D.2 Pharmacological management of motor symptoms

D.2.1 First-line treatment of motor symptoms

<table>
<tr><th>Bibliographic reference</th><th>Stern,M.B., Marek KL FAU - Friedman,Joseph, Friedman,J.FAU, Hauser RA FAU - LeWitt,Peter, LeWitt PA FAU - Tarsy,Daniel, Tarsy,D.FAU, Olanow,C.W., Double-blind, randomised, controlled trial of Rasagiline as monotherapy in early Parkinson's disease patients, Movement Disorders., 19, 916-923, 2004</th></tr>
<tr><td>Country/ies where the study was carried out</td><td>US</td></tr>
<tr><td>Study type</td><td>Double-blind randomised, placebo-controlled, parallel-group, dose-ranging study</td></tr>
<tr><td>Aim of the study</td><td>To evaluate the safety and tolerability of orally administered rasagiline, and to make a preliminary assessment of its efficacy, when administered as once-daily onotherapy in patients with early PD and who were not receiving L-dopa.</td></tr>
<tr><td>Study dates</td><td>Study date: Not reported
Study duration: 10 weeks</td></tr>
<tr><td>Source of funding</td><td>Teva Pharmaceuticals</td></tr>
<tr><td>Sample size</td><td>In total: n= 56; Rasagiline 1mg: n=15; Rasagiline 2mg: n=14; Rasagiline 4mg: n=14; Placebo: n=13</td></tr>
<tr><td>Inclusion criteria</td><td>• Between 40 to 75 years of age
• A diagnosis of idiopathic PD
• Hoehn and Yahr disease severity if less than stage III
• Required washout periods were 60 days for selegiline and 14 days for other antiparkinsonian medications, serotine reuptake inhibitors (except fluoxetine, which required 35 days), tricyclic antidepressants, opiates, and sympathomimetic agents.</td></tr>
<tr><td>Exclusion criteria</td><td>• Patients with a history of intolerance to selegiline.
• The presence of clinically significant medical or psychiatric problems, moderate or severe hypertension, or significant cognitive dysfunction compromising the patient's ability to give informed consent or to complete the study.</td></tr>
<tr><td>Details</td><td>Baseline characteristics:
<table>
<tr><td rowspan="2">Characteristics</td><td colspan="3">Selegiline group</td><td></td></tr>
<tr><td>1mg/day (n=15)</td><td>2mg/day (n=14)</td><td>4mg/day (n=14)</td><td>Placebo (n=13)</td></tr>
<tr><td>Age (yr)</td><td>59.3(8.6)</td><td>60.3(7.2)</td><td>62.0(9.7)</td><td>64.8(9.4)</td></tr>
<tr><td>Disease duration (yr)</td><td>1.3(2.6)</td><td>0.4(0.8)</td><td>0.3(0.5)</td><td>0.8(1.0)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Stern,M.B., Marek KL FAU - Friedman,Joseph, Friedman,J.FAU, Hauser RA FAU - LeWitt,Peter, LeWitt PA FAU - Tarsy,Daniel, Tarsy,D.FAU, Olanow,C.W., Double-blind, randomised, controlled trial of Rasagiline as monotherapy in early Parkinson's disease patients, Movement Disorders., 19, 916-923, 2004**

UPDRS total	18.2(6.5)	21.0(5.2)	20.2(7.4)	17.7(7.9)
UPDRS motor	9.4(3.9)	11.3(3.0)	11.6(3.8)	10.8(4.8)
UPDRS ADL	7.7(3.6)	8.4(2.8)	7.3(3.3)	6.6(3.6)
Hoehn & Yahr stage	1.5(0.4)	1.6(0.4)	1.6(0.4)	1.5(0.4)

Interventions	Group 1: Rasagiline 1 mg once daily for 10 weeks; Group 2: Rasagiline 1 mg once daily for 1 week, then rasagiline 2 mg once daily for 9 weeks; Group 3: Rasagiline 1 mg once daily for 1 week, then rasagiline 2 mg once daily for 2 weeks, followed by rasagiline 4 mg once daily for 7 weeks.
Primary outcomes	To evaluate the safety and tolerability of rasagiline as monotherapy at doses of 1, 2, or 4 mg administered once daily over a 10 week treatment period in patients with early PD and who were not receiving L-dopa.
Secondary outcomes	A preliminary assessment of the efficacy of rasagiline monotherapy as assessment of its plasma pharmacokinetics.
Results	At week 10, the mean (±SE) change from baseline in total UPDRS score was -1.8(±1.3) in the rasagiline 1mg group (9.9% improvement from baseline), -3.6(±1.7) in the rasagiline 2mg group (17% improvement), -3.6(±1.2) in the rasagiline 4mg group (17.8% improvement), and -0.5(±0.8) in those receiving placebo (2.8% improvement). Incidence of the most common adverse events in rasagiline-treated patients and of adverse events commonly associated with dopaminergic medications:

% of patients reporting adverse event (P vs. placebo)		
Adverse event	Rasagiline-treated patients	Placebo-treated patients
Pain	30%[0.48]	15%
Headache	26%[0.73]	31%
Dizziness	23%[0.71]	15%
Infection	12%[0.19]	31%

Bibliographic reference	Stern,M.B., Marek KL FAU - Friedman,Joseph, Friedman,J.FAU, Hauser RA FAU - LeWitt,Peter, LeWitt PA FAU - Tarsy,Daniel, Tarsy,D.FAU, Olanow,C.W., Double-blind, randomised, controlled trial of Rasagiline as monotherapy in early Parkinson's disease patients, Movement Disorders., 19, 916-923, 2004

Diarrhoea	12%[0.37]	23%
Insomnia	12%[0.58]	0%
Paraesthesia	12%[0.58]	0%
Nausea	7%[1.00]	8%
Somnolence	5%[1.00]	0%
Nausea & vomiting	2%[1.00]	0%
Oedema	2%[1.00]	0%
Hallucinations	2%[1.00]	0%

Overall Risk of Bias

1. Has an appropriate method of randomisation been used? Yes
2. Was there adequate concealment of allocation? Yes
3. Were the groups comparable at baseline for all major confounding/prognostic factors? Unclear
4. Did the comparison groups receive the same care apart from interventions studied? Yes
5. Were participants receiving care kept blind to treatment allocation? Yes
6. Were the individuals administering care kept blind to treatment allocation? Yes
7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Yes
8. Did the study have an appropriate length of follow up? Yes
9. Did the study use a precise definition of outcome? Yes
10. Was a valid and reliable method used to determine that outcome? Yes
11. Were investigators kept blind to participant’s exposure to the intervention? Unclear
12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

<table>
<tr><th>Bibliographic reference</th><th>Giladi,N., Boroojerdi,B.FAU, Korczyn AD FAU - Burn,David, Burn DJ FAU - Clarke,Carl, Clarke CE FAU - Schapira,Anthony, Schapira,A.H., Rotigotine transdermal patch in early Parkinson's disease: a randomised, double-blind, controlled study versus placebo and ropinirole, Movement Disorders., 22, 2398-2404, 2007</th></tr>
<tr><td>Country/ies where the study was carried out</td><td>Not reported</td></tr>
<tr><td>Study type</td><td>Multicentre, multinational, randomised, double-blind, double-dummy, placebo- and ropinirole-controlled study</td></tr>
<tr><td>Aim of the study</td><td>To investigate the efficacy and safety of the rotigotine transdermal patch in the early stages of PD.</td></tr>
<tr><td>Study dates</td><td>Study dates: Not reported.
Study duration: 41 weeks.</td></tr>
<tr><td>Source of funding</td><td>Not reported.</td></tr>
<tr><td>Sample size</td><td>In total: n= 561; Ropinirole n= 228; Rotigotine n=215; Placebo n= 118</td></tr>
<tr><td>Inclusion criteria</td><td>• 30 years or older with a diagnosis of PD based on the UK Brain Bank Criteria
• Hoehn & Yahr clinical stage of 3 or less
• UPDRS III score of at least 10
• Patients were permitted to take selegiline, amantadine, or anticholinergic agents or other CNS active drugs if maintained at stable dosages for 28 days before baseline and throughout the trial.</td></tr>
<tr><td>Exclusion criteria</td><td>• MMSE score <25
• Clinically significant psychiatric or cognitive condition
• Inability to apply and remove the patches appropriately
• A history of skin sensitivity of adhesives or other transdermal medications
• Administration of a dopamine agonist or levodopa within 28 days of the baseline visit or had ever taken levodopa for longer than 6 months
• Clinically relevant hepatic, renal, or cardiac dysfunction
• An average QTc interval of ≥450 ms for men and ≥470 ms for women in three repeated electrocardiograms performed at baseline; symptomatic orthostatic hypotension; recent exposure to monoamine oxidase A inhibitors and neuroleptics.</td></tr>
<tr><td>Details</td><td>Baseline characteristics:
<table>
<tr><td>Characteristics</td><td>Placebo (n=118)</td><td>Rotigotine (n=215)</td><td>Ropinirole (n=228)</td></tr>
<tr><td>Mean age, yr</td><td>60.4</td><td>61.1</td><td>61.6</td></tr>
<tr><td>Mean years since diagnosis</td><td>1.2</td><td>1.4</td><td>1.3</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Giladi,N., Boroojerdi,B.FAU, Korczyn AD FAU - Burn,David, Burn DJ FAU - Clarke,Carl, Clarke CE FAU - Schapira,Anthony, Schapira,A.H., Rotigotine transdermal patch in early Parkinson's disease: a randomised, double-blind, controlled study versus placebo and ropinirole, Movement Disorders., 22, 2398-2404, 2007
	Hoehn & Yahr stage, %:
	1: 25 / 24 / 27
	2: 59 / 62 / 53
	3: 15 / 13 / 21
	Mean UPDRS score:
	ADL (Part II): 8.7 / 9.3 / 9.1
	Motor (Part III): 22.6 / 23.8 / 23.2
Interventions	• Transdermal rotigotine began active treatment at 2mg/24hrs with weekly increments of 2mg/24hrs. The maximum permitted dose was 8mg/24hrs. Titration period was up to 4 weeks and there was a minimum dose-maintenance phase of 33 weeks. • Ropinirole began active treatment at 0.25mg tid with weekly increments of 0.25mg tid. The maximum permitted dose was 24mg/day. Titration period was up to 13 weeks and there was a minimum dose-maintenance phase of 24 weeks.
Primary outcomes	The proportion of patients with a minimum of 20% decrease in the combined UPDRS Part II and Part III scores.
Secondary outcomes	• Absolute change in UPDRS II + III scores from baseline visit to the end of the double-blind maintenance period • Changes in the UPDRS II and III subscale scores • Demonstration of noninferiority to ropinirole
Results	The mean decrease from baseline in UPDRS subtotal score to the end of treatment was -7.2 (SD±9.9) for patients receiving rotigotine compared with -2.2(SD±10.2) for patients receiving placebo (P<0.0001). A mean decrease of -11.0(SD±10.5) were observed for ropinirole (P<0.0001). The mean UPDRS Part II and III scores improved from baseline to end of treatment by 2.1 and 5.2, respectively, for patients receiving rotigotine and by 0.1 and 2.1 for patients receiving placebo. The difference between rotigotine transdermal patch and ropinirole for the primary efficacy parameters did not show noninferiority. Most common treatment-emergent adverse events (in%) during the overall treatment period (≥5% in any group):

Bibliographic reference	Giladi,N., Boroojerdi,B.FAU, Korczyn AD FAU - Burn,David, Burn DJ FAU - Clarke,Carl, Clarke CE FAU - Schapira,Anthony, Schapira,A.H., Rotigotine transdermal patch in early Parkinson's disease: a randomised, double-blind, controlled study versus placebo and ropinirole, Movement Disorders., 22, 2398-2404, 2007

Adverse events	Placebo (n=118)	Rotigotine (n=215)	Ropinirole (n=228)
Application-site reaction	11	38	7
Dizziness	10	14	17
Headache	8	10	9
Nausea	16	29	36
Vomiting	3	12	11
Abdominal pain	5	4	7
Constipation	4	7	9
Dyspepsia	2	3	6
Diarrhoea	4	4	6
Arthralgia	2	5	3
Back pain	8	7	5
Somnolence	20	23	28
Insomnia	5	6	6

Overall Risk of Bias

1. Has an appropriate method of randomisation been used? Yes
2. Was there adequate concealment of allocation? Unclear
3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes
4. Did the comparison groups receive the same care apart from interventions studied? Unclear
5. Were participants receiving care kept blind to treatment allocation? Yes
6. Were the individuals administering care kept blind to treatment allocation? Yes
7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Unclear
8. Did the study have an appropriate length of follow up? Yes

Bibliographic reference	Giladi,N., Boroojerdi,B.FAU, Korczyn AD FAU - Burn,David, Burn DJ FAU - Clarke,Carl, Clarke CE FAU - Schapira,Anthony, Schapira,A.H., Rotigotine transdermal patch in early Parkinson's disease: a randomised, double-blind, controlled study versus placebo and ropinirole, Movement Disorders., 22, 2398-2404, 2007
	9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Unclear 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	Mally,J., Kovacs AB,F.A.U., Stone,T.W., Delayed development of symptomatic improvement by (--)-deprenyl in Parkinson's disease, J Neurol Sci., 134, 143-145, 1995
Country/ies where the study was carried out	Not reported
Study type	Randomised, double-blind trial.
Aim of the study	To examine the effects of deprenyl (Selegiline) alone in order to be sure of distinguishing improvements due to this drug from any slowly developing changes due to L-dopa.
Study dates	Study dates: Not reported. Study duration: 6 weeks.
Source of funding	Not reported.
Sample size	In total: n=20; Selegiline: n=10; Placebo: n=10
Inclusion criteria	No other disease was evident and the patients were never on levodopa therapy.
Exclusion criteria	Not reported.
Details	Baseline characteristics: Characteristics / Selegiline n=10 / Placebo n=10 Age (yrs) / 57±2.8 / 68±2.4 Duration of disease (yrs) / 1.5±0.27 / 2.6±0.58 Hoehn-Yahr (n) / Stage 1: 2 Stage 2: 5 Stage 3: 3 / Stage 1: 2 Stage 2: 4 Stage 3: 4

<table>
<tr><th>Bibliographic reference</th><th>Mally,J., Kovacs AB,F.A.U., Stone,T.W., Delayed development of symptomatic improvement by (--)-deprenyl in Parkinson's disease, J Neurol Sci., 134, 143-145, 1995</th></tr>
<tr><td></td><td>Patients were scored on 3 different occasions before the commencement of treatment and then weekly for the next 6 weeks of drug administration.</td></tr>
<tr><td>Interventions</td><td>Selegiline: 10mg/day for 6 weeks.</td></tr>
<tr><td>Primary outcomes</td><td>Severity of symptoms as measured by UPDRS (Total, Mental, Daily activities, Motor), the North Western self-rating scale and a simple graded clinical test.</td></tr>
<tr><td>Secondary outcomes</td><td>N/A</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td></td><td>Baseline</td><td>wk1</td><td>wk2</td><td>wk3</td><td>wk4</td><td>wk5</td><td>wk6</td></tr>
<tr><td>UPDRS Daily activities</td><td>Placebo n=10</td><td>9.2±1.5</td><td>9.2±1.6</td><td>9.6±1.7</td><td>9.8±1.6</td><td>9.8±1.6</td><td>10.0±1.7</td><td>10.1±1.7</td></tr>
<tr><td></td><td>Selegiline n=10</td><td>9.1±1.5</td><td>8.9±1.6</td><td>8.4±1.4</td><td>6.0±0.9</td><td>5.8±0.5</td><td>5.3±0.3</td><td>5.3±0.3</td></tr>
<tr><td>UPDRS Motor</td><td>Placebo n=10</td><td>15.2±1.6</td><td>15.2±1.6</td><td>15.3±1.6</td><td>15.5±1.7</td><td>16.0±1.8</td><td>16.3±1.8</td><td>16.4±1.7</td></tr>
<tr><td></td><td>Selegiline n=10</td><td>15.7±2.2</td><td>15.6±2.1</td><td>12.4±1.5</td><td>11.0±1.0</td><td>9.1±1.0</td><td>8.2±0.9</td><td>8.2±0.9</td></tr>
</table>
Data are given as mean ± SE.</td></tr>
<tr><td>Overall Risk of Bias</td><td>1. Has an appropriate method of randomisation been used? Unclear
2. Was there adequate concealment of allocation? Unclear
3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes
4. Did the comparison groups receive the same care apart from interventions studied? Unclear
5. Were participants receiving care kept blind to treatment allocation? Unclear*
6. Were the individuals administering care kept blind to treatment allocation? Unclear*
7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Yes
8. Did the study have an appropriate length of follow up? No (6 weeks)
9. Did the study use a precise definition of outcome? Yes
10. Was a valid and reliable method used to determine that outcome? Yes
11. Were investigators kept blind to participant’s exposure to the intervention? Unclear*
12. Were investigators kept blind to other important confounding and prognostic factors? Unclear*</td></tr>
</table>

Bibliographic reference	Mally,J., Kovacs AB,F.A.U., Stone,T.W., Delayed development of symptomatic improvement by (--)-deprenyl in Parkinson's disease, J Neurol Sci., 134, 143-145, 1995
	*Level of blinding unclear - no details beyond description of study as "randomised, double-blind trial". Overall there is likely to be a high risk of bias.

Bibliographic reference	Adler,C.H., Sethi KD,F.A.U., Hauser RA,F.A.U., Davis TL,F.A.U., Hammerstad JP,F.A.U., Bertoni,J.FAU, Taylor RL FAU - Sanchez-Ramos,, Sanchez-Ramos,J.FAU, O'Brien,C.F., Ropinirole for the treatment of early Parkinson's disease. The Ropinirole Study Group, Neurology, 49, 393-399, 1997
Country/ies where the study was carried out	US
Study type	Prospective, randomised, multi-centre (25 sites), double-blind, placebo-controlled study
Aim of the study	To assess the efficacy and safety of ropinirole in patients with early PD.
Study dates	Study dates: Not reported Study duration: 6 months
Source of funding	SmithKline Beecham Pharmaceuticals
Sample size	In total: n=241; Ropinirole: n=116; Placebo: n=125
Inclusion criteria	• Hoehn & Yahr stages I to III • Motor symptoms of sufficient severity to warrant the introduction of dopaminergic therapy but had not received L-dopa or any dopaminergic agonist for more than 6 weeks prior to study entry. Patients entering the trial on selegiline were required to remain on stable dose of selegiline for 4 weeks prior to study entry and for the duration of the study. All other antiparkinsonian therapies, except selegiline, must be discontinued at least 4 weeks prior to study entry.
Exclusion criteria	• Treatment with vasodilators, antiarrhythmic, digoxin, calcium channel blockers, angiotensin-converting enzyme inhibitors, or other antihypertensive agents (excluding diuretics) • Previous treatment with ropinirole • History of severe dizziness or fainting • Diastolic blood pressure ≥110 mm hg • Recent history of alcoholism or drug dependence

<table>
<tr><th>Bibliographic reference</th><td>Adler,C.H., Sethi KD,F.A.U., Hauser RA,F.A.U., Davis TL,F.A.U., Hammerstad JP,F.A.U., Bertoni,J.FAU, Taylor RL FAU - Sanchez-Ramos,, Sanchez-Ramos,J.FAU, O'Brien,C.F., Ropinirole for the treatment of early Parkinson's disease. The Ropinirole Study Group, Neurology, 49, 393-399, 1997</td></tr>
<tr><td>Details</td><td>Baseline characteristics (patients were stratified by concomitant use of selegiline):
<table>
<tr><td></td><td colspan="2">Ropinirole</td><td colspan="2">Placebo</td></tr>
<tr><td>Characteristics</td><td>Nonselegiline n=58
n (%)</td><td>Selegiline n=58
n (%)</td><td>Nonselegiline n=64
n (%)</td><td>Selegiline n=61
n (%)</td></tr>
<tr><td>Mean age (years) (SD)</td><td>64.9(9.8)</td><td>59.1(10.6)</td><td>65.9(10.3)</td><td>61.6(10.6)</td></tr>
<tr><td>Mean duration of disease (months) (SD)</td><td>18.8(19.7)</td><td>30.4(19.7)</td><td>18.2(17.8)</td><td>27.5(19.8)</td></tr>
<tr><td colspan="5">Hoehn & Yahr stage:</td></tr>
<tr><td>I & I.5</td><td>14(24.1)</td><td>18(31)</td><td>19(29.7)</td><td>18(29.5)</td></tr>
<tr><td>II & II.5</td><td>35(60.4)</td><td>35(60.3)</td><td>35(54.7)</td><td>38(62.3)</td></tr>
<tr><td>III</td><td>9(15.5)</td><td>5(8.6)</td><td>10(15.6)</td><td>5(8.2)</td></tr>
<tr><td>Mean UPDRS III (SD)</td><td>19.1(8.2)</td><td>16.7(9.2)</td><td>17.6(7.7)</td><td>17.7(8.6)</td></tr>
</table></td></tr>
<tr><td>Interventions</td><td>Ropinirole: Starting dose of 0.25 mg tid, which was titrated upward at weekly intervals until an optimal therapeutic response was achieved (minimum dose was 1.5 mg tid and maximum dose was 8 mg tid). Patients were maintained at their optimal dose level for the remainder or the study.</td></tr>
<tr><td>Primary outcomes</td><td>• UPDRS III
• Adverse events</td></tr>
<tr><td>Secondary outcomes</td><td>Number (%) of patients with:
• ≥30% reduction in the UPDRS III (responders)
• scores of 1 (very much improved) or 2 (much improved) on the CGI global improvement item
• no sufficient symptomatic benefit, thereby requiring the initiation of L-dopa therapy</td></tr>
<tr><td>Results</td><td>The mean ± SD UPDRS motor examination score in all ropinirole-treated patients improved from 17.9 ± 8.8 at baseline to 13.4 ± 9.5 at endpoint. There was a statistically significant improvement of 24% in the UPDRS motor examination score in the ropinirole treated arm compared with placebo (P<0.001).</td></tr>
</table>

Bibliographic reference	**Adler,C.H., Sethi KD,F.A.U., Hauser RA,F.A.U., Davis TL,F.A.U., Hammerstad JP,F.A.U., Bertoni,J.FAU, Taylor RL FAU - Sanchez-Ramos,, Sanchez-Ramos,J.FAU, O'Brien,C.F., Ropinirole for the treatment of early Parkinson's disease. The Ropinirole Study Group, Neurology, 49, 393-399, 1997**

The placebo group experienced a 3% worsening in the UPDRS motor examination score (17.7 ±9.5 at baseline to 17.9 ±10.5 at endpoint).

Results were similar in the patients receiving selegiline compared with patients not receiving selegiline.

Adverse experiences occurring in ≥10% patients and withdrawals due to those adverse experiences:

	Incidence n (%)		Withdrawal n (%)	
Adverse event	Ropinirole n=116	Placebo n=125	Ropinirole n=116	Placebo n=125
Nausea	61(52.6)	27(21.6)	8(6.9)	2(1.6)
Dizziness	42(36.2)	23(18.4)	5(4.3)	2(1.2)
Somnolence	42(36.2)	6(4.8)	2(1.7)	0(0)
Headache	20(17.2)	19(15.2)	1(0.9)	3(2.4)
Upper respiratory tract infection	17(14.7)	18(14.4)	0(0)	0(0)
Insomnia	13(11.2)	13(10.4)	0(0)	1(0.8)
Constipation	12(10.3)	8(6.4)	0(0)	0(0)
Syncope	12(10.3)	2(1.6)	1(0.9)	0(0)

Overall Risk of Bias

1. Has an appropriate method of randomisation been used? Yes
2. Was there adequate concealment of allocation? Unclear
3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes
4. Did the comparison groups receive the same care apart from interventions studied? Unclear
5. Were participants receiving care kept blind to treatment allocation? Yes
6. Were the individuals administering care kept blind to treatment allocation? Unclear
7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Yes

Bibliographic reference	**Adler,C.H., Sethi KD,F.A.U., Hauser RA,F.A.U., Davis TL,F.A.U., Hammerstad JP,F.A.U., Bertoni,J.FAU, Taylor RL FAU - Sanchez-Ramos,, Sanchez-Ramos,J.FAU, O'Brien,C.F., Ropinirole for the treatment of early Parkinson's disease. The Ropinirole Study Group, Neurology, 49, 393-399, 1997**
	8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Unclear 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	**Hubble,J.P., Koller WC,F.A.U., Cutler NR,F.A.U., Sramek JJ,F.A.U., Friedman,J.FAU, Goetz,C.FAU, Ranhosky,A.FAU, Korts,D.FAU, Elvin,A., Pramipexole in patients with early Parkinson's disease, Clin Neuropharmacol., 18, 338-347, 1995**
Country/ies where the study was carried out	US
Study type	Four-centre randomised, parallel-group trial
Aim of the study	To evaluate the safety and efficacy of pramipexole on the motor disabilities of subjects with early PD who were not receiving levodopa treatment.
Study dates	Study dates: Not reported Study duration: 9 weeks
Source of funding	Boehringer Ingelheim Pharmaceuticals
Sample size	In total: n=55; Pramipexole n=28; Placebo n=27
Inclusion criteria	• 21 years of age or older • Had a diagnosis of early idiopathic PD (stages I-III by the Modified Hoehn and Yahr scale) • Treatment with anticholinergic agent was permitted, but no other antiparkinsonian medications were taken.
Exclusion criteria	Patients with evidence of atypical parkinsonian syndromes, clinically significant cardiac, vascular, or cerebrovascular disease, or other unstable medical condition
Details	There were no significant differences in demographic measures between the pramipexole and the placebo groups.

Characteristics	Pramipexole n=28	Placebo n=27	Total n=55
Mean age (yrs) SD	63.5(12.3)	63(8.8)	63.3(10.6)

Bibliographic reference	**Hubble,J.P., Koller WC,F.A.U., Cutler NR,F.A.U., Sramek JJ,F.A.U., Friedman,J.FAU, Goetz,C.FAU, Ranhosky,A.FAU, Korts,D.FAU, Elvin,A., Pramipexole in patients with early Parkinson's disease, Clin Neuropharmacol., 18, 338-347, 1995**
	<table><tr><td>Mean duration of disease (yrs) SD</td><td>2.1(2.5)</td><td>2.4(2.4)</td><td>2.3(2.5)</td></tr><tr><td>Mean UPDRS II</td><td>10.94</td><td>10.46 (n=25)</td><td>-</td></tr><tr><td>Mean UPDRS III</td><td>26.47</td><td>27.43 (n=25)</td><td>-</td></tr></table> All subjects received selegiline (10 mg/d) but were not treated with levodopa.
Interventions	Intervention: Selegiline 5mg bid + Pramipexole with a starting dose of 0.10mg three times daily, this was uptitrated over 6 weeks to either the maximum tolerated dose level or a maximum of 1.5mg three times daily (ascending dose schedule: 0.25, 0.5, 0.75, 1.0, 1.25 or 1.5mg three times daily). The maintenance dose interval of the trial lasted 3 weeks and was followed by a dose reduction phase during which the daily dosage was decreased by one dose level each day. Placebo: Selegiline 5mg bid
Primary outcomes	• Mean change in score UPDRS II and III comparing baseline with final maintenance visit • Adverse events
Secondary outcomes	Mean change in score from baseline to the average score of the 3 week maintenance period for UPDRS II and III
Results	Change in mean UPDRS II from baseline to maintenance average: Pramipexole (n=28): -4.84 Placebo (n=23): -2.29 Change in mean UPDRS III from baseline to maintenance average: Pramipexole (n=28): -11.96 Placebo (n=23): -8.15 Common treatment-related adverse events: No. of subjects (%) <table><tr><td>Adverse events</td><td>Pramipexole n=28</td><td>Placebo n=27</td></tr><tr><td>Total with any adverse event</td><td>28 (100%)</td><td>27 (100%)</td></tr></table>

Bibliographic reference	Hubble,J.P., Koller WC,F.A.U., Cutler NR,F.A.U., Sramek JJ,F.A.U., Friedman,J.FAU, Goetz,C.FAU, Ranhosky,A.FAU, Korts,D.FAU, Elvin,A., Pramipexole in patients with early Parkinson's disease, Clin Neuropharmacol., 18, 338-347, 1995

Asymptomatic orthostatic HTN	28 (100%)	27 (100%)
Symptomatic orthostatic HTN	7 (25%)	5 (18.5%)
Dry mouth	3 (10.7%)	0
Dizziness	12 (42.9%)	8 (29.6%)
Headache	9 (32.1%)	6 (22.2%)
Nausea	6 (21.4%)	4 (14.8%)
Insomnia	6 (21.4%)	3 (11.1%)
Hallucination	4 (14.3%)	0
Vision abnormal	3 (10.7%)	0

Overall Risk of Bias

1. Has an appropriate method of randomisation been used? Yes
2. Was there adequate concealment of allocation? Unclear
3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes
4. Did the comparison groups receive the same care apart from interventions studied? Yes
5. Were participants receiving care kept blind to treatment allocation? Yes
6. Were the individuals administering care kept blind to treatment allocation? Unclear
7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Unclear
8. Did the study have an appropriate length of follow up? Yes
9. Did the study use a precise definition of outcome? Yes
10. Was a valid and reliable method used to determine that outcome? Yes
11. Were investigators kept blind to participant’s exposure to the intervention? Unclear
12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

<table>
<tr><th>Bibliographic reference</th><th>Viallet,Francois., Pitel,S., Lancrenon,Sylvie, Blin,Olivier, Evaluation of the safety and tolerability of rasagiline in the treatment of the early stages of Parkinson's disease, Current Medical Research and Opinion, 29, 23-31, 2013</th></tr>
<tr><td>Country/ies where the study was carried out</td><td>France</td></tr>
<tr><td>Study type</td><td>Phase IV, multi-centre, randomised, double-blind study</td></tr>
<tr><td>Aim of the study</td><td>To assess the safety and tolerability of rasagiline compared with the dopaminergic agonist pramipexole in the treatment of early PD.</td></tr>
<tr><td>Study dates</td><td>Study dates: Not reported
Study duration: 15 weeks</td></tr>
<tr><td>Source of funding</td><td>Qualissima, who received a grant from Lundbeck</td></tr>
<tr><td>Sample size</td><td>In total: n=109; Rasagiline: n=53; Pramipexole: n=56</td></tr>
<tr><td>Inclusion criteria</td><td>• Patients must have never received anti-Parkinson treatment or had received levodopa for less than 12 weeks at a dose less than 200mg; patients discontinued all anti-Parkinson treatment other than the study drugs as part of the study protocol
• Patients on dopamine agonist other than pramipexole were also eligible for inclusion, on the condition that the patient was still in the titration phase at the time of inclusion, or that treatment was given for less than 6 weeks and had not been given for 2 weeks prior the time of inclusion.</td></tr>
<tr><td>Exclusion criteria</td><td>• Breastfeeding women
• Women of a childbearing age without sterilization or a reliable birth control method
• Patients with liver disease
• Patients with a concomitant disease considered to be significant by the investigator
• Patients treated with cerebral stimulation and patients with skin lesions not assessed by a dermatologist
• Patients treated with fluoxetine during the 5 weeks preceding inclusion
• Patients treated with fluvoxamine, pethidine, selegiline or any other MAOB-I during the 2 weeks preceding inclusion
• Patients likely to receive dextromethorphan or a sympathomimetic drug during the trial</td></tr>
<tr><td>Details</td><td>The two treatment groups were similar at baseline with regard to demographic variables, with the exception of pain/cramp, which was significantly higher in the pramipexole group (p=0.027).

<table><tr><td>Characteristic</td><td>Rasagiline n=53</td><td>Pramipexole n=56</td></tr><tr><td>Age (yrs)</td><td>63.2±7.3</td><td>62.1±6.2</td></tr></table></td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Viallet,Francois., Pitel,S., Lancrenon,Sylvie, Blin,Olivier, Evaluation of the safety and tolerability of rasagiline in the treatment of the early stages of Parkinson’s disease, Current Medical Research and Opinion, 29, 23-31, 2013</th></tr>
<tr><td></td><td>
<table>
<tr><td>Time since diagnosis (months)</td><td>2.5±3.8</td><td>4.3±7.3</td></tr>
<tr><td>EQ-5D original score</td><td>0.75±0.15</td><td>0.67±0.25</td></tr>
<tr><td>EQ-VAS score</td><td>67.48±16.07</td><td>63.74±18.76</td></tr>
<tr><td>PDQ-8</td><td>5.45±3.67</td><td>6.99±5.23</td></tr>
<tr><td>Tremor</td><td>7(13.2%)</td><td>13(23.2%)</td></tr>
<tr><td>Akinetic hypertonicity</td><td>12(22.6%</td><td>15(26.8%)</td></tr>
</table>
</td></tr>
<tr><td>Interventions</td><td>Rasagiline: 1mg once daily (plus placebo twice daily)
Pramipexole: three times daily, titrated from 0.375mg/day in week 1, 0.75mg/day in week 2 to a maximum dose of 1.5mg/day in week 3</td></tr>
<tr><td>Primary outcomes</td><td>Adverse events</td></tr>
<tr><td>Secondary outcomes</td><td>• The percentage of patients with sleep disorders
• The Epworth Sleepiness Scale
• Clinical Global Impression of Improvement scale
• Patient Global Impression of Improvement scale
• PDQ-8 scale
• EQ-5D
• EQ-VAS</td></tr>
<tr><td>Results</td><td>Adverse events reported by the physician in >5% of patients in either treatment group:
<table>
<tr><td>Adverse event</td><td>Rasagiline n=53</td><td>Pramipexole n=56</td></tr>
<tr><td>Total patients with an AE</td><td>36 (67.9%)</td><td>43 (76%)</td></tr>
<tr><td>Central nervous system</td><td>4 (7.5%)</td><td>6 (10.7%)</td></tr>
<tr><td>Malaise, syncope</td><td>2 (3.8%)</td><td>6 (10.7%)</td></tr>
<tr><td>Nervous system</td><td>11 (20.8%)</td><td>13 (23.2%)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Viallet,Francois., Pitel,S., Lancrenon,Sylvie, Blin,Olivier, Evaluation of the safety and tolerability of rasagiline in the treatment of the early stages of Parkinson's disease, Current Medical Research and Opinion, 29, 23-31, 2013		
	Headache	3 (5.7%)	5 (8.9%)
	Tingling	4 (7.5%)	2 (3.6%)
	Dizziness	3 (5.7%)	5 (8.9%)
	Gastrointestinal system	15 (28.3%)	27 (48.2%)
	Gastralgia	4 (7.5%)	5 (8.9%)
	Constipation	2 (3.8%)	4 (7.1%)
	Nausea, vomiting	5 (9.4%)	16 (28.6%)
	Musculo-skeletal system	12 (22.6%)	14 (25%)
	Joint pain, join disease	7 (13.2%)	12 (21.4%)
	Muscle cramps	5 (9.4%)	2 (3.6%)
	Cardiovascular system	4 (7.5%)	6 (10.7%)
	Orthostatic hypotension	1 (1.9%)	3 (5.4%)
	General disorders	11 (20.8%)	11 (19.6%)
	Weight loss	3 (5.7%)	0
	Weight gain	2 (3.8%)	4 (7.1%)
	Weakness	6 (11.3%)	7 (12.5%)
	Psychiatric disorder	18 (34%)	31 (55.4%)
	Anxiety, irritability, emotionality	4 (7.5%)	4 (7.1%)
	Mood swings	5 (9.4%)	4 (7.1%)
	Hallucinations	0	3 (5.4%)
	Sleep disorders, daytime sleepiness	9 (17%)	20 (35.7%)

Bibliographic reference	Viallet,Francois., Pitel,S., Lancrenon,Sylvie, Blin,Olivier, Evaluation of the safety and tolerability of rasagiline in the treatment of the early stages of Parkinson's disease, Current Medical Research and Opinion, 29, 23-31, 2013
	<table><tr><td>Respiratory Tract</td><td>5 (9.4%)</td><td>5 (8.9%)</td></tr><tr><td>Respiratory infection</td><td>4 (7.5%)</td><td>5 (8.9%)</td></tr><tr><td>Skin, hair and nails</td><td>8 (15.1%)</td><td>2 (3.6%)</td></tr><tr><td>Itching</td><td>3 (5.7%)</td><td>0</td></tr><tr><td>Rash</td><td>5 (9.4%)</td><td>0</td></tr></table>All values reported as n (%). Patients could have more than one type of AE. There were no significant differences in quality of life outcomes between the treatments.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Yes 2. Was there adequate concealment of allocation? Yes 3. Were the groups comparable at baseline for all major confounding/prognostic factors? No 4. Did the comparison groups receive the same care apart from interventions studied? Unclear 5. Were participants receiving care kept blind to treatment allocation? Yes 6. Were the individuals administering care kept blind to treatment allocation? Yes 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Yes 8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Yes 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	Olanow,C.Warren, Rascol,Olivier, Hauser,Robert, Feigin,Paul D., Jankovic,Joseph, Lang,Anthony, Langston,William, Melamed,Eldad, Poewe,Werner, Stocchi,Fabrizio, Tolosa,Eduardo, A Double-Blind, Delayed-Start Trial of Rasagiline in Parkinson's Disease, New England Journal of Medicine, 361, 1268-1278, 2009
Country/ies where the study was carried out	14 countries (not reported)

<table>
<tr><th>Bibliographic reference</th><td>Olanow,C.Warren, Rascol,Olivier, Hauser,Robert, Feigin,Paul D., Jankovic,Joseph, Lang,Anthony, Langston,William, Melamed,Eldad, Poewe,Werner, Stocchi,Fabrizio, Tolosa,Eduardo, A Double-Blind, Delayed-Start Trial of Rasagiline in Parkinson's Disease, New England Journal of Medicine, 361, 1268-1278, 2009</td></tr>
<tr><td>Study type</td><td>Double-blind, placebo-controlled, multicentre trial that used a delayed-start design.</td></tr>
<tr><td>Aim of the study</td><td>To examine the potential disease-modifying effects of rasagiline in Parkinson's disease.</td></tr>
<tr><td>Study dates</td><td>Study dates: Not reported.
Study duration: 72 weeks (18 months); 36 weeks per phase (2 phases in total).</td></tr>
<tr><td>Source of funding</td><td>Teva Pharmaceutical Industries</td></tr>
<tr><td>Sample size</td><td>In total: n=1176; Rasagiline 1mg/d n=288, Rasagiline 2mg/d n=293; Placebo n=595 (two placebo groups were combined for analysis).</td></tr>
<tr><td>Inclusion criteria</td><td>• Men and women between 30 and 80 years of age who were not currently receiving treatment for PD.
• The presence of at least two of the three cardinal features of the disease (resting tremor, bradykinesia, or rigidity); if resting tremor was not present, subjects had to have unilateral onset of symptoms.</td></tr>
<tr><td>Exclusion criteria</td><td>• Subjects who had previously received any antiparkinsonian medication for more than 3 weeks or who had received rasagiline or selegiline (at any dose) or coenzyme Q10 (at more than 300mg per day) within the previous 120 days.
• Disease duration of more than 18 months since diagnosis.
• A Hoehn and Yahr stage of 3 or higher and atypical or secondary Parkinsonism.</td></tr>
<tr><td>Details</td><td>The study was performed in 2 phases. In phase 1, subjects were randomly assigned to one of four study groups: rasagiline at a dose of either 1 mg or 2 mg per day (the early-start groups) or corresponding placebo. In phase 2, subjects in the early-start groups continued to receive their assigned treatment while subject in the placebo groups switched to rasagiline at a dose of 1 mg or 2 mg per day (the delayed-start groups). No concomitant anti-parkinsonian medication was permitted.

Baseline characteristics:
<table>
<tr><td rowspan="2">Characteristics</td><td colspan="2">Rasagiline 1 mg/d</td><td colspan="2">Rasagiline 2 mg/d</td></tr>
<tr><td>Placebo n=300</td><td>Treatment n=288</td><td>Placebo n=295</td><td>Treatment n=293</td></tr>
<tr><td>Age (yr)</td><td>61.9±9.7</td><td>62.4±9.7</td><td>62.4±9.7</td><td>62.3±9.6</td></tr>
<tr><td>Time since diagnosis (mo)</td><td>4.3±4.6</td><td>4.6±4.7</td><td>4.6±4.6</td><td>4.6±4.6</td></tr>
<tr><td>UPDRS Total (range, 0-176)</td><td>20.2±8.8</td><td>20.6±8.4</td><td>19.9±8.1</td><td>20.8±8.8</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Olanow,C.Warren, Rascol,Olivier, Hauser,Robert, Feigin,Paul D., Jankovic,Joseph, Lang,Anthony, Langston,William, Melamed,Eldad, Poewe,Werner, Stocchi,Fabrizio, Tolosa,Eduardo, A Double-Blind, Delayed-Start Trial of Rasagiline in Parkinson's Disease, New England Journal of Medicine, 361, 1268-1278, 2009**

UPDRS Motor (range, 0-108)	14.0±6.5	14.5±6.3	13.8±6.1	14.6±6.5
UPDRS ADL (range, 0-52)	5.3±3.1	5.1±2.8	5.1±2.9	5.4±3.1
Hoehn and Yahr stage (range, 1-5)	1.51±0.5	1.53±0.5	1.46±0.5	1.52±0.5

Visits and measurements were performed at baseline and at weeks 4, 12, 24, 36, 42, 48, 54, 60, 66, and 72.

Only available data of interest from Phase 1 (rasagiline vs. placebo) is extracted for analysis.

Interventions: Rasagiline: 1mg or 2mg per day.

Primary outcomes: The change in total UPDRS points per week between the rasagiline groups (1mg pr 2 mg per day).

Secondary outcomes:
- The change in total UPDRS score between baseline and week 72 in the early-start and delayed-start rasagiline groups (1mg or 2 mg per day).
- Adverse events

Results:

Study discontinuation after Phase 1:

1 mg placebo (n=300) - In total n=30 withdrew:

11 withdrew consent, 7 had AE, 10 needed other treatment for PD, 2 had other reason.

1 mg rasagiline (n=288) - In total 15 withdrew:

3 withdrew consent, 9 had AE, 2 needed other treatment for PD, 1 had other reason.

2 mg placebo (n=295) - In total 20 withdrew:

6 withdrew consent, 10 had AE, 2 needed other treatment for PD, 2 had other reason.

2 mg rasagiline (n=293) - In total 20 withdrew:

3 withdrew consent, 11 had AE, 2 needed other treatment for PD, 4 had other reason.

Event	Placebo*	Rasagiline 1 mg/d (no./total no. (%)	Rasagiline 2 mg/d
In >5% of subjects in any group, placebo phase			
Headache	37/595 (6.2)	14/288 (4.9)	15/293 (5.1)
Back pain	32/595 (5.4)	14/288 (4.9)	15/293 (5.1)

Bibliographic reference	Olanow,C.Warren, Rascol,Olivier, Hauser,Robert, Feigin,Paul D., Jankovic,Joseph, Lang,Anthony, Langston,William, Melamed,Eldad, Poewe,Werner, Stocchi,Fabrizio, Tolosa,Eduardo, A Double-Blind, Delayed-Start Trial of Rasagiline in Parkinson's Disease, New England Journal of Medicine, 361, 1268-1278, 2009			
	Depression	36/595 (6.1)	10/288 (3.5)	10/293 (3.4)
	Nasopharyngitis	32/595 (5.4)	12/288 (4.2)	11/293 (3.8)
	Anxiety	34/595 (5.7)	10/288 (3.5)	9/293 (3.1)
	Fatigue	17/595 (2.9)	17/288 (5.9)	10/293 (3.4)
	Related to dopaminergic therapy, placebo phase			
	Nausea or vomiting	23/595 (3.9)	12/288 (4.2)	8/293 (2.7)
	Hypertension	23/595 (3.9)	5/288 (1.7)	7/293 (2.4)
	Somnolence	9/595 (1.5)	2/288 (0.7)	4/293 (1.4)
	Orthostatic hypotension	5/595 (0.8)	2/288 (0.7)	1/293 (0.3)
	Hallucination	1/595 (0.2)	0/288	1/293 (0.3)
	Hypersexuality	0/595	0/288	1/293 (0.3)
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Yes 2. Was there adequate concealment of allocation? Unclear 3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes 4. Did the comparison groups receive the same care apart from interventions studied? Unclear 5. Were participants receiving care kept blind to treatment allocation? Unclear* 6. Were the individuals administering care kept blind to treatment allocation? Unclear* 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Yes but <10% dropout rate and no ITT analysis for efficacy outcomes 8. Did the study have an appropriate length of follow up? Yes (9 months) 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Unclear* 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear*			

Bibliographic reference	Olanow,C.Warren, Rascol,Olivier, Hauser,Robert, Feigin,Paul D., Jankovic,Joseph, Lang,Anthony, Langston,William, Melamed,Eldad, Poewe,Werner, Stocchi,Fabrizio, Tolosa,Eduardo, A Double-Blind, Delayed-Start Trial of Rasagiline in Parkinson's Disease, New England Journal of Medicine, 361, 1268-1278, 2009
	*Level of blinding unclear - no details beyond description of study as "randomised, double-blind, placebo-controlled trial". Overall there is likely high risk of bias.

Bibliographic reference	Fahn,S., The Parkinson Study Group, Does levodopa slow or hasten the rate of progression of Parkinson's disease?, Journal of Neurology, 252, 37-42, 2005
Country/ies where the study was carried out	US and Canada
Study type	A multi-centre, parallel-group, double-blind, dosage-ranging randomised, controlled clinical trial.
Aim of the study	To determine whether levodopa treatment affects the rate of progression of PD.
Study dates	Study dates: Not reported. Study duration: 40 weeks, withdrawal of treatment for 2 weeks.
Source of funding	Grants from the National Institute of Neurological Disorders and Stroke, the Department of Defence, and the General Clinical Research Centre of the National Centre for Research Resources, National Institutes of Health. Tablets were provided by Teva Pharmaceuticals (Israel).
Sample size	In total n=361 37.5/150 mg/d carbidopa-levodopa n=92 75/300 mg/d carbidopa-levodopa n=88 150/600 mg/d carbidopa-levodopa n=91 Placebo n=90
Inclusion criteria	• Subjects 30 years of age or older. • Had received a diagnosis of PD within the past 2 years. • Had a rating on modified Hoehn and Yahr scale of less than stage 3 and were not likely to require therapy for symptoms of the disease within 9 months after enrolment in the study.
Exclusion criteria	• Subjects who were receiving antiparkinsonian medication. • Had been exposed to levodopa or to any dopamine agonist for more than 14 days.

<table>
<tr><th>Bibliographic reference</th><th>Fahn,S., The Parkinson Study Group, Does levodopa slow or hasten the rate of progression of Parkinson's disease?, Journal of Neurology, 252, 37-42, 2005</th></tr>
<tr><td></td><td>• Had an identifiable cause of Parkinsonism, or had a tremor in any limb that was given a score of 3 or more on UPDRS, freezing of gait, loss of postural reflexes, major depression or dementia.</td></tr>
<tr><td>Details</td><td>The demographic and clinical characteristics of the subjects in the treatment groups were similar at baseline*:
<table>
<tr><td>Characteristics</td><td>Placebo</td><td>Carbidopa/Levodopa 37.5/ 150 mg/d</td><td>Carbidopa/Levodopa 75/300 mg/d</td><td>Carbidopa/Levodopa 150/600 mg/d</td></tr>
<tr><td>Age (yr)</td><td>64.9±10.3</td><td>64.5±10.6</td><td>63.8±12.1</td><td>65.2±10.7</td></tr>
<tr><td>Duration of disease (mo)</td><td>5.3±5.6</td><td>5.7±6.1</td><td>7.6±7.5</td><td>6.0±6.1</td></tr>
<tr><td>UPDRS Total</td><td>27.7±12</td><td>27.2±12.6</td><td>27.5±11.6</td><td>29.4±13.9</td></tr>
<tr><td>UPDRS Mental</td><td>1.4±1.5</td><td>1.3±1.5</td><td>1.3±1.4</td><td>1.4±1.6</td></tr>
<tr><td>UPDRS ADL</td><td>7.5±3.6</td><td>7.5±4.4</td><td>7.3±3.7</td><td>7.6±4.0</td></tr>
<tr><td>UPDRS Motor</td><td>18.8±8.9</td><td>18.6±9.1</td><td>18.9±8.8</td><td>20.5±10.8</td></tr>
<tr><td>Hoehn-Yahr</td><td>1.8±0.5</td><td>1.9±0.6</td><td>1.8±0.5</td><td>1.9±0.6</td></tr>
</table>
*Plus-minus values are means ± SD.</td></tr>
<tr><td>Interventions</td><td>Carbidopa-levodopa: 37.5/150 mg/d, 75/300 mg/d, or 150/600 mg/d.
The daily dose was built up gradually over a 9-week period. After 40 weeks of treatment, the patients underwent a 3-day taper of their medications, followed by a 2-week washout period during which they received no treatment for their PD.</td></tr>
<tr><td>Primary outcomes</td><td>Change in the total UPDRS score between baseline and after the washout period at week 42.</td></tr>
<tr><td>Secondary outcomes</td><td>• Changes in the scores on the UPDRS ADL, Motor, and Mental components between baseline and week 42.
• Adverse events and dropouts.</td></tr>
<tr><td>Results</td><td>Dopaminergic AEs:
<table>
<tr><td>Adverse events</td><td>Placebo (n=90)</td><td>Levodopa 150 mg/d (n=92)</td><td>Levodopa 300 mg/d (n=88)</td><td>Levodopa 600 mg/d (n=91)</td></tr>
<tr><td>Dyskinesia</td><td>3(3.3)</td><td>3(3.3)</td><td>2(2.3)</td><td>15(16.5)</td></tr>
<tr><td>Dystonia</td><td>19(21.1)</td><td>19(20.1)</td><td>14(15.9)</td><td>12(13.2)</td></tr>
<tr><td>Freezing</td><td>13(14.4)</td><td>9(9.8)</td><td>6(6.8)</td><td>5(5.5)</td></tr>
</table></td></tr>
</table>

On-off	3(3.3)	1(1.1)	0(0.0)	3(3.3)
Wearing-off	12(13.3)	15(16.3)	16(18.2)	27(29.7)

Data shown are the number of subjects (with percentages in parentheses) affected with each adverse event.

Study discontinuation:
Placebo (n=90) - 20 did not complete trial:
13 worsening symptoms, 3 AEs, 2 withdrew, 1 lost to follow-up, 1 other.
150 mg/d Carbidopa-Levodopa (n=92) - 14 did not complete trial:
5 worsening symptoms, 2 AEs, 2 withdrew, 3 lost to follow-up, 2 other.
300 mg/d Carbidopa-Levodopa (n=88) - 6 did not complete trial:
1 worsening symptoms, 2 AEs, 2 withdrew, 1 other.
600 mg/d Carbidopa-Levodopa (n=91) - 10 did not complete trial:
2 worsening symptoms, 1 AEs, 3 withdrew, 2 lost to follow-up, 2 other.

Changes in the scores on the UPDRS between baseline and week 42*:

Characteristics	Placebo (n=70)	Levodopa 150 mg/d (n=78)	Levodopa 300 mg/d (n=82)	Levodopa 600 mg/d (n=81)
Evaluation by primary rater				
UPDRS Total	27.7±12	27.2±12.6	27.5±11.6	29.4±13.9
UPDRS Mental	1.4±1.5	1.3±1.5	1.3±1.4	1.4±1.6
UPDRS ADL	7.5±3.6	7.5±4.4	7.3±3.7	7.6±4.0
UPDRS Motor	18.8±8.9	18.6±9.1	18.9±8.8	20.5±10.8
Evaluation by treating investigator				
UPDRS Total	9.0±10.4	4.0±8.2	4.0±8.4	1.0±9.9
UPDRS Mental	0.5±1.3	-0.1±1.4	0.1±1.4	0.1±1.6

Bibliographic reference	Fahn,S., The Parkinson Study Group, Does levodopa slow or hasten the rate of progression of Parkinson's disease?, Journal of Neurology, 252, 37-42, 2005

UPDRS ADL	2.5±4.0	0.8±3.1	1.0±2.8	0.3±3.5
UPDRS Motor	6.0±7.6	3.2±6.4	3.0±6.4	0.6±7.7

*Plus–minus values are means ±SD. On the UPDRS, higher scores indicate greater severity of impairment. Negative numbers indicate improvement as compared with the baseline value. The total score on the UPDRS showed a significant trend toward the reduction of symptoms with higher doses of levodopa in the evaluations by both the primary raters and the treating investigators. The post hoc analysis showed that the effects of all three doses of levodopa differed significantly from the effect of the placebo. Scores on the UPDRS showed that treatment effects were significant for activities of daily living (ADL) and the motor component but not for the mental component.

Overall Risk of Bias

1. Has an appropriate method of randomisation been used? Unclear
2. Was there adequate concealment of allocation? Unclear
3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes
4. Did the comparison groups receive the same care apart from interventions studied? Unclear
5. Were participants receiving care kept blind to treatment allocation? Unclear*
6. Were the individuals administering care kept blind to treatment allocation? Unclear*
7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? No >10% dropout rate and no ITT analysis for efficacy outcomes
8. Did the study have an appropriate length of follow up? Yes (10 months)
9. Did the study use a precise definition of outcome? Yes
10. Was a valid and reliable method used to determine that outcome? Yes
11. Were investigators kept blind to participant's exposure to the intervention? Unclear*
12. Were investigators kept blind to other important confounding and prognostic factors? Unclear*

*Level of blinding unclear - no details beyond description of study as "randomised, double-blind, placebo-controlled trial". Overall there is likely high risk of bias.

<table>
<tr><th>Bibliographic reference</th><th>Thomas,A., Bonanni,L.FAU, Di Iorio,A.FAU, Varanese S FAU - Anzellotti,Francesca, Anzellotti,F.FAU, D'Andreagiovanni,A.FAU, Stocchi,F.FAU, Onofrj,M., End-of-dose deterioration in non ergolinic dopamine agonist monotherapy of Parkinson's disease, Journal of Neurology, 253, 1633-1639, 2006</th></tr>
<tr><td>Country/ies where the study was carried out</td><td>Italy</td></tr>
<tr><td>Study type</td><td>Prospective, randomised trial</td></tr>
<tr><td>Aim of the study</td><td>To assess, in a blind protocol, the appearance of end of dose motor deterioration and eventually to understand whether WO patients had different characteristics from non-fluctuating patients (i.e. age or motor score at onset, progression of motor deterioration, need for higher drug doses).</td></tr>
<tr><td>Study dates</td><td>Study dates: Not reported.
Study duration: 24 months</td></tr>
<tr><td>Source of funding</td><td>Not reported.</td></tr>
<tr><td>Sample size</td><td>In total n=60; Ropinirole n=30 and Pramipexole n=30.</td></tr>
<tr><td>Inclusion criteria</td><td>• Patients with idiopathic PD according to the UK Brain Bank criteria.
• Patients with "de novo" PD (had never received any antiparkinsonian treatment)
• Patients were in Hoehn and Yahr stages I-II.</td></tr>
<tr><td>Exclusion criteria</td><td>Not reported.</td></tr>
<tr><td>Details</td><td>Demographic, at admission, of patients completing the study:
<table>
<tr><td>Characteristic</td><td>Total</td><td>Ropinirole (n=27)</td><td>Pramipexole (n=25)</td></tr>
<tr><td>Mean age ± SD (yr)</td><td>56.2±2.0</td><td>55.3±2.0</td><td>57.1±2.0</td></tr>
<tr><td>Hoehn/Yahr stage ± SD</td><td>1.5±0.6</td><td>1.4±0.6</td><td>1.6±0.6</td></tr>
<tr><td>UPDRS baseline ± SD</td><td>16.3±4.6</td><td>16.7±4.6</td><td>15.8±4.7</td></tr>
</table></td></tr>
<tr><td>Interventions</td><td>Ropinirole: start dose from 3-5 mg per day to 15 mg per day during the first 3 months.
Pramipexole: start dose from 0.7 mg per day to 2.1 mg per day during the first 3 months.

In the following year, daily doses could be further increased (maximum recommended dose: ropinirole to 24 mg and pramipexole to 4.2 mg) according to patients' needs.</td></tr>
<tr><td>Primary outcomes</td><td>Self-reported "wearing-off" periods confirmed by a 30% worsening in the UPDRS score during the 5 hours after a DA dose. The primary end point was therefore checked twice (subjective reports and objective observations).</td></tr>
</table>

Bibliographic reference	**Thomas,A., Bonanni,L.FAU, Di Iorio,A.FAU, Varanese S FAU - Anzellotti,Francesca, Anzellotti,F.FAU, D'Andreagiovanni,A.FAU, Stocchi,F.FAU, Onofrj,M., End-of-dose deterioration in non ergolinic dopamine agonist monotherapy of Parkinson's disease, Journal of Neurology, 253, 1633-1639, 2006**
Secondary outcomes	• Difference between fluctuating and non-fluctuating patients (WO vs. no-WO) in UPDRS scores and Hoehn and Yahr stages at the onset of the study. • Change of UPDRS scores over time and at the end of the study.
Results	Study end-point was reached in 18-21 months. UPDRS motor scores through the study:

		Baseline	3 months	12 months	Last assessment before end of study	End of study
Ropinirole						
17 patients	No WO*	15.3±4.1	7.7±3.1	10.2±2.8	10.8±2.5	12.5±3.0
10 patients	WO**	19.1±4.5	8.9±1.3	11.7±1.8	12.0±2.7	12.7±2.7
Pramipexole						
17 patients	No WO*	14.9±4.8	6.4±3.3	10.4±2.5	11.2±2.9	11.9±2.4
10 patients	WO**	17.8±4.0	7.8±2.4	11.5±1.9	11.7±2.0	12.0±2.1

*No WO=Patients unaffected by motor fluctuation during the 24-months study

Trial discontinuation due to adverse events:
Ropinirole n=3
Pramipexole n=5
In total 6 patients dropped out during the titration period because of gastrointestinal side effects and 2 patients dropped off because of excessive day time somnolence.

Of the 27 patients of the ropinirole group: 3 patients at 14 months, 1 patient at 15 and 3 patients at 16-17 moths reported transient worsening of motor symptoms, but the subjective self-assessment of worsening was not confirmed by UPDRS motor subscale scores, being lower than the 30% cut-off.
**WO="wearing-off" patients

Bibliographic reference	**Thomas,A., Bonanni,L.FAU, Di Iorio,A.FAU, Varanese S FAU - Anzellotti,Francesca, Anzellotti,F.FAU, D'Andreagiovanni,A.FAU, Stocchi,F.FAU, Onofrj,M., End-of-dose deterioration in non ergolinic dopamine agonist monotherapy of Parkinson's disease, Journal of Neurology, 253, 1633-1639, 2006**
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Yes 2. Was there adequate concealment of allocation? Unclear 3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes 4. Did the comparison groups receive the same care apart from interventions studied? Unclear 5. Were participants receiving care kept blind to treatment allocation? Unclear* 6. Were the individuals administering care kept blind to treatment allocation? No 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Yes but >10% dropout rate and no ITT analysis 8. Did the study have an appropriate length of follow up? Yes (2 years) 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Unclear* 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear* *Level of blinding unclear - no details beyond description of study as "randomised, double-blind, placebo-controlled trial". Overall there is likely high risk of bias.

Bibliographic reference	**Palhågen,S., Heinonen EH,F.A.U., Hagglund,J.FAU, Kaugesaar,T.FAU, Kontants,H.FAU, Maki-Ikola,O.FAU, Palm,R.FAU, Turunen,J., Selegiline delays the onset of disability in de novo parkinsonian patients. Swedish Parkinson Study Group, Neurology, 51, 520-525, 1998**
Country/ies where the study was carried out	Sweden
Study type	Randomised, placebo-controlled, double-blind, parallel trial.
Aim of the study	To investigate the effect of selegiline first as monotherapy and then in combination with levodopa in the early phase of PD.
Study dates	Study dates: Not reported. Study duration: Until levodopa therapy became necessary.
Source of funding	Not reported

Bibliographic reference	**Palhågen,S., Heinonen EH,F.A.U., Hagglund,J.FAU, Kaugesaar,T.FAU, Kontants,H.FAU, Maki-Ikola,O.FAU, Palm,R.FAU, Turunen,J., Selegiline delays the onset of disability in de novo parkinsonian patients. Swedish Parkinson Study Group, Neurology, 51, 520-525, 1998**
Sample size	In total n=157; Selegiline n=81; Placebo n=76.
Inclusion criteria	Patients with previously untreated idiopathic PD.
Exclusion criteria	Patients with: • Secondary parkinsonism • Unstable pulmonary, hepatic, renal or gastrointestinal disease • Major psychiatric disorders • Severe infections, • Duodenal or gastric ulcer • Evidence of severe heart disease • Malignant disease (except for basal cell carcinoma of the skin or treated in situ carcinoma of uterine cervix) • Narrow-angle glaucoma • Age more than 75 years (at inclusion) • Known allergy to selegiline or quinine (included in the placebo tablets) • Women who were pregnant or who were breast-feeding • Patients who abused drugs or alcohol • Patients who could not be followed at the intervals determined by the study protocol.
Details	Patients were assigned randomly to receive either selegiline 10 mg or matching placebo given in the morning. This regimen continued until the patient reached a level of clinical disability sufficient to warrant the initiation of levodopa therapy. At this time, the experimental treatments were withdrawn for 8 weeks, and investigators and patients were kept unaware of the treatment assignments. Thereafter, levodopa therapy was started and the study drug reinstituted. The study continued in a double-blind manner for 7 years or until the patient needed additional dopaminergic therapy. There were no statistically significant differences in the demographic data of the patients and the duration and severity of the disease between the groups. However, the mean UPDRS total score at inclusion as well as the subscores of UPDRS, the VAS tremor and the VAS motor dysfunction subscales were slightly worse in the selegiline group than the placebo group at baseline. Parameter measured | Selegiline group* | Placebo group*

<table>
<tr><th>Bibliographic reference</th><td>Palhågen,S., Heinonen EH,F.A.U., Hagglund,J.FAU, Kaugesaar,T.FAU, Kontants,H.FAU, Maki-Ikola,O.FAU, Palm,R.FAU, Turunen,J., Selegiline delays the onset of disability in de novo parkinsonian patients. Swedish Parkinson Study Group, Neurology, 51, 520-525, 1998</td></tr>
<tr><td></td><td>
<table>
<tr><td>Age (y)</td><td>63.3±9.1</td><td>64.2±6.6</td></tr>
<tr><td>Duration of PD before the study (y)</td><td>1.9±1.6</td><td>1.9±1.3</td></tr>
<tr><td>UPDRS motor</td><td>16.7±8.8</td><td>14.2±8.6</td></tr>
<tr><td>Schwab and England ADL</td><td>89.1±6.2</td><td>89.6±6.4</td></tr>
<tr><td>Hoehn and Yahr stage (%)</td><td>Stage 1: 45(55.6)
Stage 2: 34(42.0)
Stage 3: 2(2.4)</td><td>Stage 1: 49(64.5)
Stage 2: 24(31.6)
Stage 3: 3(3.9)</td></tr>
</table>
*Mean ± SD values are given.
</td></tr>
<tr><td>Interventions</td><td>Selegiline: 10mg given in the morning.</td></tr>
<tr><td>Primary outcomes</td><td>The time until the initiation of levodopa therapy became necessary, as judged by parkinsonian disability, ADL or employability.</td></tr>
<tr><td>Secondary outcomes</td><td>Assessment of progression of clinical disability using the following scales:
• UPDRS
• Schwab and England Activities of Daily Living
• Hoehn and Yahr staging
• Tremor and motor dysfunction assessed by the Visual Analogue Scale (VAS)
• MMSE
• Hamilton Depression Scale</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td rowspan="2">UPDRS</td><td colspan="2">6-Month interval (mean±SD)</td><td colspan="2">12-Month interval (mean±SD)</td></tr>
<tr><td>Selegiline n=57</td><td>Placebo n=39</td><td>Selegiline n=37</td><td>Placebo n=24</td></tr>
<tr><td>ADL</td><td>0.0±2.1</td><td>0.9±2.4</td><td>0.5±2.4</td><td>0.8±2.3</td></tr>
<tr><td>Motor</td><td>-1.5±4.7</td><td>2.5±4.4</td><td>0.7±6.1</td><td>2.6±6.8</td></tr>
</table>
The median time from inclusion until the start of washout (i.e. time to the need for addition of levodopa into the treatment regimen) was 12.7 months (quartile deviation, 9.1 months) in the selegiline group and 8.6 months (quartile deviation, 8.0 months) in the placebo group.
</td></tr>
</table>

Bibliographic reference	**Palhågen,S., Heinonen EH,F.A.U., Hagglund,J.FAU, Kaugesaar,T.FAU, Kontants,H.FAU, Maki-Ikola,O.FAU, Palm,R.FAU, Turunen,J., Selegiline delays the onset of disability in de novo parkinsonian patients. Swedish Parkinson Study Group, Neurology, 51, 520-525, 1998**
	In total 16 patients (9 in the selegiline group and 7 in the placebo group) discontinued the trial prematurely. The reasons for this were the following: 6 patients did not want to continue to study; one was lost to follow-up; 5 patients discontinued due to AEs (prostate cancer, leukaemia/lymphoma, psychiatric AEs, laboratory abnormality, broken femur, and deterioration of parkinsonian syndrome with an urgent need for levodopa therapy); and 4 patients due to protocol violation.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Unclear 2. Was there adequate concealment of allocation? Unclear 3. Were the groups comparable at baseline for all major confounding/prognostic factors? No, treatment group had slightly worse scores in UPDRS Total and Motor subscale + VAS tremor and motor dysfunction subscales 4. Did the comparison groups receive the same care apart from interventions studied? Unclear 5. Were participants receiving care kept blind to treatment allocation? Unclear* 6. Were the individuals administering care kept blind to treatment allocation? Unclear* 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? No >10% dropout rate and no ITT analysis 8. Did the study have an appropriate length of follow up? Yes (12 months) 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Unclear* 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear* *Level of blinding unclear - no details beyond description of study as "randomised, double-blind, placebo-controlled trial". Overall there is likely high risk of bias.

Bibliographic reference	**Schapira,Anthony HV, McDermott,Michael P., Barone,Paolo, Comella,Cynthia L., Albrecht,Stefan, Hsu,Helen H., Massey,Daniel H., Mizuno,Yoshikuni, Poewe,Werner, Rascol,Olivier, Marek,Kenneth, Pramipexole in patients with early Parkinson's disease (PROUD): a randomised delayed-start trial, Lancet Neurology, 12, 747-755, 2013**
Country/ies where the study was carried out	Austria, Finland, France, Germany, Italy, Japan, Spain, Sweden, the UK and the USA.
Study type	Randomised, double-blind, placebo-controlled, delayed-start trial.

Bibliographic reference	**Schapira,Anthony HV, McDermott,Michael P., Barone,Paolo, Comella,Cynthia L., Albrecht,Stefan, Hsu,Helen H., Massey,Daniel H., Mizuno,Yoshikuni, Poewe,Werner, Rascol,Olivier, Marek,Kenneth, Pramipexole in patients with early Parkinson's disease (PROUD): a randomised delayed-start trial, Lancet Neurology, 12, 747-755, 2013**
Aim of the study	To identify whether early versus delayed pramipexole initiation has clinical and neuroimaging benefits in patients with PD.
Study dates	Study dates: Not reported. Study duration: 15 months (6-9 months for period 1, pramipexole vs. placebo).
Source of funding	Boehringer Ingelheim GmbH.
Sample size	In total n=535; Pramipexole n=261, Placebo n=274.
Inclusion criteria	• Patients between 30-79 years of age. • Had idiopathic PD characterised by bradykinesia plus at least two further PD signs (resting tremor, rigidity, or asymmetry). • Were at modified Hoehn and Yahr stage 1 or 2. • Were diagnosed within the preceding 2 years and were judged unlikely to need symptomatic treatment for at least the next 6 months, preferably 9 months.
Exclusion criteria	• Patients who were currently using PD drugs. • Had used antipsychotic drugs within the preceding 6 months, or had any clinically significant abnormalities unrelated to PD in physical findings or laboratory values. • Patients with medical or psychiatric disorders capable of interfering with study participation or the interpretation of study data and those with any history of psychosis, dementia, or major or seasonal depression.
Details	The month 9 visit (which could be conducted as much as 3 months earlier) marked the transition from study period 1 (double-blind pramipexole vs. placebo) to period 2 (double-blind early vs. delayed pramipexole). Any patients needing additional PD treatment discontinued the study. Only available data of interest from period 1 (pramipexole vs. placebo) is extracted.
Interventions	Pramipexole: up-titrated over 4 weeks from 0.125 mg three times a day to 0.25 mg three times a day, and finally 0.5mg three times a day.
Primary outcomes	15-month change from baseline in total score on the UPDRS, as assessed by an independent rater (period 2 full-analysis set).
Secondary outcomes	• Total score on the UPDRS assessed at 3, 6, 9, and 15 months by a study investigator. • CGI-I and CGI-S applied at 15 months by the independent raters. • AEs.
Results	Study discontinuation during period 1: Pramipexole (n=261) - 40 discontinued:

Bibliographic reference	Schapira,Anthony HV, McDermott,Michael P., Barone,Paolo, Comella,Cynthia L., Albrecht,Stefan, Hsu,Helen H., Massey,Daniel H., Mizuno,Yoshikuni, Poewe,Werner, Rascol,Olivier, Marek,Kenneth, Pramipexole in patients with early Parkinson's disease (PROUD): a randomised delayed-start trial, Lancet Neurology, 12, 747-755, 2013

25 AEs (including 1 with worsened PD), 4 inadequate efficacy, 5 non-compliance, 5 withdrew consent, 1 other.

Placebo (n=274) - 60 discontinued:

26 AEs (including 15 worsened PD), 12 inadequate efficacy, 3 non-compliance, 16 withdrew consent, 2 lost to follow-up, 1 other.

Adverse events during period 1:

AEs	Pramipexole (n=261)	Placebo (n=274)
Any AEs	194(74%)	196(72%)
Severe AEs	34(13%)	23(8%)
Serious AEs	17(7%)	18(7%)
Study-drug-related AEs	113(43%)	72(26%)
AEs leading to discontinuation	25(10%)	26(9%)
Nausea*	54(21%)	21(8%)
Dizziness*	29(11%)	24(9%)
Somnolence*	28(11%)	9(3%)
Fatigue*	26(10%)	21(8%)
Headache*	17(7%)	23(8%)
Insomnia*	17(7%)	8(3%)
Peripheral oedema*	17(7%)	4(1%)
Constipation*	16(6%)	20(7%)
Nasopharyngitis*	16(6%)	15(5%)
Back pain*	14(5%)	13(5%)

Bibliographic reference	Schapira,Anthony HV, McDermott,Michael P., Barone,Paolo, Comella,Cynthia L., Albrecht,Stefan, Hsu,Helen H., Massey,Daniel H., Mizuno,Yoshikuni, Poewe,Werner, Rascol,Olivier, Marek,Kenneth, Pramipexole in patients with early Parkinson's disease (PROUD): a randomised delayed-start trial, Lancet Neurology, 12, 747-755, 2013

Depression*	13(5%)	12(4%)
Hallucination*	13(5%)	3(1%)
Diarrhoea*	8(3%)	15(5%)

*Event types reported in ≥5% of patients in either group.

Adjusted mean changes (SE) on UPDRS ADL and UPDRS Motor at 9 months (as measured by study investigator):

UPDRS	Early Pramipexole* n=210 or 211***	Delayed Pramipexole (Placebo)** n=200
ADL	0.4(0.2)	1.5(0.2)
Motor	-0.6(0.5)	2.7(0.5)

*Includes 45 patients who entered period 2 before 9 months.
**Includes 65 patients who entered period 2 before 9 months.
***Depending on time point.

Changes on quality of life scales and BDI (data are median change (IQR) or mean change (SE) at 9 months:

	Early Pramipexole* n=208-211***	Delayed Pramipexole (Placebo)** n=197-200***
PDQ-39 total score	-0.5(-3.6 to 2.0)	1.4(-2.2 to 5.0)
EQ-5D total score	0.0(-0.03 to 0.09)	0.0(-0.14 to 0.0)
EQVAS	0.0(-5.5 to 5.0)	-0.5(-10.0 to 5.0)
BDI, adjusted for baseline and country	-1.1(0.3)	0.3(0.3)

*Includes 45 patients who entered period 2 before 9 months.
**Includes 65 patients who entered period 2 before 9 months.
***Depending on time point.

Bibliographic reference	Schapira,Anthony HV, McDermott,Michael P., Barone,Paolo, Comella,Cynthia L., Albrecht,Stefan, Hsu,Helen H., Massey,Daniel H., Mizuno,Yoshikuni, Poewe,Werner, Rascol,Olivier, Marek,Kenneth, Pramipexole in patients with early Parkinson's disease (PROUD): a randomised delayed-start trial, Lancet Neurology, 12, 747-755, 2013
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Yes 2. Was there adequate concealment of allocation? Yes 3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes 4. Did the comparison groups receive the same care apart from interventions studied? Unclear 5. Were participants receiving care kept blind to treatment allocation? Yes 6. Were the individuals administering care kept blind to treatment allocation? Yes 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? No (apart from AEs), approximately 20% and 30% in treatment and placebo group, respectively, moved into phase 2 of the study prematurely, which involved a delayed pramipexole dosing in the placebo group + no ITT analysis. 8. Did the study have an appropriate length of follow up? Yes (9 months) 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Yes 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear* *Level of blinding unclear - no details beyond description of study as "randomised, double-blind, placebo-controlled trial". Overall there is likely low risk of bias.

Bibliographic reference	Barone, P., Santangelo, G., Morgante, L., Onofrj, M., Meco, G., Abbruzzese, G., Bonuccelli, U., Cossu, G., Pezzoli, G., Stanzione, P., Lopiano, L., Antonini, A., Tinazzi, M., A randomised clinical trial to evaluate the effects of rasagiline on depressive symptoms in non-demented Parkinson's disease patients, 22, 1184-1191, 2015
Country/ies where the study was carried out	Italy
Study type	Randomised, double-blind, placebo-controlled trial
Aim of the study	To evaluate the effects of rasagiline on depressive symptoms and cognition in non-demented PD patients with depressive symptoms.
Study dates	Study dates: 5 March 2010 to 2 July 2012

<table>
<tr><th>Bibliographic reference</th><th>Barone, P., Santangelo, G., Morgante, L., Onofrj, M., Meco, G., Abbruzzese, G., Bonuccelli, U., Cossu, G., Pezzoli, G., Stanzione, P., Lopiano, L., Antonini, A., Tinazzi, M., A randomised clinical trial to evaluate the effects of rasagiline on depressive symptoms in non-demented Parkinson's disease patients, 22, 1184-1191, 2015</th></tr>
<tr><td></td><td>Study duration: 12 weeks</td></tr>
<tr><td>Source of funding</td><td>Lundbeck Italia SpA</td></tr>
<tr><td>Sample size</td><td>In total: n=123; Rasagiline: n=58; Placebo: n=65</td></tr>
<tr><td>Inclusion criteria</td><td>• A diagnosis of PD (at least 2 of 3 cardinal signs - resting tremor, bradykinesia, rigidity - and no other known or suspected cause of parkinsonism)
• Age ≥40 and <80 years
• Hoehn and Yahr stage ≥1 and ≤3 (on treatment)
• A beck Depression Inventory score ≥15
• Should have been under stable (4 weeks prior to baseline) dopaminergic treatment.
• All stable doses of dopamine receptor agonists, levodopa/carbidopa, levodopa/benserazide and COMT inhibitors were permitted.</td></tr>
<tr><td>Exclusion criteria</td><td>• Patients with motor fluctuations (the presence of which may be associated with mood)
• Previous deep brain stimulation surgery
• MMSE <26
• A diagnosis of current or a history of major depressive episode according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) criteria within 1 year before recruitment into the study
• The presence of psychotic symptoms
• Treatment with antidepressants, antipsychotics, cholinesterase inhibitors, memantine, amantadine, anticholinergics, and the hypnotics zaleplon, zolpidem, zopiclone and antihistamines were not allowed and must have been discontinued at least 4 weeks prior to study initiation
• Patients currently or previously treated with selegiline (<90 days prior to randomisation) were also excluded</td></tr>
<tr><td>Details</td><td>Patient demographics and baseline PD characteristics were well matched, with no significant difference between groups:
<table>
<tr><td>Characteristics</td><td>Rasagiline n=58</td><td>Placebo n=65</td></tr>
<tr><td>Age (yrs), mean±SD</td><td>66.0±4.33</td><td>66.1±4.49</td></tr>
<tr><td>Duration of PD (yrs), mean ±SD</td><td>3.7±3.17</td><td>4.8±3.78</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Barone, P., Santangelo, G., Morgante, L., Onofrj, M., Meco, G., Abbruzzese, G., Bonuccelli, U., Cossu, G., Pezzoli, G., Stanzione, P., Lopiano, L., Antonini, A., Tinazzi, M., A randomised clinical trial to evaluate the effects of rasagiline on depressive symptoms in non-demented Parkinson's disease patients, 22, 1184-1191, 2015**
	Hoehn & Yahr staging, n (%) I: 9(15.5%) / 9(13.8%) I.5: 12(20.7%) / 11(16.9%) II: 29(50%) / 34(52.3%) II.5: 5(8.6%) / 6(9.2%) III: 3(5.2%) / 5(7.7%)
Interventions	Rasagiline: 1 mg daily
Primary outcomes	The change from baseline to week 12 in cognitive function as assessed by the Beck Depression Inventory total score
Secondary outcomes	• Change from baseline to week 12 in cognitive function as assessed by a comprehensive neuropsychological battery • PDQ-39 scores • Apathy Scale scores • UPDRS subscores
Results	Treatment with rasagiline significantly improved UPDRS II scores versus placebo at week 12 (marginal means difference ± SE: rasagiline -1.37±0.35 vs. placebo 0.06±0.32. P=0.003). There was no significant effect of treatment on UPDRS III subscores (rasagiline -0.88±0.56 vs. placebo 0.42±0.51, P=0.090). There was no significant effect of treatment on PDQ-39 total scores (rasagiline -6.28±2.24 vs. placebo -0.73±2.06, P=0.074. However, a post hoc analysis of PDQ-39 domains found significant differences favouring rasagiline in PDQ-mobility scores (P=0.007) and PDQ-cognition scores (P=0.026). A total of 15 vs. 17 patients (rasagiline vs. placebo group, respectively) reported at least one treatment-emergent adverse event (TEAE); most TEAEs were mild or moderate. No TEAE was reported more than two times in either group. Two patients in the rasagiline group (radius fracture; melanocytic nevus) and one in the placebo group (polyneuropathy in malignant disease and respiratory disorder) reported a serious TEAE. Four patients in the rasagiline group withdrew due to a TEAE (aggravated dyskinesia, vertigo, left trunk flexion due to PD, nausea) vs. none in the placebo group.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Yes

Bibliographic reference	Barone, P., Santangelo, G., Morgante, L., Onofrj, M., Meco, G., Abbruzzese, G., Bonuccelli, U., Cossu, G., Pezzoli, G., Stanzione, P., Lopiano, L., Antonini, A., Tinazzi, M., A randomised clinical trial to evaluate the effects of rasagiline on depressive symptoms in non-demented Parkinson's disease patients, 22, 1184-1191, 2015
	2. Was there adequate concealment of allocation? Yes 3. Were the groups comparable at baseline for all major confounding/prognostic factors? No 4. Did the comparison groups receive the same care apart from interventions studied? Yes 5. Were participants receiving care kept blind to treatment allocation? Yes 6. Were the individuals administering care kept blind to treatment allocation? Yes 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Unclear 8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Yes 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	Jankovic, Joseph, Watts, Ray L., Martin, Wayne, Boroojerdi, Babak, Transdermal rotigotine: double-blind, placebo-controlled trial in Parkinson disease, 64, 676-82, 2007
Country/ies where the study was carried out	US and Canada
Study type	Randomised, double-blind, multicentre, placebo-controlled study
Aim of the study	To assess the response to the rotigotine transdermal system in patients with early Parkinson disease.
Study dates	Study dates: Not reported Study duration: 24 weeks
Source of funding	Schwarz Pharma Ltd
Sample size	In total: n=277; Rotigotine: n= 181; Placebo: n=96
Inclusion criteria	• 30 years or older with an established diagnosis of idiopathic PD of 5 years' duration or less • With at least 2 of the following cardinal signs, without any other known or suspected causes of parkinsonism: bradykinesia, resting tremor, rigidity and postural instability • UPDRS motor score of at least 10

<table>
<tr><th>Bibliographic reference</th><th>Jankovic, Joseph, Watts, Ray L., Martin, Wayne, Boroojerdi, Babak, Transdermal rotigotine: double-blind, placebo-controlled trial in Parkinson disease, 64, 676-82, 2007</th></tr>
<tr><td></td><td>• Hoehn and Yahr stage of III or less
• MMSE score of 25 or higher
• Patients previously receiving an anticholinergic agent, monoamine oxidase-B inhibitor, or N-methyl-D-aspartate antagonist must have had a stable dose for at least 28 days before study baseline and were required to maintain that dose for the duration of the trial.</td></tr>
<tr><td>Exclusion criteria</td><td>• Patients who had:
• Previous or concurrent therapy with a dopamine agonist or with carbidopa or levodopa within 28 days of the baseline visit
• Carbidopa or levodopa therapy for more than 6 months since diagnosis
• Atypical parkinsonism
• Surgical intervention for PD
• Clinically relevant hepatic, renal, or cardiac dysfunction
• A diagnosis of epilepsy
• A history of seizures as an adult, or stroke or a transient ischemic attack within the last year
• pronounced skin hypersensitivity to adhesive or other transdermal patches or recent unresolved contact dermatitis
• Known intolerance or hypersensitivity to the antiemetic ondansetron
• Pregnancy or were nursing
• Used inadequate birth control methods
• Are receiving central nervous system active therapy unless their pharmacotherapy doses had been stable for at least 28 days before baseline and were likely to remain stable for the duration of the trial</td></tr>
<tr><td>Details</td><td>Baseline characteristics:<table><tr><td>Characteristics</td><td>Rotigotine n=181</td><td>Placebo n=96</td></tr><tr><td>Age (yrs)</td><td>62(10.3)</td><td>64.5(10.7)</td></tr><tr><td>Years since diagnosis</td><td>1.3(1.3)</td><td>1.4(1.3)</td></tr><tr><td>UPDRS II</td><td>8.3(4.6)</td><td>8.7(4.0)</td></tr><tr><td>UPDRS III</td><td>21.6(8.9)</td><td>21.3(8.2)</td></tr></table>Data are given as mean (SD) unless otherwise indicated.</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Jankovic, Joseph, Watts, Ray L., Martin, Wayne, Boroojerdi, Babak, Transdermal rotigotine: double-blind, placebo-controlled trial in Parkinson disease, 64, 676-82, 2007</th></tr>
<tr><td>Interventions</td><td>Rotigotine transdermal system: 2, 4, or 6 mg during 24 hours</td></tr>
<tr><td>Primary outcomes</td><td>Percentage of subjects achieving a 20% response or greater (reduction) as assessed with the UPDRS II and III from baseline to the end of the maintenance phase.</td></tr>
<tr><td>Secondary outcomes</td><td>• Effects on subsets of the UPDRS
• Clinical Global Impression Scale rating
• Epworth Sleepiness Scale scores
• Quality of life measures
• Serum prolactin and rotigotine plasma concentration data</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td>Rotigotine n=177</td><td>Placebo n=96</td><td>P value</td></tr>
<tr><td>Change in UPDRS II score</td><td>-0.39(0.26)</td><td>0.92(0.35)</td><td>0.002</td></tr>
<tr><td>Change in UPDRS III score</td><td>-3.58(0.54)</td><td>0.38(0.73)</td><td>0.001</td></tr>
</table>

Summary of the most common treatment-emergent adverse events with an incidence of 5% or greater:
<table>
<tr><td>Adverse event</td><td>Rotigotine n=181</td><td>Placebo n=96</td></tr>
<tr><td>Application site disorder</td><td>79(44)</td><td>11(11)</td></tr>
<tr><td>Accident, not otherwise specified</td><td>14(8)</td><td>2(2)</td></tr>
<tr><td>Fatigue</td><td>14(8)</td><td>5(5)</td></tr>
<tr><td>Pain</td><td>4(2)</td><td>7(7)</td></tr>
<tr><td>Leg pain</td><td>2(1)</td><td>6(6)</td></tr>
<tr><td>Dizziness</td><td>34(19)</td><td>12(13)</td></tr>
<tr><td>Headache</td><td>29(16)</td><td>9(9)</td></tr>
<tr><td>Tremor</td><td>11(6)</td><td>4(4)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Jankovic, Joseph, Watts, Ray L., Martin, Wayne, Boroojerdi, Babak, Transdermal rotigotine: double-blind, placebo-controlled trial in Parkinson disease, 64, 676-82, 2007

Parkinsonism aggravated	2(1)	5(5)
Nausea	75(41)	16(17)
Vomiting	16(9)	1(1)
Constipation	11(6)	4(4)
Dyspepsia	12(7)	1(1)
Diarrhoea	11(6)	2(2)
Arthralgia	10(6)	6(6)
Back pain	11(6)	3(3)
Skeletal pain	7(4)	6(6)
Somnolence	60(33)	19(20)
Insomnia	17(9)	3(3)
Coughing	9(5)	6(6)
Upper respiratory tract infection	8(4)	7(7)
Sinusitis	7(4)	6(6)
Rash	4(2)	5(5)

Data are given as number (%) of patients.

Overall Risk of Bias

1. Has an appropriate method of randomisation been used? Yes
2. Was there adequate concealment of allocation? Yes
3. Were the groups comparable at baseline for all major confounding/prognostic factors? Unclear
4. Did the comparison groups receive the same care apart from interventions studied? Unclear
5. Were participants receiving care kept blind to treatment allocation? Yes
6. Were the individuals administering care kept blind to treatment allocation? Yes

Bibliographic reference	Jankovic, Joseph, Watts, Ray L., Martin, Wayne, Boroojerdi, Babak, Transdermal rotigotine: double-blind, placebo-controlled trial in Parkinson disease, 64, 676-82, 2007
	7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Yes 8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Yes 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	Mizuno,Y., Nomoto,M., Kondo,T., Hasegawa,K., Murata,M., Takeuchi,M., Ikeda,J., Tomida,T., Hattori,N., Transdermal rotigotine in early stage Parkinson's disease: A randomised, double-blind, placebo-controlled trial, Movement Disorders.28 (10) (pp 1447-1450), 2013.Date of Publication: September 2013., 1447-1450, 2013
Country/ies where the study was carried out	Japan
Study type	Randomised, double-blind, placebo-controlled trial
Aim of the study	To determine the safety and efficacy of transdermal rotigotine in patients with early stage Parkinson's disease in Japan
Study dates	Study dates: September 2007 to April 2009 Study duration: 12 weeks
Source of funding	Otsuka Pharmaceutical Company Ltd
Sample size	In total: n=180; Rotigotine: n= 90; Placebo: n=90
Inclusion criteria	• Clinical diagnosis of PD • Patients with early PD and had no concomitant treatment with L-dopa • Age range 30-79 years • Hoehn & Yahr scale scores from I to III • UPDRS II and III scores ≥10 • Patients who had received L-dopa before study entry had to discontinue L-dopa at least 2 weeks before the date of the first treatment administration.
Exclusion criteria	Patients with any of the following symptoms:

<table>
<tr><th>Bibliographic reference</th><th>Mizuno,Y., Nomoto,M., Kondo,T., Hasegawa,K., Murata,M., Takeuchi,M., Ikeda,J., Tomida,T., Hattori,N., Transdermal rotigotine in early stage Parkinson's disease: A randomised, double-blind, placebo-controlled trial, Movement Disorders.28 (10) (pp 1447-1450), 2013.Date of Publication: September 2013., 1447-1450, 2013</th></tr>
<tr><td></td><td>• Psychiatric symptoms, including confusion, hallucination, delusion, excitation, delirium, and abnormal behaviour at entry
• Symptomatic orthostatic hypotension
• A history of epilepsy and/or convulsion
• Complications or history of serious cardiac disease and/or arrhythmia
• Severe renal or hepatic impairments
• History of deep brain stimulation
• Dementia
• Had received L-dopa for >6 months by the time of acquisition of informed consent or other drugs that could possibly affect PD symptoms from at least 4 weeks before the date of first treatment</td></tr>
<tr><td>Details</td><td>Baseline characteristics:
<table>
<tr><td>Characteristics</td><td>Rotigotine n=88</td><td>Placebo n=88</td></tr>
<tr><td>Age (yrs): <65</td><td>36(40.9)</td><td>35(39.8)</td></tr>
<tr><td>Age (yrs): ≥65</td><td>52(59.1)</td><td>53(60.2)</td></tr>
<tr><td>Duration of disease (yrs)</td><td>2.0±1.8</td><td>1.8±1.9</td></tr>
<tr><td>UPDRS II</td><td>6.8±3.9</td><td>7.4±3.8</td></tr>
<tr><td>UPDRS III</td><td>20.2±9.2</td><td>20.8±9.5</td></tr>
<tr><td>Hoehn & Yahr stage (average)</td><td>2.1±0.7</td><td>2.2±0.6</td></tr>
</table>
Values are given in means ±SD or no. of patients (%).</td></tr>
<tr><td>Interventions</td><td>Rotigotine: Starting dose of 2mg/24 hrs with a weekly increment of 2mg/24 hrs, up to a maximum of 16mg/24 hrs during the 8 week titration period.</td></tr>
<tr><td>Primary outcomes</td><td>The change in UPDRS II and III scores from baseline to the end of treatment</td></tr>
<tr><td>Secondary outcomes</td><td>Not reported</td></tr>
<tr><td>Results</td><td>Change in UPDRS III scores from baseline to end of trial differed significantly (95% CI, -5.6 to -1.6; P<0.001) between groups, but changes in UPDRS II scores did not (95% CI, -1.6 to 0.2; P=0.125).</td></tr>
</table>

Bibliographic reference	Mizuno,Y., Nomoto,M., Kondo,T., Hasegawa,K., Murata,M., Takeuchi,M., Ikeda,J., Tomida,T., Hattori,N., Transdermal rotigotine in early stage Parkinson's disease: A randomised, double-blind, placebo-controlled trial, Movement Disorders.28 (10) (pp 1447-1450), 2013.Date of Publication: September 2013., 1447-1450, 2013
	Seventy-eight patients (86.7%) in the rotigotine group and 65 patients (72.2%) in the placebo group experienced at least 1 TEAE, and most were mild or moderate in intensity.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Yes 2. Was there adequate concealment of allocation? Yes 3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes 4. Did the comparison groups receive the same care apart from interventions studied? Unclear 5. Were participants receiving care kept blind to treatment allocation? Yes 6. Were the individuals administering care kept blind to treatment allocation? Yes 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Yes 8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Yes 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	Pahwa, R., Lyons, K. E., Hauser, R. A., Fahn, S., Jankovic, J., Pourcher, E., Hsu, A., O'Connell, M., Kell, S., Gupta, S., Randomised trial of IPX066, carbidopa/levodopa extended release, in early Parkinson's disease, 20, 142-8, 2014
Country/ies where the study was carried out	US and Canada
Study type	Multicentre, multination, randomised, double-blind, parallel-group, fixed-dose, placebo-controlled trial
Aim of the study	To assess the efficacy, safety, and impact on quality of life of IPX066 (carbidopa/levodopa) in the treatment of levodopa-naive Parkinson's disease patients.
Study dates	Study dates: April 2009 to October 2010 Study duration: 30 weeks
Source of funding	Impax Pharmaceuticals
Sample size	In total: n=381; IPX066 145mg n=87; IPX066 245 n=104; IPX066 n=98; Placebo n=92

<table>
<tr><th>Bibliographic reference</th><th>Pahwa, R., Lyons, K. E., Hauser, R. A., Fahn, S., Jankovic, J., Pourcher, E., Hsu, A., O'Connell, M., Kell, S., Gupta, S., Randomised trial of IPX066, carbidopa/levodopa extended release, in early Parkinson's disease, 20, 142-8, 2014</th></tr>
<tr><td>Inclusion criteria</td><td>• ≥30 years of age at PD diagnosis
• Hoehn & Yahr stage I-III
• Levodopa- naive (not exposed to levodopa for >30 days and not within 4 weeks enrolment)
• MMSE ≥26
• Sum of UPDRS II and III scores ≥18
• Anticholinergics, amantadine, MAO-B inhibitors were allowed but dosages had to be stable for 4 weeks prior to study entry and unchanged throughout the study.</td></tr>
<tr><td>Exclusion criteria</td><td>• Atypical parkinsonism
• Females pregnant or breastfeeding
• Previous neurosurgical treatment for PD
• Use of nonselective MAO inhibitors
• Use of dopamine agonists within 30 days of screening
• Inability to tolerate a placebo regimen
• A history of sensitivity to carbidopa/levodopa
• Treatment of psychosis with any antipsychotic
• Seizure
• Active or prior medical conditions that would interfere with levodopa absorption
• Narrow-angle glaucoma
• Malignant melanoma
• Suspicious undiagnosed skin lesion
• Myocardial infarction with residual problems
• Abnormal kidney function
• Abnormal liver transaminase values</td></tr>
<tr><td>Details</td><td>There were no significant differences at baseline measures across treatment groups and patients who used non-levodopa PD medications were equally distributed across treatment groups.
<table>
<tr><td>Characteristics</td><td>Placebo n=92</td><td>145mg TID n=87</td><td>245mg TID n=104</td><td>390mg TID n=98</td></tr>
<tr><td>Age (yrs)</td><td>65.4(9.4)</td><td>63.8(9.8)</td><td>65.2(9.7)</td><td>64.8(9.3)</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><td colspan="5">Pahwa, R., Lyons, K. E., Hauser, R. A., Fahn, S., Jankovic, J., Pourcher, E., Hsu, A., O'Connell, M., Kell, S., Gupta, S., Randomised trial of IPX066, carbidopa/levodopa extended release, in early Parkinson's disease, 20, 142-8, 2014</td></tr>
<tr><td></td><td colspan="5">
<table>
<tr><td>Total PDQ-39 score</td><td>24.0(15.5)</td><td>26.0(16.9)</td><td>25.2(18.6)</td><td>25.1(17.1)</td></tr>
<tr><td>Age at PD onset (yrs)</td><td>63.7(9.5)</td><td>61.7(10.7)</td><td>63.6(10.4)</td><td>63.0(9.4)</td></tr>
<tr><td>Duration of PD (yrs)</td><td>1.8(2.0)</td><td>2.3(3.1)</td><td>1.8(1.8)</td><td>2.0(2.3)</td></tr>
<tr><td>UPDRS II</td><td>10.2(4.5)</td><td>10.3(4.5)</td><td>10.3(5.0)</td><td>9.9(4.4)</td></tr>
<tr><td>UPDRS III</td><td>26.1(9.0)</td><td>25.9(10.6)</td><td>27.8(12.2)</td><td>26.4(10.1)</td></tr>
<tr><td>Hoehn & Yahr stage:</td><td></td><td></td><td></td><td></td></tr>
<tr><td>I (n,%)</td><td>7(7.6)</td><td>6(6.9)</td><td>13(12.5)</td><td>14(14.3)</td></tr>
<tr><td>II (n,%)</td><td>69(75.0)</td><td>62(71.3)</td><td>65(62.5)</td><td>62(63.3)</td></tr>
<tr><td>III (n,%)</td><td>16(17.4)</td><td>19(21.8)</td><td>26(25.0)</td><td>22(22.4)</td></tr>
</table>
</td></tr>
<tr><td>Interventions</td><td colspan="5">IPX066 (carbidopa/levodopa) was initiated at 95 mg three times daily for all 3 intervention groups and then uptitrated to the maximum dose for each group:
Group 1: IPX066 36.25/145 mg tid
Group 2: IPX066 61.25/245 mg tid
Group 3: IPX066 97.5/390 mg tid
Group 4: Placebo tid</td></tr>
<tr><td>Primary outcomes</td><td colspan="5">• Change in UPDRS II + III from baseline to end of the study
• Adverse events</td></tr>
<tr><td>Secondary outcomes</td><td colspan="5">• Change from baseline in UPDRS I + II + III and in individual UPDRS subscores at the end of the study
• Total PDQ-39
• Patient Global Impression of Improvement
• Clinical Global Impression of Improvement</td></tr>
<tr><td>Results</td><td colspan="5">Change from baseline to end of study (p-values and 95% confidence intervals compared with placebo):
<table>
<tr><td>Efficacy measure</td><td>Placebo n=90</td><td>145mg TID n=82</td><td>245mg TID n=99</td><td>390mg TID n=90</td></tr>
<tr><td>UPDRS II</td><td>0.2</td><td>-2.8; P<0.0001; (-4.4, -1.4)</td><td>-3.1; P<0.0001; (-4.7, -1.9)</td><td>-3.9; P<0.0001; (-5.5, -2.6)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Pahwa, R., Lyons, K. E., Hauser, R. A., Fahn, S., Jankovic, J., Pourcher, E., Hsu, A., O'Connell, M., Kell, S., Gupta, S., Randomised trial of IPX066, carbidopa/levodopa extended release, in early Parkinson's disease, 20, 142-8, 2014

UPDRS III	-0.7	-8.9; P<0.0001; (-11.2, -5.2)	-9.8; P<0.0001; (-11.9, -6.2)	-11.0; P<0.0001; (-13.2, -7.4)
PDQ-39 total	0.6	-4.4; P<0.02; (9.3, -0.6)	-3.8; P<0.03; (-8.5, -0.3)	-6.0; P<0.0008; (-10.7, -2.3)

Adverse events occurring in greater than 5% of any treatment group:

Adverse event	Placebo n=92	145mg n=87	245mg n=104	390mg n=98	Total n=381
Nausea	8(8.7)	12(13.8)	20(19.2)	20(20.4)	60(15.7)
Headache	10(10.9)	6(6.9)	13(12.5)	17(17.3)	46(12.1)
Dizziness	5(5.4)	8(9.2)	20(19.2)	12(12.2)	45(11.8)
Insomnia	3(3.3)	2(2.3)	9(8.7)	6(6.1)	20(5.2)
Abnormal dreams	0	2(2.3)	6(5.8)	5(5.1)	13(3.4)
Dry mouth	1(1.1)	3(3.4)	2(1.9)	7(7.1)	13(3.4)
Vomiting	3(3.3)	2(2.3)	2(1.9)	5(5.1)	12(3.1)
Constipation	1(1.1)	2(2.3)	6(5.8)	2(2.0)	11(2.9)
Dyskinesia	0	2(2.3)	4(3.8)	5(5.1)	11(2.9)
Anxiety	0	2(2.3)	3(2.9)	5(5.1)	10(2.6)
Depression	5(5.4)	1(1.1)	2(1.9)	2(2.0)	10(2.6)
Orthostatic hypotension	1(1.1)	1(1.1)	1(1.0)	5(5.1)	8(2.1)

Overall Risk of Bias

1. Has an appropriate method of randomisation been used? Yes
2. Was there adequate concealment of allocation? Yes
3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes
4. Did the comparison groups receive the same care apart from interventions studied? Yes
5. Were participants receiving care kept blind to treatment allocation? Yes
6. Were the individuals administering care kept blind to treatment allocation? Yes

Bibliographic reference	Pahwa, R., Lyons, K. E., Hauser, R. A., Fahn, S., Jankovic, J., Pourcher, E., Hsu, A., O'Connell, M., Kell, S., Gupta, S., Randomised trial of IPX066, carbidopa/levodopa extended release, in early Parkinson's disease, 20, 142-8, 2014
	7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Unclear 8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Yes 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	Parkinson Study, Group, A controlled trial of rotigotine monotherapy in early Parkinson's disease, 60, 1721-8, 2003
Country/ies where the study was carried out	North America
Study type	Randomised, double-blind, placebo-controlled study
Aim of the study	To assess the efficacy and safety of rotigotine in patients with PD not receiving dopaminergic medications
Study dates	Study dates: Not reported Study duration: 11 weeks
Source of funding	Schwarz Pharma Inc.
Sample size	In total: n=242; Rotigotine 4.5mg n=49; Rotigotine 9mg n=47; Rotigotine 13.5mg n= 48; Rotigotine 18mg n=51; Placebo n=47
Inclusion criteria	• ≥30 years who were diagnosed as having idiopathic PD • Hoehn and Yahr stage of 3 or less • Subjects were permitted to take selegiline, amantadine, or anticholinergic agents if maintained at stable dosages for 28 days before baseline and throughout the trial.
Exclusion criteria	Patients who: • Had an MMSE score of less than 24 • Were unable to appropriately apply and remove the patches • Had a history of skin sensitivity to adhesives or other transdermal medications • Had taken a dopamine agonist or levodopa within 28 days of the baseline visit or had ever taken levodopa for longer than 6 months

<table>
<tr><th>Bibliographic reference</th><th>Parkinson Study, Group, A controlled trial of rotigotine monotherapy in early Parkinson's disease, 60, 1721-8, 2003</th></tr>
<tr><td></td><td>

Had an atypical parkinsonian syndrome
Had a clinically unstable medical or psychiatric condition
Had cardiac abnormalities such as arrhythmias, conduction blocks, congestive heart failure, QT-corrected interval of 500 milliseconds or more, unexplained syncope, symptomatic orthostatic hypotension, or a recent myocardial infarction
Had recent exposure to monoamine oxidase type A inhibitors, amphetamines, dopamine-depleting antihypertensive agents, neuroleptics, or antipsychotics or antiemetics that blocked central dopamine activity

</td></tr>
<tr><td>Details</td><td>There were no important differences among the 5 treatment groups in the baseline demographic and clinical variables.
<table>
<tr><td>Characteristics</td><td>Placebo (n=47)</td><td>Rotigotine 4.5mg (n=49)</td><td>Rotigotine 9mg (n=47)</td><td>Rotigotine 13.5mg (n=48)</td><td>Rotigotine 18mg (n=51)</td></tr>
<tr><td>Age (yrs)</td><td>62.3(10.5)</td><td>61.8(9.8)</td><td>60.9(8.3)</td><td>61.3(10.9)</td><td>60.5(10.7)</td></tr>
<tr><td>Years since PD diagnosis</td><td>1.3(1.4)</td><td>1.2(1.4)</td><td>1.5(2.0)</td><td>1.2(1.0)</td><td>1.1(1.2)</td></tr>
<tr><td colspan="6">Hoehn & Yahr stage:</td></tr>
<tr><td>I</td><td>27.7</td><td>36.7</td><td>25.5</td><td>35.4</td><td>35.3</td></tr>
<tr><td>II</td><td>57.5</td><td>57.1</td><td>70.2</td><td>56.3</td><td>56.9</td></tr>
<tr><td>III</td><td>14.9</td><td>6.1</td><td>4.3</td><td>8.3</td><td>7.8</td></tr>
<tr><td>UPDRS II</td><td>7.2(3.8)</td><td>6.9(3.3)</td><td>7.5(3.8)</td><td>7.4(4.3)</td><td>6.4(4.4)</td></tr>
<tr><td>UPDRS III</td><td>19.6(8.8)</td><td>19.8(8.9)</td><td>20.0(7.5)</td><td>19.8(10.7)</td><td>17.4(7.9)</td></tr>
</table>
Values are given as mean (SD) unless otherwise stated.</td></tr>
<tr><td>Interventions</td><td>Starting dose for all intervention groups were 4.5mg/day, then adjusted weekly by increments of 4.5mg until the maximum dosage for each group were reached:
Rotigotine patches: 4.5, 9, 13.5, or 18 mg</td></tr>
<tr><td>Primary outcomes</td><td>

The change in the sum of the scores of UPDRS II and III from baseline to the end of treatment
Adverse events and tolerability

</td></tr>
<tr><td>Secondary outcomes</td><td>

Changes in the UPDRS mental, ADL and motor subscale scores
Change in Hoehn and Yahr stage between baseline and week 11 visit

</td></tr>
</table>

Bibliographic reference	Parkinson Study, Group, A controlled trial of rotigotine monotherapy in early Parkinson's disease, 60, 1721-8, 2003

Results

Treatment effects at week 11 on UPDRS scores:

Dosage, mg	Difference in mean change between active treatment and placebo (95% CI)	P value
Motor score:		
4.5	-0.90(-3.2 to 1.40)	.44
9.0	-1.88 (-4.22 to 0.45)	.11
13.5	-3.91(-6.26 to -1.56)	.001
18.0	-3.82(-6.12 to -1.53)	.001
ADL score:		
4.5	-0.04(-1.05 to 0.97)	.94
9.0	-0.84(-1.87 to 0.18)	.11
13.5	-0.92(-1.95 to 0.11)	.08
18.0	-1.56(-2.57 to -0.56)	.003

Adverse events:

Adverse event	Placebo (n=47)	Rotigotine groups (n=195)
Nausea	7(15)	92(47)
Application site infection	10(21)	77(39)
Dizziness	6(13)	46(24)
Somnolence	2(4)	42(22)
Insomnia	5(11)	37(19)
Headache	6(13)	34(17)
Vomiting	1(2)	32(16)

Bibliographic reference	Parkinson Study, Group, A controlled trial of rotigotine monotherapy in early Parkinson's disease, 60, 1721-8, 2003
	<table><tr><td>Fatigue</td><td>1(2)</td><td>29(15)</td></tr><tr><td>Sweating</td><td>2(4)</td><td>12(6)</td></tr><tr><td>Diarrhoea</td><td>4(9)</td><td>8(4)</td></tr><tr><td>Anxiety</td><td>2(4)</td><td>9(5)</td></tr><tr><td>Peripheral oedema</td><td>0(0)</td><td>9(5)</td></tr><tr><td>Anorexia</td><td>0</td><td>9(5)</td></tr></table> Data are given as number (%) of participants.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Yes 2. Was there adequate concealment of allocation? Yes 3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes 4. Did the comparison groups receive the same care apart from interventions studied? Unclear 5. Were participants receiving care kept blind to treatment allocation? Yes 6. Were the individuals administering care kept blind to treatment allocation? Yes 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Unclear 8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Yes 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	Caraceni,T., Musicco,M., Levodopa or dopamine agonists, or deprenyl as initial treatment for Parkinson's disease. A randomised multicenter study, Parkinsonism & Related Disorders, 7, 107-114, 2001
Country/ies where the study was carried out	Italy
Study type	Multi-centre, randomised, controlled, open trial

<table>
<tr><th>Bibliographic reference</th><th>Caraceni,T., Musicco,M., Levodopa or dopamine agonists, or deprenyl as initial treatment for Parkinson's disease. A randomised multicenter study, Parkinsonism & Related Disorders, 7, 107-114, 2001</th></tr>
<tr><td>Aim of the study</td><td>To compare the occurrence of motor fluctuations and dyskinesias in previously untreated patients assigned to receive levodopa, a dopamine agonist or deprenyl.</td></tr>
<tr><td>Study dates</td><td>Study dates: Not reported
Study duration: 3 years (median follow-up of 34 months)</td></tr>
<tr><td>Source of funding</td><td>Sandoz Italy, Chiesi Farmaceutici and by Italian Ministry of Health.</td></tr>
<tr><td>Sample size</td><td>In total: 473; Levodopa plus dopa decarboxylase inhibitor n=156; Dopamine agonist n=162; Deprenyl n=155</td></tr>
<tr><td>Inclusion criteria</td><td>Clinical diagnosis of PD (when hypokinesia was associated with tremor, rigidity or both for at least 6 months)</td></tr>
<tr><td>Exclusion criteria</td><td>• Interval from diagnosis greater than 2 years
• Dementia
• Secondary parkinsonism and parkinsonian syndromes
• Taking drugs that could give rise to extrapyramidal signs
• Previous treatment for more than 4 months with any of the studied drugs</td></tr>
<tr><td>Details</td><td>Baseline characteristics:
<table>
<tr><td>Characteristics</td><td>Levodopa n=156</td><td>Dopamine agonist n=162</td><td>Deprenyl n=155</td></tr>
<tr><td>Mean age (years)</td><td>63.4</td><td>63.0</td><td>63.4</td></tr>
<tr><td colspan="4">Hoehn & Yahr stage:</td></tr>
<tr><td>I-II</td><td>104(67.3)</td><td>102(69.1)</td><td>117(75.5)</td></tr>
<tr><td>III-IV</td><td>52(32.7)</td><td>60(30.9)</td><td>38(24.5)</td></tr>
<tr><td>Mean months from disease onset</td><td>16.21</td><td>17.7</td><td>16.0</td></tr>
<tr><td>UPDRS II</td><td>9.8</td><td>10.1</td><td>9.8</td></tr>
<tr><td>UPDRS III</td><td>16.8</td><td>16.7</td><td>16.9</td></tr>
</table></td></tr>
<tr><td>Interventions</td><td>The drug doses were increased slowly over 2-4 weeks until clinical efficacy was reached or adverse effects occurred. The maximum doses were:
Levodopa + dopa decarboxylase inhibitor: 750mg</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Caraceni,T., Musicco,M., Levodopa or dopamine agonists, or deprenyl as initial treatment for Parkinson's disease. A randomised multicenter study, Parkinsonism & Related Disorders, 7, 107-114, 2001</th></tr>
<tr><td></td><td>Bromocriptine: 60mg
Lisuride: 6mg
Deprenyl: 10mg

If deprenyl or dopamine agonists were, or subsequently became, ineffective levodopa was added. In cases of intolerance, the assigned drug was substituted with another.</td></tr>
<tr><td>Primary outcomes</td><td>• Motor dyskinesias
• Motor fluctuations (wearing off and early morning akinesia)</td></tr>
<tr><td>Secondary outcomes</td><td>• Termination of the originally assigned therapy
• Initiation of add-on therapy
• A motor score worse than or equal to that recorded before the initiation of treatment</td></tr>
<tr><td>Results</td><td>Relative risks of occurrence of principal and secondary end-points by drug assigned:
<table>
<tr><td></td><td>Levodopa (n=156)</td><td>Dopamine agonist (n=162)</td><td>Deprenyl (n=155)</td></tr>
<tr><td colspan="4">Motor fluctuations:</td></tr>
<tr><td>Number (%)</td><td>46(29.7)</td><td>27(16.7)</td><td>29(18.7)</td></tr>
<tr><td>RR (95% CI)</td><td>1*</td><td>0.5(0.3-0.8)</td><td>0.6(0.4-0.9)</td></tr>
<tr><td colspan="4">Dyskinesias:</td></tr>
<tr><td>Number (%)</td><td>42(27.1)</td><td>24(14.8)</td><td>32(20.6)</td></tr>
<tr><td>RR (95% CI)</td><td>1</td><td>0.6(0.3-0.9)</td><td>0.8(0.5-1.3)</td></tr>
<tr><td colspan="4">Motor score equal to or worse than before treatment:</td></tr>
<tr><td>Number (%)</td><td>43(27.7)</td><td>60(37.0)</td><td>51(32.9)</td></tr>
<tr><td>RR (95% CI)</td><td>1*</td><td>1.4(0.9-2.1)</td><td>1.3(0.8-1.9)</td></tr>
<tr><td colspan="4">Withdrawal:</td></tr>
<tr><td>Number (%)</td><td>10(6.4)</td><td>53(32.7)</td><td>30(19.4)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Caraceni,T., Musicco,M., Levodopa or dopamine agonists, or deprenyl as initial treatment for Parkinson's disease. A randomised multicenter study, Parkinsonism & Related Disorders, 7, 107-114, 2001**
	<table><tr><td>RR (95% CI)</td><td>1*</td><td>5.8(2.5-9.3)</td><td>3.2(1.6-6.4)</td></tr><tr><td colspan="4">Add-on therapy:</td></tr><tr><td>Number (%)</td><td>20(12.9)</td><td>66(40.7)</td><td>99(63.9)</td></tr><tr><td>RR (95% CI)</td><td>1*</td><td>4.3(2.6-7.1)</td><td>9.1(5.6-14.7)</td></tr></table> *Reference group.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Unclear 2. Was there adequate concealment of allocation? Unclear 3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes 4. Did the comparison groups receive the same care apart from interventions studied? Unclear 5. Were participants receiving care kept blind to treatment allocation? No 6. Were the individuals administering care kept blind to treatment allocation? No 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Yes 8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? No 12. Were investigators kept blind to other important confounding and prognostic factors? No

Bibliographic reference	**Caraceni,T., Musicco,M., Gasparini,M., Beghi,E., Scigliano,G., Carella,F., Cossutta,E., Chiaro,C., Lovicu,G., Giminiani,G., Currado,I., Solari,A., Nicolosi,A., Agnoli,A., Nappi,G., Giuliani,G., Angeleri,A., Moro,G., Franciosi,A., A multicenter Italian randomised study on early treatment of Parkinson disease: Comparison of 1-dopa, 1-deprenyl and dopaminoagonists. Study design and short term results, Italian Journal of Neurological Sciences, 13, 735-739, 1992**
Country/ies where the study was carried out	Italy
Study type	Multicentre, randomised open trial

<table>
<tr><th>Bibliographic reference</th><th>Caraceni,T., Musicco,M., Gasparini,M., Beghi,E., Scigliano,G., Carella,F., Cossutta,E., Chiaro,C., Lovicu,G., Giminiani,G., Currado,I., Solari,A., Nicolosi,A., Agnoli,A., Nappi,G., Giuliani,G., Angeleri,A., Moro,G., Franciosi,A., A multicenter Italian randomised study on early treatment of Parkinson disease: Comparison of 1-dopa, 1-deprenyl and dopaminoagonists. Study design and short term results, Italian Journal of Neurological Sciences, 13, 735-739, 1992</th></tr>
<tr><td>Aim of the study</td><td>To find out whether early treatment of PD patients with levodopa, DA or deprenyl is associated with any difference in motor fluctuations occurrence on long term treatment.</td></tr>
<tr><td>Study dates</td><td>Study dates: November 1988 to December 1991
Study duration: 3 years (this publication reports difference between first follow-up visit (2 months) and inclusion)</td></tr>
<tr><td>Source of funding</td><td>Supported by Chiesi and by contributions from Sandoz and Shering</td></tr>
<tr><td>Sample size</td><td>In total: n=475; Levodopa + dopa decarboxylase inhibitor n=159; Bromocriptine n=77; Lisuride n= 82; Deprenyl n=157</td></tr>
<tr><td>Inclusion criteria</td><td>Diagnosis of primary PD made on clinical grounds, when hypokinesia is associated with tremor or rigidity for up to 6 months</td></tr>
<tr><td>Exclusion criteria</td><td>• An interval from diagnosis longer than 2 years
• Dementia
• Secondary parkinsonism and parkinsonian syndrome
• Previous or current therapy with drugs possibly causing extrapyramidal signs
• Previous treatment for more than 4 months with 1 of the studied drugs
• Patients were excluded if, due to health or administrative reasons, there may be difficulty in follow-up</td></tr>
<tr><td>Details</td><td>Baseline characteristics:
<table>
<tr><td>Characteristics</td><td>Levodopa</td><td>Bromocriptine</td><td>Lisuride</td><td>Deprenyl</td></tr>
<tr><td>Age (mean)</td><td>63.0</td><td>63.9</td><td>62.8</td><td>64.1</td></tr>
<tr><td>Mean duration from onset (months)</td><td>17.2</td><td>17.1</td><td>17.1</td><td>17.1</td></tr>
<tr><td>UPDRS II</td><td>9.7</td><td>9.8</td><td>10.0</td><td>9.4</td></tr>
<tr><td>UPDRS III</td><td>13.3</td><td>12.7</td><td>13.5</td><td>13.6</td></tr>
<tr><td>Hoehn & Yahr stage</td><td>1.9</td><td>1.9</td><td>2.0</td><td>2.0</td></tr>
</table></td></tr>
<tr><td>Interventions</td><td>The drug doses were increased slowly over 2-4 weeks until clinical efficacy was reached or adverse effects occurred. The maximum doses were:
• Levodopa + dopa decarboxylase inhibitor: 750mg
• Bromocriptine: 60mg</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Caraceni,T., Musicco,M., Gasparini,M., Beghi,E., Scigliano,G., Carella,F., Cossutta,E., Chiaro,C., Lovicu,G., Giminiani,G., Currado,I., Solari,A., Nicolosi,A., Agnoli,A., Nappi,G., Giuliani,G., Angeleri,A., Moro,G., Franciosi,A., A multicenter Italian randomised study on early treatment of Parkinson disease: Comparison of 1-dopa, 1-deprenyl and dopaminoagonists. Study design and short term results, Italian Journal of Neurological Sciences, 13, 735-739, 1992</th></tr>
<tr><td></td><td>• Lisuride: 3mg
• Deprenyl: 10mg
If deprenyl or dopamine agonists were, or subsequently became, ineffective levodopa was added</td></tr>
<tr><td>Primary outcomes</td><td>The occurrence of motor fluctuations, in particular of wearing-off and of early morning akinesia</td></tr>
<tr><td>Secondary outcomes</td><td>Interruption of assigned therapy for untoward side effects, add-on therapy when the assigned therapy fails to control signs and symptoms</td></tr>
<tr><td>Results</td><td>Mean difference (± SE) of UPDRS scores between first follow-up visit and inclusion:
<table>
<tr><td></td><td>Levodopa</td><td>Bromocriptine</td><td>Lisuride</td><td>Deprenyl</td></tr>
<tr><td>UPDRS II</td><td>-2.5±0.21</td><td>-1.9±0.23</td><td>-2.6±0.29</td><td>-1.4±0.16*</td></tr>
<tr><td>UPDRS III</td><td>-3.4±0.39</td><td>-2.3±0.55</td><td>-3.2±0.44</td><td>-2.4±0.38</td></tr>
</table>
*Difference between inclusion and 1st examination is significantly lower than for levodopa and DA (p=0.03).</td></tr>
<tr><td>Overall Risk of Bias</td><td>1. Has an appropriate method of randomisation been used? Unclear
2. Was there adequate concealment of allocation? Unclear
3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes
4. Did the comparison groups receive the same care apart from interventions studied? Unclear
5. Were participants receiving care kept blind to treatment allocation? No
6. Were the individuals administering care kept blind to treatment allocation? No
7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Unclear
8. Did the study have an appropriate length of follow up? Yes
9. Did the study use a precise definition of outcome? Yes
10. Was a valid and reliable method used to determine that outcome? Yes
11. Were investigators kept blind to participant’s exposure to the intervention? No
12. Were investigators kept blind to other important confounding and prognostic factors? No</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Hauser,R.A., Schapira,A.H., Rascol,O., Barone,P., Mizuno,Y., Salin,L., Haaksma,M., Juhel,N., Poewe,W., Randomised, double-blind, multicenter evaluation of pramipexole extended release once daily in early Parkinson's disease, Movement Disorders.25 (15) (pp 2542-2549), 2010.Date of Publication: November 2010., 2542-2549, 2010</th></tr>
<tr><td>Country/ies where the study was carried out</td><td>Europe, US, South America, Asia</td></tr>
<tr><td>Study type</td><td>Randomised, double-blind, placebo and active comparator-controlled, parallel group clinical trial</td></tr>
<tr><td>Aim of the study</td><td>To evaluate the efficacy and safety of pramipexole extended release (ER) administered once daily in early PD.</td></tr>
<tr><td>Study dates</td><td>Study dates: Not reported
Study duration: 18 weeks</td></tr>
<tr><td>Source of funding</td><td>Boehringer Ingelheim International</td></tr>
<tr><td>Sample size</td><td>In total: n=259; Pramipexole ER n=106; Pramipexole IR n=103; Placebo n=50</td></tr>
<tr><td>Inclusion criteria</td><td>• ≥30 years or older
• Diagnosed with PD within 5 years and exhibiting at least 2 of 3 cardinal signs
• Hoehn and Yahr stages I-III and in need of dopaminergic therapy
• Patients could not have received a dopamine agonist within the last 4 weeks or L-dopa within the last 8 weeks before baseline and could not have previously received L-dopa for a total cumulative exposure of >3 months.
• Monoamine oxidase B inhibitors, amantadine, anticholinergics, and beta-blockers were permitted at stable doses, provided the dosage had been stable for at least 4 weeks before baseline.</td></tr>
<tr><td>Exclusion criteria</td><td>• Dementia (MMSE <24)
• Atypical and secondary parkinsonisms
• Clinically relevant medical and psychiatric conditions</td></tr>
<tr><td>Details</td><td>Baseline characteristics:
<table>
<tr><td>Characteristics</td><td>Placebo (n=50)</td><td>Pramipexole ER (n=106)</td><td>Pramipexole IR (n=103)</td></tr>
<tr><td>Age (yr), mean (SD)</td><td>63.2(8.7)</td><td>61.6(9.4)</td><td>62.0(8.3)</td></tr>
<tr><td>PD known duration (yr), mean (SD)</td><td>0.8(1.1)</td><td>1.1(1.3)</td><td>0.9(1.2)</td></tr>
<tr><td colspan="4">Modified Hoehn & Yahr stage (%)</td></tr>
<tr><td>I-I.5</td><td>28.0</td><td>29.2</td><td>26.2</td></tr>
<tr><td>II-III</td><td>72.0</td><td>70.8</td><td>73.8</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Hauser,R.A., Schapira,A.H., Rascol,O., Barone,P., Mizuno,Y., Salin,L., Haaksma,M., Juhel,N., Poewe,W., Randomised, double-blind, multicenter evaluation of pramipexole extended release once daily in early Parkinson's disease, Movement Disorders.25 (15) (pp 2542-2549), 2010.Date of Publication: November 2010., 2542-2549, 2010</th></tr>
<tr><td></td><td>
<table>
<tr><td>UPDRS II</td><td>7.6(4.3)</td><td>7.9(4.3)</td><td>7.8(3.7)</td></tr>
<tr><td>UPDRS III</td><td>22.4(13.6)</td><td>22.6(10.1)</td><td>20.4(9.0)</td></tr>
</table>
</td></tr>
<tr><td>Interventions</td><td>Pramipexole ER or IR: 0.375, 0.75, 1.5, 2.25, 3.0, or 4.5 mg (7-week flexible up-titration phase)
Pramipexole ER (extended release) was administered once daily and pramipexole IR (immediate release) was administered in equally divided doses TID.</td></tr>
<tr><td>Primary outcomes</td><td>• Change from baseline to week 18 in the sum of UPDRS II and III
• Adverse events</td></tr>
<tr><td>Secondary outcomes</td><td>• Clinical Global Impression of Improvement and PGI-I responder rates at week 18
• Change from baseline to week 18 in individual UPDRS I, III, III
• PDQ-39
• EQ-5D</td></tr>
<tr><td>Results</td><td>Efficacy results:
<table>
<tr><td></td><td>Placebo</td><td>Pramipexole ER</td><td>Pramipexole IR</td></tr>
<tr><td colspan="4">UPDRS II score, adjusted mean change (SE) [p vs. placebo] :</td></tr>
<tr><td>No of subjects</td><td>50</td><td>102</td><td>101</td></tr>
<tr><td>Without levodopa data censored</td><td>-0.5(0.4)</td><td>-1.6(0.4) [0.0177]</td><td>-1.8(0.4) [0.0049]</td></tr>
<tr><td>With levodopa data censored</td><td>-0.0(0.5)</td><td>-1.5(0.4) [0.0023]</td><td>-1.8(0.4) [0.0005]</td></tr>
<tr><td colspan="4">UPDRS III score, adjusted mean change (SE) [p vs. placebo]:</td></tr>
<tr><td>No of patients</td><td>50</td><td>102</td><td>101</td></tr>
<tr><td>Without levodopa data censored</td><td>-4.6(1.0)</td><td>-6.5(0.9_ [0.0813]</td><td>-6.7(0.8) [0.0600]</td></tr>
<tr><td>With levodopa data censored</td><td>-2.7(1.0)</td><td>-5.9(0.9) [0.0039]</td><td>-5.9(0.8) [0.0038]</td></tr>
<tr><td colspan="4">PDQ-39 score, adjusted mean change (SE) [P vs. placebo]:</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Hauser,R.A., Schapira,A.H., Rascol,O., Barone,P., Mizuno,Y., Salin,L., Haaksma,M., Juhel,N., Poewe,W., Randomised, double-blind, multicenter evaluation of pramipexole extended release once daily in early Parkinson's disease, Movement Disorders.25 (15) (pp 2542-2549), 2010.Date of Publication: November 2010., 2542-2549, 2010

No of patients	49	91	95
Without levodopa data censored	-1.9(2.0)	-8.2(1.8) [0.0058]	-9.2(1.7) [0.0012]
With levodopa data censored	-1.7(2.1)	-8.2(1.8) [0.0052]	-9.2(1.7) [0.0010]
ED-5D VAS score, adjusted mean change (SE) [P vs. placebo]:			
No of patients	49	91	95
Without levodopa data censored	2.9(2.6)	7.1(2.3) [0.1445]	8.4(2.2) [0.0509]
With levodopa data censored	2.7(2.6)	6.7(2.3) [0.1631]	8.0(2.2) [0.0604]

Adverse events:

Adverse event	Placebo (n=50)	Pramipexole ER (n=106)	Pramipexole IR n=103)
Total discontinuations, n (%)	4(8.0)	21(19.8)	15(14.6)
AEs by category, n (%):			
Any	35(70.0)	81(76.4)	81(76.8)
Severea	1(2.0)	4(3.8)	6(5.8)
Seriousb	1(2.0)	5(4.7)	3(2.9)
Drug-related	19(38.0)	61(57.5)	66(64.1)
Leading to discontinuation	2(4.0)	11(10.4)	8(7.8)
AEs by type, n (%):			
Somnolence	7(14.0)	34(32.1)	34(33.0)
Nausea	2(4.0)	22(20.8)	22(21.4)

Bibliographic reference	Hauser,R.A., Schapira,A.H., Rascol,O., Barone,P., Mizuno,Y., Salin,L., Haaksma,M., Juhel,N., Poewe,W., Randomised, double-blind, multicenter evaluation of pramipexole extended release once daily in early Parkinson's disease, Movement Disorders.25 (15) (pp 2542-2549), 2010.Date of Publication: November 2010., 2542-2549, 2010

Constipation	0(0.0)	13(12.3)	16(15.5)
Fatigue	1(2.0)	7(6.6)	7(6.8)

[a]Incapacitating or causing inability to work or undertake usual activities.

[b]Fatal, life-threatening, requiring hospitalization, or resulting in significant disability.

Overall Risk of Bias

1. Has an appropriate method of randomisation been used? Yes
2. Was there adequate concealment of allocation? Yes
3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes
4. Did the comparison groups receive the same care apart from interventions studied? Yes
5. Were participants receiving care kept blind to treatment allocation? Yes
6. Were the individuals administering care kept blind to treatment allocation? Yes
7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Yes
8. Did the study have an appropriate length of follow up? Yes
9. Did the study use a precise definition of outcome? Yes
10. Was a valid and reliable method used to determine that outcome? Yes
11. Were investigators kept blind to participant’s exposure to the intervention? Unclear
12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

<table>
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<tr><td>Country/ies where the study was carried out</td><td>US and Canada</td></tr>
<tr><td>Study type</td><td>Multicentre, parallel-group, double-blind, randomised controlled trial.</td></tr>
<tr><td>Aim of the study</td><td>To compare initial treatment with pramipexole vs levodopa in early Parkinson disease, followed by levodopa supplementation, with respect to the development of dopaminergic motor complications, other adverse events, and functional and quality of life outcomes.</td></tr>
<tr><td>Study dates</td><td>Study dates: October 1996 to August 2001
Study duration: A minimum of 4 years (2 year clinical trial + an extended follow-up for at least an additional 2 years)</td></tr>
<tr><td>Source of funding</td><td>Pharmacia Corporation, Boehringer Ingelheim Pharma, The National Parkinson Foundation Center of Excellence to the Parkinson Study Group, and by the National Institutes of Health for Clinical Research Center grants RR00044 and RR01066 at the University of Rochester and the Massachusetts General Hospital, respectively.</td></tr>
<tr><td>Sample size</td><td>In total: n=301; Pramipexole n=151; Levodopa/carbidopa n=150</td></tr>
<tr><td>Inclusion criteria</td><td>• ≥30 years of age
• Idiopathic Parkinson disease for fewer than 7 years and required dopaminergic antiparkinsonian therapy at the time of enrolment.
• Hoehn and Yahr stage I-III</td></tr>
<tr><td>Exclusion criteria</td><td>Patients who had taken levodopa or a dopaminergic agonist in the 2 months prior to enrolment</td></tr>
<tr><td>Details</td><td>The 2 treatment groups were similar at baseline with regard to demographic and clinical variables, except for lower quality-of-life scores in the pramipexole group.
<table>
<tr><td></td><td colspan="2">Completed Trial</td><td colspan="2">Withdrew from trial</td></tr>
<tr><td>Characteristics</td><td>Pramipexole (n=83)</td><td>Levodopa (n=100)</td><td>Pramipexole (n=68)</td><td>Levodopa (n=50)</td></tr>
<tr><td>Age (yrs)</td><td>61.1(9.6)</td><td>60.8(9.8)</td><td>62.1(10.8)</td><td>61.0(11.9)</td></tr>
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Bibliographic reference	**Holloway,R.G., Shoulson,I., Fahn,S., Kieburtz,K., Lang,A., Marek,K., McDermott,M., Seibyl,J., Weiner,W., Musch,B., Kamp,C., Welsh,M., Shinaman,A., Pahwa,R., Barclay,L., Hubble,J., LeWitt,P., Miyasaki,J., Suchowersky,O., Stacy,M., Russell,D.S., Ford,B., Hammerstad,J., Riley,D., Standaert,D., Wooten,F., Factor,S., Jankovic,J., Atassi,F., Kurlan,R., Panisset,M., Rajput,A., Rodnitzky,R., Shults,C., Petsinger,G., Waters,C., Pfeiffer,R., Biglan,K., Borchert,L., Montgomery,A., Sutherland,L., Weeks,C., DeAngelis,M., Sime,E., Wood,S., Pantella,C., Harrigan,M., Fussell,B., Dillon,S., Alexander-Brown,B., Rainey,P., Tennis,M., Rost-Ruffner,E., Brown,D., Evans,S., Berry,D., Hall,J., Shirley,T., Dobson,J., Fontaine,D., Pfeiffer,B., Brocht,A., Bennett,S., Daigneault,S., Hodgeman,K., O'Connell,C., Ross,T., Richard,K., Watts,A., Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomised controlled trial, Archives of Neurology, 61, 1044-1053, 2004**
	Years since diagnosis: 1.4(1.3) / 1.8(1.7) / 1.6(1.6) / 1.8(1.7) UPDRS II: 8.7(4.1) / 7.8(3.8) / 9.5(4.0) / 9.2(4.2) UPDRS III: 21.9(8.9) / 20.8(9.4) / 22.7(9.5) / 24.3(9.8) No (%) of patients in Hoehn & Yahr stage: I: 12(14.5) / 18(18.0) / 8(11.8) / 5(10.0) I.5: 11(13.3) / 16(16.0) / 12(17.7) / 4(8.0) II: 43(51.8) / 58(58.0) / 35(51.5) / 26(52.0) II.5: 18(19.3) / 7(7.0) / 9(13.2) / 9(18.0) III: 1(1.2) / 1(1.0) / 4(5.9) / 6(12.0) Parkinson's Disease Quality-of-Life Scale: 28.2(9.9) / 24.5(10.4) / 30.6(13.6) / 31.0(12.2) EQ-VAS: 76.3(14.3) / 79.2(11.5) / 73.6(17.1) / 74.4(12.4) Values are expressed as mean (SD) unless otherwise indicated.
Interventions	Pramipexole: 0.25mg, 0.5mg or 1mg three times per day Carbidopa/Levodopa: 12.5/50mg or 25/100mg three times per day Subjects entered a 10-week dosage escalation period. All subjects were escalated initially to a daily dosage of 1.5mg pramipexole or 75/300mg carbidopa/levodopa. Subject requiring additional therapy could escalate to 3mg pramipexole or 112.5/450mg carbidopa/levodopa or 4.5mg pramipexole or 150/600mg carbidopa/levodopa. Thereafter (from week 11), investigators were permitted to add open-label levodopa or other antiparkinsonian medications to treat ongoing or emerging disability.

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<tr><td>Primary outcomes</td><td>• Time to the first occurrence of dopaminergic complications wearing off, dyskinesias, on-off fluctuations, and freezing
• Adverse events</td></tr>
<tr><td>Secondary outcomes</td><td>Changes in scores of the UPDRS, Parkinson's Disease Quality of Life scale the EuroQol Visual Analog Scale, as well as the need for supplemental levodopa.</td></tr>
<tr><td>Results</td><td>Treatment effects on dopaminergic end points:
<table>
<tr><td>End points</td><td>Pramipexole no (%) (n=151)</td><td>Levodopa No. (%) (n=150)</td><td>HR (95% CI)</td><td>P value</td></tr>
<tr><td>First dopaminergic complication*</td><td>78(51.7)</td><td>111(74.0)</td><td>0.48(0.35-0.66)</td><td><.001</td></tr>
<tr><td>Wearing off</td><td>71(47.0)</td><td>94(62.7)</td><td>0.68(0.49-0.93)</td><td>.02</td></tr>
<tr><td>Dyskinesias</td><td>37(24.5)</td><td>81(54.0)</td><td>0.37(0.25-0.56)</td><td><.001</td></tr>
<tr><td>On-off fluctuations</td><td>10(6.6)</td><td>12(8.0)</td><td>0.64(0.26-1.59)</td><td>.34</td></tr>
<tr><td>Freezing</td><td>56(37.1)</td><td>38(25.3)</td><td>1.70(1.11-2.59)</td><td>.01</td></tr>
<tr><td>Off-period dystonia</td><td>53(35.1)</td><td>69(46.0)</td><td>0.73(0.51-1.06)</td><td>.10</td></tr>
</table>
*Defined as the first occurrence of wearing off, dyskinesia, or on-off fluctuations.

Mean changes from baseline to month 48 in UPDRS scores:
<table>
<tr><td>Scale score</td><td>Pramipexole (n=151)</td><td>Levodopa (n=150)</td><td>Treatment effect (95% CI)</td><td>P value</td></tr>
<tr><td>Total UPDRS</td><td>-3.2(17.3)</td><td>2.0(15.4)</td><td>-5.9(-9.6, -2.1)</td><td>.003</td></tr>
<tr><td>Motor</td><td>-1.3(13.3)</td><td>3.4(12.3)</td><td>-4.9(-7.8, -1.9)</td><td>.001</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Holloway,R.G., Shoulson,I., Fahn,S., Kieburtz,K., Lang,A., Marek,K., McDermott,M., Seibyl,J., Weiner,W., Musch,B., Kamp,C., Welsh,M., Shinaman,A., Pahwa,R., Barclay,L., Hubble,J., LeWitt,P., Miyasaki,J., Suchowersky,O., Stacy,M., Russell,D.S., Ford,B., Hammerstad,J., Riley,D., Standaert,D., Wooten,F., Factor,S., Jankovic,J., Atassi,F., Kurlan,R., Panisset,M., Rajput,A., Rodnitzky,R., Shults,C., Petsinger,G., Waters,C., Pfeiffer,R., Biglan,K., Borchert,L., Montgomery,A., Sutherland,L., Weeks,C., DeAngelis,M., Sime,E., Wood,S., Pantella,C., Harrigan,M., Fussell,B., Dillon,S., Alexander-Brown,B., Rainey,P., Tennis,M., Rost-Ruffner,E., Brown,D., Evans,S., Berry,D., Hall,J., Shirley,T., Dobson,J., Fontaine,D., Pfeiffer,B., Brocht,A., Bennett,S., Daigneault,S., Hodgeman,K., O'Connell,C., Ross,T., Richard,K., Watts,A., Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomised controlled trial, Archives of Neurology, 61, 1044-1053, 2004**

ADL	-1.7(5.4)	-0.5(4.7)	-1.4(-2.5, -0.2)	.02
Mental	-0.3(1.6)	-0.8(1.6)	0.3(-0.1, 0.7)	.10

Values are mean (SD).

Adverse events by treatment group:

Adverse event	Pramipexole n (%) (n=151)	Levodopa n (%) (n=150)	P value
Oedema**	64(42.4)	22(14.7)	<.001
Peripheral oedema	34(22.5)	9(6.0)	<.001
Somnolence	56(36.4)	32(21.3)	.005
Hallucination	22(14.6)	12(8.0)	.10
Cellulitis	7(4.6)	0(0.0)	.01
Urinary frequency	5(3.3)	16(10.7)	.01
Hernia	1(0.7)	12(8.0)	.002

**Oedema includes peripheral oedema, localised oedema, generalised oedema, facial oedema, tongue oedema, periorbital oedema, and lymphedema.

Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Yes 2. Was there adequate concealment of allocation? Yes 3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes 4. Did the comparison groups receive the same care apart from interventions studied? Yes

Bibliographic reference	Holloway,R.G., Shoulson,I., Fahn,S., Kieburtz,K., Lang,A., Marek,K., McDermott,M., Seibyl,J., Weiner,W., Musch,B., Kamp,C., Welsh,M., Shinaman,A., Pahwa,R., Barclay,L., Hubble,J., LeWitt,P., Miyasaki,J., Suchowersky,O., Stacy,M., Russell,D.S., Ford,B., Hammerstad,J., Riley,D., Standaert,D., Wooten,F., Factor,S., Jankovic,J., Atassi,F., Kurlan,R., Panisset,M., Rajput,A., Rodnitzky,R., Shults,C., Petsinger,G., Waters,C., Pfeiffer,R., Biglan,K., Borchert,L., Montgomery,A., Sutherland,L., Weeks,C., DeAngelis,M., Sime,E., Wood,S., Pantella,C., Harrigan,M., Fussell,B., Dillon,S., Alexander-Brown,B., Rainey,P., Tennis,M., Rost-Ruffner,E., Brown,D., Evans,S., Berry,D., Hall,J., Shirley,T., Dobson,J., Fontaine,D., Pfeiffer,B., Brocht,A., Bennett,S., Daigneault,S., Hodgeman,K., O'Connell,C., Ross,T., Richard,K., Watts,A., Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomised controlled trial, Archives of Neurology, 61, 1044-1053, 2004
	5. Were participants receiving care kept blind to treatment allocation? Yes 6. Were the individuals administering care kept blind to treatment allocation? Yes 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Unclear 8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Unclear 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	Parkinson Study, Group, Pramipexole vs levodopa as initial treatment for Parkinson disease: A randomised controlled trial. Parkinson Study Group, JAMA 284, 1931-8, 2000
Country/ies where the study was carried out	US and Canada
Study type	Multicentre, parallel-group, double-blind, randomised controlled trial
Aim of the study	To compare the development of dopaminergic motor complications after initial treatment of early PD with pramipexole vs. levodopa.
Study dates	Study dates: Not reported Study duration: 23.5 months
Source of funding	Pharmacia Corp., the National Parkinson Foundation Center of Excellence to the Parkinson Study Group and by the National Institutes of Health for Clinical Research Center grants RR00044 and RR01066 to the University of Rochester and Massachusetts General Hospital, respectively.

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<tr><th>Bibliographic reference</th><th>Parkinson Study, Group, Pramipexole vs levodopa as initial treatment for Parkinson disease: A randomised controlled trial. Parkinson Study Group, JAMA 284, 1931-8, 2000</th></tr>
<tr><td>Sample size</td><td>In total: n=301; Pramipexole n=151; Carbidopa/Levodopa n=150</td></tr>
<tr><td>Inclusion criteria</td><td>• ≥30 years or older who had idiopathic PD for fewer than 7 years and who required dopaminergic antiparkinsonian therapy at the time of enrolment
• Hoehn and Yahr stage I-III</td></tr>
<tr><td>Exclusion criteria</td><td>Patients who had taken levodopa or a dopaminergic agonist in the 2 months prior to enrolment
Subjects who had:
• A history of a previous dopaminergic complication
• Atypical parkinsonian syndromes
• Serious concurrent illness
• Treatment with methylphenidate, cinnarizine, reserpine, amphetamine, or monoamine oxidase A inhibitors in the past 3 months
• Treatment with pramipexole in the past 4 months
• Treatment with neuroleptics, metoclopramide, alphamethyldopa, or flunarizine in the past 6 months
• An unstable dosage of selegiline, amantadine, anticholinergic therapy, or other central nervous system active therapies in the past 2 months</td></tr>
<tr><td>Details</td><td>Baseline characteristics
<table>
<tr><td>Characteristics</td><td>Pramipexole (n=151)</td><td>Levodopa (n=150)</td></tr>
<tr><td>Age (yrs)</td><td>61.5(10.1)</td><td>60.9(10.5)</td></tr>
<tr><td>UPDRS II</td><td>9.1(4.1)</td><td>8.3(4.0)</td></tr>
<tr><td>UPDRS III</td><td>22.3(9.2)</td><td>22.0(9.6)</td></tr>
<tr><td colspan="3">No. (%) of patients in Hoehn & Yahr stage:</td></tr>
<tr><td>I</td><td>27(17.9)</td><td>33(22.0)</td></tr>
<tr><td>I.5</td><td>23(15.2)</td><td>17(11.3)</td></tr>
<tr><td>II</td><td>75(49.7)</td><td>78(52.0)</td></tr>
<tr><td>II.5</td><td>21(13.9)</td><td>13(8.7)</td></tr>
</table></td></tr>
</table>

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<tr><th>Bibliographic reference</th><th>Parkinson Study, Group, Pramipexole vs levodopa as initial treatment for Parkinson disease: A randomised controlled trial. Parkinson Study Group, JAMA 284, 1931-8, 2000</th></tr>
<tr><td></td><td>
<table>
<tr><td>III</td><td>5(3.3)</td><td>9(6.0)</td></tr>
<tr><td>Parkinson's Disease Quality-of-Life Scale</td><td>30.5(10.7)</td><td>28.1(10.4)</td></tr>
<tr><td>EQ-VAS</td><td>75.1(15.6)</td><td>77.6(12.0)</td></tr>
</table>
Values are expressed as mean (SD) unless otherwise indicated.
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<tr><td>Interventions</td><td>Pramipexole: 0.25mg, 0.5mg or 1mg three times per day.
Carbidopa/Levodopa: 12.5/50mg or 25/100mg three times per day

Subjects entered a 10-week dosage escalation period. All subjects were escalated initially to a daily dosage of 1.5mg pramipexole or 75/300mg carbidopa/levodopa. Subject requiring additional therapy could escalate to 3mg pramipexole or 112.5/450mg carbidopa/levodopa or 4.5mg pramipexole or 150/600mg carbidopa/levodopa. Thereafter (from week 11), investigators were permitted to add open-label levodopa or other antiparkinsonian medications to treat ongoing or emerging disability.</td></tr>
<tr><td>Primary outcomes</td><td>Time to the first occurrence of dopaminergic complications: wearing off, dyskinesias, on-off fluctuations, and freezing
Adverse events</td></tr>
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<tr><td>End points</td><td>Pramipexole no (%) (n=151)</td><td>Levodopa No. (%) (n=150)</td><td>HR (95% CI)</td><td>P value</td></tr>
<tr><td>First dopaminergic complication*</td><td>42(27.8)</td><td>76(50.7)</td><td>0.45(0.30-0.66)</td><td><.001</td></tr>
<tr><td>Wearing off</td><td>36(23.8)</td><td>57(38.0)</td><td>0.57(0.37-0.88)</td><td>.01</td></tr>
<tr><td>Dyskinesias</td><td>15(9.9)</td><td>46(30.7)</td><td>0.33(0.18-0.60)</td><td><.001</td></tr>
<tr><td>On-off fluctuations</td><td>2(1.3)</td><td>8(5.3)</td><td>0.27(0.06-1.32)</td><td>.11</td></tr>
</table>
*Defined as the first occurrence of wearing off, dyskinesia, or on-off fluctuations.

Mean changes from baseline to month 48 in UPDRS scores:</td></tr>
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Bibliographic reference	Parkinson Study, Group, Pramipexole vs levodopa as initial treatment for Parkinson disease: A randomised controlled trial. Parkinson Study Group, JAMA 284, 1931-8, 2000

Scale score	Pramipexole (n=151)	Levodopa (n=150)	Treatment effect (95% CI)	P value
Total UPDRS	4.5(12.7)	9.2(10.8)	-5.0(-7.6 to -2.4)	<.001
Motor	3.4(8.6)	7.3(8.6)	-3.9(-5.7 to -2.1)	<.001
ADL	1.1(4.5)	2.2(3.2)	-1.4(-2.2 to -0.5)	.001
Mental	0.0(1.6)	-0.2(1.2)	0.1(-0.2 to 0.3)	.72

Values are mean (SD). Positive values indicate improvement.

Adverse events by treatment group:

Adverse event	Pramipexole n (%) (n=151)	Levodopa n (%) (n=150)
Somnolence	49(32.4)	26(17.3)a
Hallucination	14(9.3)	5(3.3)b
Generalised oedema	27(17.9)	12(8.0)b
Peripheral oedema	22(14.6)	6(4.0)a
Nausea	55(36.4)	55(36.7)
Dizziness	39(25.8)	36(24.0)
Insomnia	39(25.8)	33(22.0)
Headache	31(20.5)	23(15.3)
Constipation	31(20.5)	19(12.7)
Depression	23(15.2)	20(13.3)
Abnormal dreams	21(13.9)	19(12.7)
Anxiety	17(11.3)	10(6.7)

Bibliographic reference	Parkinson Study, Group, Pramipexole vs levodopa as initial treatment for Parkinson disease: A randomised controlled trial. Parkinson Study Group, JAMA 284, 1931-8, 2000
	Postural hypotension | 9(6.0) | 15(10) [a]p<.01 for comparison of pramipexole with levodopa. [b]p<.05 for comparison of pramipexole with levodopa.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Yes 2. Was there adequate concealment of allocation? Yes 3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes 4. Did the comparison groups receive the same care apart from interventions studied? Unclear 5. Were participants receiving care kept blind to treatment allocation? Yes 6. Were the individuals administering care kept blind to treatment allocation? Yes 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Unclear 8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Yes 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	Poewe,W., Rascol,O., Barone,P., Hauser,R.A., Mizuno,Y., Haaksma,M., Salin,L., Juhel,N., Schapira,A.H.V., Extended-release pramipexole in early Parkinson disease A 33-week randomised controlled trial, Neurology.77 (8) (pp 759-766), 2011.Date of Publication: 23 Aug 2011., 759-766, 2011
Country/ies where the study was carried out	Argentina, Austria, Czech Republic, Finland, Germany, Hungary, India, Japan, Malaysia, Russia, Slovakia, Taiwan, Ukraine, and the US
Study type	Multicentre, randomised, double-blind, parallel study
Aim of the study	To assess the clinical efficacy, safety, tolerability of a novel once-daily extended-release (ER) formulation of the dopamine agonist pramipexole as monotherapy in patients with early Parkinson disease and establish its non-inferiority vs standard immediate-release (IR) pramipexole.
Study dates	Study dates: Not reported Study duration: 33 weeks

<table>
<tr><th>Bibliographic reference</th><th>Poewe,W., Rascol,O., Barone,P., Hauser,R.A., Mizuno,Y., Haaksma,M., Salin,L., Juhel,N., Schapira,A.H.V., Extended-release pramipexole in early Parkinson disease A 33-week randomised controlled trial, Neurology.77 (8) (pp 759-766), 2011.Date of Publication: 23 Aug 2011., 759-766, 2011</th></tr>
<tr><td>Source of funding</td><td>Boehringer Ingelheim</td></tr>
<tr><td>Sample size</td><td>In total: n=539; Pramipexole ER n=223; Pramipexole IR n=213; Placebo n=103</td></tr>
<tr><td>Inclusion criteria</td><td>• A diagnosis of PD based on the presence of bradykinesia and either resting tremor or rigidity
• Hoehn & Yahr I-III
• Had disease duration of no more than 5 years
• ≥30 years of age at the time of diagnosis
• Had reached a level of clinical disability requiring initiation or augmentation of dopaminergic therapy
• Current treatment with antiparkinsonian anticholinergics, monoamine oxidase B inhibitors, amantadine or beta-blockers(when given for PD) was allowed, provided the dose had been kept stable for at least 4 weeks.
• Previous therapy with levodopa of less than 3 months total duration was also permitted if discontinued at least 8 weeks before randomisation.
• Previous dopamine agonist exposure was allowed if discontinued at least 4 weeks before randomisation.</td></tr>
<tr><td>Exclusion criteria</td><td>• MMSE score <24
• Signs suggestive of an atypical parkinsonian syndrome
• Medical or DSM-IV psychiatric disorders capable of impeding the patient's trial participation
• Clinically significant hypotension or electrocardiographic abnormalities
• Creatinine clearance <50 mL/min
• Women with childbearing potential were excluded for pregnancy or inadequate contraception</td></tr>
<tr><td>Details</td><td>Baseline demographics were similar among the 3 patient groups. Use of PD medication at baseline was also similar.
<table>
<tr><td>Characteristics</td><td>Placebo (n=103)</td><td>Pramipexole ER (n=223)</td><td>Pramipexole IR (n=213)</td></tr>
<tr><td>Mean age, y, mean (SD)</td><td>62.0(9.6)</td><td>61.3(9.8)</td><td>61.7(9.6)</td></tr>
<tr><td>Mean PD duration, y, mean (SD)</td><td>0.9(1.0)</td><td>1.0(1.2)</td><td>1.1(1.4)</td></tr>
<tr><td colspan="4">Modified Hoehn & Yahr stage, %</td></tr>
<tr><td>I-I.5</td><td>29.1</td><td>33.6</td><td>29.6</td></tr>
<tr><td>II-III</td><td>70.9</td><td>66.4</td><td>70.4</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Poewe,W., Rascol,O., Barone,P., Hauser,R.A., Mizuno,Y., Haaksma,M., Salin,L., Juhel,N., Schapira,A.H.V., Extended-release pramipexole in early Parkinson disease A 33-week randomised controlled trial, Neurology.77 (8) (pp 759-766), 2011.Date of Publication: 23 Aug 2011., 759-766, 2011

Native to PD therapy, %	38.3	40.8	36.2
UPDRS II, mean (SD)	7.6(4.4)	7.9(4.3)	7.8(3.7)
UPDRS III, mean (SD)	21.4(11.7)	21.9(9.9)	21.1(9.3)

Interventions

7-week flexible titration using the following dose escalation levels per week:
Pramipexole ER: 0.375, 0.75, 1.5, 2.25, 3.0, 3.75, or 4.5 mg once daily
Pramipexole IR: 0.125, 0.25, 0.50, 0.75, 1.0, 1.25, 1.5 mg 3 times daily

Primary outcomes

- Change from baseline to week 33 in combined score on UPDRS II and III
- Adverse events

Secondary outcomes

- Responder rates on the PGI-I and on the Clinical Global Impression Improvement scales
- UPDRS II+III responder rate
- UPDRS I, II, III scores separately
- Proportions of patients requiring levodopa rescue
- Quality of life assessment on PDQ-39 and the EQ-5D

Results

Efficacy results at week 33 with levodopa rescue censored (adjusted mean change (95% CI), p vs. placebo):

	Placebo (n=103)a	Pramipexole ER (n=213)b	Pramipexole IR (n=207)c
UPDRS II	-0.2(-0.9 to 0.4)	-2.1(-2.5 to -1.6) (<0.0001)	-2.4(-2.8 to -1.9) (<0.0001)
UPRDS III	-1.1(-2.5 to 0.3)	-6.1(-7.1 to -5.1) (<0.0001)	-6.4(-7.4 to -5.4) (<0.0001)
PDQ-39	-1.5(-4.4 to 1.5)	-3.8(-5.9 to -1.8) (0.1802)	-6.5(-8.6 to -4.5) (0.0043
EQ-5D VAS	2.1(-1.8 to 6.1)	4.2(1.5 to 7.0) (0.3820)	5.9(3.2 to 8.7) (0.1090)

Adverse events, 33-week analysis:

Adverse event	Placebo (n=103)	Pramipexole ER (n=223)	Pramipexole IR (n=213)
Total discontinuation, n (%)	12(11.7)	49(22.0)	37(17.4)

Bibliographic reference	Poewe,W., Rascol,O., Barone,P., Hauser,R.A., Mizuno,Y., Haaksma,M., Salin,L., Juhel,N., Schapira,A.H.V., Extended-release pramipexole in early Parkinson disease A 33-week randomised controlled trial, Neurology.77 (8) (pp 759-766), 2011.Date of Publication: 23 Aug 2011., 759-766, 2011

AEs by category, n (%)			
Any	80(77.7)	189(84.8)	172(80.8)
Severe*	4(3.9)	12(5.4)	11(5.2)
Serious**	4(3.9)	16(7.2)	11(5.2)
Drug-related	40(38.8)	141(63.2)	134(62.9)
Leading to discontinuation	4(3.9)	24(10.8)	20(9.4)
AEs by type, n(%)***			
Somnolence	15(14.6)	81(36.3)	70(32.9)
Nausea	9(8.7)	48(21.5)	51(23.9)
Constipation	2(1.9)	32(14.3)	25(11.7)
Dizziness	7(6.8)	26(11.7)	25(11.7)
Dry mouth	1(1.0)	12(5.4)	8(3.8)

*Incapacitating or causing inability to work or undertake usual activities.

**Fatal, immediately life-threatening, requiring or prolonging hospitalization, or resulting in significant disability.

*** With frequency ≥5% in either pramipexole group and >3 percentage points more frequent for pramipexole than for placebo.

Overall Risk of Bias

1. Has an appropriate method of randomisation been used? Yes
2. Was there adequate concealment of allocation? Yes
3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes
4. Did the comparison groups receive the same care apart from interventions studied? Unclear
5. Were participants receiving care kept blind to treatment allocation? Yes
6. Were the individuals administering care kept blind to treatment allocation? Yes
7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Unclear

Bibliographic reference	Poewe,W., Rascol,O., Barone,P., Hauser,R.A., Mizuno,Y., Haaksma,M., Salin,L., Juhel,N., Schapira,A.H.V., Extended-release pramipexole in early Parkinson disease A 33-week randomised controlled trial, Neurology.77 (8) (pp 759-766), 2011.Date of Publication: 23 Aug 2011., 759-766, 2011
	8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Unclear 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	Rascol, O., Brooks, D. J., Brunt, E. R., Korczyn, A. D., Poewe, W. H., Stocchi, F., Ropinirole in the treatment of early Parkinson's disease: a 6-month interim report of a 5-year levodopa-controlled study. 056 Study Group, Movement Disorders, 13, 39-45, 1998
Country/ies where the study was carried out	Europe, Israel and Canada
Study type	Multicentre, randomised, double-blind trial
Aim of the study	To compare the efficacies and side-effect profiles of ropinirole and L-dopa plus benserazide in patients with early PD.
Study dates	Study dates: Not reported Study duration: 6-month interim analysis of a 5-year study
Source of funding	Not reported
Sample size	In total: n=282; Ropinirole n=179; L-dopa n=89
Inclusion criteria	• ≥30 years old • Fulfilled criteria consistent with the Parkinson's disease Society of the United Kingdom Brain Tissue Bank for a clinical diagnosis of idiopathic PD • Hoehn and Yahr stages I-III • Required dopamine therapy • Patients cannot have received prior L-dopa or dopamine agonist therapy for more than 6 weeks, and any such treatment must be discontinued at least 2 weeks before study entry. • Concurrent treatment with selegiline was permitted at a constant dose but the use of other monoamine oxidase inhibitors must be discontinued at least 2 weeks before the start of treatment. Patients were allowed to continue receiving anticholinergics and amantadine, provided that the doses remained constant. Concurrent administration of other

<table>
<tr><th>Bibliographic reference</th><th>Rascol, O., Brooks, D. J., Brunt, E. R., Korczyn, A. D., Poewe, W. H., Stocchi, F., Ropinirole in the treatment of early Parkinson's disease: a 6-month interim report of a 5-year levodopa-controlled study. 056 Study Group, Movement Disorders, 13, 39-45, 1998</th></tr>
<tr><td></td><td>dopaminergic agents, apart from L-dopa rescue therapy, was not permitted, nor was the introduction of selegiline, anticholinergics, or amantadine after the start of the study.</td></tr>
<tr><td>Exclusion criteria</td><td>Patients with:
Severe systemic or psychiatric disease
A history of drug or alcohol dependence
Severe dementia or other clinically relevant abnormalities
Evidence of postural hypotension
Previous treatment with ropinirole or a contraindication to L-dopa</td></tr>
<tr><td>Details</td><td>The baseline characteristics of the two study populations were similar:
<table>
<tr><td>Characteristics</td><td>Ropinirole (n=179)</td><td>L-dopa (n=89)</td></tr>
<tr><td>Mean age (yrs)</td><td>63(9)</td><td>63(9)</td></tr>
<tr><td>Mean duration of disease (months)</td><td>30(34)</td><td>29(27)</td></tr>
<tr><td colspan="3">Hoehn & Yahr stage (%):</td></tr>
<tr><td>I</td><td>12.8</td><td>22.5</td></tr>
<tr><td>I.5</td><td>15.1</td><td>9.0</td></tr>
<tr><td>II</td><td>36.9</td><td>37.1</td></tr>
<tr><td>II.5</td><td>25.7</td><td>23.1</td></tr>
<tr><td>III</td><td>9.5</td><td>10.1</td></tr>
<tr><td>Mean baseline UPDRS III score</td><td>21.5(10.5)</td><td>21.7(11.3)</td></tr>
</table>
Values are given in mean (SD).</td></tr>
<tr><td>Interventions</td><td>Ropinirole: Starting dose of 0.25mg three times a day to a maximum of 24mg per day (8mg three times daily)
L-dopa: Starting dose of 50mg once a day to a maximum of 1200mg per day (400mg three times daily)
The doses were titrated at weekly intervals according to patient's clinical response. There were 13 dose titration levels for each treatment group. L-dopa was given twice daily at dose level 2, and tid from dose level 3 and beyond.</td></tr>
</table>

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<tr><th>Bibliographic reference</th><th>Rascol, O., Brooks, D. J., Brunt, E. R., Korczyn, A. D., Poewe, W. H., Stocchi, F., Ropinirole in the treatment of early Parkinson's disease: a 6-month interim report of a 5-year levodopa-controlled study. 056 Study Group, Movement Disorders, 13, 39-45, 1998</th></tr>
<tr><td></td><td>If therapeutic efficacy could not be maintained, open L-dopa was administered as rescue therapy.</td></tr>
<tr><td>Primary outcomes</td><td>• Percentage improvement in the UPDRS III score
• Adverse events</td></tr>
<tr><td>Secondary outcomes</td><td>• UPDRS total
• Clinical Global Impression</td></tr>
<tr><td>Results</td><td>After 6 months of treatment, the UPDRS scores were 15.7 (SD 9.0) in the ropinirole group and 13.3. (SD 8.6) in the L-dopa group. The percentage improvement was 32% in the ropinirole group and 44% in the L-dopa group, a significant difference of 12% points (-12%) (95% CI [-20%, -5%]).

Emergent adverse events occurring in >5% of patients:
<table>
<tr><td>Adverse events</td><td>Ropinirole n (%) (n=179)</td><td>L-dopa n (%) (n=89)</td></tr>
<tr><td>Nausea</td><td>70(39.1)</td><td>29(32.6)</td></tr>
<tr><td>Insomnia</td><td>22(12.3)</td><td>9(10.1)</td></tr>
<tr><td>Somnolence</td><td>22(12.3)</td><td>12(13.5)</td></tr>
<tr><td>Dizziness</td><td>21(11.7)</td><td>11(12.4)</td></tr>
<tr><td>Dyspepsia</td><td>21(11.7)</td><td>12(13.5)</td></tr>
<tr><td>Headache</td><td>19(10.6)</td><td>12(13.5)</td></tr>
<tr><td>Vomiting</td><td>17(9.5)</td><td>5(5.6)</td></tr>
<tr><td>Abnormal pain</td><td>15(8.4)</td><td>7(7.9)</td></tr>
<tr><td>Psychiatric symptoms</td><td>15(8.4)</td><td>4(4.5)</td></tr>
<tr><td>Tremor</td><td>14(7.8)</td><td>2(2.2)</td></tr>
<tr><td>Anxiety</td><td>13(7.3)</td><td>2(2.2)</td></tr>
<tr><td>Anorexia</td><td>10(5.6)</td><td>3(3.4)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Rascol, O., Brooks, D. J., Brunt, E. R., Korczyn, A. D., Poewe, W. H., Stocchi, F., Ropinirole in the treatment of early Parkinson's disease: a 6-month interim report of a 5-year levodopa-controlled study. 056 Study Group, Movement Disorders, 13, 39-45, 1998**
	<table><tr><td>Postural Hypotension</td><td>8(4.5)</td><td>5(5.6)</td></tr><tr><td>Increased sweating</td><td>8(4.5)</td><td>5(5.6)</td></tr><tr><td>Abnormal Involuntary movements</td><td>5(2.8)</td><td>10(11.2)</td></tr><tr><td>Depression</td><td>4(2.2)</td><td>5(5.6)</td></tr></table>
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Unclear 2. Was there adequate concealment of allocation? Yes 3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes 4. Did the comparison groups receive the same care apart from interventions studied? Yes 5. Were participants receiving care kept blind to treatment allocation? Yes 6. Were the individuals administering care kept blind to treatment allocation? Yes 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Unclear 8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant’s exposure to the intervention? Unclear 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	**Rascol, O., Brooks, D. J., Korczyn, A. D., De Deyn, P. P., Clarke, C. E., Lang, A. E., A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa, New England Journal of Medicine, 342, 1484-91, 2000**
Country/ies where the study was carried out	Europe, Israel and Canada
Study type	Multicentre, randomised, double-blind trial
Aim of the study	To compare the risk of dyskinesia in early Parkinson's disease among patients treated with ropinirole with that among patients treated with a combination of levodopa and benserazide over a period of 5 years.

<table>
<tr><th>Bibliographic reference</th><th>Rascol, O., Brooks, D. J., Korczyn, A. D., De Deyn, P. P., Clarke, C. E., Lang, A. E., A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa, New England Journal of Medicine, 342, 1484-91, 2000</th></tr>
<tr><td>Study dates</td><td>Study dates: Not reported
Study duration: 5 years</td></tr>
<tr><td>Source of funding</td><td>SmithKline Beecham Pharmaceuticals</td></tr>
<tr><td>Sample size</td><td>In total: n=268; Ropinirole n=179; Levodopa n=89</td></tr>
<tr><td>Inclusion criteria</td><td>• ≥30 years old
• Hoehn and Yahr stages I-III
• Prior short-term treatment with levodopa or dopamine agonists was limited to a maximum of 6 weeks and had to be discontinued at least 2 weeks before study entry.</td></tr>
<tr><td>Exclusion criteria</td><td>Patients with:
• Severe dizziness or fainting
• Severe systemic disease
• Major psychosis
• Severe dementia
• Alcoholism or drug dependence
• A contraindication to levodopa
• Treatment with a monoamine oxidase inhibitor within 2 weeks before study entry (with the exception of selegiline) or previous treatment with ropinirole</td></tr>
<tr><td>Details</td><td>The demographic characteristics of the two groups were similar:
<table>
<tr><td>Characteristics</td><td>Ropinirole (n=179)</td><td>L-dopa (n=89)</td></tr>
<tr><td>Mean age (yrs)</td><td>63(9)</td><td>63(9)</td></tr>
<tr><td>Mean duration of disease (months)</td><td>30(34)</td><td>29(27)</td></tr>
<tr><td colspan="3">Hoehn & Yahr stage (%):</td></tr>
<tr><td>I</td><td>23(12.8)</td><td>20(22.5)</td></tr>
<tr><td>I.5</td><td>27(15.1)</td><td>8(9.0)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Rascol, O., Brooks, D. J., Korczyn, A. D., De Deyn, P. P., Clarke, C. E., Lang, A. E., A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa, New England Journal of Medicine, 342, 1484-91, 2000**
	II 66(36.9) 33(37.1) II.5 46(25.7) 19(21.3) III 17(9.5) 9(10.1) Mean baseline UPDRS III score 21.5(10.5) 21.7(11.3) Mean baseline UPDRS II score 8.0(5.0) 8.0(4.6) Values are given in mean (SD).
Interventions	Ropinirole: Starting dose of 0.25mg three times a day to a maximum of 24mg per day (8mg three times daily) L-dopa: Starting dose of 50mg once a day to a maximum of 1200mg per day (400mg three times daily) The doses were titrated at weekly intervals according to patient's clinical response. There were 13 dose titration levels for each treatment group. L-dopa was given twice daily at dose level 2, and tid from dose level 3 and beyond. If therapeutic efficacy could not be maintained, open L-dopa was administered as rescue therapy.
Primary outcomes	• Dyskinesia • Adverse events
Secondary outcomes	• Scores of UPDRS II and III • UPDRS item 39 assessing "Wearing off" period • UPDRS item 14 assessing "Freezing when walking"
Results	Hazard ratio for remaining free dyskinesia in the ropinirole group, as compared with the levodopa group, 2.82; 95% CI, 1.78 to 4.44; P<0.001. Overall, dyskinesia developed in 36 of the 177 patients in the ropinirole group (20%) and in 40 of the 88 in the levodopa group (45%), as assessed by item 32 in the UPDRS and by reports of adverse events. Before the addition of supplementary levodopa, 9 of 177 patients in the ropinirole group (5%) and 32 of 88 in the levodopa group (36%) had dyskinesia. Adverse events occurring in 10% or more of either group in the ITT analysis: Adverse event* Ropinirole n (%) (n=179) Levodopa n (%) (n=89)

Bibliographic reference	Rascol, O., Brooks, D. J., Korczyn, A. D., De Deyn, P. P., Clarke, C. E., Lang, A. E., A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa, New England Journal of Medicine, 342, 1484-91, 2000		
	Nausea	87(48.6)	44(49.4)
	Somnolence	49(27.4)	17(19.1)
	Insomnia	45(25.1)	21(23.6)
	Aggravated PD	40(22.3)	18(20.2)
	Dyspepsia	37(20.7)	15(16.9)
	Dizziness	36(20.1)	17(19.1)
	Hallucinations	31(17.3)	5(5.6)
	Vomiting	29(16.2)	10(11.2)
	Tremor	29(16.2)	11(12.4)
	Abdominal pain	27(15.1)	13(14.6)
	Depression	26(14.5)	20(22.5)
	Headache	25(14.0)	16(18.0)
	Edema of the legs	25(14.0)	5(5.6)
	Ataxia	25(14.0)	8(9.0)
	Anxiety	21(11.7)	8(9.0)
	Postural hypotension	21(11.7)	11(12.4)
	Constipation	17(9.5)	11(12.4)
	Dyskinesia	16(8.9)	23(25.8)
	Dystonia	12(6.7)	11(12.4)
	Increased sweating	11(6.1)	9(10.1)

Bibliographic reference	Rascol, O., Brooks, D. J., Korczyn, A. D., De Deyn, P. P., Clarke, C. E., Lang, A. E., A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa, New England Journal of Medicine, 342, 1484-91, 2000
	*Patients often had more than one adverse event.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Yes 2. Was there adequate concealment of allocation? Yes 3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes 4. Did the comparison groups receive the same care apart from interventions studied? Unclear 5. Were participants receiving care kept blind to treatment allocation? Yes 6. Were the individuals administering care kept blind to treatment allocation? Yes 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Unclear 8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Unclear 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	Whone, A. L., Watts, R. L., Stoessl, A. J., Davis, M., Reske, S., Nahmias, C., Lang, A. E., Rascol, O., Ribeiro, M. J., Remy, P., Poewe, W. H., Hauser, R. A., Brooks, D. J., Slower progression of Parkinson's disease with ropinirole versus levodopa: The REAL-PET study, Annals of Neurology, 54, 93-101, 2003
Country/ies where the study was carried out	Not reported
Study type	Randomised, double-blind, multinational study
Aim of the study	To compare the rates of loss of dopamine-terminal function in de novo patients with clinical and F-dopa PET evidence of early PD.
Study dates	Study dates: June 1997 to April 1999 Study duration: 2 years
Source of funding	GlaxoSmithKline
Sample size	In total: n=162; Ropinirole n= 87; L-dopa n=75

<table>
<tr><th>Bibliographic reference</th><th>Whone, A. L., Watts, R. L., Stoessl, A. J., Davis, M., Reske, S., Nahmias, C., Lang, A. E., Rascol, O., Ribeiro, M. J., Remy, P., Poewe, W. H., Hauser, R. A., Brooks, D. J., Slower progression of Parkinson's disease with ropinirole versus levodopa: The REAL-PET study, Annals of Neurology, 54, 93-101, 2003</th></tr>
<tr><td>Inclusion criteria</td><td>• Aged 30 to 75 years with a clinical diagnosis of idiopathic PD
• Hoehn and Yahr stages I-II.5 with a symptom duration of 2 years or less
• Patients who had not previously received treatment with L-dopa or dopamine agonist and were considered by their local neurologist to require such therapy
• Amantadine and anticholinergic antiparkinsonian medications were permitted but at a fixed dose from study onset. Concomitant selegiline was not allowed and was discontinued at least 6 weeks before the study started.</td></tr>
<tr><td>Exclusion criteria</td><td>Patients with:
• Pronounced head tremor or postural dizziness
• Potentially producing difficulty with imaging
• Severe psychiatric or severe systemic physical illness, including diabetes and other severe endocrine disorders</td></tr>
<tr><td>Details</td><td>Baseline demographics and disease characteristics of the groups were similar:
<table>
<tr><td>Characteristics</td><td>Ropinirole, mean (SD) (n=87)</td><td>L-dopa, mean (SD) (n=75)</td></tr>
<tr><td>Age (yr)</td><td>61.0(8.60)</td><td>59.9(9.23)</td></tr>
<tr><td>Age range (yr)</td><td>34-79</td><td>32-76</td></tr>
<tr><td>Symptom of duration (months)</td><td>15.6(6.79)</td><td>16.3(6.55)</td></tr>
<tr><td>Symptom of duration range (months)</td><td>1-27</td><td>3-35</td></tr>
<tr><td colspan="3">Hoehn & Yahr score, n (%):</td></tr>
<tr><td>I</td><td>19(21.8%)</td><td>22(29.3%)</td></tr>
<tr><td>I.5</td><td>13(14.9%)</td><td>9(12.0%)</td></tr>
<tr><td>II</td><td>39(44.8%)</td><td>34(45.3%)</td></tr>
<tr><td>II.5</td><td>16(18.4%)</td><td>10(13.3%)</td></tr>
<tr><td>UPDRS III</td><td>19.2(8.74)</td><td>17.7(8.20)</td></tr>
<tr><td>UPDRS III range</td><td>5+40</td><td>3-38</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Whone, A. L., Watts, R. L., Stoessl, A. J., Davis, M., Reske, S., Nahmias, C., Lang, A. E., Rascol, O., Ribeiro, M. J., Remy, P., Poewe, W. H., Hauser, R. A., Brooks, D. J., Slower progression of Parkinson's disease with ropinirole versus levodopa: The REAL-PET study, Annals of Neurology, 54, 93-101, 2003**
Interventions	Ropinirole: Initial doses of 0.75mg/d (0.25mg three times a day) Carbidopa/L-dopa: 50mg/day Over the first 4 weeks of the study, doses were escalated to three times daily regimens of ropinirole, 3mg/day, or L-dopa, 300mg/day. Titration was then flexible, based on clinical response and tolerability, to a maximum 24mg/day ropinirole or 1000mg/day L-dopa. If symptoms were inadequately controlled, patients could receive open-label, supplementary L-dopa.
Primary outcomes	The rates of loss of dopamine-terminal function
Secondary outcomes	• Change from baseline to completion in UPDRS III (motor) scores • The proportion of patients scoring 1 or 2 on the Clinical Global Impression Improvement scale • Incidence and time to development of dyskinesias
Results	Incidence of dyskinesia: Significantly fewer patients in the ropinirole group (3/87, 3.4%; one receiving open-label L-dopa) developed dyskinesias compared with the L-dopa group (20/75, 26.7%; OR, 0.09; 95% CI, 0.02-0.29; p<0.001). There was also a significant difference in favour of ropinirole in the time to develop dyskinesias (hazard ratio, 8.28; 95% CI, 2.46-27.93, p<0.001). Adverse events: Similar proportions of patients (87 ropinirole, 75 L-dopa) reported nonserious adverse events (ropinirole, 95.4%l L-dopa, 86.7%). nausea and somnolence were the most commonly reported adverse events, and both were more common in patients receiving ropinirole than in those receiving L-dopa. Hallucinations, depression, and confusion occurred in less than 10% of patients on each treatment (six and one patients; six and seven patients, five and one patients, ropinirole vs. L-dopa, respectively). Serious adverse events were experienced by 18 ropinirole and 17 L-dopa-treated patients with no contribution of concern from any one event.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Yes 2. Was there adequate concealment of allocation? Unclear 3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes 4. Did the comparison groups receive the same care apart from interventions studied? Unclear 5. Were participants receiving care kept blind to treatment allocation? Yes 6. Were the individuals administering care kept blind to treatment allocation? Yes

Bibliographic reference	Whone, A. L., Watts, R. L., Stoessl, A. J., Davis, M., Reske, S., Nahmias, C., Lang, A. E., Rascol, O., Ribeiro, M. J., Remy, P., Poewe, W. H., Hauser, R. A., Brooks, D. J., Slower progression of Parkinson's disease with ropinirole versus levodopa: The REAL-PET study, Annals of Neurology, 54, 93-101, 2003
	7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Yes 8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Unclear 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	Gray,R.FAU, Ives,N.FAU, Rick,C.FAU, Patel S FAU - Gray,Alastair, Gray,A.FAU, Jenkinson,C.FAU, McIntosh E FAU - Wheatley,Keith, Wheatley,K.FAU, Williams,A.FAU, Clarke,C.E., Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial, Lancet, -1196, 2014
Country/ies where the study was carried out	UK, Czech Republic, Russia
Study type	Open-label, pragmatic, randomised trial
Aim of the study	To establish which of the three classes of drug, as initial treatment, provides the most effective long-term control of symptoms and best quality of life for people with early Parkinson's disease.
Study dates	Study dates: 09 Nov 2000 to 22 Dec 2009 Study duration: 7 years
Source of funding	UK National Institute for Health Research Health Technology Assessment Programme, UK department of Health, UK Medical Research Council, Parkinson's UK.
Sample size	In total: 1620; Levodopa n=528; Dopamine agonist n=632; MAOBI n=460
Inclusion criteria	• People diagnosed with idiopathic Parkinson's disease • Previously untreated or had been treated for less than 6 months with dopaminergic drugs and if there was uncertainty as which class of drug to use.
Exclusion criteria	• Dementia • Inability to complete questionnaires

Bibliographic reference	**Gray,R.FAU, Ives,N.FAU, Rick,C.FAU, Patel S FAU - Gray,Alastair, Gray,A.FAU, Jenkinson,C.FAU, McIntosh E FAU - Wheatley,Keith, Wheatley,K.FAU, Williams,A.FAU, Clarke,C.E., Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial, Lancet, -1196, 2014**
Details	1058 (65%) of 1620 were randomly assigned three ways between dopamine agonists, MAOBI, and levodopa, 348 (21%) were assigned two ways between dopamine agonists and levodopa, and 214 (13%) were assigned two ways between dopamine agonists and MAOBI. Therefore, in total, 1406 were randomised between levodopa-sparing therapy and levodopa, and 919 between the two levodopa-sparing therapies, dopamine agonists and MAOBI. Patients assigned only between dopamine agonists and MAOBI had less severe disease and were younger. Other patient characteristics were balanced between randomisation and treatment groups:

Characteristics	Levodopa vs. levodopa sparing comparison		Levodopa-sparing comparison (dopamine agonist vs. MAOBI)	
	Levodopa (n=528)	Levodopa-sparing (n=878)	Dopamine agonist (n=459)	MAOBI (n=460)
Age (years)	71(34-94)	71(42-92)	69(27-92)	69(36-92)
Duration of PD (years)	0.6(0-10)	0.6(0-13)	0.6(0-6)	0.7(0-13)
Hoehn & Yahr stage:				
I-I.5	254(48%)	414(47%)	232(51%)	235(51%)
II	155(29%)	262(30%)	130(28%)	130(28%)
II.5-V	119(23%)	202(23%)	97(21%)	95(21%)
Previously received anti-PD treatments	46(9%)	74(8%)	37(8%)	38(8%)
PDQ-39 mobility score	31.2(25.5)	30.5(26.2)	28.3(26.5)	27.7(24.6)
PDQ-39 summary index	22.6(13.2)	22.3(14.0)	21.7(13.5)	21.4(13.2)

Data are in mean (range), n(%), or mean (SD).

<table>
<tr><th>Bibliographic reference</th><th>Gray,R.FAU, Ives,N.FAU, Rick,C.FAU, Patel S FAU - Gray,Alastair, Gray,A.FAU, Jenkinson,C.FAU, McIntosh E FAU - Wheatley,Keith, Wheatley,K.FAU, Williams,A.FAU, Clarke,C.E., Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial, Lancet, -1196, 2014</th></tr>
<tr><td>Interventions</td><td>Levodopa: Mean daily dose was 347 (SD 139) at 1 year rising to 531mg (SD 229) at 7 years
Dopamine agonists;
Ropinirole: Mean daily dose was 9mg/day (SD 4.5) at 1 year rising to 13mg/day (SD 6.7) at 7 years
Pramipexole: Mean daily dose was 2.2mg/day (SD 1.10; salt) at 1 year rising to 3.4mg/day (SD 1.5) at 7 years
MAOBI:
Selegiline: 8.4mg/day (SD 3.1) at 1 year and 8.6mg/day (SD 2.7) at 7 years
Rasagiline: 1mg/day (SD 0.1) at 1 and 7 years.</td></tr>
<tr><td>Primary outcomes</td><td>• Patient-rated functional status on the mobility subscale of the PDQ-39
• Cost-effectiveness</td></tr>
<tr><td>Secondary outcomes</td><td>• QALYs derived from the EQ-5D generic quality-of-life measure and a resource usage questionnaire
• PDQ-39 domains and overall score and compliance
• MMSE
• Onset of dementia
• Dyskinesias
• Motor fluctuations
• Admissions to hospital or institutional care
• Mortality</td></tr>
<tr><td>Results</td><td>Exposure to levodopa was similar in the dopamine agonists and MAOBI groups: averaging in all patients at 1 year, 96mg/d (SD 157) for dopamine agonists and 131mg/d (SD 172) for MAOBI, rising at 7 years to 526mg/d (SD 266) for dopamine agonists and 489mg/d (SD 246) for MAOBI. The mean daily dose in patients allocated to levodopa was 347mg (SD 139 at 1 year rising to 531mg (SD 229) at 7 years.

Estimated average differences between levodopa and levodopa-sparing groups, and between dopamine agonist and MAOBI, in the different PDQ-39 subscales and in EQ-5D:
<table>
<tr><td rowspan="2"></td><td colspan="2">Levodopa vs. levodopa-sparing</td><td colspan="2">Dopamine agonist vs. MAOBI</td><td rowspan="2">MID*</td></tr>
<tr><td>Estimate+ (95% CI)</td><td>p value</td><td>Estimate++ (95% CI)</td><td>p value</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Gray,R.FAU, Ives,N.FAU, Rick,C.FAU, Patel S FAU - Gray,Alastair, Gray,A.FAU, Jenkinson,C.FAU, McIntosh E FAU - Wheatley,Keith, Wheatley,K.FAU, Williams,A.FAU, Clarke,C.E., Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial, Lancet, -1196, 2014

Mobility	1.8 (0.5 to 3.0)	0.005	1.4 (0.0 to 2.9)	0.05	3.2
ADL	1.9 (0.7 to 3.0)	0.002	0.3 (-1.1 to 1.7)	0.7	4.4
Emotional wellbeing	-0.2 (-1.1 to 0.7)	0.7	0.3 (-0.8 to 1.4)	0.6	4.2
Stigma	1.3 (0.2 to 2.3)	0.02	1.3 (0.0 to 2.5)	0.06	5.6
Social support	0.1 (-0.6 to 0.8)	0.8	0.8 (-0.1 to 1.7)	0.07	11.4
Cognition	1.0 (0.0 to 2.0)	0.05	1.7 (0.5 to 2.9)	0.005	1.8
Communication	0.9 (0.0 to 1.8)	0.05	0.5 (-0.6 to 1.5)	0.4	4.2
Bodily discomfort	1.4 (0.3 to 2.4)	0.01	0.7 (-0.6 to 2.0)	0.3	2.1
PDQ-39 summary index	1.0 (0.3 to 1.7)	0.008	0.8 (0.0 to 1.7)	0.05	1.6
EQ-5D utility score	0.03 (0.01 to 0.05)	0.0002	0.004 (-0.01 to 0.02)	0.6	-

*MID=minimally important difference.

+Positive numbers favour levodopa.

++Positive numbers favour MAOBI.

The side effects (mainly psychological, sleep disturbance, and gastrointestinal) were usually mild, only 16 patients (9 given dopamine agonists, 4 given MAOBI, and 3 given levodopa) had serious adverse events believed to be possibly related to trial treatment.

Patients in the levodopa group were more likely to develop dyskinesias than those in the levodopa-sparing group: HR: 1.52, 95% CI 1.16 to 2.00, p=0.003) but there was no difference in motor fluctuations (1.11, 0.90 to 1.37, p=0.3).

Rates of dyskinesias were similar (HR: 0.85, 95% CI 0.60 to 1.22, p=0.4) but motor fluctuations were higher (HR: 1.32, 95% CI 1.01 to 1.72, p=0.04) in the dopamine agonist group than in the MAOBI group.

Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Yes 2. Was there adequate concealment of allocation? No

Bibliographic reference	Gray,R.FAU, Ives,N.FAU, Rick,C.FAU, Patel S FAU - Gray,Alastair, Gray,A.FAU, Jenkinson,C.FAU, McIntosh E FAU - Wheatley,Keith, Wheatley,K.FAU, Williams,A.FAU, Clarke,C.E., Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial, Lancet, -1196, 2014
	3. Were the groups comparable at baseline for all major confounding/prognostic factors? No 4. Did the comparison groups receive the same care apart from interventions studied? No 5. Were participants receiving care kept blind to treatment allocation? No 6. Were the individuals administering care kept blind to treatment allocation? No 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Yes 8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? No 12. Were investigators kept blind to other important confounding and prognostic factors? No

Bibliographic reference	Parkinson Study Group, Safety and efficacy of pramipexole in early Parkinson disease. A randomised dose-ranging study. Parkinson Study Group, JAMA, 125-130, 1997
Country/ies where the study was carried out	Not reported
Study type	Multicentre, multidosage, parallel-group, double-blind, placebo-controlled, randomised clinical trial
Aim of the study	To evaluate dose-response relationships for tolerability, safety, and efficacy of the synthetic dopamine agonist pramipexole.
Study dates	Study dates: April to September 1994 Study duration: 11 weeks
Source of funding	Pharmacia & Upjohn, Inc.
Sample size	In total: n=264; Pramipexole 1.5mg/d n=54; Pramipexole 3.0mg/d n=50; Pramipexole 4.5mg/d n=54; Pramipexole 6.0mg/d n=55; Placebo n=51
Inclusion criteria	• Adults who had idiopathic PD for less than 7 years • Did not require anti-PD treatment with levodopa or dopamine agonists and had not taken such medication within the 3 months prior to enrolment

<table>
<tr><th>Bibliographic reference</th><th>Parkinson Study Group, Safety and efficacy of pramipexole in early Parkinson disease. A randomised dose-ranging study. Parkinson Study Group, JAMA, 125-130, 1997</th></tr>
<tr><td></td><td>• Hoehn & Yahr stage I-III
• The use of levodopa or other dopamine agonists was not permitted during the study; however, selegiline, anticholinergics and amantadine were permitted if administered at a stable dosage for 30 days prior to and throughout the duration of the study.</td></tr>
<tr><td>Exclusion criteria</td><td>Subjects with:
• Atypical parkinsonian syndromes
• Dementia, as defined by a MMSE score of 22 or less
• Serious concurrent illness, such as active cardiac, renal, liver or neoplastic disease
• Age younger than 30 years
• Treatment with an antipsychotic, neuroleptic, metoclopramide, methyldopa, flunarizine, methylphenidate, cinnarizine, reserpine, or amphetamine in the past 6 months</td></tr>
<tr><td>Details</td><td>Baseline characteristics:
<table>
<tr><td>Characteristics</td><td>Placebo (n=51)</td><td>Pramipexole 1.5mg/d (n=54)</td><td>Pramipexole 3.0mg/d (n=50)</td><td>Pramipexole 4.5mg/d (n=54)</td><td>Pramipexole 6.0mg/d (n=55)</td></tr>
<tr><td>Age, mean (SD), y</td><td>60.4(12.0)</td><td>60.3(10.5)</td><td>62.2(11.1)</td><td>62.8(10.5)</td><td>62.8(11.4)</td></tr>
<tr><td>Time since onset of symptoms, mean (SD), y</td><td>1.7(1.5)</td><td>1.8(1.5)</td><td>2.0(1.6)</td><td>1.9(1.5)</td><td>2.2(1.8)</td></tr>
<tr><td>UPDRS Total, mean (SD)</td><td>28.7(12.3)</td><td>29.0(13.7)</td><td>28.3(11.9)</td><td>27.3(12.9)</td><td>32.9(18.6)</td></tr>
<tr><td>Hoehn & Yahr stage, mean (SD)</td><td>1.8(0.5)</td><td>1.8(0.6)</td><td>1.9(0.5)</td><td>1.8(0.5)</td><td>1.9(0.6)</td></tr>
</table></td></tr>
<tr><td>Interventions</td><td>Pramipexole: 1.5, 3.0, 4.5, or 6.0mg per day.
A 6-week dosage escalation period was followed by a 4-week maintenance period and a 1-week period during which active treatment was withdrawn.</td></tr>
<tr><td>Primary outcomes</td><td>• The proportion of subjects completing the study on the assigned treatment
• Change from baseline to 10 weeks in the total score of UPDRS</td></tr>
<tr><td>Secondary outcomes</td><td>• Changes between baseline and 8 and 10 weeks in the mental, motor and activities of daily living subscale scores of the UPDRS
• Changes between baseline and 10 weeks in Hoehn and Yahr scores</td></tr>
</table>

Bibliographic reference	**Parkinson Study Group, Safety and efficacy of pramipexole in early Parkinson disease. A randomised dose-ranging study. Parkinson Study Group, JAMA, 125-130, 1997**
	• Adverse events
Results	Changes from baseline to 10 weeks in Total UPDRS score:

Pramipexole dosage, mg/d	Difference* between treatment group mean and placebo group mean (98.75% CI)
1.5	-5.24 (-8.95 to -1.54)
3.0	-5.08 (-8.86 to -1.29)
4.5	-5.86 (-9.59 to -2.13
6.0	-5.24 (8.96 to -1.53

*Negative values indicate improvement.

The same pattern of treatment effect was apparent for the UPDRS II and UPDRS III score (data not reported in this publication).

Adverse effects:

Adverse event	Placebo n(%) (n=51)	Pramipexole 1.5mg/d, n(%) (n=54)	Pramipexole 3.0mg/d, n(%) (n=50)	Pramipexole 4.5mg/d, n(%) (n=54)	Pramipexole 6.0mg/d n(%) (n=55)	Combined pramipexole groups, n(%) (n=213)
Any event	40(78.4)	43(79.6)	42(84.0)	47(87.0)	49(89.1)	181(85.0)
Any event (moderate and severe intensity)	19(37.3)	24(44.4)	18(36.0)	23(42.6)	37(67.3)	102(47.9)
Somnolence	7(13.7)	9(16.7)	15(30.0)	17(31.5)	17(30.9)	58(27.2)
Dizziness	10(19.6)	10(18.5)	10(20.0)	9(16.7)	10(18.2)	39(18.3)
Nausea	5(9.8)	9(16.7)	9(18.0)	12(22.2)	12(21.8)	42(19.7)
Musculoskeletal pain	10(19.6)	8(14.8)	6(12.0)	3(5.6)	4(7.3)	21(9.8)
Headache	5(9.8)	5(9.2)	7(14.0)	8(14.8)	4(7.3)	24(11.3)
Constipation	3(5.9)	4(7.4)	6(12.0)	3(5.6)	10(18.2)	23(10.8)

Bibliographic reference	Parkinson Study Group, Safety and efficacy of pramipexole in early Parkinson disease. A randomised dose-ranging study. Parkinson Study Group, JAMA, 125-130, 1997

Insomnia	4(7.8)	2(3.7)	2(4.0)	7(13.0)	5(9.1)	16(7.5)
Fatigue	5(9.8)	4(7.4)	2(4.0)	2(3.7)	6(10.9)	14(6.6)
Hallucination	0(0)	4(7.4)	4(8.0)	1(1.9)	5(9.1)	14(6.6)
Confusion	0(0)	3(5.6)	2(4.0)	1(1.9)	3(5.5)	9(4.2)

Overall Risk of Bias

1. Has an appropriate method of randomisation been used? Yes
2. Was there adequate concealment of allocation? Yes
3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes
4. Did the comparison groups receive the same care apart from interventions studied? Unclear
5. Were participants receiving care kept blind to treatment allocation? Yes
6. Were the individuals administering care kept blind to treatment allocation? Yes
7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Yes
8. Did the study have an appropriate length of follow up? Yes
9. Did the study use a precise definition of outcome? Yes
10. Was a valid and reliable method used to determine that outcome? Yes
11. Were investigators kept blind to participant's exposure to the intervention? Unclear
12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	Parkinson Study Group, A controlled trial of rasagiline in early Parkinson disease: the TEMPO Study, Arch Neurol., 1937-1943, 2002
Country/ies where the study was carried out	US and Canada
Study type	Multi-centre, parallel-group, randomised, double-blind, placebo-controlled clinical trial.
Aim of the study	To evaluate the safety and efficacy of the selective monoamine oxidase type B inhibitor rasagiline on parkinsonian characteristics in untreated patients with early PD who had not developed sufficient disability to require dopaminergic therapy.
Study dates	Study dates: November 1997 to June 1999 Study duration: 26 weeks

<table>
<tr><th>Bibliographic reference</th><th>Parkinson Study Group, A controlled trial of rasagiline in early Parkinson disease: the TEMPO Study, Arch Neurol., 1937-1943, 2002</th></tr>
<tr><td>Source of funding</td><td>Teva Pharmaceuticals Industries, Ltd and Teva Neuroscience LLC</td></tr>
<tr><td>Sample size</td><td>In total: n=404; Rasagiline 1mg/d n=134; Rasagiline 2mg/d n=132; Placebo n=138</td></tr>
<tr><td>Inclusion criteria</td><td>• Older than 35 years who had the presence of at least 2 of the cardinal signs of PD
• Hoehn & Yahr I-III
• Patients could be treated with anticholinergic medications, but other antiparkinsonian medications, including levodopa, dopamine agonists, selegiline or amantadine were not permitted.</td></tr>
<tr><td>Exclusion criteria</td><td>Patients who had:
• Atypical or secondary parkinsonism
• Unstable medical problems, including congestive heart failure of New York Heart Association class II or greater
• Psychiatric problems that compromised the ability of the subjects to give informed consent
• An MMSE score of 23 or less
• Clinically significant depression
• Patients on antidepressants and sympathomimetics</td></tr>
<tr><td>Details</td><td>Baseline characteristics:
<table>
<tr><td>Characteristics</td><td>Placebo (n=138)</td><td>Rasagiline 1mg/d (n=134)</td><td>Rasagiline 2mg/d (n=132)</td><td>P value</td></tr>
<tr><td>Age (yrs)</td><td>60.5(10.8)</td><td>61.6(10.3)</td><td>60.4(11.4)</td><td>.76</td></tr>
<tr><td>Disease duration (yrs)</td><td>0.94(1.10)</td><td>0.92(1.24)</td><td>1.15(1.32)</td><td>.35</td></tr>
<tr><td>UPDRS II</td><td>6.2(3.5)</td><td>5.9(3.4)</td><td>6.7(3.2)</td><td>.04</td></tr>
<tr><td>UPDRS III</td><td>17.6(8.8)</td><td>17.9(8.9)</td><td>18.0(7.5)</td><td>.71</td></tr>
<tr><td>Hoehn and Yahr stage</td><td>1.9(0.5)</td><td>1.9(0.5)</td><td>1.9(0.5)</td><td>.93</td></tr>
<tr><td>PDQUALIF scale</td><td>26.9(15.7)</td><td>28.3(15.2)</td><td>30.2(16.8)</td><td>.29</td></tr>
<tr><td>Beck Depression Inventory</td><td>2.54(2.79)</td><td>2.39(2.47)</td><td>3.05(3.22)</td><td>.33</td></tr>
</table>
Data are presented as mean (SD) unless otherwise indicated.</td></tr>
<tr><td>Interventions</td><td>Rasagiline: 1mg or 2mg per day. A 1-week escalation period was followed by a 25-week maintenance period.</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Parkinson Study Group, A controlled trial of rasagiline in early Parkinson disease: the TEMPO Study, Arch Neurol., 1937-1943, 2002</th></tr>
<tr><td>Primary outcomes</td><td>The change in the UPDRS Total score between baseline and 26 weeks of treatment, comparing active treatment group with the placebo group.</td></tr>
<tr><td>Secondary outcomes</td><td>Changes in:
Mental, ADL and motor subscales of the UPDRS as well as symptom-based subscores (tremor, rigidity, bradykinesia, and postural instability/gait disorder)
Hoehn & Yahr stage
Schwab-England ADL scale
Beck Depression Inventory score
Timed motor tests
PDQUALIF scale</td></tr>
<tr><td>Results</td><td>Changes between baseline and 26 weeks:
<table>
<tr><td></td><td colspan="2">Effect size (95% CI)</td></tr>
<tr><td>Characteristic</td><td>Rasagiline 1mg/d vs. placebo</td><td>Rasagiline 2mg/d vs. placebo</td></tr>
<tr><td>UPDRS III</td><td>-2.71 (-3.86 to -1.55)</td><td>-1.68 (-2.84 to -0.51</td></tr>
<tr><td>UPDRS II</td><td>-1.04 (-1.60 to -0.48)</td><td>-1.22 (-1.78 to -0.65)</td></tr>
<tr><td>PDQUALIF scale</td><td>-2.91 (-5.19 to -0.64)</td><td>-2.74 (-5.02 to -0.45)</td></tr>
<tr><td>Beck Depression Inventory</td><td>-0.35 (-0.86 to 0.16)</td><td>-0.21 (-0.72 to 0.30)</td></tr>
</table>
Adverse events by treatment group:
<table>
<tr><td>Adverse events</td><td>Placebo, n(%) (n=138)</td><td>Rasagiline 1mg/d, n(%) (n=134)</td><td>Rasagiline 2mg/d, n(%) (n=132)</td><td>Combined rasagiline groups, n(%) (n=266)</td></tr>
<tr><td>Any event</td><td>110(79.7)</td><td>109(81.3)</td><td>111(84.1)</td><td>220(82.7)</td></tr>
<tr><td>Any event (moderate or severe intensity)</td><td>63(45.7)</td><td>58(43.3)</td><td>60(45.5)</td><td>118(44.4)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Parkinson Study Group, A controlled trial of rasagiline in early Parkinson disease: the TEMPO Study, Arch Neurol., 1937-1943, 2002

Infection	22(15.9)	20(14.9)	21(15.9)	41(15.4)
Headache	14(10.1)	19(14.2)	16(12.1)	35(13.2)
Accidental injury	14(10.1)	10(7.5)	10(7.6)	20(7.5)
Dizziness	15(10.9)	9(6.7)	10(7.6)	19(7.1)
Asthenia*	15(10.9)	6(4.5)	6(4.5)	12(4.5)
Nausea	10(7.2)	7(5.2)	9(6.8)	16(6.0)
Arthralgia	6(4.3)	5(3.7)	14(10.6)	19(7.1)
Back pain	7(5.1)	7(5.2)	8(6.1)	15(5.6)
Pain	8(5.8)	8(6.0)	6(4.5)	14(5.3)

*P=.03 for the difference between placebo and combined groups; P=.05 difference between placebo and each of the individual treatment groups.

Overall Risk of Bias

1. Has an appropriate method of randomisation been used? Yes
2. Was there adequate concealment of allocation? Yes
3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes
4. Did the comparison groups receive the same care apart from interventions studied? Unclear
5. Were participants receiving care kept blind to treatment allocation? Yes
6. Were the individuals administering care kept blind to treatment allocation? Yes
7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Yes
8. Did the study have an appropriate length of follow up? Yes
9. Did the study use a precise definition of outcome? Yes
10. Was a valid and reliable method used to determine that outcome? Yes
11. Were investigators kept blind to participant's exposure to the intervention? Unclear
12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	**Watts,R.L., Jankovic,J.FAU, Waters,C.FAU, Rajput,A.FAU, Boroojerdi,B.FAU, Rao,J., Randomised, blind, controlled trial of transdermal rotigotine in early Parkinson disease, Neurology, 272-276, 2007**
Country/ies where the study was carried out	US and Canada
Study type	Phase III, multi-centre, randomised, double-blind, placebo-controlled, two-arm, parallel-group clinical trial.
Aim of the study	To compare safety and therapeutic effects between transdermally applied rotigotine and placebo in patients with early-stage PD.
Study dates	Study dates: November 2001 to April 2003 Study duration: 28 weeks
Source of funding	Schwarz Pharma
Sample size	In total: 277; Rotigotine n=181; Placebo n=96
Inclusion criteria	• ≥30 years old • A diagnosis of idiopathic PD of less than or equal to 5 years in duration • UPDRS III score of at least 10 at baseline • Hoehn & Yahr stage score I-III • Two or more of the cardinal signs of PD • MMSE score of 25 or more • No other known or suspected cause of parkinsonism • Patients previously receiving an anticholinergic agent, monoamine oxidase B inhibitor, or an N-methyl-D-aspartate antagonist (amantadine) must have been on a stable dose for at least 28 days prior to study baseline and must be maintained on that dose for the duration of the trial
Exclusion criteria	• Prior or concurrent therapy with a dopamine agonist or carbidopa/levodopa therapy within 28 days of the baseline visit • Carbidopa/levodopa therapy lasting for more than 6 months since diagnosis • Atypical parkinsonism • Surgical intervention for PD • Clinically relevant hepatic, renal, or cardiac dysfunction • A diagnosis of epilepsy • A history of seizures as an adult, stroke, a TIA within the last year • Significant skin hypersensitivity to adhesive or other intolerance/hypersensitivity to the antiemetic ondansetron • Pregnancy or nursing

<table>
<tr><th>Bibliographic reference</th><th>Watts,R.L., Jankovic,J.FAU, Waters,C.FAU, Rajput,A.FAU, Boroojerdi,B.FAU, Rao,J., Randomised, blind, controlled trial of transdermal rotigotine in early Parkinson disease, Neurology, 272-276, 2007</th></tr>
<tr><td></td><td>• Inadequate birth control methods
• Patients receiving CNS active therapy were excluded unless their pharmacotherapy dose(s) had been stable for at least 28 days prior to baseline and was likely to remain stable for the duration of the trial</td></tr>
<tr><td>Details</td><td>Baseline characteristics:
<table>
<tr><td>Characteristics</td><td>Placebo n=96</td><td>Rotigotine n=181</td></tr>
<tr><td>Mean (SD) age, years</td><td>64.5(10.7)</td><td>62.0(10.3)</td></tr>
<tr><td>Mean (SD) years since diagnosis</td><td>1.4(1.3)</td><td>1.3(1.3)</td></tr>
<tr><td colspan="3">Hoehn & Yahr stage:</td></tr>
<tr><td>I</td><td>19(18)</td><td>27(49)</td></tr>
<tr><td>II</td><td>63(60)</td><td>54(97)</td></tr>
<tr><td>III</td><td>19(18)</td><td>19(34)</td></tr>
</table></td></tr>
<tr><td>Interventions</td><td>Rotigotine: starting at 2mg/day, titrated weekly up to 6mg/day, and then maintained for 6 months.</td></tr>
<tr><td>Primary outcomes</td><td>• The change in UPDRS II and III from baseline to end of treatment
• Responder rates (patients with ≥20% improvement)</td></tr>
<tr><td>Secondary outcomes</td><td>Not reported.</td></tr>
<tr><td>Results</td><td>Superior scoring in the UPDRS III was the greatest numerical contributor for the rotigotine group's subtotal improvements: the mean change in UPDRS III from baseline to end of the maintenance phase was -3.50 (±7.26) and the mean change in the UPDRS II score was -0.30 (±3.54).

Summary of the most common treatment-emergent adverse events:
<table>
<tr><td>Adverse event</td><td>Placebo n (%) (n=95)</td><td>Rotigotine n (%) (n=181)</td></tr>
<tr><td>Application site disorders*</td><td>11(12)</td><td>79(44)</td></tr>
<tr><td>Accident NOS*</td><td>2(2)</td><td>14(8)</td></tr>
<tr><td>Fatigue*</td><td>5(5)</td><td>14(8)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Watts,R.L., Jankovic,J.FAU, Waters,C.FAU, Rajput,A.FAU, Boroojerdi,B.FAU, Rao,J., Randomised, blind, controlled trial of transdermal rotigotine in early Parkinson disease, Neurology, 272-276, 2007

Pain	7(7)	4(2)
Leg pain	6(6)	2(1)
Dizziness*	12(13)	34(19)
Headache*	9(9)	29(16)
Tremor*	4(4)	11(6)
PD aggravated	5(5)	2(1)
Nausea*	16(17)	75(41)
Vomiting*	1(1)	16(9)
Constipation*	4(4)	11(6)
Dyspepsia*	1(2	12(7)
Diarrhoea*	2(2)	11(6)
Arthralgia*	6(6)	10(6)
Back pain*	3(3)	11(6)
Skeletal pain	6(6)	7(4)
Somnolence*	19(20)	60(33)
Insomnia*	3(3)	17(9)
Coughing*	6(6)	9(5)
Upper respiratory tract infection	7(7)	8(4)
Sinusitis	6(6)	7(4)
Rash	5(5)	4(2)

*Adverse events with an incidence of >5% in the rotigotine-treatment group.

Bibliographic reference	**Watts,R.L., Jankovic,J.FAU, Waters,C.FAU, Rajput,A.FAU, Boroojerdi,B.FAU, Rao,J., Randomised, blind, controlled trial of transdermal rotigotine in early Parkinson disease, Neurology, 272-276, 2007**
	NOS=not otherwise specified
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Yes 2. Was there adequate concealment of allocation? Yes 3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes 4. Did the comparison groups receive the same care apart from interventions studied? Yes 5. Were participants receiving care kept blind to treatment allocation? Yes 6. Were the individuals administering care kept blind to treatment allocation? Yes 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Unclear 8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Yes 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	**Zhang,Z., Shang,H., Hu,X., Chen,S., Zhao,Z., Du,Z., Surmann,E., Bauer,L., Asgharnejad,M., Rotigotine transdermal patch in Chinese patients with early Parkinson's disease: a randomized, double-blind, placebo-controlled pivotal study, Parkinsonism and Related Disorders, 28,29-55, 2016**
Country/ies where the study was carried out	China
Study type	Randomised, double-blind, placebo-controlled trial
Aim of the study	To determine the efficacy and safety of transdermal rotigotine in Chinese patients with early stage Parkinson's disease
Study dates	Study dates: June 2012 to May 2014 Study duration: 24 weeks
Source of funding	UCB Pharma
Sample size	In total: n=247; Rotigotine: n= 124; Placebo: n=123
Inclusion criteria	• Idiopathic Parkinson's disease of less than 5 years duration • Hoehn and Yahr stage ≤3

<table>
<tr><th>Bibliographic reference</th><th>Zhang,Z., Shang,H., Hu,X., Chen,S., Zhao,Z., Du,Z., Surmann,E., Bauer,L., Asgharnejad,M., Rotigotine transdermal patch in Chinese patients with early Parkinson’s disease: a randomized, double-blind, placebo-controlled pivotal study, Parkinsonism and Related Disorders, 28,29-55, 2016</th></tr>
<tr><td></td><td>• MMSE ≥25
• UPDRS III ≥10
• Patients who were being treated with anticholinergics, MAOBIs and amantadine has to be on stable doses at least 28 days prior to the start of trial and maintain those doses for its duration</td></tr>
<tr><td>Exclusion criteria</td><td>Patients with any of the following symptoms:
• Dementia
• Active psychosis or hallucinations
• Severe depression
• Evidence of an impulse control disorder
• History of epilepsy or stroke
• Hepatic, renal or cardiac dysfunction</td></tr>
<tr><td>Details</td><td>Baseline characteristics:
<table>
<tr><td>Characteristics</td><td>Rotigotine n=124</td><td>Placebo n=123</td></tr>
<tr><td>Mean age (years)</td><td>59.1 (10.3)</td><td>59.7 (10.1)</td></tr>
<tr><td>Male (%)</td><td>74 (60)</td><td>76 (62)</td></tr>
<tr><td>Duration of disease (years)</td><td>0.94 (1.17)</td><td>1.08 (1.27)</td></tr>
</table>
Values are given in means (SD) or no. of patients (%).</td></tr>
<tr><td>Interventions</td><td>Rotigotine: Starting dose of 2mg/24 hrs with a weekly increment of 2mg/24 hrs, up to a maximum of 8mg/24 hrs during the 4 week titration period.</td></tr>
<tr><td>Primary outcomes</td><td>The change in UPDRS II + III scores from baseline to the end of treatment</td></tr>
<tr><td>Secondary outcomes</td><td>• Clinical global impression
• PDQ-8</td></tr>
<tr><td>Results</td><td>Significantly greater reduction in UPDRS II + III scores with rotigotine versus placebo</td></tr>
<tr><td>Overall Risk of Bias</td><td>1. Has an appropriate method of randomisation been used? Yes
2. Was there adequate concealment of allocation? Yes</td></tr>
</table>

Bibliographic reference	Zhang,Z., Shang,H., Hu,X., Chen,S., Zhao,Z., Du,Z., Surmann,E., Bauer,L., Asgharnejad,M., Rotigotine transdermal patch in Chinese patients with early Parkinson's disease: a randomized, double-blind, placebo-controlled pivotal study, Parkinsonism and Related Disorders, 28,29-55, 2016
	3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes 4. Did the comparison groups receive the same care apart from interventions studied? Unclear 5. Were participants receiving care kept blind to treatment allocation? Yes 6. Were the individuals administering care kept blind to treatment allocation? Yes 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Yes 8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Yes 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear