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The Parkinson–Control Study: A 1-Year Randomized, Double-Blind Trial Comparing Piribedil (150 mg/day) With Bromocriptine (25 mg/day) in Early Combination With Levodopa in Parkinson's Disease

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Abstract: Dopamine agonists have been recommended as early treatment for Parkinson's disease (PD), alone or combined with levodopa. Piribedil is a non-ergot selective D_2/D_3 agonist with α_2 antagonist properties shown to be effective in the treatment of PD. This 12-month international, randomized, double-blind trial aimed to assess the efficacy of piribedil 150 mg versus bromocriptine 25 mg, in early combination with levodopa in Stage I to III PD patients. Motor efficacy was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS III, Items 18–31) as improvement from baseline. Response rate was defined as a 30% improvement. Among the 425 randomly assigned patients, 178 were also included in a substudy on cognitive follow-up evaluated by a dysexecutive syndrome oriented battery. A relevant improvement in UPDRS III over the 12-month study duration was observed both in the piribedil and bromocriptine groups (-7.9 ± 9.7 points from baseline versus -8.0 ± 9.5; not significant [n.s.]) with a response rate of 58.4% and 55.3% (n.s.), respectively. Piribedil and bromocriptine resulted in similar improvement on all UPDRS III subscores. Piribedil patients required less levodopa dose increase than those on bromocriptine. Cognitive performance remained generally unchanged in both groups, with a significant effect of piribedil limited to the Wisconsin Card Sorting Test. An overall good tolerability of piribedil was observed. Early combination of piribedil 150 mg with levodopa resulted in significant long-term improvement of all motor symptoms in PD patients insufficiently controlled by levodopa alone. Taking into account both efficacy and acceptability in the long-term, piribedil proved in this bromocriptine controlled study to be an effective and safe treatment for PD. © 2005 Movement Disorder Society

Key words: dopamine agonists; piribedil; levodopa; Parkinson's disease; bromocriptine

Dopamine agonists, which have long been used as adjunctive treatments in the later stages of Parkinson's disease (PD),[1–4] are now recommended as first-line symptomatic monotherapy,[5–7] because they have the potential to delay or to reduce levodopa-induced complications. This strategy has been justified on the basis of their L-dopa–sparing effect, by a more constant stimulation of central dopamine receptors, and by a putative neuroprotection.[2,5–8]

Bromocriptine, the first clinically introduced dopamine agonist, is a D_2-type agonist with partial D_1 antag-

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onist activity.[1,2] Bromocriptine has been shown to control L-dopa–induced clinical fluctuations[8,9] and is used both as an adjunct therapy in advanced disease and in early therapy.

Piribedil ([(methylenedioxy-3,4 benzyl)-4 pyperazinyl-1]-2 pyrimidine) is a non-ergot, centrally acting dopamine agonist with a balanced affinity for D_2 and D_3 receptors with α_2 antagonist properties.[10–13] In 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) -treated marmosets, repeated oral administration of piribedil compared with an equieffective dose of L-dopa is less likely to induce dyskinesia than L-dopa.[14] After repeated oral administration of 150 mg/day to parkinsonian patients, piribedil plasma levels remain stable over 24 hours, the median terminal half-life being 21 hours.[15,16]

Previous clinical studies have shown that piribedil is effective either as monotherapy or in combination in the treatment of PD.[17–21] Ziegler and colleagues[22] recently reported that the combination of piribedil with L-dopa significantly improved parkinsonian motor symptoms with a good tolerability, thus leading to definitive acknowledgment of piribedil efficacy versus placebo before any adjustment of L-dopa dose.[23] Still more recently, significant motor efficacy versus placebo over long-term was reported on true monotherapy conditions for daily doses of piribedil from 150 to 300 mg.[24,25]

The present 12-month, international, multicenter, randomized, double-blind study was carried out to confirm, in a large cohort, the therapeutic benefit of piribedil (150 mg) on motor function in PD compared with bromocriptine (25 mg) in early combination with L-dopa. The effects of piribedil on cognitive performance were also investigated in a subset of patients.

PATIENTS AND METHODS

This study was conducted in accordance with the Principles of Good Clinical Practice and the Declaration of Helsinki. The protocol was approved by the relevant institutional ethics committees, and all patients freely gave their written informed consent before participation.

Patients

Male and female patients, 40 to 77 years of age, with a clinical diagnosis of idiopathic PD (according to the UK Parkinson's Disease Society Brain Bank) Stages I to III on the Hoehn and Yahr scale[26] were recruited. Previous treatment with dopamine agonists, anticholinergic agents, and amantadine had to be discontinued for at least 1 month before screening. Eligible patients had to be receiving L-dopa + carbidopa or benserazide immediate release treatment for more than 3 months and less than 5 years, on a stable dosage $\leq$ 600 mg/day (inclusion of patients previously treated with L-dopa + carbidopa 750 mg/day; with L-dopa + carbidopa controlled-release 850 mg/day or L-dopa + benserazide controlled-release 1,000 mg/day was allowed). Additionally, their motor symptoms, with or without fluctuations, had to be insufficiently controlled and they had to require therapeutic adaptation. Patients treated with selegiline were allowed to participate as long as they were on a stable dosage before enrollment. Current treatments with antidepressant drugs (except for monoamine oxidase inhibitors, amineptine, medifoxamine, and fluphenazine with nortriptyline) were continued unchanged throughout the trial.

Exclusion criteria were the following: patients frequently falling according to Unified Parkinson's Disease Rating Scale (UPDRS) II Item 13; previous neurosurgery for PD; patients suffering from psychotic symptoms or visual hallucinations; patients with intellectual impairment defined as Mini-Mental Status of Folstein score lower than 23 or reporting confusion episodes; severe cardiovascular diseases, including uncontrolled coronary ischemic heart disease, recent acute myocardial infarction, past history of symptomatic orthostatic hypotension, unexplained loss of consciousness; uncontrolled hypertension within the past 2 months before day 0 (D0); cancer of any type, severe or uncontrolled diabetes, renal or hepatic disease, gastric or duodenal ulcer; past history of significant psychiatric disease or current major depressive episode with Hamilton Psychiatric rating scale for depression (HDRS) score higher than 16.

Study Design

This study was carried out in 105 centers: in the UK (5 centers), Belgium (16 centers), France (44 centers), Spain (15 centers), Germany (10 centers), Italy (6 centers), Argentina (5 centers), and Portugal (4 centers). The study used a randomized, double-blind, two-group parallel design. Patients underwent a run-in placebo period of 15 days and then were randomly assigned to piribedil plus L-dopa or bromocriptine plus L-dopa.

The main objective of the study was to assess the efficacy of piribedil in comparison with bromocriptine in early combination with L-dopa in patients with PD. The primary efficacy criterion was the improvement of the UPDRS III score from baseline on an intention-to-treat basis over 12 months, expressed as the change from baseline to the last observed value, and secondly as the response rate defined by a 30% or more decrease on the UPDRS III score at the last value.[27,28]

Secondary criteria included the last change versus baseline in: L-dopa dose, severity of the disease (Hoehn and Yahr stage), UPDRS II (Activities of Daily Living,

ADL) score, clinical global impressions (CGI) scores, and quality of life.

An ancillary cognitive protocol including Stroop test, semantic and lexical fluency, block design (Wechsler Adult Intelligence Scale-Revised), Wisconsin Card Sorting Test (WCST), and Benton visual retention test was implemented in Argentina, France, Spain, and the United Kingdom. Centers participated if standardized translations of tests were available in the country's language and a trained neuropsychologist worked in the center. Cognitive assessments were performed at D0, month 3 (M3), M6, and M12 and expressed in terms of change between D0 and M12.

EXPERIMENTAL PROCEDURES

Piribedil was given as 50-mg tablets. The starting dose of piribedil was 50 mg/day, increased every 2 weeks in increments of 50 mg up to 150 mg/day. Bromocriptine was prescribed at increased dosage from 1.25 mg/day at D0 to 25 mg/day at D28. The L-dopa dose was kept stable until D28, could be decreased if necessary in the titration period until D42, and thereafter decreased or increased during the rest of the study. Domperidone (60 mg/day) was prescribed to prevent gastrointestinal disorders 2 days before the inclusion until D14, and thereafter the daily dose could be adjusted.

The selection visit included a complete medical history with particular attention to the stability of symptoms throughout the day. Clinical efficacy and safety assessments were performed at baseline and after 2, 4, and 6 weeks, 3, 6, 9, and 12 months.

Safety evaluations included vital sign measurements (weight, blood pressure, and heart rate), adverse events, and biological parameters. At each visit, an open-question interview concerning unexpected events was carried out and compliance was calculated by the count of unused medication.

Statistical Analysis and Sample Size Considerations

Main analyses were performed on the full analysis set and the per-protocol sets at 6 and 12 months. The full analysis set is defined (in accordance with the intention-to-treat principle) as randomly assigned patients having taken at least one dose of medication and having at least one postbaseline assessment of UPDRS III. The per-protocol set is defined as all randomly assigned patients having taken at least one dose of study medication, having an evaluation at M12 (or M6) for the primary efficacy criteria, and without protocol deviation that may interfere with the assessment of efficacy.

The comparison adequacy of the two groups was tested at baseline for the main endpoints and clinical characteristics. The piribedil and bromocriptine groups were compared over the 6-and 12-month periods by a two-tailed Student *t* test. Secondary statistical analyses included two-way analysis of variance (treatment, time) with repeated measures over time (D0, M3, M6, M9, M12).

A χ^2 test was carried out for the response to treatment between groups. Change of L-dopa dose and the last observation carried forward (LOCF) were described for each group. Descriptive analyses by group were performed for other secondary criteria (ADL, CGI, Hoehn and Yahr stage). Effects on cognitive performance were analyzed on an intergroup basis by the Mann–Whitney tests and on an intragroup basis by the Wilcoxon test.

In a two-sided approach with a minimal difference of three points between the two groups on UPDRS III change from baseline, a standard deviation estimated at nine points and an α risk of 0.05, at least 162 patients, with at least one UPDRS III score assessment during the treatment, were planned in each group. A post hoc noninferiority interpretation was carried out on the main efficacy criterion UPDRS III Motor score, in the per-protocol population both at 6 and 12 months of treatment. This analysis was based on a limit of less than a two-point difference in change from baseline and less than 10% in terms of response to treatment, after verifying conditions of applicability were met according to the "Points to consider on switching between superiority and noninferiority",[29] "on adjustment for covariates".[30] Power calculations and statistical analyses were carried out by the Institut de Recherches Internationales Servier.

RESULTS

Demographic Data

A total of 425 patients with idiopathic PD Hoehn & Yahr Stage I to III were included in centers located in France (110 patients), Portugal (27 patients), Spain (119 patients), Argentina (89 patients), Germany (24 patients), Belgium (38 patients), Italy (7 patients), and the United Kingdom (11 patients; Tables 1 and 2). Treatment groups were homogenous at inclusion (Table 1). Most of the patients had no family history of PD (88.6% in the piribedil group and 93.5% in the bromocriptine group). Clinical symptoms reported at the onset of PD were tremor (55.2%), bradykinesia (14.8%), and rigidity (9.5%) with no clinically relevant difference between the two treatment groups for the first onset of symptoms.

A total of 178 nondepressed (Hamilton Depression Rating Scale $>$ 16 points) and nondemented patients (Mini-Mental Status of Folstein score $\geq$ 23) recruited from 21 centers were enrolled for the substudy on cog-

TABLE 1. *Demographics and characteristics of the randomized population at baseline (D0)*

Parameters	Piribedil (n = 210)	Bromocriptine (n = 215)
Men (%)	55.7	55.3
Age (yr)	65.3 ± 7.6	65.1 ± 7.9
UPDRS III	23.8 ± 9.4	24.1 ± 10.6
UPDRS II (ADL)	9.3 ± 4.4	9.2 ± 4.5
Duration of the disease (mo.)	37 ± 24	39 ± 29
L-Dopa daily dose at D0 (mg)	395 ± 127	391 ± 122
Hoehn and Yahr stage	2.02 ± 0.5	2.01 ± 0.5
Previous dopamine agonists (%)	19	19.5
Previous selegiline (%)	30	27
Previous amantadine (%)	7.1	5.6

Values are expressed as mean ± SD, unless otherwise indicated.
UPDRS, Unified Parkinson's Disease Rating Scale; ADL, Activities of Daily Living.

nitive performance and underwent at least one cognitive assessment. Demographic and disease characteristics (motor symptoms) of this subpopulation were similar in the two treatment groups.

Patients

Among 458 selected patients, 425 patients were randomly assigned in the study (Fig. 1). Ninety-nine patients (23.2%) withdrew from the study (Table 2). Of the 178 patients enrolled in the substudy on cognitive performance, the patients who had at least one postbaseline evaluation in one of the cognitive tests were defined as sub–full analysis set (FAS) groups. Homogeneity and relevance of the sub-FAS WCST (n = 119) was validated by a centralized procedure and 110 of 119 patients who had a valid cognitive assessment at M12 were finally analyzed for WCST.

Efficacy

UPDRS III score decreased similarly in both groups over 12 months (Table 3). The percentages of change

TABLE 2. *Distribution of patients*

	Piribedil	Bromocriptine	Entire population
Selected	—	—	458
Randomized	210	215	425
Withdrawn, n (%)	52	47	99 (23.2)
Due to adverse event	41	33	74 (17.4)
Due to non-medical reason	6	8	14 (3.3)
Due to protocol deviation	2	2	4 (0.9)
Due to lack of efficacy	3	4	7 (1.6)
Completed month 12	158	168	326 (76.7)
Full analysis set	209	215	424
Per-protocol set (M1, M12)	124	140	264
Per-protocol set (M2, M6)	143	152	295
Safety set	210	215	425

Data presented as percentage of randomized set.
M, month.

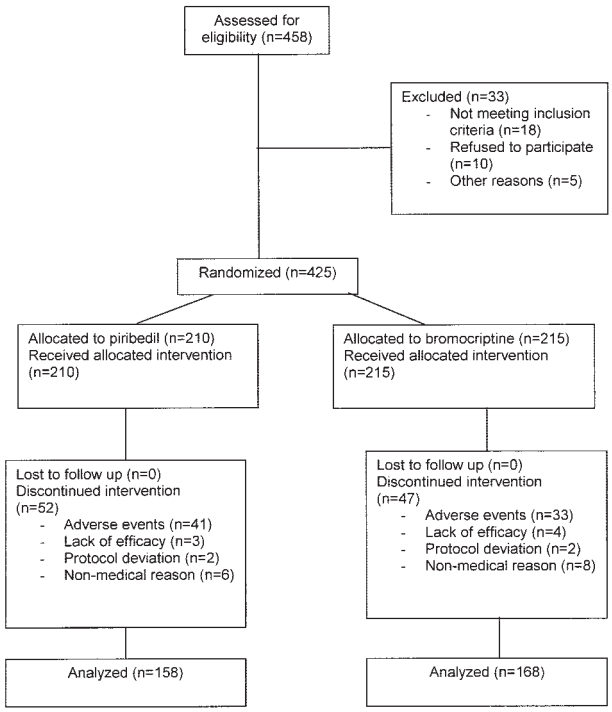

FIG. 1. Flow diagram of the Parkinson–Control study.

began to have a clinical impact from D42, with 34.7 ± 28.9% in the piribedil group versus 38.7 ± 27.9% in the bromocriptine group. The last percentages of variation on treatment were 36.6 ± 38.9% in the piribedil group and 35.3 ± 35.6% in the bromocriptine group, showing the clinical efficiency of both treatments. Regarding the percentage of responders, the last response over 12 months was 58.4% on piribedil versus 55.3% on bromocriptine (not significant [n.s.]) and the last response on treatment was 60.8% versus 58.1%, respectively (n.s.; Fig. 2). All subscores of the UPDRS III (tremor at rest, action on postural tremor, rigidity, bradykinesia, posture and gait, axial symptoms) decreased similarly in both groups (Table 4).

TABLE 3. *UPDRS III decrease from baseline for each expression in the full analysis set (n = 424)*

Change over 12 months	Piribedil (mean ± SD)	Bromocriptine (mean ± SD)	*P**
Full analysis set	n = 209	n = 215	
Last change (main analysis)	−7.9 ± 9.7	−8.0 ± 9.5	0.94
Last change under treatment	−8.7 ± 9.1	−8.6 ± 9.1	0.92
Last change before L-dopa dose increase	−7.9 ± 9.5	−7.7 ± 9.8	0.81

*Two-tailed Student's *t* test for independent samples. None of the comparison is statistically significant.
UPDRS, Unified Parkinson's Disease Rating Scale.

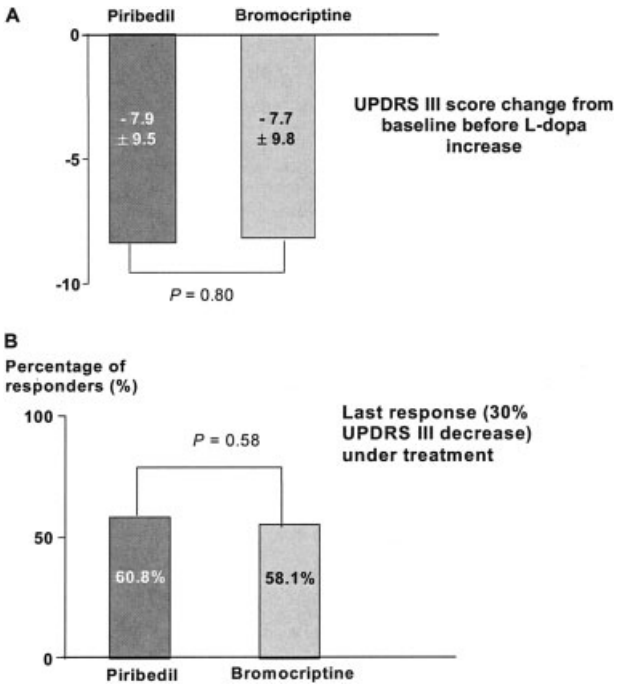

FIG. 2. Efficacy analysis at day 42 (D42; before possible L-dopa increase, reflecting the real effect of each dopamine agonist, the full analysis set, n = 424) **A:** Change from baseline in Unified Parkinson's Disease Rating Scale (UPDRS) III score. **B:** Percentage of responders. Last response under treatment, defined as a 30% decrease from baseline on the UPDRS III score.

L-Dopa prescription initially decreased in both groups and more on piribedil than on bromocriptine: at D42, -7.1 ± 64.4 mg versus -2.1 ± 15.9 mg (n.s.). A modest increase of L-dopa daily dose was observed over 12 months: this dose was slightly less with piribedil than with bromocriptine (7.6 ± 121.9 mg vs. 16.7 ± 91.3 mg; n.s.).

UPDRS II (ADL) scores decreased similarly in both groups (-2.6 ± 5.2 on piribedil vs. -2.7 ± 3.9 on bromocriptine). CGI scores for illness severity at D0 were 2.8 ± 1.1 for the piribedil group and 2.7 ± 1.2 for the bromocriptine group and showed a comparable decrease with scores at M12 of 2.3 ± 1.1 versus 2.2 ± 1.2, respectively.

As expected, cognitive assessment at baseline revealed subtle cognitive impairment, approximately 1 standard deviation below expected values for age in the entire subpopulation. After 12 months, cognitive status was overall unchanged, with no significant difference between piribedil and bromocriptine on most of the tests, except for a significant effect of piribedil on the WCST. This finding was more prominent in the younger patients (50 to 70 years of age). The number of fulfilled criteria increased in patients on piribedil (from 3.2 (2.0) to 3.6 (1.9)), whereas it slightly decreased in the bromocriptine group (from 4.0 (1.9) to 3.7 (2.1)). Intergroup analysis for the number of criteria was in favor of piribedil (Mann–Whitney; $P < 0.032$). Intragroup analysis demonstrated a significant effect of piribedil (Wilcoxon; $P = 0.035$) and no effect of bromocriptine ($P = 0.247$). No significant difference on number of total errors was found between groups. Similar results were found after 6 months, excluding the sole explanation of a retest effect. A significant negative correlation between the improvement in the number of fulfilled criteria and age was found only in the piribedil-treated patients ($P < 0.042$; $r = -0.305$).

In light of the substantial similarity in motor effects observed in the two treatment groups, corresponding to relevant clinical improvement of patients over the study duration, a post hoc noninferiority interpretation was considered for the main efficacy parameter, the UPDRS III, on the baseline change and on the percentage of responders. For both UPDRS III expressions (bromocriptine piribedil difference of mean changes and difference in response rate), the 95% confidence intervals were found, respectively, lower than 2 (or even 1.5) points and much lower than 10% percentage (Figs. 3 and 4), thus demonstrating the noninferiority of piribedil (150 mg/day) versus bromocriptine (25 mg/day).

Safety and Tolerability

A total of 74 patients (17.4%) reported at least one adverse event resulting in treatment discontinuation, 41 being in the piribedil group (19.5%) and 33 in the bromocriptine group (15.3%). Emergent gastrointestinal adverse events resulted in treatment discontinuation slightly more frequently in the bromocriptine group (6.5% vs. 5.2%) and hallucinations in the piribedil group (2.9% vs. 1.4%).

During the study, 81.9% of the patients reported at least one emergent adverse event, i.e., 175 patients (83.3%) in the piribedil group and 173 patients (80.5%) in the bromocriptine group. Table 5 reports the most frequently (> 3.5% of patients) reported emergent symptoms. The incidence of hallucinations (8.1% vs. 2.8%) was higher for piribedil than for bromocriptine. Interestingly, dyskinesia was infrequently observed over 1-year (2.9% on piribedil vs. 4.7% on bromocriptine), and none being severe in either group.

Forty-four patients (10.4%), 25 (11.9%) from the piribedil group and 19 (8.8%) from the bromocriptine group, reported at least one serious emergent adverse event. Most of the serious emergent adverse events were psychiatric disorders (2.4% of patients on piribedil vs. 0.5%) and cardiovascular disorders (1.9% vs. 0.5%).

TABLE 4. *Subscore decreases of UPDRS III, last change at M12, and last change under treatment ([a]), full analysis set (n = 424)*

UPDRS Part III subscores	Piribedil (n = 209)	Bromocriptine (n = 215)	Intergroup comparison (*P*)
Tremor at rest	−1.2 ± 2.3	−1.2 ± 2.0	0.90
	−1.4 ± 2.1[a]	−1.3 ± 1.9[a]	0.53
Action or postural tremor	−0.3 ± 1.0	−0.4 ± 1.0	0.19
	−0.3 ± 1.0[a]	−0.5 ± 1.0[a]	0.10
Rigidity	−1.9 ± 2.9	−2.1 ± 2.9	0.41
	−2.1 ± 2.8[a]	−2.3 ± 2.8[a]	0.46
Bradykinesia	−3.5 ± 5.0	−3.0 ± 4.8	0.29
	−3.7 ± 4.7[a]	−3.3 ± 4.7[a]	0.31
Postural and gait	−0.5 ± 1.5	−0.6 ± 1.4	0.50
	−0.6 ± 1.4[a]	−0.7 ± 1.4[a]	0.67
Axial score	−0.5 ± 1.5	−0.7 ± 1.4	0.25
	−0.6 ± 1.4[a]	−0.7 ± 1.4[a]	0.38

Values are expressed as mean ± SD. Differences are not statistically significant for any comparison.
[a]Values under treatment.
UPDRS, Unified Parkinson's Disease Rating Scale.

Two patients in the piribedil group died during the study period: one from a myocardial infarction, which came abruptly (with no clinical signs in favor of an hypothetical underlying valvular disease) and was judged unrelated to treatment; the second patient presented with a psychotic episode, a neuroleptic treatment was initiated, and the antiparkinsonian treatment was stopped. The patient died 8 days later from a cardiovascular arrest, and the event was considered as probably related.

DISCUSSION

The present randomized, double-blind, 12-month trial in L-dopa–treated patients is one of the larger therapeutic trials versus reference compound conducted in PD, and the first one to compare two dopamine agonists at fixed doses. It confirms piribedil (150 mg) as a powerful treatment that maintains its efficacy in the long-term. Several clinical studies have already demonstrated the efficacy of piribedil in combination with L-dopa[18,21,22] in improving parkinsonian motor symptoms in stable patients with approximately a 5-year history of PD. The present study further confirms that there is no significant difference in efficacy between piribedil and bromocriptine. Other comparative trials in PD have indicated equal efficacy of nonergoline compounds and bromocriptine.[31–33] However, in those trials, the doses of each dopamine agonist could vary at any time. The change in the UPDRS III score between baseline and last evalua-

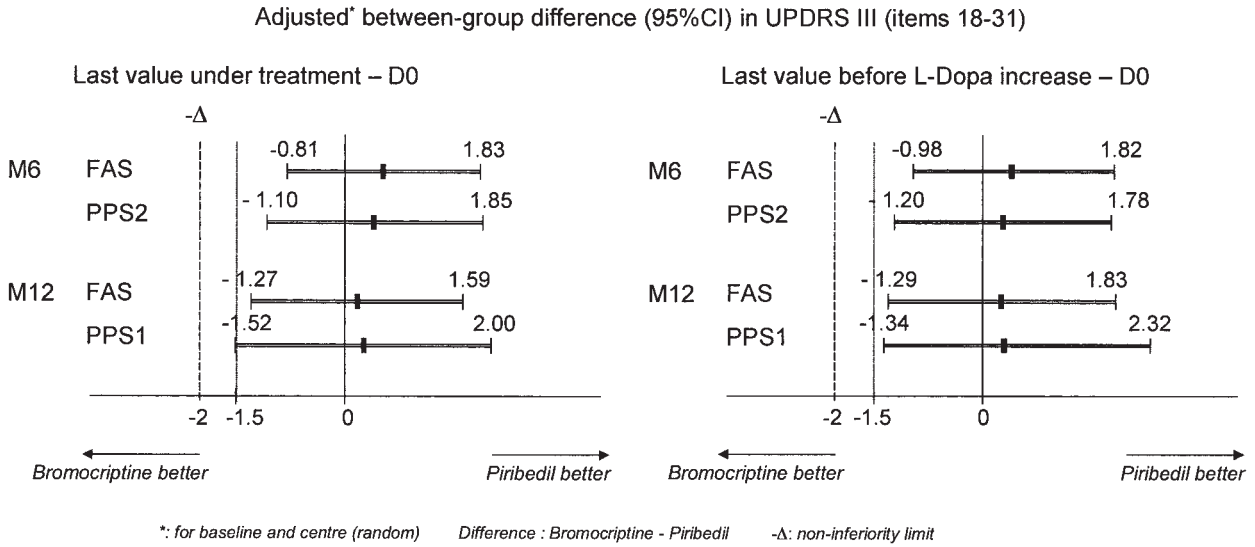

FIG. 3. Noninferiority interpretation. Change in Unified Parkinson's Disease Rating Scale (UPDRS) III (LAST − D0). CI, confidence interval; FAS, full analysis set; PPS1, per-protocol set at 12 months; PPS2, per-protocol set at 6 months.

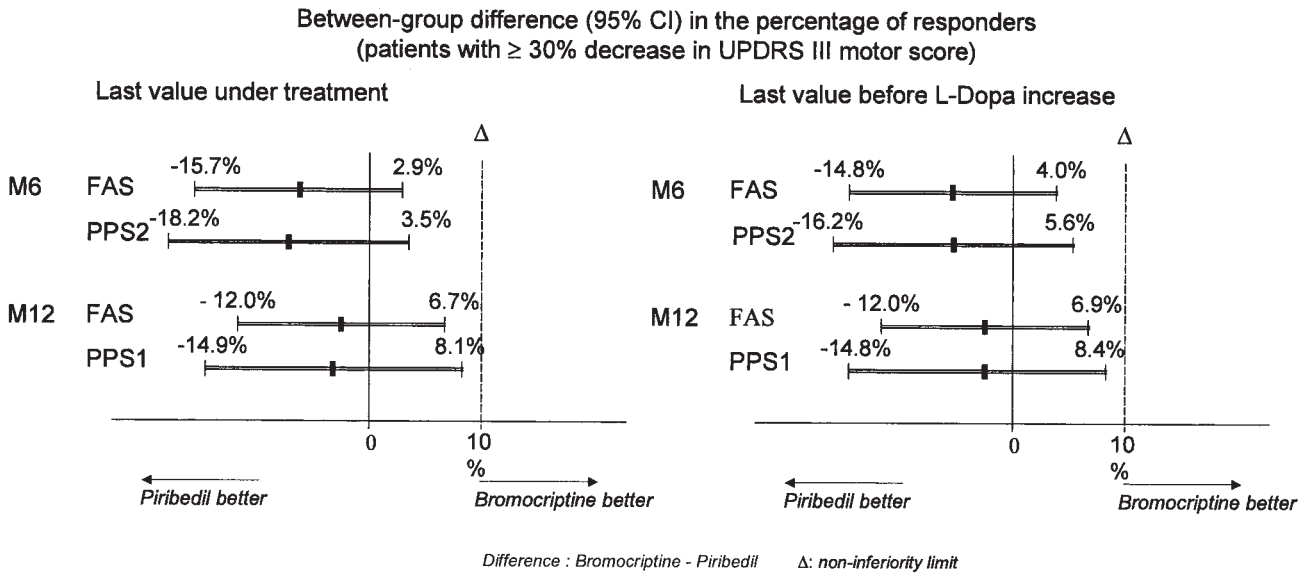

FIG. 4. Noninferiority analyses. Percentage of responders. UPDRS, Unified Parkinson's Disease Rating Scale; CI, confidence interval; FAS, full analysis set; PPS1, per-protocol set at 12 months; PPS2, per-protocol set at 6 months.

tion in the mentioned trials was around eight points, as in the present study. Bromocriptine-controlled studies with pergolide, generally with a limited number of patients and short-term assessment, also reported no or a very modest difference of efficacy between treatments.[34–36]

The present trial also reveals a trend toward a higher number of responders and a lower L-dopa increase after a 1-year treatment in favor of piribedil, which means that the motor efficacy persists with time. Subscore analyses over 12 months of UPDRS III showed slight advantage of piribedil for bradykinesia and slight advantage of bromocriptine for rigidity. Regarding other secondary criteria, piribedil and bromocriptine similarly improved ADL and CGI scores.

After verifying conditions of applicability, a post hoc noninferiority switch was carried out for the main efficacy criterion in the more sensitive per-protocol populations at 6 and 12 months of treatment, based on a noninferiority limit of a two-point difference for UPDRS III change from baseline and 10% in terms of response to treatment. Results (Figs. 3 and 4) showed a lower limit higher than the previously established noninferiority of 2 (or even 1.5) points and much lower than 10% for the percentage of responders. These post hoc results demonstrate statistically the noninferiority of piribedil (150 mg/day) versus bromocriptine (25 mg/day). This finding was confirmed in different study populations (FAS and per- protocol) and on different expressions, demonstrating good internal coherence of results. Thus, both treatments provide comparable therapeutic efficacy, which allows to say that 25 mg of bromocriptine are equivalent to 150 mg of piribedil in its sustained release formulation.

The methodology used in the Control study is robust and strictly in line with recommended scientific standards[28]; Part III of the UPDRS was chosen because it is widely validated and has good interrater reliability,[37] and response defined by at least a 30% reduction from baseline is believed to represent a clinically relevant improvement. A 20% decrease in the UPDRS III score was chosen for the ropinirole study,[31,32] a decrease of 10 points in the UPDRS III score was chosen in the pramipexole study,[33] and a simplified UPDRS (21 items) evaluation was chosen in the major pergolide study.[36].

PD is characterized not only by the classic motor symptoms but also by cognitive deficits, even at early stages of the disease.[38,39] Cognitive dysfunction in PD patients presents frequently as impairment of executive functions (planning, concept formation, set shifting, behavioral adaptation to environmental changes), attention, and visual–spatial deficits. In the present study, a battery of tests mostly oriented toward executive function evaluation was administered to a subgroup of 178 nondepressed, nondemented elderly parkinsonian patients. Among the many tests for cognitive evaluation, the WCST is widely used because it is usually the first test able to detect early impairments and because it requires the participation of all cognitive processes needed for executive functions.[38]

TABLE 5. *Most frequent (>3.5%) treatment emergent adverse events over D0–M12 in the safety set (n = 425)*

System organ class	Piribedil (n = 210)	Bromocriptine (n = 215)
Gastrointestinal system disorders		
Nausea	36 (17.1)	40 (18.6)
Constipation	14 (6.7)	22 (10.2)
Dyspepsia	14 (6.7)	11 (5.1)
Vomiting	9 (4.3)	12 (5.6)
Diarrhea	8 (3.8)	11 (5.1)
Central and peripheral nervous system disorders		
Dizziness	31 (14.7)	30 (13.9)
Headache	9 (4.3)	8 (3.7)
Dyskinesia	6 (2.9)	10 (4.7)
Psychiatric disorders		
Hallucinations	17 (8.1)	6 (2.8)
Somnolence	14 (6.7)	9 (4.2)
Insomnia	10 (4.8)	11 (5.1)
Anxiety	7 (3.3)	10 (4.7)
Depression and depression aggravated	5 (2.4)	8 (3.7)
Body as a whole, general disorders		
Back pain	11 (5.2)	17 (7.9)
Edema peripheral	10 (4.8)	10 (4.7)
Influenza-like symptoms	8 (3.8)	5 (2.3)
Syncope	5 (2.4)	8 (3.7)
Leg pain	2 (1.0)	9 (4.2)
Asthenia	2 (1.0)	8 (3.7)
Cardiovascular disorders		
Hypotension	16 (7.6)	20 (9.3)
Hypertension	15 (7.1)	9 (4.2)
Respiratory system disorders		
Bronchitis	5 (2.4)	8 (3.7)
Metabolic and nutritional disorders		
Weight decrease	4 (1.9)	8 (3.7)
Musculoskeletal system disorders		
Arthralgia	8 (3.8)	2 (0.9)
Skin and appendages disorders		
Sweating increased	8 (3.8)	0 (0)

Values are expressed as n (%), where n = number of patients with at least one emergentadverse event in a given system organ class.
D0, day 0; M12, month 12.

At baseline, as expected, the entire sample of patients did exhibit subtle cognitive changes with respect to normal values for age. After 12 months, piribedil showed a significant effect on the WCST, with a more prominent amelioration in younger patients (<70 years), whereas bromocriptine showed no effect. In both groups there was no correlation between the UPDRS III Motor scores and cognitive results, suggesting a difference in the mode of action between the two compounds. Because the WCST is particularly sensitive to frontal cortex dysfunction, and impaired performance is usually not responsive to dopaminergic replacement,[38–40] the positive effect of piribedil may be related to its additional noradrenergic α_2-antagonistic properties, which have been shown to reinforce corticolimbic adrenergic and cholinergic transmission.[13,14] Such an effect was not observed with bromocriptine. This explanation is further supported by the existence of attention deficits in PD, mainly related to nondopaminergic neuronal systems, which certainly influence the performance of patients on cognitive tests assessing frontal lobe function.[41,42] As the patient population was at a relatively early stage of the disease and the cognitive follow-up was not the main endpoint of the study, these results warrant further confirmation in a specifically designed study upon a larger cohort of PD patients with a clear-cut cognitive dysfunction.[43].

The present study shows that the global efficacy of piribedil on motor symptoms is associated with good tolerability and adverse event withdrawals comparable to bromocriptine. The pattern of emergent adverse events observed with piribedil was basically the same as with other dopamine agonists, being mainly digestive symptoms.[31–36] Hallucinations were more frequently reported for piribedil (8.1%) than for bromocriptine (2.8%); the relatively low incidence of hallucinations in patients on bromocriptine is somewhat surprising, as other studies

using similar doses, such as that by Korczyn and associates comparing ropinirole with bromocriptine, reported incidence rates of 11% and 9%, respectively.[32].

CONCLUSION

Whereas most previous studies of piribedil mainly explored its therapeutic efficacy on tremor, the present trial assessed global, long-term motor efficacy of piribedil versus bromocriptine. The results of this double-blind, randomized trial confirm that the early combination of piribedil with L-dopa significantly improves all motor symptoms in PD patients insufficiently controlled by L-dopa alone and that efficacy is maintained over 1 year. Additional benefits on cognitive performance are suggested by this study at least on executive functions. Taking into account both efficacy and acceptability in the long-term, piribedil in this bromocriptine controlled study proved to be an effective and safe treatment for PD.

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APPENDIX

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