2. What did you understand was the chance of receiving placebo (50:50, one in three, etc.)?
3. Did you feel you improved during the treatment?
   a. Markedly
   b. At least mildly
   c. No
4. Did you think you were assigned placebo during the trial? Yes/No
5. How did you react to the news of being assigned placebo?
   a. Shock
   b. Surprise
   c. No feeling
   d. I suspected as much
   e. I was sure all along
6. How do you feel about having been assigned the placebo ?
   a. Disappointed
   b. Happy
   c. Neutral
   d. Other_____
7. Which are important true statements:
   a. I was hoping for the study drug.
   b. I wasted my time.
   c. I spent money to participate and got nothing.
   d. I inconvenienced other people.
   e. I feel manipulated like a guinea pig.
   f. No special reason, I just feel let down.
   g. I helped advance science.
   h. I avoided possible side effects.
   i. I liked the experience, education and attention.
   j. I did it for other patients as much or more than for myself.
   k. No special reason, I just feel happy.
   l. Other_____
8. If you were informed about another placebo-controlled study in Parkinson's disease, would you be interested?
   a. Definitely
   b. Likely
   c. Maybe
   d. Probably not
   e. No

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Randomized, Double-Blind Study of Pramipexole with Placebo and Bromocriptine in Advanced Parkinson's Disease

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Abstract: **We compared the efficacy and safety of pramipexole (PPX) with placebo in the treatment of advanced Parkinson's disease (PD) as an adjunct to levodopa. A bromocriptine (BR) group was included to enable determination of the noninferiority of PPX relative to BR as the standard treatment.** © 2003 Movement Disorder Society

Key words: Parkinson's disease; pramipexole; bromocriptine; levodopa; drug comparison; randomized controlled trial (RCT)

Dopamine agonists are known for their efficacy as an adjunct to levodopa treatment in patients with advanced

†See Acknowledgments for a full list of study participants.

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Parkinson's disease (PD).[1] However, older dopamine agonists such as bromocriptine (BR) and pergolide induce activity in adrenergic and serotonergic receptors resulting in side effects,[2] as well as certain serious adverse events due to their common ergot chemical structure.[1,2]

Pramipexole (PPX) is a novel nonergoline dopamine agonist of the D_2 receptor family with preferential affinity to the D_3 receptor subtype.[3,4] In North American and European countries, PPX was demonstrated to be effective and safe in early[5,6] and advanced[7] PD compared with placebo. In addition, in a comparative trial with a placebo and BR, the effect of PPX was shown to be significantly superior to that of the placebo and was similar to that of BR in patients with advanced PD in a study involving mainly European countries.[8] To determine whether the efficacy of PPX is significantly superior to that of a placebo and not statistically inferior to BR in patients with advanced PD as an adjunct to levodopa therapy, we conducted a three-arm double-blind comparative study in Japan.

SUBJECTS AND METHODS

Design

This study design was a multicenter, controlled, double-blind, randomized, parallel-group study in patients with advanced PD. Thirty-eight sites were involved in this study throughout Japan. The duration of the trial was 12 weeks (the ascending dose period: up to 8 weeks; the maintenance dose period: at least 4 weeks) followed by a 1- to 4-week dose reduction period. The three treatment groups were PPX, up to 4.5 mg per day; BR, up to 22.5 mg per day; or a placebo. The maximum daily dose of BR was adapted to the dosage and usage approved in Japan.

Patient Selection

Patients of both sexes at least 20 years of age were enrolled in this study. Patients were diagnosed as having PD.[9,10] In addition, patients who exhibited any therapeutically problematic issues based on levodopa therapy such as wearing-off phenomena, on–off phenomena, and freezing phenomena, or in whom the suboptimal dose of levodopa had been administered due to side effects or therapeutic strategy were included. Patients had received an individual dosage of levodopa (plus a decarboxylase inhibitor) and were stable for at least 28 days before the initial administration of the study medication. Before enrollment, all patients gave written informed consent to participate in this study.

Exclusion criteria included patients who had received any dopamine agonists during the 28 days before the investigator obtaining informed consent. Patients with a medical history of hypersensitivity to ergoline derivatives or seizure were excluded. Patients suffering from psychiatric symptoms such as confusion, hallucination, delusion, agitation, delirium or abnormal behavior, symptomatic orthostatic hypotension, hypotension in which systolic blood pressure was less than 100 mm Hg, Raynaud's disease, peptic ulcer, or a clinically significant heart, liver, or kidney disease were also excluded. Treatment with the following drugs during administration of the trial medication was not permitted: alpha methyldopa, reserpine, flunarizine, cinnarizine, lisuride, neuroleptics such as phenothiazine derivatives, butyrophenone derivatives, and benzamide derivatives, clebopride, and metoclopramide. Women with childbearing potential or nursing mothers were not permitted to participate. Patients who had dementia precluding the signing of the informed consent form as well as patients participating in other studies of other investigational drugs within 6 months of baseline were also excluded.

Clinical Procedures

The screening and baseline assessments included medical history, physical examination, modified Hoehn and Yahr Staging[11] *on* Scale, blood pressure, pulse rate, laboratory tests, and Unified Parkinson's Disease Rating Scale[11] (UPDRS, I to IV). Patients were then assigned randomly to one of three treatment groups, namely PPX, BR, or placebo in the identical ratio by an independent third party for enrollment, according to a computer-generated code prepared by the external statistician, "the drug assignment director." A block of every 6 patients was used to ensure close balance of the numbers in each treatment group. All study personnel and participants were blinded to the study medication. The drug assignment director confirmed the blindness at the end of the study.

TABLE 1. *Ascending dose schedule*

Dose level	Week	Period (day)	Total PPX daily dose (mg)	Total BR daily dose (mg)
1	1	3	0.25	1.25
2	1	4	0.5	2.5
3	2	7	1.0	5.0
4	3	7	1.5	7.5
5	4	7	2.0	10.0
6	5	7	2.5	12.5
7	6	7	3.0	15.0
8	7	7	3.5	17.5
9	8	7	4.5	22.5

PPX, pramipexole group; BR, bromocriptine group.

The ascending dose period was up to a maximum of 8 weeks after baseline (Table 1). Patients were titrated to the maximal tolerated dose of the study medication. If an adverse event occurred that could not be tolerated, the patient entered the maintenance dose period at the highest previously tolerated dose.

The duration of the maintenance dose period was at least 4 weeks. Hospital visits occurred every 2 weeks and included assessments of blood pressure, pulse rate, modified Hoehn and Yahr Staging *on* Scale, and UPDRS. In addition, laboratory tests were performed at the beginning, at the eighth week, and at the final maintenance (12th W) or upon discontinuation, and electrocardiograms (ECG) were performed at the beginning and at the final maintenance (12th W) or upon discontinuation. During this study, concomitant medication for the treatment of PD such as anticholinergics, amantadine, droxidopa, and deprenyl were maintained at fixed doses for at least 28 days before the initial administration of the study medication. Domperidone was allowed to alleviate any gastrointestinal adverse effects caused by the study medication.

Efficacy Endpoints

The primary endpoints were the change from the baseline on the final maintenance of the total score of UPDRS II; Activities of Daily Living (ADL) Scale (average of *on* and *off* scores), and the total score of UPDRS III, Motor Examination Scale. Motor examinations were performed during *on* time with the last dose of levodopa.

Secondary endpoints included the total score of UPDRS I, IV, and I to III, modified Hoehn and Yahr Staging Scale, Clinical Global Impression on Efficacy (CGI), and the responder analysis on the changes of UPDRS II and III, and I to IV total scores.

Safety

Safety evaluation was based on the number of patients who experienced adverse events and abnormalities of laboratory or physical examination, if any.

Statistical Methods

According to the outcomes of a prior study,[8] the assumption that the equivalence margins delta for the two primary variables, UPDRS II and UPDRS III, were 1 and 2 would be appropriate. The sample size sufficient to detect noninferiority in the group concomitantly treated with levodopa was estimated to be approximately 90 patients per group ($\alpha = 0.05$, power = 0.8, one-sided). The aim of this study was to confirm two hypotheses. First, that PPX is superior to the placebo in treatment effect. Second, that PPX is not inferior to BR in treatment effect. The hypotheses were to hold only if both endpoints were statistically significant, and adjustment for multiplicity was not performed. Data were analyzed by two different methods. The primary analysis was for full analysis set (FAS) with the application of the last observation carried forward method. The secondary analysis focused on the observed cases, which comprised patients with complete data. Patients with at least one dose of the study medication and at least one complete postbaseline assessment were considered suitable for FAS.

For testing the first hypothesis, a nonparametric approach based on the Wilcoxon-Mann-Whitney test was used. For the second hypothesis, 90% confidential intervals of the mean difference were calculated. The equivalence margins delta for the two primary variables, UPDRS II and UPDRS III, were 1 and 2, respectively. The other statistical methods used for the secondary endpoints included Fisher's exact test.

RESULTS

A total of 325 patients were randomized into the study and 315 participated in the study medication (Fig. 1). Patients were recruited from April 1999 to March 2000. For FAS analysis, 313 patients were included. The reasons for excluding 2 patients from FAS were lack of the UPDRS assessment after study medication and incorrect value of UPDRS III at baseline in that the examiner had evaluated *off* time UPDRS III. Although a few protocol deviations were observed in remaining 313 patients, none should be excluded from the FAS. There was no statistical imbalance among the three groups based on sex, age, duration of PD, Modified Hoehn and Yahr Staging *on* Scale, the total score of UPDRS II and III, and the daily dose of levodopa (Table 2).

The average daily dose of the PPX group at the final maintenance of this study was 3.24 mg (SD = 1.33) and that of the BR group was 17.75 mg (SD = 5.76).

The primary outcome measures are shown in Figure 2a and b. The total scores of both UPDRS II and III were significantly reduced in the PPX group ($P < 0.001$) compared to the placebo group. The efficacy of the PPX group on both primary endpoints was not statistically inferior to that of the BR group (UPDRS II: delta = 1, 90% confidence interval [CI] = −0.16 to 1.63; UPDRS III: $\delta = 2$, 90% CI = −0.56 to 4.09). BR treatment was also significantly better than the placebo group, but the magnitude of the response was less than that observed with the PPX group. This study was not empowered to detect differences between the two active treatment groups.

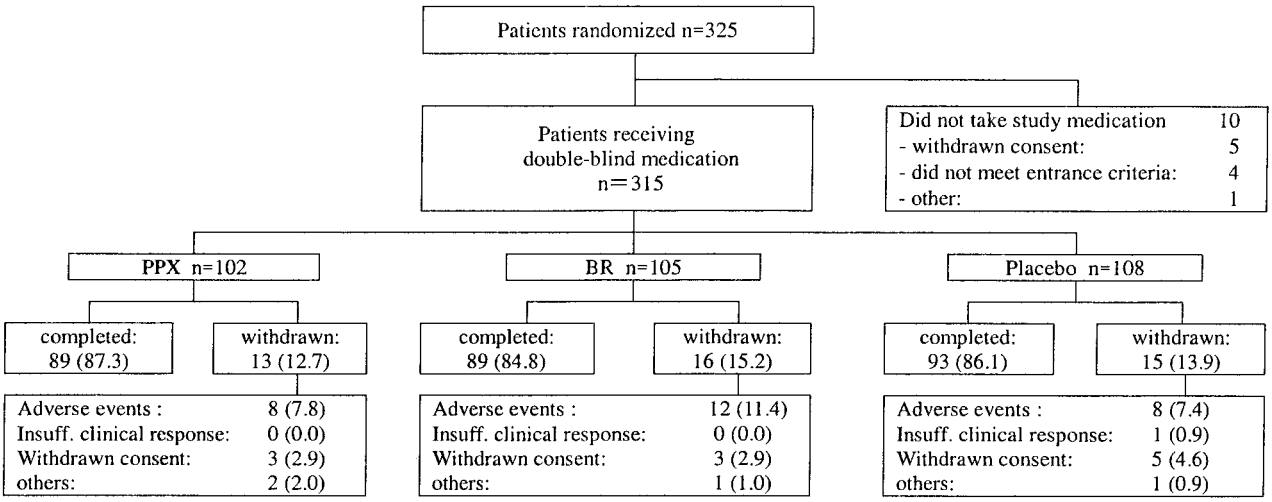

FIG. 1. Patients randomized to each treatment group, patients who completed, withdrawals, and reasons for withdrawals. PPX, pramipexole; BR, bromocriptine. Numbers in parentheses indicate percentages.

The mean changes in UPDRS II and III scores for the PPX group as shown in Figure 3a and b were greater for each visit throughout the treatment period than for the placebo group and the BR group (BR: UPDRS II, after week 4).

The results of secondary endpoints are summarized in Table 3. There was no significant difference for the PPX group in the analysis of UPDRS I when compared with the placebo group ($P = 0.169$) and the BR group ($P = 0.323$). Analysis of UPDRS IV indicated a significant difference favoring placebo over PPX ($P = 0.006$), but there was no significant difference between the PPX group and the BR group ($P = 0.789$) in this analysis. The PPX group showed a significant improvement compared with the placebo group ($P < 0.001$) and a trend toward significant improvement compared with the BR group ($P = 0.053$) in the analysis of the modified Hoehn and Yahr Staging Scale. Significance was noted in the CGI, with greater improvement in the PPX group compared with both the BR group ($P = 0.022$) and the placebo group ($P < 0.001$). Improvement rates, defined as "effective" and/or "very effective", for the CGI were 61.8%

TABLE 2. *Summary of baseline demographic information (FAS)*

	PPX	BR	Placebo	Total
Patients (n)	102	104	107	313
Sex, n (%)				
Male	60 (58.8)	49 (47.1)	56 (52.3)	165 (52.7)
Female	42 (41.2)	55 (52.9)	51 (47.7)	148 (47.3)
Age (yr), mean (SD)	65.46 (9.45)	64.53 (7.47)	63.96 (8.64)	64.64 (8.55)
Duration of PD (yr), mean (SD)	4.79 (4.07)	5.03 (3.96)	5.73 (7.05)	5.19 (5.25)
Modified H&Y stage, mean (SD)	2.66 (0.70)	2.59 (0.74)	2.64 (0.82)	2.63 (0.75)
UPDRS II				
Median	9.00	10.00	9.00	9.00
Range	1–45	1–25	0–44	0–45
Mean	10.44	10.29	10.36	10.36
SD	6.54	5.28	7.09	6.34
UPDRS III				
Median	26.50	26.00	26.00	26.00
Range	2–63	5–72	4–72	2–72
Mean	27.11	27.20	27.36	27.22
SD	12.53	11.78	13.53	12.60
Daily dose of levodopa (mg), mean (SD)	404.90 (275.17)	377.88 (237.79)	422.43 (330.33)	401.92 (283.88)

PPX, pramipexole group; BR, bromocriptine group; PD, Parkinson's disease; H&Y, Hoehn and Yahr; UPDRS, Unified Parkinson's Disease Rating Scale.

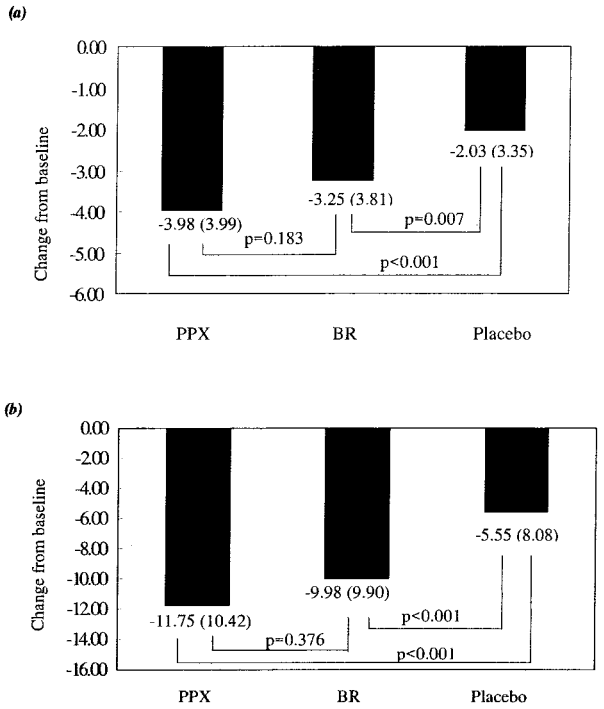

FIG. 2. a: Unified Parkinson's Disease Rating Scale II (UPDRS II, Activities of Daily Living) change in mean score at final maintenance from baseline. **b:** UPDRS III (Motor) change in mean score at final maintenance from baseline. PPX, pramipexole; BR, bromocriptine. Numbers indicate the mean score decreases, and the standard deviations are in parentheses. The differences between the placebo and bromocriptine and placebo and pramipexole were statistically significant both in UPDRS II and III. But the difference between bromocriptine and pramipexole did not reach statistical significance in both endpoints, although the pramipexole group showed greater decrease in the mean score in UPDRS II. The statistical analysis between bromocriptine and placebo were not planned in the original protocol. However, for the sake of clear comparison, this additional analysis has been done. Statistical analyses used were full analysis set and last observation carried forward analyses. The statistical analysis between bromocriptine and placebo was not planned in original protocol.

in the PPX group, 47.1% in the BR group, and 28.0% in the placebo group. The proportions of responders, defined as showing a 30% or more reduction in UPDRS II and III, and I to IV total scores from baseline, were significantly larger in the PPX group than in the placebo group for each variable ($P < 0.001$). No significant difference was observed between PPX and BR in these response rates. The rates of responders in PPX, BR, and placebo were 56.9%, 49.0%, and 29.9% in UPDRS II, 63.7%, 60.6%, and 36.4% in UPDRS III, 61.8%, 51.9%, and 36.4% in UPDRS I to IV total scores, respectively.

Adverse events, which were reported by more than 10% of patients, in each group are presented in Table 4. The rate of patients with adverse events in the PPX group (85.3%) showed no significant difference compared with the BR group (90.5%) and the placebo group (76.9%). Three patients in the PPX group had serious adverse events (fracture after a fall, dehydration, and colon cancer), but these findings were not considered related to the study drug. A hallucination was experienced by 1 patient in the BR group and was considered as a drug-related serious adverse event. The "sudden onset of sleep" was observed in 1 patient in the BR group. The number of withdrawals in each treatment group due to adverse events was 8, 12, and 9 patients in the PPX, the BR, and the placebo groups, respectively. The majority of withdrawals in all treatment groups was dropout during the ascending dose period. Some abnormal changes or findings in blood pressure, pulse rate, or ECG were observed in a few patients in all groups, but none were considered major clinical problems.

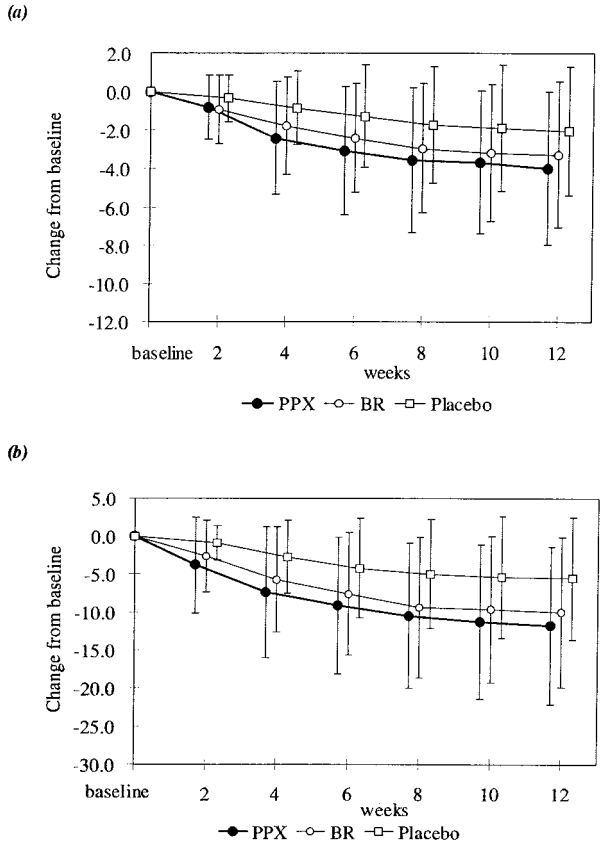

FIG. 3. a: Unified Parkinson's Disease Rating Scale II (UPDRS II, Activities of Daily Living [ADL]) change in mean score at each visit from baseline to the end of maintenance period. **b:** UPDRS III (Motor score) change in mean score at each visit from baseline to the end of maintenance period. The ordinates indicate UPDRS II (ADL) score changes (a) and UPDRS Part III (Motor) score changes (b). The abscissae indicate weeks after the start of dosing. The mean value and standard deviation of each visit are described. PPX, pramipexole; BR, bromocriptine.

TABLE 3. *Secondary endpoints (LOCF, FAS)*

	PPX	BR	Placebo
Subjects (n)	102	104	107
UPDRS I, total score, change from baseline			
Decrease	26 (25.5)	19 (18.3)	16 (15.0)
No change	71 (69.6)	76 (73.1)	85 (79.4)
Increase	5 (4.9)	9 (8.7)	6 (5.6)
P-value vs. PPX[a]	—	0.323	0.169
UPDRS IV, total score, change from baseline			
Decrease	20 (19.6)	19 (18.3)	17 (15.9)
No change	52 (51.0)	58 (55.8)	76 (71.0)
Increase	30 (29.4)	27 (26.0)	14 (13.1)
P-value vs. PPX[a]	—	0.789	0.006
Modified Hoehn & Yahr stages, change from baseline			
Decrease	61 (59.8)	46 (44.2)	33 (30.8)
No change	40 (39.2)	56 (53.8)	71 (66.4)
Increase	1 (1.0)	2 (1.9)	3 (2.8)
P-value vs. PPX[a]	—	0.053	<0.001
Clinical global impression[b]			
Effective or better	63 (61.8)	49 (47.1)	30 (28.0)
P-value vs. PPX[c]	—	0.022	<0.001
Responder rate[d]			
UPDRS II	58 (56.9)	51 (49.0)	32 (29.9)
P-value vs. PPX[a]	—	0.268	<0.001
UPDRS III	65 (63.7)	63 (60.6)	39 (36.4)
P-value vs. PPX[a]	—	0.668	<0.001
UPDRS I–IV	63 (61.8)	54 (51.9)	39 (36.4)
P-value vs. PPX[a]	—	0.162	<0.001

Values are expressed as n (%), unless otherwise indicated.

[a]Fisher's exact test; [b]Wilcoxon two-sample test for original five categories.

[c]Clinical global impression of efficacy included five categories: markedly effective, effective, slightly effective, ineffective, and undesirable.

[d]Thirty percent decrease in each total score from baseline was defined as "Responders".

LOCF, last observation carried forward; FAS, full analysis set; PPX, pramipexole group; BR, bromocriptine group.

The dose reduction period was set for the safety of the patients participating, but the dose reduction period was not a part of the test period. Therefore, data for this period are not reported apart from adverse events. No serious adverse events occurred during the dose reduction period.

TABLE 4. *Main adverse events reported in more than 10% of subjects*

	PPX	BR	Placebo
Subjects treated (N)	102 (100)	105 (100)	108 (100)
Adverse event	87 (85.3)	95 (90.5)	83 (76.9)
Central and peripheral nervous system disorders			
Dyskinesia	16 (15.7)	9 (8.6)	6 (5.6)
Dizziness	18 (17.6)	32 (30.5)	14 (13.0)
Headache	12 (11.8)	16 (15.2)	10 (9.3)
Somnolence	15 (14.7)	26 (24.8)	14 (13.0)
Psychiatric disorders			
Hallucination	14 (13.7)	16 (15.2)	4 (3.7)
Autonomic nervous system disorders			
Mouth dry	11 (10.8)	13 (12.4)	12 (11.1)
Gastrointestinal system disorders			
Anorexia	18 (17.6)	20 (19.0)	16 (14.8)
Dyspepsia	26 (25.5)	23 (21.9)	19 (17.6)
Nausea	24 (23.5)	32 (30.5)	24 (22.2)
Vomiting	11 (10.8)	7 (6.7)	3 (2.8)
Constipation	19 (18.6)	19 (18.1)	13 (12.0)

Values are expressed as n (%), unless otherwise indicated.

PPX, pramipexole group; BR, bromocriptine group.

DISCUSSION

In this study, PPX showed superiority to placebo on the UPDRS II (ADL) and III (Motor) scores. Our results are consistent with those of previous placebo-controlled comparative studies of PPX in patients with advanced PD as adjunctive therapy to levodopa.[7,12–14] UPDRS has been used for primary variables in international clinical studies of PPX.[5–9] In Japan, however, to date, no clinical studies have been conducted using UPDRS for efficacy endpoint. Upon conducting our study, we had prepared the Japanese version of UPDRS based on the original[11] and confirmed its reliability.[15] Most of the Phase III DBT of other dopamine agonists in Japan had been conducted by parallel group comparison with BR as a standard treatment using clinical global impression as the primary endpoint. Accordingly, our trial is notable as being the first clinical trial for Parkinson's disease in Japan using more reliable methods. The results of the primary measures in both of our study and the European study,[9] which was a parallel group comparison of three treatment groups (PPX, BR, and placebo) like ours, were comparable.

With respect to comparison with the BR group, the PPX group showed noninferiority to the BR group but no significant difference was observed. This result is probably attributable to insufficient patient numbers. The magnitude of the observed changes in the UPDRS ADL and Motor scores were greater in the PPX group than in the BR group.

Comparison of the mean changes in these scores from baseline to each subsequent visit suggested that the PPX group experienced earlier onset of response and greater improvement than the BR group throughout the treatment period.

The secondary endpoints, responder rates and CGI, endorsed PPX's superiority. The responder rates in both UPDRS II and III were greater in the PPX group than in the BR group. The higher improvement rate of PPX in CGI in efficacy seems to be related to the finding that patients on PPX responded particularly well in UPDRS II and the Modified Hoehn and Yahr Staging Scale as well as the earlier onset of efficacy.

The BR comparative clinical trials of other dopamine agonists such as pergolide, cabergoline and ropinirole for advanced PD have been conducted in Japan using CGI as a primary endpoint.[16–18] None of the results of their trials could disclose superiority to BR. The significant outcome on CGI in our trial may indicate that PPX has an advantage over the other dopamine agonists. All these trials and our trial of PPX used a 22.5-mg daily dose as the maximal dose of BR, according to the approved dose in Japan, which was low compared to that in the United States and Europe (40 mg daily).

Comparing different dopamine agonists is an interesting strategy. However, very few well-designed randomized studies addressed this approach. To date, there is no evidence indicating that one dopamine agonist is superior to another,[19–23] except for the present study, as shown in the secondary endpoints. Our results warrant further studies to see different profiles of dopamine agonists being used.

In our study, significant differences in UPDRS IV scores were seen between the PPX and placebo groups, but not between the PPX and BR groups. One reason underlying the difference between the PPX and the placebo groups may be that the rate of both "increasing" and "decreasing" was greater than placebo group, whereas the majority of patients in the placebo group experienced "no change." The higher rate of "increasing" and "decreasing" was also observed in the BR group. Therefore, dopamine activation by PPX and BR might affect subscores A (dyskinesias) and B (clinical fluctuations) and indicated the significant difference in this analysis.

There were no unexpected adverse events noted in this study. Both PPX and BR were well tolerated. Adverse events in the PPX group that were at least 10% higher than in the placebo group were dyskinesia and hallucination, which were regarded as dopaminergic complications. In the BR group, dizziness, somnolence, and hallucination occurred at a higher rate ($\geq$10%) than in the placebo group. The safety profiles of PPX are considered to be comparable with the other dopamine agonists. The sudden onset of sleep, which has been reported internationally under PPX medication,[24,25] was not observed in the PPX group. However, it should be remembered that excessive daytime sleepiness and sleep attacks can occur as a result of the use of any dopamine agonists.

In conclusion, our study shows that PPX was significantly more effective than the placebo and not inferior to BR in patients with advanced Parkinson's disease as an adjunct to levodopa therapy, with no particular safety concerns noted.

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