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A fixed-dose, dose–response study of ropinirole prolonged release in early stage Parkinson's disease

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

Summary points

- A prolonged release (PR) formulation of ropinirole was developed to allow once-daily dosing, simple dose titration and potentially early onset of efficacy in Parkinson's disease (PD).
- This Phase IV, double-blind, placebo-controlled, dose-ranging, parallel-group multi-center study aimed to characterize the dose–response and tolerability of fixed doses of ropinirole PR.
- Subjects with early PD were randomized to placebo or ropinirole PR 2, 4, 8, 12 or 24 mg once daily up-titrated for 13 weeks and maintained for 4 weeks.
- In total, 229 subjects were screened, of whom 186 entered the study; 154 (83%) of these completed the study.
- The primary end point (change from baseline in Unified Parkinson's Disease Rating Scale [UPDRS] motor score) was not met, but ropinirole PR 8 and 12 mg showed a greater numerical reduction in UPDRS motor score than placebo ($p = 0.091$ and $p = 0.124$, respectively).
- In a prespecified nonparametric analysis of covariance (ANCOVA), ropinirole PR 12 and 8 mg showed significantly ($p = 0.047$) and numerically ($p = 0.060$) greater changes in UPDRS motor score, respectively.
- Nonparametric ANCOVA by actual modal dose showed significant effects of 6–8 mg and 12–16 mg doses on UPDRS motor score.
- Significantly greater improvements in UPDRS score (parts II and III combined), total UPDRS score, percentage of UPDRS responders and percentage of Clinical Global Impression–Global Improvement responders were seen for ropinirole PR 12 mg versus placebo.
- The safety profile was consistent with the published prescribing information and with that previously described with the flexible dosing regimen for ropinirole PR in early PD.
- Results from the first fixed-dose, dose–response study conducted with ropinirole PR suggest the 8 and 12 mg doses were effective in treating the motor symptoms of early PD.

Aim: This Phase IV, double-blind, randomized, parallel-group study characterized the dose–response and tolerability of fixed doses of ropinirole prolonged release (PR).

Patients & methods: Subjects with early Parkinson's disease (PD) received placebo or ropinirole PR 2, 4, 8, 12 or 24 mg once daily, up-titrated to randomized or highest tolerated dose, maintained for 4 weeks. **Results:** The primary end point was not met (change from baseline in Unified PD Rating Scale motor score). However, because the data were not normally distributed, prespecified nonparametric analysis of covariance suggested ropinirole PR (8 and 12 mg/day) was effective in treating motor symptoms. The adverse event profile was consistent with the known safety profile of ropinirole PR.

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; tzesiewi@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

Results (cont.): There was no impulse control disorder reported. Although a higher than previously reported rate of sudden onset of sleep events was reported, these were not dose dependent and were likely to have been influenced by the method of data collection. **Conclusion:** The adverse event profile was consistent with the known safety profile of ropinirole PR and ropinirole PR (8 or 12 mg/day) improved motor symptoms of early PD.

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KEYWORDS

• dose–response
• Parkinson’s disease
• ropinirole • ropinirole prolonged release • Unified Parkinson’s Disease Rating Scale

Ropinirole is a nonergoline dopamine agonist developed for the treatment of early and advanced Parkinson’s disease (PD) [1–3]. The immediate release formulation is registered in >60 countries as monotherapy for early PD and as adjunctive therapy to levodopa (L-dopa) for advanced PD. The efficacy and safety profile of ropinirole in early PD has been well characterized. Most adverse events (AEs) associated with treatment are related to peripheral dopaminergic activity [4]. Monotherapy may delay the onset of dyskinesia by 5–10 years [5,6].

Ropinirole immediate release is administered three times daily, with dose titration required to reach a dose that balances efficacy and tolerability. To achieve the maximum daily dose of 24 mg, ≥13 titration steps may be required. A prolonged release (PR) formulation was developed with a dose range of 2–24 mg/day, allowing once-daily dosing, a simpler dose-titration regimen and potentially an earlier onset of efficacy [7,8]. Ropinirole PR has been shown to be efficacious as monotherapy in patients with early stage PD (Hoehn and Yahr stages I–III) [8] and as adjunctive treatment to L-dopa in patients with advanced PD (Hoehn and Yahr stages II–IV) [9]. The formulation was first approved for use in PD in 2008, by both the US FDA [3] and the EMA [10].

Phase III pivotal trials for both ropinirole immediate release and ropinirole PR utilized flexible dosing, enabling a balance to be achieved between upward titration to effect and tolerability [8,9]. However, while flexible dosing may mirror clinical practice, it does not provide the information needed for a dose–response analysis. The objectives of this study were to characterize the dose–response and tolerability of fixed doses of ropinirole PR as monotherapy in subjects with early PD.

Patients & methods

• Study design

This Phase IV study was a double-blind, fixed-dose, placebo-controlled, dose-ranging,

parallel-group design (NCT01485172; GSK study identifier: ROP111662). Subjects were enrolled at 28 centers across the Russian Federation, the USA, Estonia, Republic of Korea and Slovakia. Following an initial screening period of 1–2 weeks, subjects were randomized via an Interactive Voice Recognition System 3:1:3:3:3:1 to receive placebo or ropinirole PR at fixed ‘target doses’ of 2, 4, 8, 12 or 24 mg once daily. Following randomization, subjects entered the up-titration period (13–17 weeks), passing through 1–8 titration stages to reach their target randomized dose or highest tolerated dose. The up-titration period was followed by a 4–7-week maintenance period, during which subjects received their target or highest tolerated dose for 4 weeks. If poor tolerability was experienced during the titration or maintenance period, back-titration was permitted before a re-challenge, but only one re-challenge was permitted in each of the up-titration and maintenance periods. The dose taken on the greatest number of days per subject during the maintenance period was termed as the actual modal dose. After the maintenance period, subjects entered a down-titration period of 1 week, followed by a follow-up period lasting 1–2 weeks after the last dose was administered. The study ran for a maximum of 29 weeks per subject.

The study received ethical approval and was conducted in accordance with the Declaration of Helsinki 2008 and the International Conference on Harmonisation and Good Clinical Practice guidelines. All subjects provided written informed consent prior to study participation.

• Subjects

Subjects must have had a diagnosis of idiopathic PD (modified Hoehn and Yahr criteria stages I–III), must have been ≥30 years old at screening and must have had a baseline Unified Parkinson’s Disease Rating Scale (UPDRS) motor score ≥10. Subjects were excluded if dopaminergic therapy was not warranted at

screening, if they had 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), if they were withdrawing, inducing or changing dose of hormone replacement therapy and/or drugs known to inhibit or induce CYP450 CYP1A2 activity, or were pregnant or breastfeeding.

• Prior & concomitant medications

Metoclopramide, domperidone (in countries where it was approved) and other peripherally acting anti-nausea medications were permitted during the up-titration period to treat the symptoms of AEs caused by peripheral dopaminergic effects. The following were not permitted during the study: L-dopa medication (3 months prior use of moderate-to-low doses was permitted if discontinued 4 weeks before screening), dopamine agonists (6 months prior use was permitted if discontinued 4 weeks before screening), monoamine oxidase A/B inhibitors, apomorphine and introduction of catechol *O*-methyltransferase inhibitors, neuroleptics or deep brain stimulation.

• Outcomes & assessments

The primary efficacy end point was the change from baseline in UPDRS part III (motor score) at week 4 of the maintenance period. UPDRS scores were clinician-rated and evaluated using a combination of data collected by interview and examination of the subject. The UPDRS part III motor score was performed with the subject in the ‘On’ state. Secondary efficacy end points included UPDRS responders (i.e., subjects with $\geq 30\%$ reduction in baseline UPDRS motor score), change from baseline in UPDRS parts II and III combined, UPDRS activities of daily living, total UPDRS score (parts I–III), UPDRS part I (mentation), Clinical Global Impression–Global Improvement (CGI-I) scale responders (i.e., subjects with a score of much improved or very much improved) and percentage of subjects withdrawn from the study owing to lack of efficacy. All secondary end points measuring a change from baseline were evaluated at week 4 of the maintenance period.

Safety assessments included monitoring of AEs, clinical laboratory tests, vital signs, ECG, physical, neurological, dermatological examinations and pregnancy testing. AEs of

special interest included the Minnesota Impulse Disorders Interview (MIDI), Questionnaire for Sudden Onset Of sleep (SOOS) and the Columbia Suicide Severity Rating Scale (C-SSRS). The C-SSRS was administered via touch-tone telephone and the report was reviewed with the subject before leaving the study site.

• Statistical analyses

The study was powered to detect a difference in change from baseline UPDRS motor score between the placebo and ropinirole PR 4, 8 and 12 mg groups, respectively. A sample size of 32 subjects per group provided 80% power to detect a difference of 5 points, assuming a standard deviation of 7 (two-sided significance level of 5%). The ropinirole PR 2 and 24 mg doses were not powered for significance, but provided further information on the shape of the dose–response relationship.

The primary analysis was conducted on all subjects with a nonmissing efficacy observation during the maintenance period, using the observed cases dataset in the intent-to-treat (ITT) population. Data were analyzed according to randomized treatment. A mixed-effect model repeated measures (MMRM) model was used, including terms for baseline UPDRS motor score, treatment, visit and treatment-by-visit interaction as fixed effects, regardless of their statistical significance. Prespecified additional analysis (nonparametric ranked analysis of covariance [ANCOVA]) of the primary end point was conducted on all subjects with a nonmissing efficacy observation during the maintenance period, using last maintenance observation carried forward imputation for subjects entering but not completing the maintenance period.

Unless otherwise stated, responder rates were analyzed using the generalized estimating equations model, and UPDRS secondary end points were analyzed using the MMRM model (both models used observed case data for all subjects with a nonmissing efficacy observation during the maintenance period, ITT population by randomized treatment).

The safety population included all subjects who received at least one dose of study medication. The ITT population included all subjects in the safety population who had a baseline and at least one postbaseline efficacy assessment and was used for all primary and secondary efficacy analyses.

Results

• Study population

In total, 229 subjects were screened, of whom 186 entered the study; 154 (83%) of these completed the study while 32 (17%) withdrew (Figure 1). The proportion who withdrew was higher in the ropinirole PR 24 mg group (31%) than other groups (18, 8, 17, 20 and 13% for the placebo, 2, 4, 8 and 12 mg groups, respectively). The most common reasons for withdrawal overall were AEs, protocol deviation and withdrawal of consent. The majority of the withdrawals due to AEs occurred during the up-titration period.

Demographic and baseline characteristics were similar among the treatment groups, although there was a higher proportion of Asian and female subjects in the ropinirole PR 8 mg group (Table 1).

• Efficacy

Efficacy results are presented by randomized dose and by actual modal dose. The actual modal dose matched the randomized dose in 85–92% of subjects in all ropinirole PR groups (safety population), except the ropinirole PR 24 mg group (62% of subjects).

• Change in UPDRS motor score

Using the primary analysis (MMRM model) the study did not meet its primary end point (Figure 2); there was no significant difference in change in UPDRS motor score from baseline to week 4 of the maintenance period between placebo and any ropinirole PR group (MMRM model). However, both ropinirole PR 8 and 12 mg demonstrated a numerically greater change in UPDRS motor score than placebo ($p = 0.091$ and $p = 0.124$, respectively). In the primary analysis MMRM model, demographic covariates were tested for inclusion and race was found to be a significant covariate.

Because data were not normally distributed, prespecified additional analyses were performed with/without stratification by race (Table 2). Nonparametric ANCOVA analysis of randomized dose without stratification by race revealed a significantly greater reduction in UPDRS motor score at week 4 of the maintenance period with ropinirole PR 12 mg versus placebo ($p = 0.047$). There was also a numerically greater reduction with ropinirole PR 8 mg versus placebo ($p = 0.060$). When including stratification by race, nonparametric ANCOVA analysis revealed a significantly greater reduction

in UPDRS motor score with ropinirole PR 8 mg versus placebo ($p = 0.032$), and a numerically greater reduction with ropinirole PR 12 mg versus placebo ($p = 0.051$). Nonparametric ANCOVA analysis of actual modal dose (regardless of stratification by race) revealed significantly greater reduction in UPDRS motor score with ropinirole PR 6–8 mg and 12–16 mg versus placebo (p -values all <0.04 ; Table 2).

• Secondary efficacy endpoints

Motor

At week 4 of the maintenance period, the UPDRS motor score responder rate was significantly higher with ropinirole PR 12 mg (39%) versus placebo (18%) (odds ratio [OR]: 2.960; 95% CI: 1.02, 8.55; $p = 0.045$).

Nonmotor

At week 4 of the maintenance period, ropinirole PR 12 mg was associated with a significantly greater improvement in total UPDRS score (parts I–III) ($p = 0.040$) and in UPDRS parts II and III combined ($p = 0.048$; Table 3), versus placebo. There was a numerically greater improvement in UPDRS activities of daily living with ropinirole PR 12 mg versus placebo ($p = 0.117$) and in UPDRS part I with ropinirole PR 2 and 8 mg versus placebo ($p = 0.102$ and $p = 0.084$, respectively).

At week 4 of the maintenance period, the CGI-I responder rate was significantly higher with ropinirole PR 8 mg (55%) and 12 mg (61%) versus placebo (22%) ([OR: 4.204; 95% CI: 1.46, 12.07; $p = 0.008$] and [OR: 5.456; 95% CI: 1.93, 15.46; $p = 0.001$], respectively).

• Safety

More subjects receiving ropinirole PR, experienced a treatment-emergent AE (50%) than those receiving placebo (43%; Table 4). No consistent dose-related trends in AE reporting were noted and as the study progressed, the frequency of AEs reported, decreased (Table 4). The most frequently reported AEs during the study period were nausea, somnolence, headache and dizziness (Table 4).

Overall, ten (7%) subjects receiving any dose of ropinirole PR withdrew from the study owing to an AE, versus two (5%) randomized to placebo. Of the ropinirole PR-treated withdrawals, three (8%) were randomized to 8 mg, two each were randomized to 4, 12 and 24 mg (5, 5 and 15%, respectively) and one (8%) was randomized

Figure 1. Study population: screening, allocation, follow-up and analysis. Six of the ten subjects noted as withdrawn due to ‘protocol deviation’ were from site 83 (Slovakia). Owing to quality issues, enrollment at the site was halted and subsequent to this, the site terminated all ongoing subjects. The site was closed on schedule when country enrollment ended. One of the ten subjects noted as withdrawn due to ‘protocol deviation’ received levodopa during the study and was withdrawn. Two subjects were withdrawn due to reaching protocol-defined stopping criteria. One subject was noncompliant; another had unstable hepatitis C and should not have been enrolled.

[†]One subject in the placebo group provided reason for withdrawal of ‘withdrew consent’; however, the specified text suggested lack of efficacy.

[‡]One subject in the 8 mg group provided reason for withdrawal of ‘withdrew consent’; however, it is noted in the dataset that the subject had an AE of nausea that led to withdrawal.

[§]One subject in the 12 mg group provided reason for withdrawal of ‘investigator discretion’; however, the specified text suggested withdrawal due to an AE of nausea.

[¶]One subject in the 12 mg group provided reason for withdrawal of ‘withdrew consent’; however, the specified text suggested withdrawal due to an AE of sedation.

[#]One additional subject in the 24 mg group, completed maintenance but discontinued before follow-up, and was counted as withdrawn.

AE: Adverse event; PR: Prolonged release.

to 2 mg. Nausea and somnolence were the most frequent AEs leading to discontinuation.

Three serious AEs (SAEs) were reported during the study, all occurring during the

up-titration period in subjects randomized to ropinirole PR: chest pain (one subject randomized to ropinirole PR 4 mg who received ropinirole PR 8 mg in error), coronary artery

Table 1. Summary of subject demographics and baseline characteristics (all randomized subjects).

Characteristics	Placebo (n = 40)	ROP 2 mg (n = 13)	ROP 4 mg (n = 41)	ROP 8 mg (n = 40)	ROP 12 mg (n = 39)	ROP 24 mg (n = 13)	Total (n = 186)
Age (years):							
– Mean (SD)	63.1 (8.82)	58.2 (11.12)	62.1 (11.38)	60.3 (11.72)	61.7 (10.78)	62.5 (12.88)	61.6 (10.85)
– Min, max	47, 86	34, 76	43, 89	33, 85	38, 89	31, 82	31, 89
Gender:							
– Female, n (%)	17 (43)	5 (38)	16 (39)	28 (70)	19 (49)	6 (46)	91 (49)
Race:							
– n	40	13	41	40	38	13	185
– African–American/African heritage, n (%)	2 (5)	0	0	0	0	0	2 (1)
– Asian, n (%)	2 (5)	0	2 (5)	6 (15)	2 (5)	1 (8)	13 (7)
– White, n (%)	36 (90)	13 (100)	39 (95)	34 (85)	36 (92)	12 (92)	170 (91)
Ethnicity:							
– Hispanic/Latino, n (%)	0	1 (8)	1 (2)	2 (5)	1 (3)	0	5 (3)
Modified Hoehn and Yahr stage (during ‘Off’ time), n (%):							
– n	40	13	41	39	39	13	185
– 0	0	0	0	0	0	0	–
– 1	4 (10)	1 (8)	10 (24)	5 (13)	6 (15)	2 (15)	–
– 1.5	11 (28)	4 (31)	12 (29)	11 (28)	9 (23)	3 (23)	–
– 2	18 (45)	6 (46)	13 (32)	18 (45)	17 (44)	5 (38)	–
– 2.5	4 (10)	0	5 (12)	3 (8)	6 (15)	3 (23)	–
– 3	3 (8)	2 (15)	1 (2)	2 (5)	1 (3)	0	–
– 4	0	0	0	0	0	0	–
– 5	0	0	0	0	0	0	–
BL UPDRS motor score (subjects with a nonmissing efficacy observation during the maintenance period):							
– n	35	13	35	33	34	10	–
– Mean (SD)	22.4 (8.12)	23.3 (9.31)	21.1 (9.86)	20.9 (6.42)	23.5 (9.90)	25.0 (10.35)	–
BL UPDRS score – parts II and III combined (subjects with a nonmissing efficacy observation during the maintenance period):							
– n	35	13	35	33	34	10	–
– Mean (SD)	29.7 (12.61)	30.8 (13.13)	27.9 (13.96)	28.2 (8.65)	31.9 (12.61)	32.9 (12.65)	–
BL UPDRS score – parts I–III (subjects with a nonmissing efficacy observation during the maintenance period):							
– n	35	13	35	33	34	10	–
– Mean (SD)	30.8 (13.53)	31.7 (14.29)	28.7 (14.06)	29.3 (8.77)	33.1 (13.01)	33.8 (12.92)	–
BL UPDRS score – activities of daily living (subjects with a nonmissing efficacy observation during the maintenance period):							
– n	29	11	29	28	25	7	–
– Mean (SD)	7.7 (5.87)	7.2 (5.00)	5.8 (4.01)	7.3 (3.57)	8.5 (3.99)	7.7 (3.64)	–
BL UPDRS – part I (mentation) (subjects with a nonmissing efficacy observation during the maintenance period):							
– n	35	13	35	33	34	10	–
– Mean (SD)	1.1 (1.51)	0.8 (1.57)	0.8 (0.88)	1.2 (1.18)	1.2 (1.41)	0.9 (0.88)	–

BL: Baseline; ROP: Ropinirole prolonged release; SD: Standard deviation; UPDRS: Unified Parkinson's Disease Rating Scale.

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

Characteristics	Actual modal dose						
	Placebo (n = 41)	ROP 2 mg (n = 19)	ROP 4 mg (n = 37)	ROP 6–8 mg (n = 41)	ROP 12–16 mg (n = 39)	ROP 20–24 mg (n = 8)	Total (n = 185)
BL UPDRS motor score (subjects with a nonmissing efficacy observation during the maintenance period):							
– n	35	14	33	33	37	8	–
– Mean (SD)	22.4 (8.12)	22.7 (9.47)	20.4 (8.96)	22.2 (7.80)	22.9 (9.61)	27.0 (10.60)	–
BL : Baseline; ROP: Ropinirel prolonged release; SD: Standard deviation; UPDRS: Unified Parkinson's Disease Rating Scale							

BL: Baseline; ROP: Ropinirole prolonged release; SD: Standard deviation; UPDRS: Unified Parkinson's Disease Rating Scale.

disease and cerebral infarction (one subject each randomized to ropinirole PR 12 mg). All SAEs were judged by study investigators to be unrelated to study treatment. No fatal SAEs were reported.

Overall, no clear effects on hematology, clinical chemistry, urinalysis, ECG, semi-supine or standing systolic or diastolic blood pressure (BP), heart rate or neurological examination were observed. Few subjects were found to have orthostatic hypotension at baseline, and none of these had a systolic BP decrease ≥ 40 mmHg.

Orthostatic hypotension was reported most frequently during the up-titration period (systolic BP drops ≥ 20 mmHg reported in 10% and 12% of subjects randomized to placebo and any dose of ropinirole PR, respectively). During this period, only one subject ($<1\%$; randomized to ropinirole PR 4 mg) had a systolic BP decrease ≥ 40 mmHg. During the maintenance period, one subject randomized to placebo (3%) and six randomized to any dose of ropinirole PR (5%) had systolic BP drops ≥ 20 mmHg and one subject randomized to placebo (3%) and

Figure 2. Change in Unified Parkinson's Disease Rating Scale motor score. Mixed-effect model repeated measure model, randomized dose, observed cases data with all subjects with a nonmissing efficacy observation during the maintenance period and by randomized treatment [intent-to-treat population]. ROP PR 24 and 4 mg were not statistically tested.

ROP PR: Ropinirole prolonged release; UPDRS: Unified Parkinson's Disease Rating Scale.

Table 2. Change in Unified Parkinson's Disease Rating Scale motor score (intent-to-treat population, subjects with a nonmissing efficacy observation during the maintenance period): (ANCOVA[†] and nonparametric ANCOVA^{‡§} models)

End point	Randomized dose					
	Placebo <i>n</i> = (40)	ROP PR 2 mg (<i>n</i> = 13)	ROP PR 4 mg (<i>n</i> = 40)	ROP PR 8 mg (<i>n</i> = 40)	ROP PR 12 mg (<i>n</i> = 39)	ROP PR 24 mg (<i>n</i> = 13)
Change (maintenance week 4):						
– <i>n</i>	35	13	35	33	34	10
– Mean	-3.9	-4.5	-4.6	-5.5	-6.6	-5.8
– Min, max	-30, 9	-16, 7	-24, 8	-18, 3	-35, 2	-17, 3
ANCOVA model [†] :						
– LS mean (95% CI)	-2.24 (-4.56, 0.08)	-2.15 (-5.67, 1.37)	-3.23 (-5.60, -0.86)	-4.61 (-6.83, -2.39)	-4.56 (-6.90, -2.21)	-3.35 (-7.17, 0.47)
– SE	1.17	1.78	1.20	1.12	1.19	1.93
– 95% CI for the difference [¶]	–	-3.61, 3.79	-3.71, 1.73	-5.15, 0.40	-5.06, 0.42	-5.20, 2.97
– <i>p</i> -value	–	0.962	0.475	0.093	0.096	0.590
Nonparametric rank ANCOVA:						
– <i>p</i> -value [‡]	–	0.439	0.177	0.060	0.047	0.407
– <i>p</i> -value [§]	–	0.599	0.253	0.032	0.051	0.331
End point	Actual modal dose					
	Placebo (<i>n</i> = 41)	ROP PR 2 mg (<i>n</i> = 19)	ROP PR 4 mg (<i>n</i> = 37)	ROP PR 6–8 mg (<i>n</i> = 41)	ROP PR 12–16 mg (<i>n</i> = 39)	ROP PR 20–24 mg (<i>n</i> = 8)
Change (maintenance week 4):						
– <i>n</i>	35	14	33	33	37	8
– Mean	-3.9	-3.5	-4.2	-6.3	-6.5	-5.8
– Min, max	-30, 9	-16, 7	-13, 8	-24, 3	-35, 3	-17, 3
– LS mean (95% CI) [¶]	-2.18 (-4.47, 0.12)	-1.3 (-4.69, 2.08)	-3.00 (-5.39, -0.61)	-4.99 (-7.19, -2.80)	-4.60 (-6.87, -2.34)	-2.73 (-6.90, 1.45)
– SE [†]	1.16	1.71	1.21	1.11	1.15	2.11
– 95% CI for the difference ^{†¶}	–	-2.69, 4.45	-3.56, 1.92	-5.56, 0.07	-5.08, 0.23	-4.99, 3.89
– <i>p</i> -value [‡]	–	0.628	0.554	0.045	0.073	0.807
Nonparametric rank ANCOVA:						
– <i>p</i> -value [‡]	–	0.740	0.174	0.030	0.037	0.716
– <i>p</i> -value [§]	–	0.940	0.238	0.015	0.039	0.582

Intent-to-treat population, subjects with a nonmissing efficacy observation during the maintenance period.
[†]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 without stratification.
[§]Nonparametric rank ANCOVA stratified by race.
[¶]95% CI for the difference in LS means between each ROP PR group and placebo.
ANCOVA: Analysis of covariance; LS: Least squares; ROP PR: Ropinirole prolonged release; SE: Standard error.

one subject randomized to ropinirole PR 12 mg (3%) had a systolic BP drop ≥ 40 mmHg on standing.

Throughout the study period, seven subjects randomized to any dose of ropinirole PR and no subjects randomized to placebo experienced ≥ 1 AE of SOOS. Five subjects reported one AE each of SOOS during the up-titration period. Two of these subjects were randomized to ropinirole PR 4 mg (SOOS events reported while receiving the 4 mg dose) and three were randomized to ropinirole PR 12 mg (SOOS events reported while receiving actual doses of 2, 6–8 and 12–16 mg). The mean duration of SOOS events during the up-titration period was

35 min and two (40%) events were preceded by sleepiness or drowsiness. During the maintenance period, three subjects reported AEs of SOOS; two were randomized to ropinirole PR 12 mg (each subject reported 2 events) and one was randomized to ropinirole PR 24 mg. All maintenance period SOOS events were reported while patients were receiving an actual dose of 12–16 mg. The mean duration of SOOS events during the maintenance period was 18 min and two (40%) events were preceded by sleepiness or drowsiness. One subject reported events in both up-titration and maintenance periods. No SOOS events were reported during the down-titration period.

No subjects scored positive for impulse control disorder as assessed by MIDI. Two subjects (one randomized to placebo and one randomized to ropinirole PR 12 mg) reported suicidal ideation during the study, as assessed by C-SSRS. No possible suicidality-related AEs were reported by the investigators. One ropinirole PR subject (<1%) experienced dyskinesia and one (<1%) experienced hallucinations. One subject (<1%) experienced syncope, which led to study discontinuation. No subjects developed melanoma after exposure to ropinirole PR.

Discussion

This study aimed to characterize the dose–response and tolerability of fixed doses of ropinirole PR in subjects with early PD.

Using an MMRM model, no statistically significant differences were found for any of the treatment groups versus placebo in the primary efficacy end point of change in UPDRS motor score. However, because data normality was not supported, a nonparametric ranked ANCOVA was conducted, in line with the analysis plan. This analysis demonstrated significantly greater improvements in UPDRS motor score (vs placebo) with ropinirole PR 12 mg when the analysis was run without stratification by race; the analysis showed significantly greater improvements in UPDRS motor score (vs placebo) with ropinirole PR 8 mg when stratified by race. Nonparametric ANCOVA analyses conducted by actual modal dose demonstrated significant effects of ropinirole PR 6–8 mg and 12–16 mg doses on UPDRS motor score, with or without stratification by race.

Analysis of the secondary efficacy end points revealed significantly greater improvements in UPDRS score (parts II and III combined), total UPDRS score and percentage of UPDRS responders for ropinirole PR 12 mg versus placebo. The number of CGI-I responders was also significantly greater with ropinirole PR 8 and 12 mg than with placebo. The 24 mg dose group was not powered for comparison with placebo, so conclusions relating to dose–response at the higher end of the dose range should be treated with caution. The results of this study suggest however, that in subjects with early stage PD, further benefit may not be afforded by dose escalation beyond ropinirole PR 12 mg once daily. This observation is consistent with the findings of a previous study in early stage PD [8] and the associated pharmacokinetic and pharmacodynamic evaluation [11], which suggested that doses of ropinirole of 8–12 mg are likely to be efficacious and that higher doses are likely to be unnecessary in most subjects. The authors of this study commented that subjects should be titrated with ropinirole PR to clinical effect and maintained on the lowest dose that achieved symptom control; any further changes should be made only when symptoms change.

Of note, the improvement in UPDRS score of approximately four points with placebo was higher than expected [4] and contributing to this were a 20- and 30-point improvement in the UPDRS motor score at the end of the maintenance period in two placebo-treated subjects. These two subjects were confirmed as not having inadvertently received ropinirole PR, and it remains unclear why such a marked improvement in the UPDRS motor score occurred. Importantly, however, significant benefit of ropinirole PR was

Table 3. Change in Unified Parkinson's Disease Rating Scale parts II and III combined (intent-to-treat population, subjects with a nonmissing efficacy observation during the maintenance period): mixed-effect model repeated measure[†] model.

End point	Randomized dose					
	Placebo (n = 40)	ROP PR 2 mg (n = 13)	ROP PR 4 mg (n = 40)	ROP PR 8 mg (n = 40)	ROP PR 12 mg (n = 39)	ROP PR 24 mg (n = 13)
n	35	13	35	33	34	10
Mean	-5.0	-4.6	-5.1	-6.8	-9.2	-6.8
Min, max	-39, 15	-20, 16	-25, 10	-27, 6	-39, 2	-15, 1
LS mean (95% CI)	-2.88 (-5.87, 0.10)	-1.81 (-6.18, 2.57)	-3.81 (-6.76, -0.85)	-5.63 (-8.44, -2.81)	-6.62 (-9.51, -3.72)	-3.87 (-8.68, 0.94)
SE	1.51	2.21	1.50	1.42	1.47	2.43
95% CI for the difference [‡]	–	-3.78, 5.93	-4.63, 2.77	-6.50, 1.01	-7.43, -0.04	-6.32, 4.35
p-value	–	0.662	0.621	0.150	0.048	0.715

[†]Mixed-effect model repeated measure 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.

LS: least squares; ROP PR: Ropinirole prolonged release; SE: Standard error.

Table 4. Summary of most common adverse events reported in $\geq 10\%$ of subjects in any randomized treatment group (safety population).

Preferred term	Placebo, n (%)	ROP PR 2 mg, n (%)	ROP PR 4 mg, n (%)	ROP PR 8 mg, n (%)	ROP PR 12 mg, n (%)	ROP PR 24 mg, n (%)	Any ROP PR, n (%)
Whole study period:	40	13	41	40	39	13	146
– Any event	17 (43)	5 (38)	19 (46)	24 (60)	18 (46)	7 (54)	73 (50)
– Nausea	3 (8)	1 (8)	6 (15)	13 (33)	4 (10)	2 (15)	26 (18)
– Somnolence	2 (5)	2 (15)	5 (12)	4 (10)	3 (8)	1 (8)	15 (10)
– Headache	1 (3)	1 (8)	4 (10)	3 (8)	2 (5)	2 (15)	12 (8)
– Dizziness	2 (5)	0	2 (5)	4 (10)	3 (8)	1 (8)	10 (7)
– Sudden onset of sleep	0	0	2 (5)	0	4 (10)	1 (8)	7 (5)
– Hypertension	0	0	2 (5)	2 (5)	1 (3)	2 (15)	7 (5)
– Vomiting	2 (5)	0	2 (5)	4 (10)	0	0	6 (4)
– Back pain	1 (3)	0	2 (5)	1 (3)	1 (3)	2 (15)	6 (4)
Up-titration period:	40	13	41	40	39	13	146
– Any event	16 (40)	4 (31)	17 (41)	23 (58)	17 (44)	7 (54)	68 (47)
– Nausea	3 (8)	1 (8)	5 (12)	11 (28)	4 (10)	2 (15)	23 (16)
– Somnolence	2 (5)	2 (15)	4 (10)	4 (10)	3 (8)	1 (8)	14 (10)
– Headache	1 (3)	1 (8)	4 (10)	3 (8)	2 (5)	2 (15)	12 (8)
– Dizziness	2 (5)	0	2 (5)	4 (10)	3 (8)	0	9 (6)
– Hypertension	0	0	2 (5)	2 (5)	1 (3)	2 (15)	7 (5)
– Vomiting	2 (5)	0	1 (2)	4 (10)	0	0	5 (3)
Maintenance period:	35	13	35	33	34	10	125
– Any event	2 (6)	2 (15)	9 (26)	5 (15)	3 (9)	3 (30)	22 (18)
– Sudden onset of sleep	0	0	0	0	2 (6)	1 (10)	3 (2)
– Headache	0	0	0	1 (3)	0	1 (10)	2 (2)
– Dizziness	0	0	0	0	0	1 (10)	1 (<1)
– Skeletal injury	0	0	0	0	0	1 (10)	1 (<1)
Down-titration period [†] :	37	12	36	35	36	11	130
– Any event	2 (5)	1 (8)	5 (14)	2 (6)	1 (3)	2 (18)	11 (8)

[†]No individual category of adverse event occurred in $\geq 10\%$ of subjects during the down-titration period.

ROP PR: Ropinirole prolonged release.

demonstrated in this study and the size of the placebo response is not likely to have influenced the shape of the dose–response curve.

The safety profile was consistent with the published prescribing information [3,10] and with that previously described with the flexible dosing regimen for ropinirole PR in early PD [8]. In previous studies conducted in subjects with advanced PD, the proportion of subjects reporting ≥ 1 AE was slightly higher than in the present study (64% [9] and 72% [7] compared with 54% in the present study), and dyskinesia was one of the most common AEs, being reported by 11% [7] and 13% [9] of subjects. These differences with the present study may be a reflection of a patient population with more advanced disease and the associated concomitant treatment with L-dopa in advanced PD. In another study in early PD [8], dyskinesia was not reported as an AE (GlaxoSmithKline

[GSK] data on file). No new safety signals were detected during the study, and no clear dose-related effect on AEs was noted. No deaths were reported during the study. The AEs reported were mostly mild or moderate.

Ten SOOS events were reported by ropinirole PR subjects during the current study. This incidence is greater than reported previously [1], although this is likely to have been influenced by the methods of data collection. In the current study, a specific questionnaire was used to evaluate any suspected SOOS event whereas in previous studies evaluation of SOOS relied on review of AE reporting after completion of the study. Of note, there was no clear dose–response relationship for SOOS events.

An AE of orthostatic hypotension was reported in one subject receiving placebo and in two subjects in the titration phase who had

been randomized to ropinirole PR 12 mg. In addition, an orthostatic fall in systolic BP ≥ 40 mmHg was noted in two subjects receiving ropinirole PR (one each during the up-titration and maintenance periods) and one receiving placebo. One occurrence of syncope was reported in a ropinirole PR subject ($<1\%$), which is in line with reports in subjects with advanced PD ($<1\%$) [9].

Conclusion

In summary, this was the first fixed-dose, dose–response study conducted with ropinirole PR, and the results suggest that the 8 and 12 mg doses were effective in treating the motor symptoms of early PD. The 24 mg dose was not powered for comparison against placebo but clear evidence of additional benefit of the higher dose was not demonstrated. These findings are consistent with information on the dose–response relationship indicated in a previous study in subjects with early stage PD [8].

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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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