In view of the potential for drug complications in PD, the initiation of treatment is customarily delayed until the symptoms of PD significantly impair the individual's ability to function at work or in daily living. There is increasing evidence to challenge this traditional recommendation:

- The use of clinical deterioration to a Hoehn and Yahr stage 3a (a decline of at least 2 points in Unified Parkinson's Disease Rating Scale [UPDRS] points in the first year after diagnosis), supporting this in a frame of opportunity for treatment intervention 2
- Earlier rather than delayed initiation of PD treatment may lead to better long-term motor benefits. 3,4
- Delayed treatment may result in the loss of abilities that cannot be regained 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

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), supporting this in a frame of opportunity for treatment intervention 2
- Earlier rather than delayed initiation of PD treatment may lead to better long-term motor benefits. 3,4
- Delayed treatment may result in the loss of abilities that cannot be regained in the disease course, and thus early treatment may lead to better long-term benefit.

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Comparative advantage of the study design compared to previous trials:

- The SP512 study 7 was a long-term, open-labeled extension of the SP512 study, 8,9 a 6-month, randomized, double-blind, placebo-controlled study in PIs with early-stage PD. Continuous transdermal delivery of rotigotine was well tolerated for up to 12 months, with sustained efficacy (UPDRS II + III total score) for at least 2 years. 7

- The SP702 study was a long-term, open-label extension of the SP512 study. 8,9 It consisted of an initial 6-month, double-blind placebo-controlled trial followed by open-label rotigotine maintenance for up to 6 years. 7

- The SP702 study enrolled patients who had received rotigotine during the initial 6-month, double-blind study. Initiation of rotigotine treatment in the open-label study was at the discretion of the investigator, after an in-person consultation with the patient and agreement on the treatment choice. 7

- The effect of early vs. delayed start rotigotine on change from double-blind baseline UPDRS II + III total score was evaluated for all patients. All patients received rotigotine in the open-label extension. 7

- 217 of 277 (78%) patients completed the double-blind study and entered the open-label extension. 7

- 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. 7

- 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. 7

- Patients in the early-start group had earlier onset of PD (median age at disease diagnosis of 61 ± 7 years vs 66 ± 8 years for the delayed-start group). 7

- More patients in the early-start group were male (63% vs 48%). 7

- More patients in the early-start group had a higher Hoehn and Yahr stage at baseline (21% vs 13% in the delayed-start group) 7

- The mean change scores of early-start patients remained below those of the delayed-start patients by 2 to 3 points for the entire duration of rotigotine treatment. 7

Concomitant Levodopa Treatment in the SP702 Study

- In the subgroup of patients with early PD, the mean UPDRS II + III scores at double-blind baseline and after 66 months of rotigotine treatment were 36 ± 4 in the early-start group and 38 ± 5 in the delayed-start group. 7

Early- vs Delayed-Start Rotigotine

<table>
<thead>
<tr>
<th>Months of rotigotine treatment</th>
<th>Early-start: open-label rotigotine</th>
<th>Delayed-start patients: double-blind placebo/open-label rotigotine (n=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>36</td>
<td>36 ± 6 (n=78)</td>
<td>42 ± 7 (n=79)</td>
</tr>
<tr>
<td>48</td>
<td>38 ± 6 (n=76)</td>
<td>46 ± 7 (n=77)</td>
</tr>
<tr>
<td>60</td>
<td>40 ± 7 (n=74)</td>
<td>48 ± 8 (n=77)</td>
</tr>
</tbody>
</table>

Conclusions

- 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 significant 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 better timed.

- Early treatment may lead to better long-term motor benefits (Table 1).

- 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 trials are required to investigate this further.

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

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

<table>
<thead>
<tr>
<th>Safety set (n=216)</th>
<th>Early-start patients</th>
<th>Delayed-start patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63 ± 9</td>
<td>66 ± 8</td>
</tr>
<tr>
<td>Male (%)</td>
<td>63%</td>
<td>48%</td>
</tr>
<tr>
<td>Median age at diagnosis (years)</td>
<td>61 ± 7</td>
<td>66 ± 8</td>
</tr>
<tr>
<td>UPDRS II + III at baseline (n=137)</td>
<td>Early-start: 39 ± 5</td>
<td>Delayed-start: 41 ± 6</td>
</tr>
<tr>
<td>UPDRS II + III at baseline (n=79)</td>
<td>Early-start: 39 ± 5</td>
<td>Delayed-start: 41 ± 6</td>
</tr>
</tbody>
</table>

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.

- 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.

- Patients in the early-start group had earlier onset of PD (median age at disease diagnosis of 61 ± 7 years vs 66 ± 8 years for the delayed-start group).

- More patients in the early-start group were male (63% vs 48%).

- More patients in the early-start group had a higher Hoehn and Yahr stage at baseline (21% vs 13% in the delayed-start group).

- The mean change scores of early-start patients remained below those of the delayed-start patients by 2 to 3 points for the entire duration of rotigotine treatment.

Figure 1. SP702 study design

Figure 2. Rotigotine Transdermal System in Patients With Early-Stage, Idiopathic Parkinson’s Disease