity.

In total, 20 (7%) subjects randomized to ropinirole PR versus three (4%) subjects to placebo withdrew from the study due to an AE. Of the subjects treated with ropinirole PR, one (4%) subject was randomized to 4 mg, seven (9%) subjects to 8 mg, six (8%) subjects to 12 mg, six (8%) subjects to 16 mg and no subjects to 24 mg. All AEs leading to withdrawal, emerged during the up-titration period. Most subjects who withdrew, did not achieve their randomized dose target. Hallucination was the most frequent AE leading to discontinuation in a total of five subjects (ropinirole PR 4 mg [$n = 1$]; 8 mg [$n = 1$]; 12 mg [$n = 3$]).

Serious AEs (SAEs) were reported in four subjects, all during up-titration (rectal hemorrhage,

hernia, severe impulsive behavior and gastric adenocarcinoma, all $n = 1$). The latter two subjects were withdrawn from study but only the incidence of impulsive behavior was considered treatment related. This subject's randomized ropinirole PR dose was 8 mg (actual dose 8 mg). No fatal SAEs were reported.

Overall, hematology, clinical chemistry, urinalysis, ECG, dermatological and neurological examinations were similar between treatments groups, and no pregnancies were reported. An orthostatic fall in systolic blood pressure (BP) ≥ 20 mmHg was most frequently reported during the up-titration period, in 9 and 12% of subjects treated with ropinirole PR and placebo, respectively. In one subject who was treated with placebo, a systolic BP decrease of ≥ 40 mmHg was reported. During the maintenance period, an orthostatic systolic BP decrease of ≥ 20 mmHg was reported by 5 and 6% of subjects randomized to any dose of ropinirole PR and placebo, respectively, and no subjects had an orthostatic systolic BP decrease of ≥ 40 mmHg.

In total, ten (4%) and two (3%) subjects randomized to any ropinirole PR dose or placebo,

respectively, reported at least one AE of SOOS. No dose-related trend was found, with an SOOS AE reported in two subjects randomized to ropinirole PR 4 mg, four to ropinirole PR 8 mg, three to ropinirole PR 12 mg, one to ropinirole PR 16 mg and none to ropinirole PR 24 mg. During the up-titration period, 11 SOOS events were reported in subjects randomized to ropinirole PR (sleepiness or drowsiness preceded five events) and two events were reported for placebo. During the maintenance period, two SOOS events were reported, one each in the ropinirole PR 8 and 12 mg groups. No events were experienced during the down-titration period.

There was no clear difference in suicidal ideation assessed by C-SSRS between treatment groups: ropinirole PR 4 (4%), 8 (3%), 12 (1%), 16 (1%) and 24 mg (4%), and placebo (3%). One (1%) subject (ropinirole PR 8 mg, receiving 2–4 mg at the time of the event) reported two possible suicidality related AEs. An additional AE of suicidal ideation was identified in one (1%) subject randomized to ropinirole PR 16 mg (receiving 12 mg). One subject (randomized to

Figure 2. Change from baseline in total awake time ‘Off’ at week 4 of the maintenance period – mixed-effect model for repeated measures – observed cases data set – intent-to-treat population (all subjects with a nonmissing efficacy observation during the maintenance period and by randomized treatment). Numerical values represent the least squares means; the ROP PR 4 and 24 mg doses were not statistically tested; x-axis group numbers represent the number of patients in each treatment group at week 4 of the maintenance period.

[†]Statistically significant compared with placebo.

ROP PR: Ropinirole prolonged release.

Table 2. Change from baseline in total awake time 'Off' at week 4 of the maintenance period (intent-to-treat population, subjects with a nonmissing efficacy observation during the maintenance period).

End point	Randomized dose					
	Placebo (n = 73)	ROP PR 4 mg (n = 25)	ROP PR 8 mg (n = 76)	ROP PR 12 mg (n = 73)	ROP PR 16 mg (n = 75)	ROP PR 24 mg (n = 25)
Change (maintenance week 4):						
– n	65	21	59	60	63	25
– Mean	-2.05	-1.92	-2.85	-2.50	-2.52	-2.44
MMRM model [†] :						
– LS mean (95% CI)	-1.91 (-2.46, -1.35)	-2.04 (-3.02, -1.06)	-2.92 (-3.50, -2.34)	-2.34 (-2.91, -1.76)	-2.80 (-3.36, -2.24)	-2.37 (-3.26, -1.47)
– SE	(0.28)	(0.50)	(0.29)	(0.29)	(0.28)	(0.45)
– 95% CI for the difference [‡]	–	(-1.26, 0.99)	(-1.82, -0.21)	(-1.23, 0.37)	(-1.68, -0.10)	(-1.51, 0.59)
– p-value	–	0.814	0.013	0.287	0.027	0.390
ANCOVA model [§] :						
– LS mean (95% CI)	-1.90 (-2.45, -1.34)	-2.05 (-3.02, -1.07)	-2.92 (-3.50, -2.35)	-2.35 (-2.93, -1.78)	-2.80 (-3.36, -2.25)	-2.36 (-3.26, -1.47)
– SE	(0.28)	(0.50)	(0.29)	(0.29)	(0.28)	(0.45)
– 95% CI for the difference [‡]	–	(-1.27, 0.98)	(-1.83, -0.22)	(-1.25, 0.34)	(-1.70, -0.12)	(-1.52, 0.59)
– p-value	–	0.795	0.012	0.261	0.025	0.386
Nonparametric rank ANCOVA model [¶] :						
– p-value	–	0.844	0.030	0.437	0.034	0.808
End point	Actual modal dose					
	Placebo (n = 75)	ROP PR 2–4 mg (n = 36)	ROP PR 6–8 mg (n = 84)	ROP PR 12 mg (n = 70)	ROP PR 16mg (n = 60)	ROP PR 20–24 mg (n = 22)
MMRM model [†] :						
– n	65	21	66	64	59	22
– LS mean (95% CI)	-1.91 (-2.46, -1.35)	-2.04 (-3.02, -1.06)	-2.89 (-3.44, -2.34)	-2.40 (-2.96, -1.84)	-2.76 (-3.34, -2.17)	-2.36 (-3.32, -1.41)
– SE	0.28	0.50	0.28	0.29	0.30	0.49
– 95% CI for the difference [‡]	–	(-1.26, 0.99)	(-1.77, -0.20)	(-1.28, 0.30)	(-1.66, -0.04)	(-1.56, 0.65)
– p-value	–	0.818	0.014	0.223	0.039	0.418
†MMRM model by randomized treatment, observed cases data with all subjects with a nonmissing efficacy observation during the maintenance period (intent-to-treatpopulation). ‡95% CI for the difference in LS means between each ROP PR group and placebo. §ANCOVA model, maintenance last observation carried forward; data with all subjects with a nonmissing efficacy observation during the maintenance period (intent-to-treat population). ¶Nonparametric rank ANCOVA model, maintenance last observation carried forward; data with all subjects with a nonmissing efficacy observation during the maintenance period (intent-to-treatpopulation). †MMRM model observed data with all subjects with a nonmissing efficacy observation during the maintenance period by actual modal dose. ‡Least squares; MMRM: Mixed-effect model repeated measures; ROP PR: Ropinrole prolonged release; SE: Standard error.						

[†]MMRM model by randomized treatment; observed cases data with all subjects with a nonmissing efficacy observation during the maintenance period (intent-to-treat population).

[‡]95% CI for the difference in LS means between each ROP PR group and placebo.

[§]ANCOVA model; maintenance last observation carried forward; data with all subjects with a nonmissing efficacy observation during the maintenance period (intent-to-treat population).

[¶]Nonparametric rank ANCOVA model; maintenance last observation carried forward; data with all subjects with a nonmissing efficacy observation during the maintenance period (intent-to-treat population).

^{††}MMRM model observed data with all subjects with a nonmissing efficacy observation during the maintenance period by actual modal dose.

ANCOVA: Analysis of covariance; LS: Least squares; MMRM: Mixed-effect model repeated measures; ROP PR: Ropinirole prolonged release; SE: Standard error.

Table 3. Secondary outcomes at week 4 of the maintenance period by randomized dose (intent-to-treat population, subjects with a nonmissing efficacy observation during the maintenance period).

	Randomized dose					
	Placebo (n = 73)	ROP PR 4 mg (n = 25)	ROP PR 8 mg (n = 76)	ROP PR 12 mg (n = 73)	ROP PR 16 mg (n = 75)	ROP PR 24 mg (n = 25)
CGI-I responders (GEE model) [†] :						
– n (%)	26 (36)	7 (28)	30 (39)	31 (42)	35 (47)	14 (56)
– LS mean rate (95% CI)	40.0 (28.9, 52.3)	33.3 (16.8, 55.3)	50 (37.6, 62.4)	52.4 (39.9, 64.6)	54.5 (42.3, 66.1)	56.0 (36.6, 73.7)
– SE	6.08	10.29	6.45	6.43	6.17	9.93
– p-value	–	0.586	0.262	0.164	0.100	0.174
Change from baseline in percentage of awake time spent ‘Off’ (MMRM model):						
– LS mean (95% CI)	-12.43 (-16.03, -8.84)	-11.60 (-17.93, -5.27)	-18.41 (-22.16, -14.66)	-15.36 (-19.08, -11.64)	-17.81 (-21.43, -14.20)	-15.01 (-20.81, -9.22)
– SE	1.83	3.21	1.91	1.89	1.84	2.95
– 95% CI for the difference [‡]	–	(-6.45, 8.12)	(-11.17, -0.77)	(-8.10, 2.25)	(-10.49, -0.27)	(-9.40, 4.24)
– p-value	–	0.822	0.025	0.267	0.039	0.458
Subjects with ≥1-h reduction in baseline ‘Off-time’ (GEE model):						
– n (%)	47 (64)	14 (56)	46 (61)	44 (60)	50 (67)	20 (80)
– LS mean rate (95% CI)	72.1 (59.5, 82.0)	70.1 (48.6, 85.4)	80.6 (68.7, 88.7)	73.5 (59.6, 83.9)	83.2 (72.1, 90.5)	81.4 (62.3, 92.0)
– SE	5.79	9.72	5.10	6.28	4.63	7.52
– p-value	–	0.861	0.277	0.869	0.140	0.362
Subjects with ≥2-h reduction in baseline ‘Off-time’ (GEE model):						
– n (%)	36 (49)	9 (36)	38 (50)	33 (45)	36 (48)	13 (52)
– LS mean rate (95% CI)	53.7 (39.8, 67.1)	45.6 (26.8, 65.8)	68.2 (54.8, 79.2)	53.6 (39.3, 67.3)	63.2 (49.6, 75.0)	51.3 (30.1, 72.0)
– SE	7.14	10.48	6.33	7.35	6.61	11.41
– p-value	–	0.525	0.130	0.992	0.329	0.856
Change from baseline in absolute awake time spent ‘On’ without troublesome dyskinesia, hours (MMRM model):						
– LS mean (95% CI)	1.76 (1.15, 2.36)	1.21 (0.15, 2.27)	2.69 (2.06, 3.31)	2.16 (1.54, 2.78)	2.49 (1.89, 3.10)	2.24 (1.27, 3.21)
– SE	0.31	0.54	0.32	0.32	0.31	0.49
– 95% CI for the difference [‡]	–	-1.77, 0.67	0.06, 1.80	-0.46, 1.27	-0.11, 1.59	-0.66, 1.63
– p-value	–	0.376	0.036	0.362	0.089	0.403
Change from baseline in UPDRS motor score with subjects in an ‘On state’ (MMRM model):						
– LS mean (95% CI)	-4.75 (-6.78, -2.72)	-10.38 (-13.94, -6.82)	-8.43 (-10.54, -6.32)	-8.34 (-10.43, -6.24)	-8.86 (-10.88, -6.85)	-10.06 (-13.37, -6.75)
– SE	1.03	1.81	1.07	1.06	1.02	1.68
– 95% CI for the difference [‡]	–	-9.73, -1.53	-6.61, -0.75	-6.50, -0.67	-6.98, -1.25	-9.20, -1.42
– p-value	–	0.007	0.014	0.016	0.005	0.008

[†]Responder rate was defined as the proportion of subjects with a score of ‘much improved’ or ‘very much improved’ on the CGI-I scale.

[‡]95% CI for the difference in LS means between each ROP PR group and placebo.

CGI-I: Clinical Global Impression–Global Improvement; GEE: Generalized estimating equation; ITT: Intent-to-treat; LS: Least squares; MMRM: Mixed-effect model repeated measures; ROP PR: Ropinirole prolonged release; SE: Standard error; UPDRS: Unified Parkinson's Disease Rating Scale.

Table 3. Secondary outcomes at week 4 of the maintenance period by randomized dose (intent-to-treat population, subjects with a nonmissing efficacy observation during the maintenance period) (cont.).

	Randomized dose					
	Placebo (n = 73)	ROP PR 4 mg (n = 25)	ROP PR 8 mg (n = 76)	ROP PR 12 mg (n = 73)	ROP PR 16 mg (n = 75)	ROP PR 24 mg (n = 25)
Percent change from baseline in total sleep time during the night time hours of sleep (MMRM model):						
– LS mean (95% CI)	3.67 (0.23, 7.11)	1.97 (-4.0, 8.02)	3.63 (0.04, 7.22)	2.47 (-1.09, 6.04)	0.54 (-2.93, 4.00)	1.54 (-4.00, 7.09)
– SE	1.75	3.07	1.83	1.81	1.76	2.82
– 95% CI for the difference*	–	-8.66, 5.26	-5.01, 4.93	-6.15, 3.75	-8.02, 1.75	-8.65, 4.39
– p-value	–	0.631	0.987	0.635	0.208	0.521

*Responder rate was defined as the proportion of subjects with a score of ‘much improved’ or ‘very much improved’ on the CGI-I scale.

*95% CI for the difference in LS means between each ROP PR group and placebo.

CGI-I: Clinical Global Impression–Global Improvement; GEE: Generalized estimating equation; ITT: Intent-to-treat; LS: Least squares;

MMRM: Mixed-effect model repeated measures; ROP PR: Ropinirole prolonged release; SE: Standard error; UPDRS: Unified Parkinson's Disease Rating Scale.

ropinirole PR 12 mg but receiving ropinirole PR 8 mg at the time of event) reported a positive score (pathological gambling) postbaseline for MIDI assessed impulse control during the titration period, leading to withdrawal. Additionally, another subject (randomized to and receiving ropinirole PR 8 mg) experienced an SAE of impulsive behavior leading to withdrawal.

Discussion

The primary analysis indicated that ropinirole PR 16 mg significantly improved total awake ‘Off-time’ from baseline at week 4 of the maintenance period versus placebo. Subsequent prespecified hierarchical testing of the 12 mg dose found no statistically significant improvement versus placebo in ‘Off-time’. This was potentially due to the higher proportion of patients with Hoehn and Yahr stages 3 and 4, indicating more severe PD in this group compared with other dose groups. The 8 mg dose was the lowest dose associated with efficacy, based on inspection of the LS means. The LS mean for this dose level was similar to those for the higher ropinirole PR dose groups, suggesting that this was also the lowest maximally effective dose. The 4 and 24 mg dose groups were not powered to demonstrate superiority versus placebo in this study.

These results were supported by actual modal dose and prespecified nonparametric ANCOVA analyses. These results are also consistent with previous studies in advanced PD, which demonstrated similar, approximately 2-h improvements in ‘Off-time’ with flexible dose regimens of ropinirole [7,10].

The results of the secondary efficacy end point analyses were generally consistent with those of the primary end point. The percentage awake ‘Off-time’ was decreased with ropinirole PR 8 and 16 mg compared with placebo. Absolute awake time spent ‘On’ without troublesome dyskinesia was increased; this may be considered surprising as the dose of L-dopa was not scheduled to be reduced during the study. Additionally, UPDRS motor scores were decreased with all doses of ropinirole PR versus placebo, suggesting improvements in motor impairments and disability. In contrast, the proportion of CGI-I responders, the proportion of subjects with a ≥ 1 or ≥ 2 -h reduction in ‘Off-time’ and total sleep time during the night hours of sleep were not significantly greater with ropinirole compared with placebo. However, the proportion of CGI-I responders did increase with increasing dose of ropinirole PR. Of note, the highest LS mean CGI-I responder rate was noted in the ropinirole PR 24 mg group, suggesting that some subjects may benefit from this dose. However, the 24 mg dose was not powered to demonstrate superiority versus placebo and a statistical difference was not demonstrated.

The potential benefit of higher ropinirole doses is supported by the results of a previous pharmacokinetic/pharmacodynamic analysis of flexible ropinirole dosing in advanced PD [13]. This study found that a mean dose of ropinirole PR 18.8 mg per day significantly improved the total awake time ‘Off’ at week 24 [13]. The pharmacokinetic/pharmacodynamic analysis in this study noted that both the awake time ‘Off’ and UPDRS motor scores showed no evidence

Table 4. Summary of most common adverse events reported in ≥5% of subjects in any treatment group: safety population.

Preferred term	Placebo, n (%)	ROP PR 4 mg, n (%)	ROP PR 8 mg, n (%)	ROP PR 12 mg, n (%)	ROP PR 16 mg, n (%)	ROP PR 24 mg, n (%)	Any ROP PR, n (%)
Whole study period:	74	25	76	75	75	25	276
– Any event	34 (46)	12 (48)	38 (50)	40 (53)	43 (57)	12 (48)	145 (53)
– Somnolence	4 (5)	1 (4)	4 (5)	9 (12)	8 (11)	0	22 (8)
– Dyskinesia	1 (1)	1 (4)	3 (4)	5 (7)	8 (11)	1 (4)	18 (7)
– Dizziness	2 (3)	2 (8)	3 (4)	6 (8)	4 (5)	1 (4)	16 (6)
– Headache	4 (5)	0	2 (3)	3 (4)	4 (5)	1 (4)	10 (4)
– SOOS	2 (3)	2 (8)	4 (5)	3 (4)	1 (1)	0	10 (4)
– Nausea	8 (11)	1 (4)	5 (7)	8 (11)	7 (9)	2 (8)	23 (8)
– Constipation	4 (5)	0	0	0	0	0	0
– Nasopharyngitis	1 (1)	0	2 (3)	2 (3)	0	2 (8)	6 (2)
– Insomnia	0	0	0	1 (1)	4 (5)	0	5 (2)
– Arthralgia	0	0	2 (3)	0	2 (3)	2 (8)	6 (2)
– Hypertension	1 (1)	2 (8)	1 (1)	1 (1)	3 (4)	2 (8)	9 (3)
– Fall	4 (5)	0	1 (1)	3 (4)	2 (3)	0	6 (2)
Up-titration period:	74	25	76	75	75	25	276
– Any event	29 (39)	12 (48)	31 (41)	32 (43)	42 (56)	11 (44)	128 (46)
– Somnolence	4 (5)	1 (4)	4 (5)	9 (12)	7 (9)	0	21 (8)
– Dyskinesia	1 (1)	1 (4)	3 (4)	5 (7)	7 (9)	1 (4)	17 (6)
– Dizziness	2 (3)	2 (8)	3 (4)	5 (7)	3 (4)	1 (4)	14 (5)
– Headache	4 (5)	0	1 (1)	1 (1)	4 (5)	1 (4)	7 (3)
– SOOS	1 (1)	2 (8)	3 (4)	2 (3)	1 (1)	0	8 (3)
– Nausea	7 (9)	1 (4)	5 (7)	8 (11)	6 (8)	2 (8)	22 (8)
– Constipation	4 (5)	0	0	0	0	0	0
– Insomnia	0	0	0	1 (1)	4 (5)	0	5 (2)
– Arthralgia	0	0	2 (3)	0	2 (3)	2 (8)	6 (2)
– Nasopharyngitis	1 (1)	0	2 (3)	2 (3)	0	2 (8)	6 (2)
– Hypertension	1 (1)	2 (8)	1 (1)	1 (1)	3 (4)	2 (8)	9 (3)
Maintenance period:	65	21	60	61	65	25	232
– Any event	5 (8)	1 (5)	7 (12)	10 (16)	10 (15)	2 (8)	30 (13)
– Influenza	1 (2)	1 (5)	0	0	1 (2)	0	2 (<1)
Down-titration period:	70	24	66	68	72	25	255
– Any event	8 (11)	2 (8)	5 (8)	11 (16)	5 (7)	2 (8)	25 (10)

ROP PR: Ropinirole prolonged release; SOOS: Sudden Onset of Sleep.

of a dose-dependent increase in response with increasing ropinirole exposure. However, logistic regression analysis found that the probability of being a responder for total awake time ‘Off’ (20% reduction from baseline) and UPDRS motor score responder (30% reduction in score from baseline) was increased at higher ropinirole exposure levels, in parallel with a possible reduction in L-dopa dose.

The safety profile of ropinirole PR in the current study is broadly consistent with the summary of product characteristics and previous studies using flexible dose regimens, with no dose-related trends in AEs observed and no new safety signals identified [4–5,7,10]. There were four nonfatal SAEs during the study (all ropinirole PR), one of which was considered related

to study medication (impulsive behavior). The incidence of orthostatic hypotension was low, with one subject reporting a systolic BP decrease ≥40 mmHg (placebo). The incidence of SOOS, an AE noted in the medication leaflet, was greater with ropinirole PR (4%) in this study than noted previously (<1%) [4,5]. This is possibly due to the use of a specific questionnaire to assess SOOS in the current study and consequently a greater awareness of this event compared with earlier studies. No clear dose–response relationship was observed. Impulse control disorders were uncommon, being reported in two subjects, both randomized to ropinirole.

The ropinirole PR 4 and 24 mg doses were not powered for assessing statistical significance

versus placebo, which limits the conclusions that can be drawn for these doses. The use of fixed randomized target doses may have also resulted in some subjects having a maintenance dose not optimal for their needs. Finally, the stipulation to maintain the same baseline dose of L-dopa throughout the study makes comparisons with previous studies difficult.

Conclusion

In conclusion, in this fixed-dose, dose-response study, hierarchical testing indicated that the 16 mg ropinirole PR dose was effective at reducing 'Off-time' and has an acceptable safety profile. Examination of LS means suggests that the 8 mg dose may be the lowest maximally effective dose. These findings are consistent with previous studies on ropinirole PR in subjects with advanced PD in which subjects were titrated to their individual optimum dose based on both efficacy and tolerability.

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Author contributions

S Chriscoe, T Jimenez and S VanMeter contributed to the study concept and design. TA Zesiewicz was involved in data acquisition. All authors participated in data analysis and interpretation, were involved in preparation and review of the manuscript, and approved the final version prior to submission.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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