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Early Piribedil Monotherapy of Parkinson's Disease: A Planned Seven-Month Report of the REGAIN Study

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Abstract: Piribedil is a D_2 dopamine agonist, which has been shown to improve symptoms of Parkinson's disease (PD) when combined with L-dopa. The objective of this study was to compare the efficacy of piribedil monotherapy to placebo in patients with early PD over a 7-month period. Four hundred and five early PD patients were randomized (double-blind) to piribedil (150–300 mg/day) or placebo. L-dopa open-label supplementation was permitted. Unified Parkinson Disease Rating Scale part III (UPDRS III) score as the last observation on monotherapy over 7 months was the primary outcome measure. Secondary outcomes were proportion of responders (UPDRS III improvement $>$ 30%), patients remaining on monotherapy after 7 months, UPDRS III subscores, and UPDRS II. UPDRS III improved on piribedil (-4.9 points) versus a worsening on placebo (2.6 points; estimated effect = 7.26 points; 95% CI = 5.38–9.14; $P < 0.0001$). The proportion of responders was significantly higher for piribedil (42%) than for placebo (14%) (OR = 4.69; 95% CI = 2.82–7.80; $P < 0.001$). Piribedil significantly improved several UPDRS III subscores. UPDRS II improved on piribedil by -1.2 points, while it deteriorated by 1.5 points on placebo (estimated effect = 2.71; 95% CI = 1.8–3.62; $P < 0.0001$). The proportion of patients remaining on monotherapy after 7 months was greater in the piribedil group (OR = 3.72; 95% CI = 2.26–6.11; $P < 0.001$). Safety was consistent with that reported for other dopamine agonists, gastrointestinal side effects being the most common (22% of patients in piribedil group vs. 14% on placebo). Piribedil is effective and safe as early PD therapy. © 2006 Movement Disorder Society

Key words: piribedil; L-dopa; Parkinson's disease; monotherapy

Although L-dopa therapy improves motor symptoms of patients with Parkinson's disease (PD), the emergence of motor fluctuations and dyskinesias poses a major therapeutic challenge.[1–3] The early use of a dopamine agonist delays or prevents the development of motor complications[4,5] for at least 5 years.

Piribedil [(methylenedioxy-3,4-benzyl)-4 pyperazinyl-1-2 pyrimidine], a centrally acting nonergoline dopamine agonist[6] with affinity for D2 and D3 receptors[7,8] and significant activity on animal models of PD,[9] has been used for many years in the treatment of PD.[10] Controlled studies have demonstrated piribedil efficacy in combination with L-dopa,[11–13] but only one open-label 3-month study has reported a favorable therapeutic profile of piribedil monotherapy in de novo patients.[14]

The REGAIN (Early Treatment of Idiopathic PD With the Dopaminergic Agonist Trivastal 50 Retard in Monotherapy) multicenter randomized double-blind placebo-controlled study was carried out to confirm the therapeu-

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tic efficacy of piribedil as monotherapy in de novo patients. We now report the results of the planned 7-month analysis of a 2-year study.

PATIENTS AND METHODS

This multinational multicenter study used a randomized double-blind two-group parallel design and was conducted in agreement with the principles of Good Clinical Practice and the Declaration of Helsinki. The protocol was approved by the relevant institutional ethics committees. All patients freely gave their written informed consent before participation.

Patients

Patients aged 30 to 77 years with a diagnosis of idiopathic PD (according to Queen Square Brain Bank for Neurological Disorders criteria)[15] at stage 1 to 3 on the Hoehn and Yahr's scale[16] were eligible. Previous treatment with dopamine agonists for less than 3 months and L-dopa for less than 6 weeks was permitted. Dopamine agonists, anticholinergics, selegiline, and amantadine had to be discontinued for at least 1 month (60 days in case of selegiline) prior to screening.

Ongoing treatments with anxiolytic, hypnotic, and antidepressant drugs were continued unchanged throughout the trial. Selective serotonin reuptake inhibitors were authorized if started at least 3 months before and at stable daily dose. Treatment with nonselective monoamine oxidase inhibitors, amineptine, imipramine, and derivates were the exclusion criteria.

Study Design

Patients underwent a run-in single-blind placebo period of 30 days and then were randomized to one of the two treatment arms, piribedil or placebo. Three main visits, when a full clinical evaluation was performed, were scheduled: at day 0 (inclusion visit), after 7 months, and after 24 months. Double-blind conditions were kept from randomization up to the end of the 2-year study (Fig. 1A). The present report focuses on the clinical and safety assessments performed at baseline, day 28, day 42, and after 4 and 7 months. All criteria were evaluated either over the 7-month period under piribedil monotherapy condition or until the last visit prior to L-dopa rescue (last change, LOCF; planned analysis, main study objective).

The primary efficacy endpoint was the mean change at endpoint versus baseline of the Unified Parkinson Disease Rating Scale part III (UPDRS III) score.[17] Secondary motor endpoint included the percentage of responders, defined by a 30% decrease from baseline on the UPDRS III score.[17] Other secondary criteria were UPDRS III subscores [tremor at rest (item 20), action or postural tremor score (item 21), rigidity score (item 22), bradykinesia score (items 23–27, 31), axial score (items 18, 28–30), and UPDRS II score (activities of daily living)]. Other exploratory endpoints included the time to failure (defined as the number of days from day 0 to the introduction of L-dopa), the percentage of patients on L-dopa, the L-dopa daily dose, Montgomery and Asberg Depression Rating Scale (MADRS) scores, Beck Depression Inventory total scores, and quality of life of patients (PDQL) total scores expressed as raw values. Cognitive evaluations, performed at inclusion and after a 7- and 24-month period, included the Stroop test, the Wisconsin Card Sorting Test, Verbal fluency, Digit Ordering, and Reversed Digit Symbol. Results of these last evaluations will be presented in a separate paper.

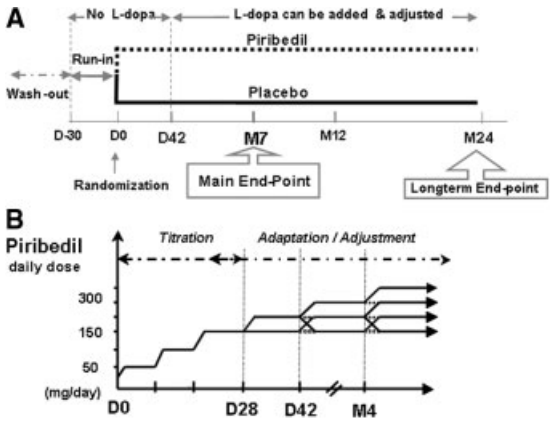

FIG. 1. A: Study design. **B:** Study treatment.

Safety evaluations included blood pressure, heart rate, and an open-question interview. Adherence was calculated by a count of unused medication. Standard biological analyses were performed at inclusion and after 7 months.

Piribedil was taken as 50 mg tablets, or identical matching placebo tablets. The starting dose was 50 mg o.d., which was then increased every week in increments of 50 mg up to 150 mg t.i.d. by day 21. The daily dose could be increased thereafter in increments of 50 mg every 14 days in the event of lack of effect, with three possible stable dose regimens (150, 200, and 250 mg/day) up to month 4. During this period, piribedil could be also downtitrated by steps of 50 mg in the event of intolerance. After month 4, the investigator was allowed to increase the medication to a maximal level of 300 mg per day (Fig. 1B). After day 42, open-label rescue treatment with L-dopa was permitted. Domperidone (up to 60 mg/day) was prescribed to control gastrointestinal symp-

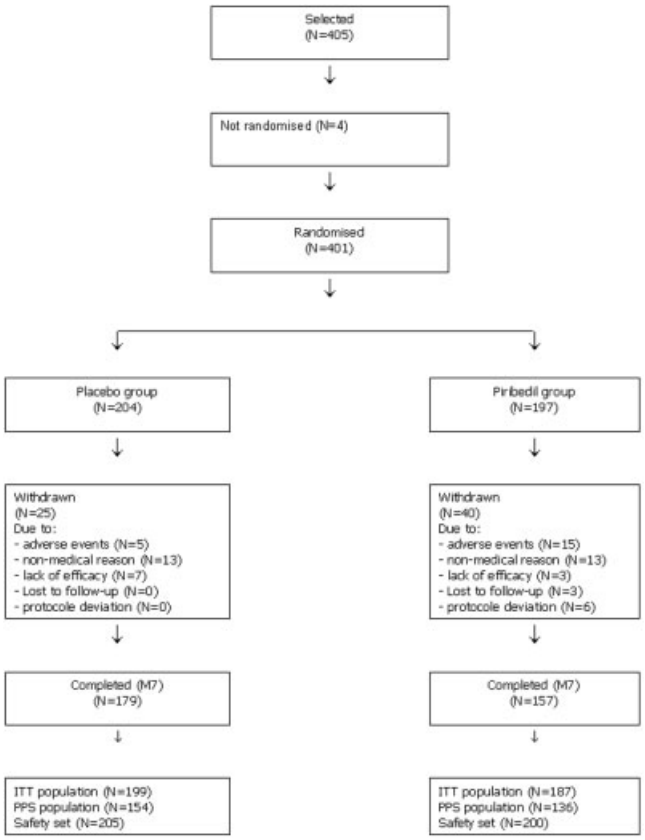

FIG. 2. Disposition of patients.

toms up to day 42 and could be continued thereafter, depending on clinical need.

Statistical Analysis and Sample Size Considerations

Randomization procedures were performed via IVRS (by Clinphone, Nottingham, U.K.). Main analyses were performed on an intention-to-treat (ITT) basis [all randomized patients who received at least one dose of treatment and had fully recorded baseline (D0) data]. Piribedil and placebo groups were compared over the 7-month period in true monotherapy conditions by using an analysis of covariance by group, presence of previous L-dopa treatment, and country as fixed effects and with baseline value as a covariate. In case of L-dopa supplementation before M7, the last monotherapy value was considered for analysis (LOCF).

In planning the trial, it was calculated that a trial with 200 patients per arm would have 88% power to detect a 3-point difference at the 2.5% level one-sided given an assumed standard deviation of 9.5 points.[18] The main analysis was performed at a 2.5% one-sided level significance. This one-sided approach was justified by the long-term open-label utilization of piribedil as an antiparkinson drug and by the positive results of controlled trials in L-dopa–treated PD patients. All other tests were performed at a level of 5% (two-sided comparisons). As there was only one main analysis for the primary endpoint, no adjustments for multiplicity were needed.

The difference between treatments in the percentage of responders was compared using a logistic regression with baseline UPDRS III score and country as covariates. Difference between treatments for time to failure (introduction of L-dopa) was analyzed using a Cox proportional-hazards model with baseline UPDRS III score and country as covariates. Differences between treatments for the percentage of patients on L-dopa, as well as the last prescribed L-dopa daily dose, were compared by using a Cochran–Mantel–Haenszel (CMH) test. In order to avoid involuntary biases, two different teams of statisticians were in charge of the short-term (7-month) and the long-term (24-month) analyses.

RESULTS

Four hundred and five patients recruited by 52 centers in seven countries (Argentina, India, France, Mexico, South Africa, Spain, and Portugal) participated in the trial. One hundred and ninety-seven patients were randomized in the piribedil group and 204 in the placebo group (Fig. 2). Treatment groups were matched at inclusion (Table 1).

Efficacy

A total of 179 (88%) of 204 patients in the placebo group and 157 (80%) of 197 in the piribedil group completed the 7-month period (Fig. 2). A total of 187 patients in the piribedil group and 199 in the placebo group were included in the ITT main analysis.

At endpoint, the mean daily dose of piribedil was 240 ± 55 mg/day. UPDRS III score improved by −4.9 ± 9.8 points on piribedil, while the score deterio-

TABLE 1. *Characteristics of the population at baseline*

	Placebo (n = 204)	Piribedil (n = 197)
Age (yr)	62.3 ± 10.3	62.4 ± 9.5
Male sex	128 (62.7%)	116 (58.9%)
PD duration (yr)	2.0 ± 2.0	2.0 ± 1.8
Hoehn and Yahr	2 ± 0.5	2.1 ± 0.5
Class 1-1.5	58 (28.4)	47 (23.9%)
Class 2-2.5	128 (62.7%)	133 (67.5%)
Class 3	18 (8.8%)	16 (8.1%)
MADRS score	6.5 ± 7.2	7.7 ± 7.2
UPDRS III score	23.1 ± 11.5	25.9 ± 11.7
UPDRS III axial score	2.3 ± 1.6	2.7 ± 1.6

Values are mean ± SD or n (%).

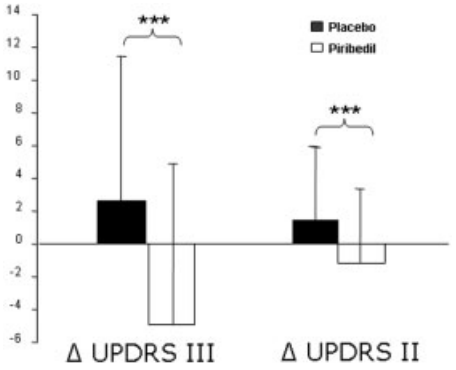

FIG. 3. UPDRS III and II changes between baseline and endpoint on piribedil or placebo monotherapy (month 7 or last monotherapy value before L-dopa supplementation being carried forward).

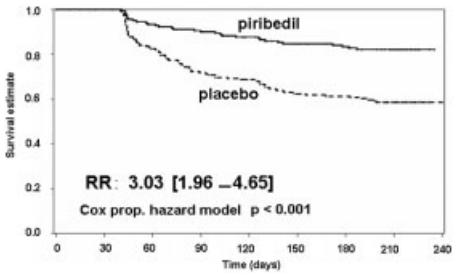

FIG. 4. Time to introduction of L-dopa.

rated by 2.6 ± 8.9 points on placebo (estimated effect = 7.26; 95% CI = 5.38–9.14; $P < 0.0001$; Fig. 3). The number of responders was also greater with piribedil (42% vs. 14% with placebo, logistic regression; odds ratio = 4.69; 95% CI = 2.82–7.80; $P < 0.001$).

When compared to placebo, piribedil significantly improved UPDRS II by −1.2 ± 4.6 points from baseline, while the score deteriorated by 1.5 ± 4.4 points on placebo (estimated effect = 2.71; 95% CI = 1.8–3.62; $P < 0.0001$; Fig. 3). Piribedil also significantly improved all UPDRS III subscores (Table 2).

The rate of patients taking L-dopa was significantly higher (odds ratio = 3.72) in the placebo group than in patients receiving piribedil ($P < 0.001$). At M7, 17% of piribedil-treated patients received L-dopa rescue treatment compared with 40% in the placebo arm ($P < 0.0001$; Fig. 4). In the patients who needed L-dopa supplementation, the mean last prescribed dose was 346 ± 148 mg/day in the placebo group (n = 80) and 344 ± 141 mg/day in the piribedil group (n = 31). Overall in the study population, a significant difference in the last prescribed L-dopa daily dose was demonstrated in favor of piribedil (estimated effect = 81.39 ± 16.72; $P < 0.0001$).

Safety and Tolerability

Sixty-nine percent of the patients in the piribedil group and 57% in the placebo group reported at least one emergent adverse event, but medication was stopped in only 4.7% of patients (2.0% in placebo and 7.5% in the piribedil group) because of adverse events.

The most common treatment emergent adverse events were gastrointestinal symptoms (61 [31%] of 200 patients on piribedil; 29 [14%] of 205 patients on placebo), psychiatric disorders (46 [23%] of 200 patients on piribedil; 36 [18%] of 205 patients on placebo), and body as a whole general disorders (41 [21%] of 200 patients on piribedil; 28 [14%] of 205 patients on placebo). The most frequently occurring emergent adverse events are reported in Table 3. After 7 months, 42 patients (10.4%) experienced at least one serious adverse event: 10 patients (4.9%) in placebo group and 17 patients (8.5%) in piribedil group.

Adverse events led to discontinuation of the study medication in 15 piribedil- and 5 placebo-treated patients. Gastrointestinal symptoms (5 patients) and psychiatric symptoms, including hallucinations (4 patients; 1.0%), were the most frequent reason for discontinuation in the active treatment group, whereas in the placebo group, the most common reason for adverse event-related withdrawal was the aggravation of specific motor symptoms (2 patients).

Over 7 months in the safety set (n = 405), irrespective of the introduction of L-dopa, vital signs mean values

TABLE 2. *Effects of piribedil on the main subscores of UPDRS III at 7 months*

	Placebo (n = 199)	Piribedil (n = 187)	Estimated effect	*P*
Tremor at rest (item 20a–20e)	0.4 (2.2)	−1 (2.2)	1.33 ± 0.21	< 0.0001
Action or postural tremor (item 21a–21b)	0.1 (1.3)	−0.2 (1.3)	0.31 ± 0.12	< 0.01
Rigidity (item 22a–22e)	0.3 (2.7)	−0.7 (2.6)	0.96 ± 0.26	< 0.0005
Bradykinesia (items 23a, 23b, 24a, 24b, 25a, 25b, 26a, 26b, 27, 31)	1.4 (4.4)	−2.4 (5)	3.57 ± 0.48	< 0.0001
Axial score (items 18, 28-30)	0.3 (1.2)	−0.3 (1.3)	0.47 ± 0.12	< 0.0005

Last change versus baseline in monotherapy condition.

TABLE 3. *Emergent adverse events occurring in > 5% of patients*

Adverse event	Placebo (n = 205)		Piribedil (n = 200)	
	n	%	n	%
Nausea	8	3.9	24	12.0
Hypertension	9	4.4	19	9.5
Dizziness	9	4.4	15	7.5
Anxiety	9	4.4	13	6.5
Hypotension postural	8	3.9	13	6.5
Insomnia	6	2.9	13	6.5
Constipation	6	2.9	13	6.5
Depression	12	5.9	7	3.5
Somnolence	6	2.9	12	6.0
Edema peripheral	7	3.4	10	5.0
Abdominal pain	4	2.0	12	6.0

Safety set (n = 405).

remained stable from baseline to the last observation in both treatment arms.

DISCUSSION

The dopamine agonist piribedil has been used for many years for the treatment of PD in several countries. However, there is a lack of data regarding the efficacy of piribedil in monotherapy in de novo patients based on randomized double-blind placebo-controlled results. The present results demonstrate that piribedil monotherapy is more efficacious than placebo over 7 months in de novo patients, as determined by changes in UPDRS II and III and need for L-dopa supplementation.

Piribedil (150–300 mg/day) as monotherapy decreased the UPDRS III score with a significant treatment effect of 7.26 points versus placebo ($P < 0.0001$). This effect size may be compared with the results reported in comparable populations and comparable trial design with other dopamine agonists such as ropinirole (effect size of about 5 points),[19] pramipexole (effect size of about 6 points),[20] pergolide (effect size of about 5 points),[21] or rotigotine (effect size of about 4 points).[22] The lack of head-to-head comparison prevents, however, any definite conclusions regarding relative efficacy across trials and across agonists. The piribedil effect size observed in the REGAIN study was also greater than the one reported with MAO-B inhibitors such as selegiline or rasagiline (effect size of 2–3 points.[23,24] However, the same cautiousness should apply before drawing any conclusion in term of relative efficacy.

While it is a frequent empirical observation that piribedil is highly effective on tremor, the present study also demonstrated global efficacy on all motor symptoms, including rigidity, bradykinesia, and axial symptoms. The relationship between axial symptoms and dopaminergic or nondopaminergic mechanisms remains controversial.[25,26] Therefore, the respective contribution of the adrenergic versus the dopaminergic activities of piribedil to its actions on axial symptoms remains uncertain and requires further clarification.

Piribedil is currently used at a dose of 150 to 250 mg/day in the countries where it is marketed. Uptitrating piribedil to 300 mg/day was permitted in the REGAIN trial in order to maintain monotherapy as long as possible. Thus, the mean daily dose at the last visit was 244 mg/day. The aim of this strategy was to try to reduce the risk of dyskinesia by delaying L-dopa rescue. The impact of this strategy on the incidence of dyskinesias will be assessed in the 2-year analysis, but the present data demonstrate that the early use of such a dose of piribedil is a feasible option to delay the introduction of L-dopa since the number of patients needing L-dopa rescue was greater for the placebo group (RR = 3.02; $P < 0.0001$).

The present study also showed that piribedil, administered over 7 months up to a dose of 300 mg/day, was well tolerated in patients with early PD aged 77 years or less. Of the 197 patients who received piribedil, only 7.5% withdrew because of adverse events. The adverse events reported (i.e., in more than 5% of treated patients) with piribedil are typical of the safety profile of an active dopaminergic drug and comparable to other dopamine agonists.[18,27] Piribedil, however, has not so far been reported to be associated with fibrotic reactions as seen with ergoline agonists.[28]

APPENDIX

The following members of the Parkinson REGAIN Study Group participated in this study and were authors of this report.

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