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Clinical evaluation of ropinirole controlled-release formulation at 18–24 mg/day in Japanese patients with Parkinson's disease

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ABSTRACT

Introduction: There has been no clinical data on Japanese patients with Parkinson's disease with which to examine whether motor symptoms improve and to assess the safety profile after the dose of ropinirole was increased in those who had not achieved an optimal response to the ropinirole immediate-release formulation 15 mg/day or the controlled-release (CR) formulation 16 mg/day.
Methods: This was a multicenter, randomized, double-blind study, followed by an open-label, long-term study. Participants were randomized at a ratio of 3:1 to the high-dose ropinirole CR (18–24 mg/day) group or the maintenance ropinirole CR 16 mg/day group.
Results: In the high-dose ropinirole CR group (N = 61), the Japanese unified Parkinson's disease rating scale Part III total score at week 12 was significantly decreased compared with the baseline total score (−4.8 ± 5.95, [95% CI, −6.3 to −3.2], $p < 0.001$). However, a comparable decrease was also observed in the maintenance ropinirole CR 16 mg/day group (N = 20) (−5.7 ± 5.18, [95% CI, −8.1 to −3.3]), with no statistically significant difference in the adjusted mean change between the high-dose and maintenance groups (0.5 [95% CI, −2.4 to 3.4]). Plasma drug concentrations increased at doses higher than 16 mg/day, but did not increase significantly in a dose-dependent manner at doses of 18–24 mg/day. No adverse events were found that would affect the known safety profile of ropinirole.
Conclusion: This study did not demonstrate the difference in efficacy between the high-dose ropinirole CR group and the maintenance ropinirole CR group.
Clinical trial registration: ClinicalTrials.gov identifier: NCT01929317.

1. Introduction

Ropinirole hydrochloride (JAN) developed by SmithKline Beecham, UK, (currently GlaxoSmithKline) is a non-ergot alkaloid dopamine receptor agonist that has selective affinity for the dopamine D2 receptor system. The ropinirole controlled-release (CR) formulation, which is an extended-release version of ropinirole hydrochloride, was approved in Japan for the treatment of Parkinson's disease in June 2012.

In Japan, ropinirole CR can be administered to a maximum dose of 16 mg/day, which is deemed equivalent to a maximum dose of 15 mg/day for the preceding ropinirole immediate-release (IR) formulation. In other countries, however, both ropinirole CR and IR can be administered to a maximum dose of 24 mg/day [1–3], with differences in the approved dose between Japan and other countries. According to published reports of ropinirole hydrochloride administered at a maximum dose of 24 mg/day, ropinirole improved “wearing off” and dyskinesia [4], and delayed the need for stereotactic surgery or continuous apomorphine infusion [5]. Previous studies of ropinirole CR in Japan have shown that there are no clear ethnic differences in the pharmacokinetic profile between Japanese and non-Japanese patients with Parkinson's disease [Company internal document].

In the present study, therefore, the efficacy and safety of ropinirole CR administered at doses of 18–24 mg once daily were

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evaluated in Japanese patients with Parkinson's disease who had not achieved an optimal response to ropinirole IR 15 mg/day or ropinirole CR 16 mg/day to determine whether a dose increase from 16 mg, the maximum daily dose of ropinirole CR approved for Parkinson's disease in Japan, to 24 mg, the equivalent approved in other countries, would yield additional clinical benefits or raise new safety concerns. In addition, the long-term safety was evaluated. Incidentally, there has been no comparison study between high-dose and standard-dose controlled formulation of the other dopamine agonists in Japanese or Asian population.

2. Methods

2.1. Ethics

This was a multicenter study in Japanese patients with Parkinson's disease, conducted at 17 medical institutions from August 2013 to June 2015. The protocol, informed consent documents, and other aspects of this study requiring prior approval were reviewed and approved by the Institutional Review Board as specified in the "Good Clinical Practice (GCP) for Drugs." The study was implemented in compliance with GCP. Furthermore, all applicable requirements for the protection of participants' privacy and the Declaration of Helsinki were adhered to by protecting participants' personal information and data. Written informed consent was obtained from all participants.

2.2. Trial design

This was a multicenter, randomized, double-blind study followed by an open-label long-term study. It comprised a 4-weeks screening phase, 12-weeks dose increase effect verification phase, 1-week down titration phase 1, 39-weeks long-term phase, a 1- to 2-weeks down titration phase 2, and follow-up phase (1–4 weeks after the end of study treatment) (Supplemental Figure). The first 60 participants who completed the dose increase effect verification phase entered the down titration phase 1 and then the long-term phase. The remaining participants who completed the dose increase effect verification phase entered the down titration phase 2 and then completed the study. Participants were randomly assigned at a ratio of 3:1 to either the high-dose ropinirole CR group (18–24 mg/day) or maintenance ropinirole CR 16 mg/day group. Stratified randomization according to concomitant L-dopa (ropinirole monotherapy or L-dopa adjunct therapy) was used.

The maintenance ropinirole CR 16 mg/day group was included in the study to confirm the efficacy and safety at the maximum dose (16 mg/day) approved in Japan in the same study. However, because a large sample size was required for a parallel-group comparison study to verify the superiority of high-dose ropinirole CR to the maintenance dose of 16 mg/day, the primary evaluation was a comparison before versus after the dose increase of ropinirole CR in the high-dose ropinirole CR group.

2.3. Study population

Patients who met all of the following criteria were eligible for the study: those who were diagnosed with Parkinson's disease in stages I-IV on the modified Hoehn and Yahr scale during the "on" period; those who were receiving ropinirole IR 15 mg/day or CR 16 mg/day and had a unified Parkinson's disease rating scale (UPDRS) Part III total score (during "on") of 10 or more at the start of screening; and those who were expected to show clinical improvement by increasing the dose of ropinirole CR (to 18–24 mg/day).

Participants receiving ropinirole monotherapy had never received L-dopa, or had previously received L-dopa at doses up to 450 mg/day for up to 3 months in total and had been withdrawn from L-dopa for a minimum of 4 weeks prior to screening. Participants on L-dopa adjunct therapy had received L-dopa (up to 450 mg/day) for at least 4 weeks prior to screening. We were concerned that if L-dopa dosage was too high, it may difficult to obtain the effect of high-dose ropinirole CR compared to standard dose (16 mg). Therefore L-dopa dosage was limited up to 450 mg/day.

The following patients with Parkinson's disease were excluded from the study: those with advanced disease characterized by severe peak dose or biphasic dyskinesia, or unpredictable symptomatic fluctuations despite treatment with a stable dose of L-dopa; those with symptomatic orthostatic hypotension (e.g., dizziness, syncope); those with severe dementia as indicated by a UPDRS Part I, item 1 (intellectual function) score of 3 or 4; those with current or prior severe psychosis (e.g., schizophrenia, psychotic depression) as indicated by a UPDRS Part I, item 2 (thought disorder) or item 3 (depression) score of 3 or 4; and those who had previously received surgical treatment for Parkinson's disease (e.g., pallidectomy, deep brain stimulation).

2.4. Treatment

During the screening phase, all participants received ropinirole CR 16 mg/day. Ropinirole CR (or placebo) was orally administered once daily at the same time each day, preferably in the morning for maximum benefit.

2.4.1. Dose increase effect verification phase (double-blind)

The daily dose of ropinirole CR or placebo was adjusted to 18–24 mg by 2 mg/day at intervals of 1 week or longer from week 0 to week 7, depending on the clinical response/tolerance of each participant. After week 8, the participants received treatment at the same dose level for 4 consecutive weeks.

2.4.2. Long-term phase (open-label)

To enter the long-term phase without disrupting the treatment assignment in the dose increase effect verification phase, the daily dose of ropinirole CR was reduced to 18–20 mg during the down titration phase 1 after the dose increase effect verification phase was completed. The long-term treatment with ropinirole CR was then started at a dose of 18 mg. The daily dose of ropinirole CR was increased to 18–24 mg by 2 mg/day at intervals of 1 week or longer, depending on the clinical response/tolerance of each participant.

2.5. Outcomes

2.5.1. Efficacy

The primary endpoint was the change in the Japanese UPDRS Part III total score from week 0 to week 12 in the high-dose ropinirole CR group during the dose increase effect verification phase. The secondary endpoints were the UPDRS Part I, II, and IV total scores, modified Hoehn and Yahr severity, "on"/"off" time (only participants on L-dopa adjunct therapy), clinical global impression-improvement(CGI-I) (7 grades from "very much improved" to "very much worse"), and proportion of participants remaining in the study. For the on/off time, participants were instructed to record in the diary the off time, on time, on time with troublesome dyskinesia, and asleep times over 2 days before a given day of evaluation.

2.5.2. Pharmacokinetics (PK)

Plasma ropinirole concentrations were measured after administration of ropinirole CR at doses of 16–24 mg. Blood sampling for pharmacokinetics was conducted immediately before

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