The Long-Term Impact of Early Versus Delayed Treatment with Rotigotine Transdermal System in Patients With Early-Stage, Idiopathic Parkinson's Disease

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Background

- Parkinson's disease (PD) is a progressive neurodegenerative disorder; however, symptomatic therapy can provide benefit for many years.
- In view of the potential for drug complications in PD, the initiation of treatment is customarily delayed until the symptoms of PD significantly limit the patient's ability to function at work or socially.[1] There is increasing evidence to challenge this traditional recommendation:
  - The rate of clinical deterioration in PD is rapid in the early stages (a decline of 8 to 10 Unified Parkinson's Disease Rating Scale [UPDRS] points in the first year after diagnosis), suggesting this is a time of opportunity for treatment intervention[2]
  - Earlier rather than delayed initiation of PD treatment may lead to better long-term motor benefit.[3,4]
- Delayed treatment may result in the loss of abilities that cannot be regained later in the disease course, and thus early treatment may lead to better long-term benefit.
- Rotigotine* is a unique dopamine agonist with activity across D1 through D5 receptors as well as select adrenergic and serotonergic sites;[5] continuous transdermal delivery of rotigotine maintains stable plasma levels over 24 hours with a single daily application.[6]
- The SP702 study[7] was a long-term, open-label extension of the SP512 study,[8,9] a 6-month, randomized, double-blind, placebo-controlled study of rotigotine in patients with early-stage PD. Continuous transdermal delivery of rotigotine was well tolerated for up to 6 years, with sustained efficacy (UPDRS II + III total score) for at least 2 years.[7]

Objective

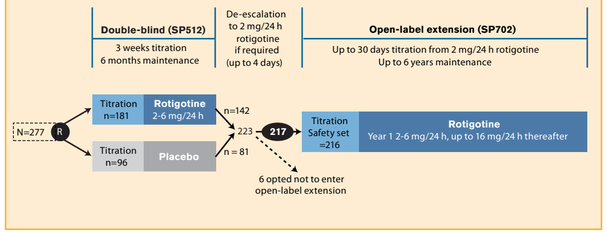
- This post hoc analysis of the SP702 study investigates the long-term impact of early vs delayed treatment with rotigotine transdermal system in early-stage PD.

Methods

SP512 and SP702 Study Design

- In SP512, a 6-month, double-blind study, patients were randomized in a 2:1 ratio to rotigotine or placebo titrated to optimal dose (2, 4, or 6 mg/24 h).
- In SP702 (ClinicalTrials.gov: NCT00594165), an open-label extension of the double-blind study, patients received rotigotine (up to 16 mg/24 h) for up to 6 years.

Figure 1. SP702 study design



Patient Eligibility

- Double-blind study (SP512):
  - Early-stage idiopathic PD (≤5 years' duration)
  - Hoehn and Yahr Stage I to III
  - No previous or concurrent therapy with a dopamine agonist, or with carbidopa/levodopa within 28 days of baseline.
- Open-label extension (SP702):
  - Completion of the double-blind maintenance period
  - No ongoing serious adverse event related to trial medication
  - Concomitant levodopa permitted, if required, after 1 month of open-label rotigotine maintenance therapy.

Early- vs Delayed-Start Rotigotine

In this post hoc analysis:

- Early-start patients were those who had received rotigotine during the 6-month, double-blind study; initiation of rotigotine treatment started in the double-blind study.
- Delayed-start patients were those who had received placebo during the 6-month, double-blind study; initiation of rotigotine treatment started in the open-label study.
- The effect of early- vs delayed-start rotigotine on change from double-blind baseline UPDRS II+III total score is reported for:
  - All SP702 patients
  - A subgroup of SP702 patients with very early PD (Hoehn and Yahr Stage I to II).
- Efficacy analyses were performed on the safety set, defined as all patients who received at least one dose of rotigotine in the open-label extension.

Results

Patients

- 217 of 277 (78%) patients completed the double-blind study and entered the open-label extension.
- 60 (22%) patients did not enter the extension; 54 were ineligible because of non-completion of the double-blind study and six opted not to participate.
- 47% of patients remained in the study upon closure by the sponsor; 24% withdrew prematurely because of adverse events, 6% because of lack of efficacy.

Table 1. SP702 (open-label extension) demographic and baseline characteristics (double-blind baseline)

Safety set* (n=216)	Early-start patients (double-blind rotigotine) (n=137)	Delayed-start patients (double-blind placebo) (n=79)
Age, mean ± SD, years	61.7 ± 10.2	65.8 ± 10.0
Male, n (%)	98 (72)	49 (62)
Mean duration of PD (range), years	1.3 (0-6)	1.4 (0-5)
UPDRS Part II score, mean ± SD (range)	7.9 ± 4.5 (1-22)	8.4 ± 3.9 (1-17)
UPDRS Part III score, mean ± SD (range)	21.5 ± 8.4 (8-48)	20.4 ± 8.1 (5-50)
UPDRS Part II+III total score, mean ± SD (range)	29.4 ± 11.4 (10-69)	28.8 ± 10.4 (7-61)
Hoehn and Yahr Stage, n (%)		
I	35 (26)	17 (22)
II	76 (55)	48 (61)
III	26 (19)	14 (18)
Prior and concomitant PD medications, n (%)	59 (43)	38 (48)

* One subject received open-label trial medication at the final visit of the double-blind phase, but never returned to the clinic and was therefore excluded from the safety set

Concomitant Levodopa Treatment in the SP702 Study

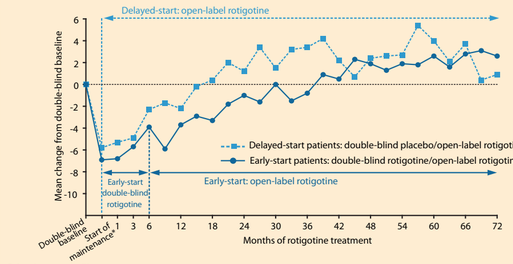
- During up to 6 years of open-label rotigotine treatment, a similar proportion of patients in each subgroup started concomitant levodopa treatment: 75% of early-start patients and 70% of delayed-start patients.
- The mean ± SD dose of concomitant levodopa used during the open-label study was also similar: 365.4 ± 158.5 mg/day (early-start patients) and 388.1 ± 224.6 mg/day (delayed-start patients).

UPDRS II+III Total Scores (Early- vs Delayed-Start Rotigotine)

All Patients From the SP702 Study

- Mean ± SD UPDRS II+III total scores at double-blind baseline were similar between groups: 29.4 ± 11.4 (early-start patients) and 28.8 ± 10.4 (delayed-start patients).
- Upon initiation of rotigotine maintenance, mean changes from double-blind baseline UPDRS II+III total scores were -6.9 ± 6.5 for early-start patients (where rotigotine maintenance started in the double-blind study) and -5.8 ± 7.2 for delayed-start patients (where rotigotine maintenance started in the open-label extension) (Figure 2).
- After this initial improvement, mean change scores declined, but remained below double-blind baseline for 36 months for early-start patients and for 15 months for the delayed-start patients (Figure 2).

Figure 2. All patients from SP702 study: mean change from double-blind baseline in UPDRS II+III total scores (safety set, as observed)



Delayed-start: n=	79	76	67	60	54	44	41	36	24	
Early-start: n=	136	135	136	110	108	104	83	77	66	

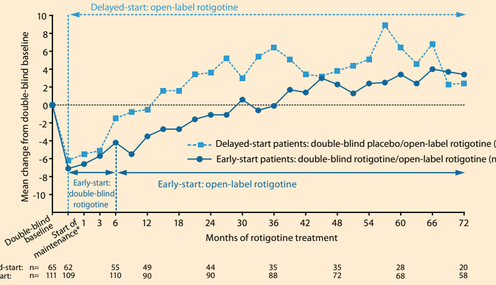
*For early-start patients: rotigotine maintenance starts after double-blind titration; delayed-start patients: rotigotine maintenance starts after open-label titration

- The mean change scores of early-start patients remained below (indicating less decline) those of delayed-start patients (by between 0.8 and 5.0 points) for 42 months of rotigotine treatment.

Subgroup of Patients With Very Early PD

- 111 of 137 (81%) early-start patients and 65 of 79 (82%) delayed-start patients had very early PD (Hoehn and Yahr Stage I to II) at double-blind baseline.
- In this subgroup of patients with very early PD, mean ± SD UPDRS II+III total scores at double-blind baseline were similar between early-start (28.0 ± 10.7) and delayed-start (26.8 ± 8.4) patients.
- In the subgroup of patients with very early PD, after an initial improvement at the start of rotigotine maintenance, mean change from baseline UPDRS II+III total scores declined but remained below double-blind baseline for 27 months for early-start patients and for 12 months for delayed-start patients (Figure 3).

Figure 3. Patients with very early PD: mean change from double-blind baseline in UPDRS II+III total scores (safety set, as observed)



Delayed-start: n=	65	62	55	49	44	35	35	28	20	
Early-start: n=	111	109	110	90	90	88	72	68	58	

*For early-start patients: rotigotine maintenance starts after double-blind titration; delayed-start patients: rotigotine maintenance starts after open-label titration

- The mean change scores of early-start patients remained below those of the delayed-start patients (by between 0.2 and 6.5 points) for 66 months of rotigotine treatment.

Conclusions

- In this post hoc exploratory analysis of the SP702 study, a 6-month earlier initiation of rotigotine treatment resulted in less decline of UPDRS II+III scores for approximately 3 years, suggesting that if initiation of treatment is delayed, patients may not have the opportunity to attain maximal benefits because of disease progression in the early stages of PD.
- A similar effect was observed in the subgroup of patients with very early PD, suggesting that there does not appear to be a threshold for early initiation of treatment, and supporting the concept that treatment intervention in the very early stages of PD, when there is a rapid rate of deterioration, may be beneficial.[2]
- This post hoc exploratory analysis suggests that a 6-month earlier initiation of rotigotine treatment may be associated with improved long-term benefits in patients with early-stage PD.
- Prospective studies are required to investigate this further.

*Rotigotine transdermal system (Neupro®, a registered trademark of the UCB Group of Companies) is licensed by the FDA for the treatment of early stage idiopathic Parkinson's disease, but not for the treatment of advanced stage idiopathic Parkinson's disease. Rotigotine transdermal system is not currently on the US market.
In the European Union, rotigotine transdermal patch is approved for the treatment of early and advanced stage idiopathic Parkinson's disease, as well as moderate to severe idiopathic restless legs syndrome in adults.

References
1. Miyasaki JM, Martin W, Suchowersky O, et al. Practice parameter: initiation of treatment for Parkinson's disease: an evidence-based review: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2002;58(1):11-17. **2.** Schapira AH, Obeso J. Timing of treatment initiation in Parkinson's disease: a need for reappraisal? *Ann Neurol*. 2006;59(3):559-562. **3.** Olanow CW, Rascol O, Hauser R, et al. A double-blind, delayed-start trial of rasagiline in Parkinson's disease. *N Engl J Med*. 2009;361(13):1268-1278. **4.** Parkinson Study Group. A controlled, randomized, delayed-start study of rasagiline in early Parkinson disease. *Arch Neurol*. 2004;61(4):561-566. **5.** Jenner P. A novel dopamine agonist for the transdermal treatment of Parkinson's disease. *Neurology*. 2005;65(2 Suppl 1):S3-S5. **6.** Braun M, Andreas JO, Elshoff JP, et al. Steady-state plasma concentration profile of transdermal rotigotine [Submitted for publication]. **7.** Watts R, Boroojerdi B, Jankovic J, et al. Open-label extension to the double-blind SP512 trial to assess the safety of long-term treatment of rotigotine in subjects with early-stage idiopathic Parkinson's disease. Poster presented at the American Academy of Neurology 2010 – 62nd Annual Meeting. April 10-17, 2010, Toronto, Canada. **8.** Jankovic J, Watts RL, Martin W, et al. Transdermal rotigotine: double-blind, placebo-controlled trial in Parkinson disease. *Arch Neurol*. 2007;64(5):676-682. **9.** Watts RL, Jankovic J, Waters C, et al. Randomized, blind, controlled trial of transdermal rotigotine in early Parkinson disease. *Neurology*. 2007;68(4):272-276.

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