Article Title: Sustained efficacy of apomorphine in Japanese patients with advanced Parkinson's disease

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See the appendix for a list of 6500-004 study group.

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Short title: SC Apomorphine for Parkinson's Disease

Key words: Parkinson's disease; dopamine agonist; apomorphine; randomized controlled study

Abstract

Background: This report presents data from one of the first trials of apomorphine rescue treatment for advanced Parkinson's disease (PD) conducted in Japan. This 3 month trial aimed to evaluate the sustainability of efficacy of intermittent apomorphine rescue treatment.

Methods: A phase III, double-blind, placebo-controlled trial was conducted in PD patients (n = 31) with motor fluctuations in spite of individually titrated treatment with levodopa and other anti PD. Intermittent treatment was titrated to the maintenance dose with a subsequent unblind 12-week outpatient phase. At the week-12 visit, response to apomorphine or placebo was assessed as primary efficacy endpoint using the Unified Parkinson's Disease Rating Scale (UPDRS) part III (Motor Examination) under double-blind crossover conditions.

Results: In the crossover phase (n = 28), least squares mean changes in the the UPDRS part III score from pre-dose were -24.5 points with apomorphine and -2.3 points with placebo, showing that apomorphine, compared with placebo, provided a significantly greater improvement in the UPDRS part III score change (difference between treatments: -22.1 [95% confidence interval, -27.8, -16.4]; $P < 0.001$). The most frequently reported adverse events during the study were increased eosinophil count (8 patients), nausea (7), somnolence (6), dyskinesia (5), yawning (5), and decreased blood pressure (3).

Conclusions: Our results indicate that a 3-month use of intermittent apomorphine is an effective rescue therapy for "off" episodes in advanced PD patients.

Introduction

Apomorphine injection, although not marketed for intermittent use in Japan, has been used overseas including in US, UK, Germany and France as a fast-acting rescue treatment for “off” episodes in advanced Parkinson’s disease (PD) patients with symptoms refractory to individually titrated oral medications.

Reports of several studies on the efficacy and safety of long-term apomorphine use have been published [1-3]. The placebo-controlled Study APO302 by Ronald et al. showed that apomorphine administered for 3 months or longer was effective in PD patients [4]. Hughes et al. concluded from their 5-year follow-up study that the reduction in the duration of “off” state by intermittent apomorphine was stable and long-lasting [3].

This double-blind, placebo controlled and crossover study (Study 6500-004) aimed to confirm the sustainability of efficacy after 3-months apomorphine treatment in Japanese apomorphine-naïve patients with advanced PD.

Patients and methods

- Study overview

This study was conducted in sixteen neurology centers in Japan. It consisted of (i) an open-label dose-escalation titration phase, (ii) a 12-week open-label outpatient phase and (iii) a randomized, double-blinded, placebo-controlled, crossover phase with the study was approved by the appropriate institutional review boards, and all subjects provided written informed consent.

- Patients

1 Eligibility criteria were as follows: age ≥ 20 years; diagnosis of PD; modified Hoehn and Yahr Stage 4-5 in
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4 “off” state and 0-3 in “on” state [5]; a sufficient response to levodopa defined as more than 30% reduction
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6 from pre-dose in the Unified Parkinson’s Disease Rating Scale (UPDRS) part III score; and a stable PD
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8 medication regimen including levodopa and other PD medication with a levodopa dosing frequency of at
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10 least 3 times per day for at least 28 days. Key exclusion criteria included: prior apomorphine use, a Mini
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12 Mental State Examination score ≤ 23 , or treatment with central dopamine receptor-blocking agent or
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14 antipsychotic medication within 3 months.
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21 The package inserts for Apo-go and Apokyn, brand names for subcutaneous apomorphine in the UK and
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23 the US, require that an antiemetic such as domperidone or trimethobenzamide be started prior to the initial
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25 apomorphine dose [6, 7]. No clear evidence, however, has shown that the prophylactic use of antiemetics is
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27 necessary. Patients with advanced PD may have acquired a high threshold for nausea or vomiting because
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29 of decreased sensitivity to dopamine stimulation caused by long-term use of dopamine agonists. For this
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31 reason antiemetic use were prohibited for prophylactic use for 28 days prior to the first dose of study drug
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33 and during the study to evaluate tolerance without prophylactic antiemetics. Patients who were prescribed
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35 an antiemetic over 28 days prior to the first dose of study drug were prohibited from modifying the dosage
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37 regimen. Antiemetics were permitted to treat nausea that occurred during study drug use. No dosage
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39 regimen modifications were to anti- PD agents were allowed in the 28 days prior to the first dose of study
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41 drug and during the titration phase. Antipsychotic agents were prohibited during the study.
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57 • Treatment
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59 Apomorphine hydrochloride 10 mg/mL was supplied in 3 mL cartridges packaged in un-blinded cartons for
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1 the titration and outpatient phases. Apomorphine and matching placebo were supplied in identical
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3 cartridges and blinded cartons for the crossover phase. Apomorphine was subcutaneously injected with a
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5 dosing injector in the abdomen, thigh or upper arm to treat “off” episodes. No more than 5 doses were
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7 allowed per day at intervals of at least 120 minutes.
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11 During the pre-study period, performed 35 days or less before the titration started, each patient’s response
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13 to his or her usual dose of oral levodopa was assessed in the “off” state. In the titration phase, each
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15 patient’s response to apomorphine 20-40 min after injection was evaluated in 1-mg increments from 1 mg
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17 up to 6 mg. Administration of the same doses was allowed, and dose reduction to any level was also
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19 permitted when needed. Treatment was titrated to an optimal maintenance dose deemed adequately
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21 effective and well tolerated by the investigator. They judged the efficacy based on the parameters including
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23 UPDRS part III scores and duration of “on” states. The trial was terminated in patients for whom no
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25 optimal maintenance dose of apomorphine was achieved in the range of 1–6 mg.
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29 After self injection training, patients began apomorphine use on an as-needed basis for 12 weeks
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31 (outpatient phase). At week-2, 4 and 8 visits, efficacy and tolerability were evaluated, with apomorphine
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33 dose adjustments allowed up to 10 weeks. At week 12, active and placebo drugs were administered at the
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35 week-10 level of maintenance dose in a randomized, double-blind, crossover fashion. Patients were
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37 allocated to group A (to receive active first, and placebo second) or group B (to receive placebo first, and
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39 active second) at the 8-week visit. At the week-12 visit, the first study drug was assessed for efficacy
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41 during an observed “off” state, and on or after the next day, the second study drug was administered during
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43 a similar “off” state. A window of $\pm$ 1-week was allowed for each visit.
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1 • Evaluation

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3 The primary efficacy variable was change from pre-dose in UPDRS part III score 20–40 minutes after
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6 dosing during the double-blind crossover phase.
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9 Secondary endpoints included change from pre-dose in UPDRS motor score at optimal maintenance dose
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12 in the titration phase and time to onset and duration of “on” state in the titration and crossover phases. In
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15 the outpatient phase, patients recorded the daily apomorphine injection times in diaries.
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18 Safety assessments included the recording of adverse events (AEs) during the study, vital signs at every
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21 visit and laboratory evaluations and ECG in the titration phase and at week-4 and 12 visits.
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27 • Statistical analysis

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29 Data analysis was performed on hierarchical sets of subject samples, including the safety set (patients who
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32 had at least one dose of study drug), full analysis set (FAS; patients who were randomized, received at least
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35 one double-blind study drug and had at least one set of pre- and post-dose UPDRS motor data in the
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38 crossover phase), and per protocol set (patients who were randomized, received two double-blind study
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41 drugs and had two sets of pre- and post-dose UPDRS motor data in the crossover phase and who had no
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44 major protocol deviations).
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47 Sample size was calculated based on an expected reduction in UPDRS motor score of –20 points for
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50 apomorphine and –3 points for the placebo groups,. We calculated that we would need a sample size of 8
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53 patients per group to detect a reduction in UPDRS part III total score at a 5% significance level and a
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56 power of 90%, assuming intra-subject standard deviations are 18.5 for apomorphine group and 6.0 for
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59 placebo group. The final sample size was determined to be 20 patients or more, given an anticipated
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dropout rate of 20%.

Analysis of covariance was applied to the change from pre-dose UPDRS part III score, which constituted the primary efficacy measure, with drug, group (A or B), timing of dose (first and second) and pre-dose UPDRS part III score as fixed effects and subject as random effect. The least squares (LS) mean and its 95% confidence interval (CI) were calculated for each treatment to evaluate the efficacy of apomorphine relative to that of placebo.

A brief description is provided on the analysis of secondary endpoints including difference between pre- and post-dose UPDRS part III scores at the maintenance dose in the titration phase and time to onset and duration of “on” state before and after dosing in the titration and crossover phases.

For safety assessment, AEs were presented without distinguishing whether the subject was on apomorphine or placebo.

Subject eligibility was determined before the database lock as appropriate.

Results

- Study population

Subjects were recruited between February and July 2010. Of 36 subjects screened, 31 met the inclusion criteria and started apomorphine titration. Three subjects dropped out: 1 for AEs and 2 for withdrawal of consent. Of 28 subjects randomized, 15 were allocated to group A and 13 to group B. All 31 subjects exposed to apomorphine were evaluated for safety, while the 28 subjects who completed the study were included in the FAS and per protocol set for efficacy evaluation.

Table 1 shows the baseline demographic and clinical characteristics. Groups A and B were generally well

matched in baseline characteristics.

- Exposure to study drug

The maintenance dose determined in the titration phase averaged 2.6 mg (range 1–5 mg, n = 30). Of the 30 subjects who proceeded to the outpatient phase, 4 changed their dose between weeks 0 and 4: 1-mg increase in 3 and 2-mg decrease in 1. The maintenance doses in the crossover phase were 1 (n = 6), 2 (n = 8), 3 (n = 4), 4 (n = 9) and 5 mg (n = 1) and the average dose was 2.7 mg (n = 28). In the outpatient phase, the mean of the individual average number of daily doses was 1.55 (0.2–4.6), the mean of the individual average daily dose was 4.49 mg (0.2–18.5 mg) and the average duration of treatment was 79.4 days.

- Efficacy of subcutaneous apomorphine

Crossover phase

In the crossover phase after 12 weeks of apomorphine treatment, the study drug was administered twice on separate days to evaluate UPDRS part III scores pre-dose and 20 - 40 minutes post-dose.

Apomorphine markedly reduced UPDRS part III scores to 16.9 ± 15.2 (mean $\pm$ standard deviation [SD]) 20 - 40 minutes post-dose from 41.0 ± 17.4 pre-dose. The placebo had no effect on UPDRS part III scores, which were 42.5 ± 16.8 pre-dose and 39.9 ± 18.6 20 - 40 minutes post-dose. The LS mean changes (95% CI) in UPDRS part III score were -24.5 (-28.5 , -20.4) for the apomorphine group and -2.3 (-6.4 , 1.7) for the placebo group (Fig. 1). The point estimate (95% CI) of differences between apomorphine and placebo groups in score change was -22.1 (-27.8 , -16.4), showing that the reduction in UPDRS part III score with apomorphine was significantly and statistically greater than that with placebo ($p < 0.001$).

Table 2 summarizes times to onset and durations of “on” state in the FAS in the crossover phase.

Apomorphine induced an “on” state in 25 (89.3%) of 28 subjects, with a mean time to onset of 14.2 (range 2–34) minutes and a mean duration of 62.6 (30–127) minutes. The placebo also induced an “on” state in 5 (17.9%) of 28 subjects; mean time to onset 11.4 (2–25) minutes and mean duration 51.4 (25–73) minutes.

Titration phase

Mean changes in patients’ UPDRS part III score from pre-dose score and the maintenance dose were –28.7, with 1 mg –32.8, with 2 mg –17.0, with 3 mg –31.3 with 4 mg and –16.0 with 5 mg, averaging -28.2 ± 13.5 (mean $\pm$ SD). “On” states occurred 16.8 ± 9.3 minutes after apomorphine treatment and lasted 68.7 ± 33.1 minutes on average (Table 2).

- Safety of subcutaneous apomorphine

Of the 31 subjects exposed to apomorphine, 27 (87.1%) experienced AEs. The most frequent events were raised eosinophil count in 8 subjects (25.8%), followed by nausea in 7 (22.6%), somnolence in 6 (19.4%) and dyskinesia and yawning in 5 (16.1%) each. No severe AEs were reported. AEs were moderate in severity in 4 subjects. Two patients experienced nausea and decreased blood pressure, and one patient experienced vomiting, one somnolence, one yawning and one cold sweats. Most events occurred during the titration phase, whereas the eosinophil count increase first occurred in or after the outpatient phase in 7 of 8 subjects. Incidence was not dose-related for any of the events. One subject (3.2%) discontinued treatment due to AEs: decreased blood pressure, postural dizziness and headache. These occurred the 3 mg dose during the titration phase and resolved within a day of discontinuation. The severity was moderate

(decreased blood pressure) and mild (postural dizziness, headache). AEs requiring dose reduction were reported in 6 subjects (19.4%): somnolence in 2 (6.5%) and decreased blood pressure, dizziness postural, nausea, dyskinesia and yawning in 1 (3.2%) each.

In this study, prophylactic use of antiemetics was prohibited except in those who had been on antiemetic treatment before the start of study. Of the 31 subjects exposed to apomorphine, 5 were using concomitant antiemetic at the beginning of titration phase, while the remaining 26 were not. Nausea occurred in 7 (22.6%) of the 31 subjects analyzed for safety. In one (3.2%) subject nausea was complicated by vomiting. Action was taken in only 3 of the 7 subjects who experienced nausea/vomiting: domperidone was added in 2 (10 mg three times a day in 1 patient and 10 mg once a day in another patient) and apomorphine dose reduced in 1. No subject discontinued the study due to gastrointestinal upset. Of the 26 subjects who did not use antiemetics, 6 (23.1%) had nausea, with 1 of them complicated by vomiting; none of the remaining 20 had any gastrointestinal upset.

Some laboratory variables in a few subjects showed higher or lower values than reference ranges, but they were clinically insignificant. ECG tracings were normal in all subjects.

Discussion

In this study, we showed that apomorphine is still effective at week 12 of treatment, showing an effect similar in magnitude to that of levodopa. A mean time to onset of about 15 minutes at week 12 in the crossover phase and a mean duration of about 1 hour for the induced “on” state indicated that apomorphine is sufficiently effective and fast acting to be a rescue therapy for “off” episodes. Although apomorphine is used as a rescue treatment, it could be used regularly in advanced PD patients over the long-term. The

1 sustained efficacy of apomorphine after a 3-month treatment suggests that continuous administration of
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3 apomorphine is effective. Although the proportion of AEs was high, discontinuation was only reported in
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5 one subject and dose reduction in 6 subjects. AEs requiring dose reduction disappeared with no other action
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7 taken within 4 days and without recurrence. Apomorphine was well tolerated without requiring
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9 modifications to the dosing regimen of daily oral PD drugs.
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15 The findings concerning motor improvement and time to onset and duration of “on” state in this study are
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17 consistent with those reported in Study APO302 [4], a placebo-controlled, parallel-group comparative study
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19 conducted in the US to assess the efficacy of apomorphine after at least 12 weeks of administration.
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24 Prophylactic use of antiemetics was prohibited except in those who had been receiving antiemetic treatment
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26 before the start of study. Approximately 20% of the subjects reported gastrointestinal AEs, including nausea
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28 and vomiting. Some of them required an antiemetic or apomorphine dose reduction and disappeared soon
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30 after these action taken, but none discontinued the study for gastrointestinal AEs, suggesting that it is
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32 feasible to start apomorphine without pre-treatment with antiemetics. One possible explanation is that many
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34 of the subjects could have developed tolerance to the adverse effects of dopamine agonists following long-
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36 term treatment with other anti-PD drugs [8]. A longer dosing interval (120 minutes) and a starting titration
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38 dose of as small as 1 mg may contribute to the prevention of gastrointestinal events.
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47 The mean maintenance dose per injection (2.6 mg) in this study was a little lower than that of 3 to 5 mg
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49 reported in open-label studies in advanced PD patients in other countries [9]. This finding justified a
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51 starting dose of 1 mg and subsequent dose increases in 1-mg increments. The gradual titration in 1-mg
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53 increments may have allowed more precise estimations of the effective dose than titrations in 2-mg
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55 increments from a starting dose of 2 mg recommended for Apokyn™ in the US.
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1 In this study, apomorphine was successfully titrated to an individual optimal dose in most subjects (30 of
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4 31) exposed to apomorphine. A total of 28 subjects continued apomorphine treatment for 12 weeks with
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7 good tolerance and persistent efficacy. Apomorphine can be expected to be an effective option for the
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10 rescue treatment of “off” episodes in advanced PD patients in Japan just as in countries where it is
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12 prescribed for this indication.
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18 **Full financial disclosures**

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21 Nobutaka Hattori, MD (Juntendo University School of Medicine); Nobutaka Hattori is an advisory board
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23
24 member for Kyowa Hakko-Kirin pharmaceutical Company and he received personal compensation when
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26
27 he attended advisory board meetings. Nobutaka Hattori has received grants from the Japanese Ministry of
28
29
30 Education, Culture, Sports, Science, and Technology, the Japanese Ministry of Health, Labor and Welfare
31
32
33 (20261501, 22140501 and 22140901), the Health and Labor Scientific Research, JST and CREST, Grant-in-Aid
34
35
36 for Scientific Research (21390272 and 80218510), and Scientific Research on Innovative Areas (23111003),
37
38
39 Grants-in-Aid from Research on Measures for Intractable Diseases and Research on Health Sciences focusing on
40
41
42 Drug Innovation. Nobutaka Hattori has received honoraria from FP Pharmaceutical Company, Novartis
43
44
45 Pharma, Nihon Medi-Physics Company, Zeria Pharmaceutical Company, Boehringer-Ingelheim Japan,
46
47
48 Benesis Corporation, Astellas Pharmaceutical Company, Mitsubishi Tanabe Pharmaceutical Company,
49
50
51 Pfizer Japan, Sanofi, MSD and Takeda Pharmaceutical Company.
52

53
54 Masahiro Nomoto, MD (Ehime University Graduate School of Medicine); Masahiro Nomoto consulted for
55
56
57 Hisamitsu Pharmaceutical Company, Kyowa Hakko-Kirin Pharmaceutical Company and Otsuka
58
59
60 Pharmaceutical Company. Masahiro Nomoto is an advisory board member for Kyowa Hakko-Kirin
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Pharmaceutical Company and he received personal compensation when he attended advisory board meetings. Masahiro Nomoto has received grants from the Japanese Ministry of Health, Labour and Welfare. Masahiro Nomoto received honoraria from Dainippon-Sumitomo Pharmaceutical Company, GlaxoSmithKline, Novartis Pharma and Ono Pharmaceutical Company.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgment

We greatly appreciate the study investigators, study coordinators, and participating subjects. This study supported by Kyowa Hakko-Kirin Pharmaceuticals.

Appendix

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Clinic), Nishikawa N (Ehime University Hospital), Tsuboi Y (Fukuoka University Hospital), Ohya Y
(University Hospital, University of the Ryukyus).

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Table 1 Baseline demographic and PD characteristics

	Safety evaluation population (n=31)	Crossover population (FAS)	
		Group A	Group B
		Placebo/apomorphine (n=15)	Apomorphine/placebo (n=13)
Gender (n)			
Men	18 (58.1%)	7 (46.7%)	8 (61.5%)
Women	13 (41.9%)	8 (53.3%)	5 (38.5%)
Age (y)	61.6 (10.6)	64.3 (10.9)	58.5 (9.9)
Body weight (kg)	56.7 (13.9)	54.3 (14.5)	56.3 (13.0)
Duration of PD (y)	12.1 (6.5)	12.5 (5.2)	12.2 (8.5)
Time since onset of motor complication (y)	6.0 (4.5)	7.3 (5.8)	4.6 (2.8)
Baseline levodopa dose (mg/day)	491.9 (192.4)	446.7 (123.2)	542.3 (240.5)
“Off” state frequency per day	3.7 (1.3)	3.6 (1.2)	3.9 (1.6)
Baseline “off” state, Hoehn and Yahr stage (n)			
4	25 (80.6%)	13 (86.7%)	10 (76.9%)
5	6 (19.4%)	2 (13.3%)	3 (23.1%)
Baseline “on” state, Hoehn and Yahr stage (n)			
0	6 (19.4%)	4 (26.7%)	2 (15.4%)
1	2 (6.5%)	0 (0.0%)	0 (0.0%)
1.5	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	2 (6.5%)	0 (0.0%)	2 (15.4%)
2.5	9 (29.0%)	3 (20.0%)	5 (38.5%)
3	12 (38.7%)	8 (53.3%)	4 (30.8%)
Baseline UPDRS motor score			
“Off” state	41.8 (17.4)	43.2 (19.6)	41.8 (16.3)
“On” state	17.5 (11.5)	17.3 (12.7)	18.5 (10.9)
Baseline PD medications (n)			
Dopamine agonists	27 (87.1%)	14 (%)	11 (84.6%)
MAO-B inhibitors	15 (48.4%)	9 (60.0%)	4 (30.8%)
COMT inhibitors	25 (80.6%)	13 (86.7%)	9 (69.2%)
Baseline use of antiemetics (n)			
Domperidone	2 (6.5%)	1 (6.7%)	0 (0.0%)
Mosapride citrate	3 (9.7%)	2 (13.3%)	1 (7.7%)

Data are expressed as number (%) or mean (SD).

SD: standard deviation; PD: Parkinson’s disease; UPDRS: Unified Parkinson’s disease Rating Scale; FAS: full analysis set

Table 2

Time to onset and duration of “on” state in the titration and crossover phases

	Titration phase		Crossover phase	
	Apomorphine	Placebo	Apomorphine	
	(n=30)	(n=28)	(n= 28)	
"On" manifestation (n) (%)	30 (100%)	5 (17.9%)	25 (89.3%)	
Time to onset (minute)*	16.8 (1-50)	11.4 (2-25)	14.2 (2-34)	
Duration of "on" (minute)*	68.7 (34-215)	51.4 (25-73)	62.6 (30-127)	

* Data are given as mean (range) of “on”-manifesting population.

Fig 1. Change from pre-dose UPDRS part III score (The least squares mean and 95% confidence interval). Crossover doses were evaluated at 20-40 minutes post-dose at week-12 visit.