



## Clinical trial results:

### A fixed dose, dose response study for ropinirole prolonged release (PR) in patients with early stage Parkinson's Disease.

#### Summary

EudraCT number	2011-002827-17
Trial protocol	EE SK
Global end of trial date	30 April 2014

#### Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	10 May 2015

#### Trial information

##### Trial identification

Sponsor protocol code	ROP111662
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01485172
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, +1 8664357343,
Scientific contact	GSK Response Center, GlaxoSmithKline, +1 8664357343,

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 January 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	30 April 2014
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To characterize the dose response of fixed doses of ropinirole PR as monotherapy in patients with early stage Parkinson's disease.

Protection of trial subjects:

All subjects signed an Informed Consent form to participate in the study. Subjects were allowed to titrate to their randomized dose, and if they experienced AEs, they could remain at a lower dose for the duration of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 January 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Slovakia: 12
Country: Number of subjects enrolled	Estonia: 19
Country: Number of subjects enrolled	Korea, Republic of: 11
Country: Number of subjects enrolled	Russian Federation: 102
Country: Number of subjects enrolled	United States: 42
Worldwide total number of subjects	186
EEA total number of subjects	31

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	118

From 65 to 84 years	64
85 years and over	4

## Subject disposition

### Recruitment

Recruitment details:

Eligible participants (par.) were diagnosed with early stage Parkinson's disease (according to modified Hoehn and Yahr criteria Stages I-III) and randomized at Screening into one of six treatment arms to receive placebo or ropinirole Prolonged Release (PR) tablets.

### Pre-assignment

Screening details:

After Screening, par. underwent a 13 Week Up-Titration Period until reaching their target dose then continued on their target dose during a 4 Week Maintenance Period up to Week 17. All par. underwent a 1 Week Down-Titration Period and then a Follow-Up Visit 1-2 Weeks after receiving the last dose of treatment.

### Period 1

Period 1 title	Overall Study (Up to 29 Weeks) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Treatment Group A: Placebo

Arm description:

Participants (par.) were administered a matching Prolonged Release (PR) placebo tablet Once Daily (OD) for up to 17 weeks. Par. completed a Follow-up visit 2 weeks after receiving the last dose of study medication.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

For the ropinirole PR tablets and matching placebo the oral prolonged release / extended release tablets are white aqueous film coated capsule shaped tablets, 12.62mm x 6.91mm, with 'SB' debossed on both sides. The Investigational product will be supplied to the clinic in white HDPE 85cc bottles with a 33mm induction heat sealed child resistant cap. Each bottle will contain 18 tablets of either ropinirole PR 2mg, 4mg, 8mg or placebo to match. Subjects will be required to take one tablet per day from each dispensed bottle of medication. Each bottle will be sufficient for 14 days dosing with 4 days overage to allow some flexibility of participant visits. Participants will be instructed to take the medication at the same time every day.

<b>Arm title</b>	Treatment Group B: 2 mg/day
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Arm description:

Par. were administered a ropinirole PR tablet totalling 2 milligrams per day (mg/day), OD up to Study Week 17. Par. reaching their target dose and completing the maintenance period or withdrawing prematurely were switched to placebo for down-titration for 1 week before completing a Follow-up visit 2 weeks after receiving the last dose of study medication.

Arm type	Experimental
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Investigational medicinal product name	Ropinirole PR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

**Dosage and administration details:**

For the ropinirole PR tablets and matching placebo the oral prolonged release / extended release tablets are white aqueous film coated capsule shaped tablets, 12.62mm x 6.91mm, with 'SB' debossed on both sides. The Investigational product will be supplied to the clinic in white HDPE 85cc bottles with a 33mm induction heat sealed child resistant cap. Each bottle will contain 18 tablets of either ropinirole PR 2mg, 4mg, 8mg or placebo to match. Subjects will be required to take one tablet per day from each dispensed bottle of medication. Each bottle will be sufficient for 14 days dosing with 4 days overage to allow some flexibility of participant visits. Participants will be instructed to take the medication at the same time every day.

<b>Arm title</b>	Treatment Group C: 4 mg/day
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**Arm description:**

Par. were administered a ropinirole PR tablet totalling 2 mg/day, OD for one week. Par. were up-titrated to 4 mg/day at Week 2 and continued this dose up to Study Week 17. Par. reaching their target dose and completing the maintenance period or withdrawing prematurely were down-titrated to 2 mg for 4 days and then switched to placebo for 3 days for down-titration before completing a Follow-up visit 2 weeks after receiving the last dose of study medication.

Arm type	Experimental
Investigational medicinal product name	Ropinirole PR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

**Dosage and administration details:**

For the ropinirole PR tablets and matching placebo the oral prolonged release / extended release tablets are white aqueous film coated capsule shaped tablets, 12.62mm x 6.91mm, with 'SB' debossed on both sides. The Investigational product will be supplied to the clinic in white HDPE 85cc bottles with a 33mm induction heat sealed child resistant cap. Each bottle will contain 18 tablets of either ropinirole PR 2mg, 4mg, 8mg or placebo to match. Subjects will be required to take one tablet per day from each dispensed bottle of medication. Each bottle will be sufficient for 14 days dosing with 4 days overage to allow some flexibility of participant visits. Participants will be instructed to take the medication at the same time every day.

<b>Arm title</b>	Treatment Group D: 8 mg/day
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**Arm description:**

ar. were administered a ropinirole PR tablet totalling 2 mg/day, OD for one week. Par. were up-titrated to 4 mg/day at Week 2, 6 mg/day at Week 3, and 8 mg/day at Week 4. Par. continued this dose up to Study Week 17. Par. reaching their target dose and completing the maintenance period or withdrawing prematurely were down-titrated for 1 week before completing a Follow-up visit 2 weeks after receiving the last dose of study medication.

Arm type	Experimental
Investigational medicinal product name	Ropinirole PR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

**Dosage and administration details:**

For the ropinirole PR tablets and matching placebo the oral prolonged release / extended release tablets are white aqueous film coated capsule shaped tablets, 12.62mm x 6.91mm, with 'SB' debossed on both sides. The Investigational product will be supplied to the clinic in white HDPE 85cc bottles with a 33mm induction heat sealed child resistant cap. Each bottle will contain 18 tablets of either ropinirole PR 2mg, 4mg, 8mg or placebo to match. Subjects will be required to take one tablet per day from each dispensed bottle of medication. Each bottle will be sufficient for 14 days dosing with 4 days overage to allow some flexibility of participant visits. Participants will be instructed to take the medication at the same time every day.

<b>Arm title</b>	Treatment Group E: 12 mg/day
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Arm description:

Par. were administered a ropinirole PR tablet totalling 2 mg/day, OD for one week. Par. were up-titrated to 4 mg/day at Week 2, 6 mg/day at Week 3, 8 mg/day at Week 4, and 12 mg/day at Week 6. Par. continued this dose up to Study Week 17. Par. reaching their target dose and completing the maintenance period or withdrawing prematurely were down-titrated for 1 week before completing a Follow-up visit 2 weeks after receiving the last dose of study medication.

Arm type	Experimental
Investigational medicinal product name	Ropinirole PR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

For the ropinirole PR tablets and matching placebo the oral prolonged release / extended release tablets are white aqueous film coated capsule shaped tablets, 12.62mm x 6.91mm, with 'SB' debossed on both sides. The Investigational product will be supplied to the clinic in white HDPE 85cc bottles with a 33mm induction heat sealed child resistant cap. Each bottle will contain 18 tablets of either ropinirole PR 2mg, 4mg, 8mg or placebo to match. Subjects will be required to take one tablet per day from each dispensed bottle of medication. Each bottle will be sufficient for 14 days dosing with 4 days overage to allow some flexibility of participant visits. Participants will be instructed to take the medication at the same time every day.

<b>Arm title</b>	Treatment Group F: 24 mg/day
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Arm description:

Par. were administered a ropinirole PR tablet totalling 2 mg/day, OD for one week. Par. were up-titrated to 4 mg/day at Week 2, 6 mg/day at Week 3, 8 mg/day at Week 4, 12 mg/day at Week 6, 16 mg/day at Week 8, 20 mg/day at Week 10, and 24 mg/day at Week 12. Par. continued this dose up to Study Week 17. Par. reaching their target dose and completing the maintenance or withdrawing prematurely were down-titrated for 1 week before completing a Follow-up visit 2 weeks after receiving the last dose of study medication.

Arm type	Experimental
Investigational medicinal product name	Ropinirole PR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

For the ropinirole PR tablets and matching placebo the oral prolonged release / extended release tablets are white aqueous film coated capsule shaped tablets, 12.62mm x 6.91mm, with 'SB' debossed on both sides. The Investigational product will be supplied to the clinic in white HDPE 85cc bottles with a 33mm induction heat sealed child resistant cap. Each bottle will contain 18 tablets of either ropinirole PR 2mg, 4mg, 8mg or placebo to match. Subjects will be required to take one tablet per day from each dispensed bottle of medication. Each bottle will be sufficient for 14 days dosing with 4 days overage to allow some flexibility of participant visits. Participants will be instructed to take the medication at the same time every day.

<b>Number of subjects in period 1</b>	Treatment Group A: Placebo	Treatment Group B: 2 mg/day	Treatment Group C: 4 mg/day
Started	40	13	41
Completed	33	12	34
Not completed	7	1	7
Consent withdrawn by subject	2	-	-
Physician decision	-	-	-
Adverse event, non-fatal	2	1	2
Protocol defined stopping criteria	1	-	-
Lost to follow-up	-	-	1
Lack of efficacy	2	-	-
Protocol deviation	-	-	4

<b>Number of subjects in period 1</b>	Treatment Group D: 8 mg/day	Treatment Group E: 12 mg/day	Treatment Group F: 24 mg/day
Started	40	39	13
Completed	32	34	9
Not completed	8	5	4
Consent withdrawn by subject	1	1	1
Physician decision	-	1	-
Adverse event, non-fatal	2	1	2
Protocol defined stopping criteria	-	1	-
Lost to follow-up	-	-	1
Lack of efficacy	-	-	-
Protocol deviation	5	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	Treatment Group A: Placebo
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Reporting group description:

Participants (par.) were administered a matching Prolonged Release (PR) placebo tablet Once Daily (OD) for up to 17 weeks. Par. completed a Follow-up visit 2 weeks after receiving the last dose of study medication.

Reporting group title	Treatment Group B: 2 mg/day
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Reporting group description:

Par. were administered a ropinirole PR tablet totalling 2 milligrams per day (mg/day), OD up to Study Week 17. Par. reaching their target dose and completing the maintenance period or withdrawing prematurely were switched to placebo for down-titration for 1 week before completing a Follow-up visit 2 weeks after receiving the last dose of study medication.

Reporting group title	Treatment Group C: 4 mg/day
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Reporting group description:

Par. were administered a ropinirole PR tablet totalling 2 mg/day, OD for one week. Par. were up-titrated to 4 mg/day at Week 2 and continued this dose up to Study Week 17. Par. reaching their target dose and completing the maintenance period or withdrawing prematurely were down-titrated to 2 mg for 4 days and then switched to placebo for 3 days for down-titration before completing a Follow-up visit 2 weeks after receiving the last dose of study medication.

Reporting group title	Treatment Group D: 8 mg/day
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Reporting group description:

Par. were administered a ropinirole PR tablet totalling 2 mg/day, OD for one week. Par. were up-titrated to 4 mg/day at Week 2, 6 mg/day at Week 3, and 8 mg/day at Week 4. Par. continued this dose up to Study Week 17. Par. reaching their target dose and completing the maintenance period or withdrawing prematurely were down-titrated for 1 week before completing a Follow-up visit 2 weeks after receiving the last dose of study medication.

Reporting group title	Treatment Group E: 12 mg/day
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Reporting group description:

Par. were administered a ropinirole PR tablet totalling 2 mg/day, OD for one week. Par. were up-titrated to 4 mg/day at Week 2, 6 mg/day at Week 3, 8 mg/day at Week 4, and 12 mg/day at Week 6. Par. continued this dose up to Study Week 17. Par. reaching their target dose and completing the maintenance period or withdrawing prematurely were down-titrated for 1 week before completing a Follow-up visit 2 weeks after receiving the last dose of study medication.

Reporting group title	Treatment Group F: 24 mg/day
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Reporting group description:

Par. were administered a ropinirole PR tablet totalling 2 mg/day, OD for one week. Par. were up-titrated to 4 mg/day at Week 2, 6 mg/day at Week 3, 8 mg/day at Week 4, 12 mg/day at Week 6, 16 mg/day at Week 8, 20 mg/day at Week 10, and 24 mg/day at Week 12. Par. continued this dose up to Study Week 17. Par. reaching their target dose and completing the maintenance or withdrawing prematurely were down-titrated for 1 week before completing a Follow-up visit 2 weeks after receiving the last dose of study medication.

Reporting group values	Treatment Group A: Placebo	Treatment Group B: 2 mg/day	Treatment Group C: 4 mg/day
Number of subjects	40	13	41
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	63.1 ± 8.82	58.2 ± 11.12	62.1 ± 11.38

Gender categorical Units: Subjects			
Female	17	5	16
Male	23	8	25
Race, Customized Units: Subjects			
African American/African Heritage	2	0	0
Asian - East Asian Heritage	2	0	1
Asian - Japanese Heritage	0	0	1
Asian - South East Asian Heritage	0	0	0
White - White/Caucasian/European Heritage	36	13	39
Missing	0	0	0

<b>Reporting group values</b>	Treatment Group D: 8 mg/day	Treatment Group E: 12 mg/day	Treatment Group F: 24 mg/day
Number of subjects	40	39	13
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	60.3	61.7	62.5
standard deviation	± 11.72	± 10.78	± 12.88
Gender categorical Units: Subjects			
Female	28	19	6
Male	12	20	7
Race, Customized Units: Subjects			
African American/African Heritage	0	0	0
Asian - East Asian Heritage	5	2	1
Asian - Japanese Heritage	0	0	0
Asian - South East Asian Heritage	1	0	0
White - White/Caucasian/European Heritage	34	36	12
Missing	0	1	0

<b>Reporting group values</b>	Total		
Number of subjects	186		
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	-		
standard deviation			
Gender categorical Units: Subjects			
Female	91		
Male	95		

Race, Customized			
Units: Subjects			
African American/African Heritage	2		
Asian - East Asian Heritage	11		
Asian - Japanese Heritage	1		
Asian - South East Asian Heritage	1		
White - White/Caucasian/European Heritage	170		
Missing	1		

## End points

### End points reporting groups

Reporting group title	Treatment Group A: Placebo
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Reporting group description:

Participants (par.) were administered a matching Prolonged Release (PR) placebo tablet Once Daily (OD) for up to 17 weeks. Par. completed a Follow-up visit 2 weeks after receiving the last dose of study medication.

Reporting group title	Treatment Group B: 2 mg/day
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Reporting group description:

Par. were administered a ropinirole PR tablet totalling 2 milligrams per day (mg/day), OD up to Study Week 17. Par. reaching their target dose and completing the maintenance period or withdrawing prematurely were switched to placebo for down-titration for 1 week before completing a Follow-up visit 2 weeks after receiving the last dose of study medication.

Reporting group title	Treatment Group C: 4 mg/day
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Reporting group description:

Par. were administered a ropinirole PR tablet totalling 2 mg/day, OD for one week. Par. were up-titrated to 4 mg/day at Week 2 and continued this dose up to Study Week 17. Par. reaching their target dose and completing the maintenance period or withdrawing prematurely were down-titrated to 2 mg for 4 days and then switched to placebo for 3 days for down-titration before completing a Follow-up visit 2 weeks after receiving the last dose of study medication.

Reporting group title	Treatment Group D: 8 mg/day
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Reporting group description:

ar. were administered a ropinirole PR tablet totalling 2 mg/day, OD for one week. Par. were up-titrated to 4 mg/day at Week 2, 6 mg/day at Week 3, and 8 mg/day at Week 4. Par. continued this dose up to Study Week 17. Par. reaching their target dose and completing the maintenance period or withdrawing prematurely were down-titrated for 1 week before completing a Follow-up visit 2 weeks after receiving the last dose of study medication.

Reporting group title	Treatment Group E: 12 mg/day
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Reporting group description:

Par. were administered a ropinirole PR tablet totalling 2 mg/day, OD for one week. Par. were up-titrated to 4 mg/day at Week 2, 6 mg/day at Week 3, 8 mg/day at Week 4, and 12 mg/day at Week 6. Par. continued this dose up to Study Week 17. Par. reaching their target dose and completing the maintenance period or withdrawing prematurely were down-titrated for 1 week before completing a Follow-up visit 2 weeks after receiving the last dose of study medication.

Reporting group title	Treatment Group F: 24 mg/day
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Reporting group description:

Par. were administered a ropinirole PR tablet totalling 2 mg/day, OD for one week. Par. were up-titrated to 4 mg/day at Week 2, 6 mg/day at Week 3, 8 mg/day at Week 4, 12 mg/day at Week 6, 16 mg/day at Week 8, 20 mg/day at Week 10, and 24 mg/day at Week 12. Par. continued this dose up to Study Week 17. Par. reaching their target dose and completing the maintenance or withdrawing prematurely were down-titrated for 1 week before completing a Follow-up visit 2 weeks after receiving the last dose of study medication.

### Primary: Change From Baseline (BL) in Unified Parkinson Disease (PD) Rating Scale (UPDRS) Motor Score

End point title	Change From Baseline (BL) in Unified Parkinson Disease (PD) Rating Scale (UPDRS) Motor Score
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End point description:

The UPDRS is a clinician based rating scale used to measure motor impairments and disability assessing six features of PD impairment. These are evaluated with data collected by interview and examination of the participant. One of the six features include the Part III–Motor Examination where scores range 0-108 and the maximum score indicates the worse condition. BL is defined as the last non-missing value on or before the first dose date. The change from BL was calculated by subtracting the BL values from the individual post-randomization values. The least squares(LS) means were estimated using the mixed model repeated measures(MMRM) adjusting for BL UPDRS motor score and race(white versus other) or by using the non-parametric rank analysis of covariance(ANCOVA). Intent to Treat (ITT) Population: all

randomized participants who received at least one dose of study medication, had a BL efficacy assessment for the specific outcome, and at least one respective post-BL efficacy assessment.

End point type	Primary
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End point timeframe:

Baseline (BL) and Week 4 of the Maintenance Period (Study Week 17)

End point values	Treatment Group A: Placebo	Treatment Group B: 2 mg/day	Treatment Group C: 4 mg/day	Treatment Group D: 8 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33 <sup>[1]</sup>	13 <sup>[2]</sup>	34 <sup>[3]</sup>	33 <sup>[4]</sup>
Units: Score on a scale				
least squares mean (confidence interval 95%)	-1.91 (-4.15 to 0.34)	-1.58 (-5.02 to 1.86)	-2.76 (-5.04 to -0.49)	-4.31 (-6.48 to -2.15)

Notes:

[1] - Intent to Treat (ITT) Population

[2] - Intent to Treat (ITT) Population

[3] - Intent to Treat (ITT) Population

[4] - Intent to Treat (ITT) Population

End point values	Treatment Group E: 12 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34 <sup>[5]</sup>	10 <sup>[6]</sup>		
Units: Score on a scale				
least squares mean (confidence interval 95%)	-4.07 (-6.32 to -1.82)	-2.83 (-6.61 to 0.95)		

Notes:

[5] - Intent to Treat (ITT) Population

[6] - Intent to Treat (ITT) Population

## Statistical analyses

<b>Statistical analysis title</b>	Statistical analysis 1
Statistical analysis description: LS Mean Difference vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group B: 2 mg/day
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.864 <sup>[7]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.41
upper limit	4.05

Notes:

[7] - P-values are from a Mixed Model Repeated Measures analysis.

<b>Statistical analysis title</b>	Statistical analysis 2
Statistical analysis description: LS Mean Difference vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group C: 4 mg/day
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.539 [8]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.61
upper limit	1.9

Notes:

[8] - P-values are from a Mixed Model Repeated Measures analysis.

<b>Statistical analysis title</b>	Statistical analysis 3
Statistical analysis description: LS Mean Difference vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group D: 8 mg/day
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.091 [9]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.21
upper limit	0.39

Notes:

[9] - P-values are from a Mixed Model Repeated Measures analysis.

<b>Statistical analysis title</b>	Statistical analysis 4
Statistical analysis description: LS Mean Difference vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group E: 12 mg/day

Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.124 <sup>[10]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.93
upper limit	0.6

Notes:

[10] - P-values are from a Mixed Model Repeated Measures analysis.

<b>Statistical analysis title</b>	Statistical analysis 5
Statistical analysis description: LS Mean Difference vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.658 <sup>[11]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.04
upper limit	3.19

Notes:

[11] - P-values are from a Mixed Model Repeated Measures analysis.

<b>Statistical analysis title</b>	Statistical analysis 6
Comparison groups	Treatment Group A: Placebo v Treatment Group B: 2 mg/day
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.439 <sup>[12]</sup>
Method	ANCOVA

Notes:

[12] - P-values are from nonparametric rank ANCOVA without stratifications.

<b>Statistical analysis title</b>	Statistical analysis 7
Comparison groups	Treatment Group A: Placebo v Treatment Group C: 4 mg/day

Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.177 <sup>[13]</sup>
Method	ANCOVA

Notes:

[13] - P-values are from nonparametric rank ANCOVA without stratifications.

<b>Statistical analysis title</b>	Statistical analysis 8
Comparison groups	Treatment Group A: Placebo v Treatment Group D: 8 mg/day
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.06 <sup>[14]</sup>
Method	ANCOVA

Notes:

[14] - P-values are from nonparametric rank ANCOVA without stratifications.

<b>Statistical analysis title</b>	Statistical analysis 9
Comparison groups	Treatment Group A: Placebo v Treatment Group E: 12 mg/day
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.047 <sup>[15]</sup>
Method	ANCOVA

Notes:

[15] - P-values are from nonparametric rank ANCOVA without stratifications.

<b>Statistical analysis title</b>	Statistical analysis 10
Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.407 <sup>[16]</sup>
Method	ANCOVA

Notes:

[16] - P-values are from nonparametric rank ANCOVA without stratifications.

### **Secondary: Number of participants with a $\geq 5$ points reduction from Baseline in UPDRS motor score**

End point title	Number of participants with a $\geq 5$ points reduction from Baseline in UPDRS motor score
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End point description:

The UPDRS motor scores can range from 0-108 where the maximum score indicates the worse condition. Baseline is defined as the last non-missing assessment measured on or before the first dose date. The change from Baseline will be calculated by subtracting the Baseline values from the individual post-randomization values. All participants with a non-missing efficacy observation at Baseline and during the maintenance period were analyzed.

End point type	Secondary
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End point timeframe:

Baseline and Week 4 of the Maintenance Period (Study Week 17)

<b>End point values</b>	Treatment Group A: Placebo	Treatment Group B: 2 mg/day	Treatment Group C: 4 mg/day	Treatment Group D: 8 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35 <sup>[17]</sup>	13 <sup>[18]</sup>	35 <sup>[19]</sup>	33 <sup>[20]</sup>
Units: Participants				
number (not applicable)	9	6	14	16

Notes:

[17] - ITT Population

[18] - ITT Population

[19] - ITT Population

[20] - ITT Population

<b>End point values</b>	Treatment Group E: 12 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34 <sup>[21]</sup>	10 <sup>[22]</sup>		
Units: Participants				
number (not applicable)	19	5		

Notes:

[21] - ITT Population

[22] - ITT Population

### Statistical analyses

<b>Statistical analysis title</b>	Statistical analysis 1
Comparison groups	Treatment Group A: Placebo v Treatment Group B: 2 mg/day
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.397
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	2.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	9.98

<b>Statistical analysis title</b>	Statistical analysis 2
Comparison groups	Treatment Group A: Placebo v Treatment Group C: 4 mg/day

Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.131
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	2.242
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	6.4

<b>Statistical analysis title</b>	Statistical analysis 3
Comparison groups	Treatment Group A: Placebo v Treatment Group D: 8 mg/day
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.018
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	3.515
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.25
upper limit	9.92

<b>Statistical analysis title</b>	Statistical analysis 4
Comparison groups	Treatment Group A: Placebo v Treatment Group E: 12 mg/day
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.02
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	3.607
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.22
upper limit	10.64

<b>Statistical analysis title</b>	Statistical analysis 5
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Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.202
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	2.679
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	12.16

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**Secondary: Number of participants with a  $\geq 10$  points reduction from Baseline in UPDRS motor score**

End point title	Number of participants with a $\geq 10$ points reduction from Baseline in UPDRS motor score
End point description:	The UPDRS motor scores can range from 0-108 where the maximum score indicates the worse condition. Baseline is defined as the last non-missing assessment measured on or before the first dose date. The change from Baseline will be calculated by subtracting the Baseline values from the individual post-randomization values. All participants with a non-missing efficacy observation at Baseline and during the maintenance period were analyzed
End point type	Secondary
End point timeframe:	Baseline and Week 4 of the Maintenance Period (Study Week 17)

<b>End point values</b>	Treatment Group A: Placebo	Treatment Group B: 2 mg/day	Treatment Group C: 4 mg/day	Treatment Group D: 8 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35 <sup>[23]</sup>	13 <sup>[24]</sup>	35 <sup>[25]</sup>	33 <sup>[26]</sup>
Units: Participants				
number (not applicable)	5	3	7	7

Notes:

[23] - ITT Population

[24] - ITT Population

[25] - ITT Population

[26] - ITT Population

<b>End point values</b>	Treatment Group E: 12 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34 <sup>[27]</sup>	10 <sup>[28]</sup>		
Units: Participants				
number (not applicable)	9	2		

Notes:

[27] - ITT Population

[28] - ITT Population

### Statistical analyses

<b>Statistical analysis title</b>	Statistical analysis 1
Comparison groups	Treatment Group A: Placebo v Treatment Group B: 2 mg/day
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.662
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	1.544
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	10.84

<b>Statistical analysis title</b>	Statistical analysis 2
Comparison groups	Treatment Group A: Placebo v Treatment Group C: 4 mg/day
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.557
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	1.485
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	5.55

<b>Statistical analysis title</b>	Statistical analysis 3
Comparison groups	Treatment Group A: Placebo v Treatment Group D: 8 mg/day

Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.347
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	1.855
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	6.72

<b>Statistical analysis title</b>	Statistical analysis 4
Comparison groups	Treatment Group A: Placebo v Treatment Group E: 12 mg/day
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.379
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	1.776
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	6.38

<b>Statistical analysis title</b>	Statistical analysis 5
Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.851
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	1.194
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	7.63

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**Secondary: Number of participants with a  $\geq 10$  points reduction from Baseline in**

## UPDRS Parts II and III combined

End point title	Number of participants with a $\geq 10$ points reduction from Baseline in UPDRS Parts II and III combined
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### End point description:

The UPDRS Part II is the Activities of Daily Living (ADL) score and can range from 0-52 as determined by the physician. The UPDRS Part III is the Motor Examination (Total Motor Score [TMS]) and is defined as the total score, ranging from 0-108 as determined by the physician, of the tests given in the motor examination section. The combined scores of Parts II and III can range from 0-160 with the higher score indicating the worse condition. Tests were performed when the participant is in the "on" state of Parkinson's. Baseline is defined as the last non-missing assessment measured on or before the first dose date. All participants with a non-missing efficacy observation at Baseline and during the maintenance period were analyzed.

End point type	Secondary
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### End point timeframe:

Baseline and Week 4 of the Maintenance Period (Study Week 17)

End point values	Treatment Group A: Placebo	Treatment Group B: 2 mg/day	Treatment Group C: 4 mg/day	Treatment Group D: 8 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35 <sup>[29]</sup>	13 <sup>[30]</sup>	35 <sup>[31]</sup>	33 <sup>[32]</sup>
Units: Participants				
number (not applicable)	6	3	7	10

### Notes:

[29] - ITT Population

[30] - ITT Population

[31] - ITT Population

[32] - ITT Population

End point values	Treatment Group E: 12 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34 <sup>[33]</sup>	10 <sup>[34]</sup>		
Units: Participants				
number (not applicable)	12	5		

### Notes:

[33] - ITT Population

[34] - ITT Population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Responder rate defined as participants with a $\geq 30\%$ reduction in Baseline UPDRS motor score

End point title	Responder rate defined as participants with a $\geq 30\%$ reduction in Baseline UPDRS motor score
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### End point description:

The responder rate is defined as the percentage of participants with a greater than or equal to ( $\geq$ )30% reduction in their individual Baseline UPDRS motor score at Week 4 of the Maintenance Period (Study Week 17). Baseline is defined as the last non-missing assessment measured on or before the first dose date. The change from Baseline will be calculated by subtracting the Baseline values from the individual post-randomization values. All participants with a non-missing efficacy observation at Baseline and

during the maintenance period were analyzed.

End point type	Secondary
End point timeframe:	
Baseline and Week 4 of the Maintenance Period (Study Week 17)	

<b>End point values</b>	Treatment Group A: Placebo	Treatment Group B: 2 mg/day	Treatment Group C: 4 mg/day	Treatment Group D: 8 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35 <sup>[35]</sup>	13 <sup>[36]</sup>	35 <sup>[37]</sup>	33 <sup>[38]</sup>
Units: Percentage of participants				
number (not applicable)	18	31	23	30

Notes:

[35] - ITT Population

[36] - ITT Population

[37] - ITT Population

[38] - ITT Population

<b>End point values</b>	Treatment Group E: 12 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34 <sup>[39]</sup>	10 <sup>[40]</sup>		
Units: Percentage of participants				
number (not applicable)	38	31		

Notes:

[39] - ITT Population

[40] - ITT Population

## Statistical analyses

<b>Statistical analysis title</b>	Statistical analysis 1
Comparison groups	Treatment Group B: 2 mg/day v Treatment Group A: Placebo
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.54
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	1.591
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	7.03

<b>Statistical analysis title</b>	Statistical analysis 2
Comparison groups	Treatment Group A: Placebo v Treatment Group C: 4 mg/day

Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.494
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	1.473
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	4.47

<b>Statistical analysis title</b>	Statistical analysis 3
Comparison groups	Treatment Group A: Placebo v Treatment Group D: 8 mg/day
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.115
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	2.391
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	7.06

<b>Statistical analysis title</b>	Statistical analysis 4
Comparison groups	Treatment Group A: Placebo v Treatment Group E: 12 mg/day
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.045
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	2.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.02
upper limit	8.55

<b>Statistical analysis title</b>	Statistical analysis 5
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Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.221
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	2.506
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	10.9

### Secondary: Change from Baseline in UPDRS Parts II and III combined

End point title	Change from Baseline in UPDRS Parts II and III combined
End point description:	The UPDRS Part II is the Activities of Daily Living (ADL) score and can range from 0-52 as determined by the physician. The UPDRS Part III is the Motor Examination (Total Motor Score [TMS]) and is defined as the total score, ranging from 0-108 as determined by the physician, of the tests given in the motor examination section. The combined scores of Parts II and III can range from 0-160 with the higher score indicating the worse condition. Tests were performed when the participant is in the "on" state of Parkinson's. Baseline is defined as the last non-missing assessment measured on or before the first dose date. The change from Baseline will be calculated by subtracting the Baseline values from the individual post-randomization values. All participants with a non-missing efficacy observation at Baseline and during the maintenance period were analyzed.
End point type	Secondary
End point timeframe:	Baseline and Week 4 of the Maintenance Period (Study Week 17)

End point values	Treatment Group A: Placebo	Treatment Group B: 2 mg/day	Treatment Group C: 4 mg/day	Treatment Group D: 8 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28 <sup>[41]</sup>	13 <sup>[42]</sup>	32 <sup>[43]</sup>	31 <sup>[44]</sup>
Units: Scores on a scale				
least squares mean (confidence interval 95%)	-2.88 (-5.87 to 0.1)	-1.81 (-6.18 to 2.57)	-3.81 (-6.76 to -0.85)	-5.63 (-8.44 to -2.81)

Notes:

[41] - ITT Population

[42] - ITT Population

[43] - ITT Population

[44] - ITT Population

End point values	Treatment Group E: 12 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32 <sup>[45]</sup>	10 <sup>[46]</sup>		

Units: Scores on a scale				
least squares mean (confidence interval 95%)	-6.62 (-9.51 to -3.72)	-3.87 (-8.68 to 0.94)		

Notes:

[45] - ITT Population

[46] - ITT Population

## Statistical analyses

<b>Statistical analysis title</b>	Statistical analysis 1
Statistical analysis description: LS Mean Difference vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group B: 2 mg/day
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.662 [47]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.78
upper limit	5.93

Notes:

[47] - The P-value was calculated using Mixed Model Repeated Measures analysis

<b>Statistical analysis title</b>	Statistical analysis 2
Statistical analysis description: LS Mean Difference vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group C: 4 mg/day
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.621 [48]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.63
upper limit	2.77

Notes:

[48] - The P-value was calculated using Mixed Model Repeated Measures analysis

<b>Statistical analysis title</b>	Statistical analysis 3
Statistical analysis description: LS Mean Difference vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group D: 8 mg/day

Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.15 <sup>[49]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.5
upper limit	1.01

Notes:

[49] - The P-value was calculated using Mixed Model Repeated Measures analysis

<b>Statistical analysis title</b>	Statistical analysis 4
Statistical analysis description: LS Mean Difference vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group E: 12 mg/day
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.048 <sup>[50]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.43
upper limit	-0.04

Notes:

[50] - The P-value was calculated using Mixed Model Repeated Measures analysis

<b>Statistical analysis title</b>	Statistical analysis 5
Statistical analysis description: LS Mean Difference vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.715 <sup>[51]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.32
upper limit	4.35

Notes:

[51] - The P-value was calculated using Mixed Model Repeated Measures analysis

## Secondary: Change from Baseline in UPDRS Activities of Daily Living

End point title	Change from Baseline in UPDRS Activities of Daily Living
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End point description:

The UPDRS Part II is the Activities of Daily Living (ADL) score and can range from 0-52 as determined by the physician. The higher score indicates the worse condition. Tests were performed when the participant is in the "on" state of Parkinson's. Baseline is defined as the last non-missing assessment measured on or before the first dose date. The change from Baseline will be calculated by subtracting the Baseline values from the individual post-randomization values. All participants with a non-missing efficacy observation at Baseline and during the maintenance period were analyzed.

End point type	Secondary
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End point timeframe:

Baseline and Week 4 of the Maintenance Period (Study Week 17)

End point values	Treatment Group A: Placebo	Treatment Group B: 2 mg/day	Treatment Group C: 4 mg/day	Treatment Group D: 8 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27 <sup>[52]</sup>	11 <sup>[53]</sup>	28 <sup>[54]</sup>	28 <sup>[55]</sup>
Units: Score on a scale				
least squares mean (confidence interval 95%)	-0.26 (-1.23 to 0.72)	0.91 (-0.58 to 2.41)	-0.73 (-1.74 to 0.27)	-1.13 (-2.08 to -0.17)

Notes:

[52] - ITT Population

[53] - ITT Population

[54] - ITT Population

[55] - ITT Population

End point values	Treatment Group E: 12 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25 <sup>[56]</sup>	7 <sup>[57]</sup>		
Units: Score on a scale				
least squares mean (confidence interval 95%)	-1.27 (-2.32 to -0.22)	-0.99 (-2.77 to 0.79)		

Notes:

[56] - ITT Population

[57] - ITT Population

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

LS Mean Difference vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group B: 2 mg/day
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Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.158 <sup>[58]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.46
upper limit	2.81

Notes:

[58] - The P-value was calculated using Mixed Model Repeated Measures analysis

<b>Statistical analysis title</b>	Statistical Analysis 2
Statistical analysis description: LS Mean Difference vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group C: 4 mg/day
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.446 <sup>[59]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.71
upper limit	0.76

Notes:

[59] - The P-value was calculated using Mixed Model Repeated Measures analysis

<b>Statistical analysis title</b>	Statistical Analysis 3
Statistical analysis description: LS Mean Difference vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group D: 8 mg/day
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.163 <sup>[60]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	0.36

Notes:

[60] - The P-value was calculated using Mixed Model Repeated Measures analysis

<b>Statistical analysis title</b>	Statistical Analysis 4
Statistical analysis description: LS Mean Difference vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group E: 12 mg/day
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.117 <sup>[61]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.27
upper limit	0.25

Notes:

[61] - The P-value was calculated using Mixed Model Repeated Measures analysis

<b>Statistical analysis title</b>	Statistical Analysis 5
Statistical analysis description: LS Mean Difference vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.456 <sup>[62]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.67
upper limit	1.2

Notes:

[62] - The P-value was calculated using Mixed Model Repeated Measures analysis

### **Secondary: Change from Baseline in the total UPDRS score (Parts I-III)**

End point title	Change from Baseline in the total UPDRS score (Parts I-III)
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End point description:

The total UPDRS score was calculated by the sum of the values for each component (Part I + Part II + Part III) as determined by the physician. The UPDRS Part I scores mentation, behavior and mood and scores can range from 0-16. The UPDRS Part II is the Activities of Daily Living (ADL) score and can range from 0-52. The UPDRS Part III is the Motor Examination (Total Motor Score [TMS]) and scores range from 0-108. The total UPDRS (Part I + II + III) scores can range from 0-176 with the higher score indicating the worse condition. Tests were performed when the participant is in the "on" state of Parkinson's. Baseline is defined as the last non-missing assessment measured on or before the first dose date. The change from Baseline will be calculated by subtracting the Baseline values from the individual

postrandomization values. All participants with a non-missing efficacy observation at Baseline and during the maintenance period were analyzed.

End point type	Secondary
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End point timeframe:

Baseline and Week 4 of the Maintenance Period (Study Week 17)

End point values	Treatment Group A: Placebo	Treatment Group B: 2 mg/day	Treatment Group C: 4 mg/day	Treatment Group D: 8 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28 <sup>[63]</sup>	13 <sup>[64]</sup>	32 <sup>[65]</sup>	31 <sup>[66]</sup>
Units: Score on a scale				
least squares mean (confidence interval 95%)	-2.74 (-5.79 to 0.31)	-2.18 (-6.65 to 2.29)	-3.83 (-6.85 to -0.81)	-5.93 (-8.8 to -3.06)

Notes:

[63] - ITT Population

[64] - ITT Population

[65] - ITT Population

[66] - ITT Population

End point values	Treatment Group E: 12 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32 <sup>[67]</sup>	10 <sup>[68]</sup>		
Units: Score on a scale				
least squares mean (confidence interval 95%)	-6.68 (-9.64 to -3.71)	-3.4 (-8.3 to 1.5)		

Notes:

[67] - ITT Population

[68] - ITT Population

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

LS Mean Difference vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group B: 2 mg/day
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.823 <sup>[69]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.38
upper limit	5.5

Notes:

[69] - The P-value was calculated using Mixed Model Repeated Measures analysis

<b>Statistical analysis title</b>	Statistical Analysis 2
Statistical analysis description: LS Mean Difference vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group C: 4 mg/day
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.568 <sup>[70]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.86
upper limit	2.68

Notes:

[70] - The P-value was calculated using Mixed Model Repeated Measures analysis

<b>Statistical analysis title</b>	Statistical Analysis 3
Statistical analysis description: LS Mean Difference vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group D: 8 mg/day
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.101 <sup>[71]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.01
upper limit	0.63

Notes:

[71] - The P-value was calculated using Mixed Model Repeated Measures analysis

<b>Statistical analysis title</b>	Statistical Analysis 4
Statistical analysis description: LS Mean Difference vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group E: 12 mg/day

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.04 [72]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.7
upper limit	-0.18

Notes:

[72] - The P-value was calculated using Mixed Model Repeated Measures analysis

<b>Statistical analysis title</b>	Statistical Analysis 5
Statistical analysis description: LS Mean Difference vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.811 [73]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.08
upper limit	4.77

Notes:

[73] - The P-value was calculated using Mixed Model Repeated Measures analysis

### **Secondary: Change from Baseline in the UPDRS Part I (mentation)**

End point title	Change from Baseline in the UPDRS Part I (mentation)
End point description: The UPDRS Part I scores mentation, behavior and mood as determined by a physician and participants were tested during the "on" phase of Parkinson's. This component of the UPDRS is the total score for 4 items (the items 1- 4 include intellectual impairment, thought disorder, motivation/initiative, and depression) and may have a value ranging from 0 to 16 as determined by a physician where 16 indicates the maximum score and the worse condition. All 4 items have to be present for a total score to be calculated. If one or more items are missing, the total score for the component will also be missing. Baseline is defined as the last non-missing assessment measured on or before the first dose date. The change from Baseline will be calculated by subtracting the Baseline values from the individual post-randomization values. All participants with a non-missing efficacy observation at Baseline and during the maintenance period were analyzed.	
End point type	Secondary
End point timeframe: Baseline and Week 4 of the Maintenance Period (Study Week 17)	

<b>End point values</b>	Treatment Group A: Placebo	Treatment Group B: 2 mg/day	Treatment Group C: 4 mg/day	Treatment Group D: 8 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33 <sup>[74]</sup>	13 <sup>[75]</sup>	34 <sup>[76]</sup>	33 <sup>[77]</sup>
Units: Score on a scale				
least squares mean (confidence interval 95%)	0.05 (-0.24 to 0.34)	-0.34 (-0.78 to 0.1)	-0.01 (-0.31 to 0.28)	-0.26 (-0.54 to 0.02)

Notes:

[74] - ITT Population

[75] - ITT Population

[76] - ITT Population

[77] - ITT Population

<b>End point values</b>	Treatment Group E: 12 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34 <sup>[78]</sup>	10 <sup>[79]</sup>		
Units: Score on a scale				
least squares mean (confidence interval 95%)	-0.02 (-0.31 to 0.27)	0.5 (0.02 to 0.98)		

Notes:

[78] - ITT Population

[79] - ITT Population

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Statistical analysis description: LS Mean Difference vs. Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group B: 2 mg/day
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.102 <sup>[80]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.86
upper limit	0.08

Notes:

[80] - The P-value was calculated using Mixed Model Repeated Measures analysis

<b>Statistical analysis title</b>	Statistical Analysis 2
Statistical analysis description: LS Mean Difference vs. Placebo	

Comparison groups	Treatment Group A: Placebo v Treatment Group C: 4 mg/day
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.723 <sup>[81]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.41
upper limit	0.29

Notes:

[81] - The P-value was calculated using Mixed Model Repeated Measures analysis

<b>Statistical analysis title</b>	Statistical Analysis 3
Statistical analysis description: LS Mean Difference vs. Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group D: 8 mg/day
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.084 <sup>[82]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.66
upper limit	0.04

Notes:

[82] - The P-value was calculated using Mixed Model Repeated Measures analysis

<b>Statistical analysis title</b>	Statistical Analysis 4
Statistical analysis description: LS Mean Difference vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group E: 12 mg/day
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.697 <sup>[83]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.07

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	0.28

Notes:

[83] - The P-value was calculated using Mixed Model Repeated Measures analysis

<b>Statistical analysis title</b>	Statistical Analysis 5
Statistical analysis description: LS Mean Difference vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.086 <sup>[84]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.97

Notes:

[84] - The P-value was calculated using Mixed Model Repeated Measures analysis

### **Secondary: Responder rate according to the Clinical Global Impression – Global Improvement (CGI-I) scale**

End point title	Responder rate according to the Clinical Global Impression – Global Improvement (CGI-I) scale
End point description: The CGI-I scale allows the investigator to rate the participant's total improvement since the beginning of treatment (Baseline). Baseline is defined as the last non-missing assessment measured on or before the first dose date. The scale is rated from 1-7 where 1 = "very much improved", 2 = "much improved", 3 = "minimally improved", 4 = "no change", 5 = "minimally worse", 6 = "much worse", and 7 = "very much worse". The responder rate is defined as the percentage of participants with a score of 1 or 2. All participants with a non-missing efficacy observation at Baseline and during the maintenance period were analyzed.	
End point type	Secondary
End point timeframe: Week 4 of the Maintenance Period (Study Week 17)	

<b>End point values</b>	Treatment Group A: Placebo	Treatment Group B: 2 mg/day	Treatment Group C: 4 mg/day	Treatment Group D: 8 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40 <sup>[85]</sup>	13 <sup>[86]</sup>	40 <sup>[87]</sup>	40 <sup>[88]</sup>
Units: Percentage of participants				
number (not applicable)	20	15	28	45

Notes:

[85] - ITT Population

[86] - ITT Population

[87] - ITT Population

[88] - ITT Population

<b>End point values</b>	Treatment Group E: 12 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39 <sup>[89]</sup>	13 <sup>[90]</sup>		
Units: Percentage of participants				
number (not applicable)	56	23		

Notes:

[89] - ITT Population

[90] - ITT Population

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Comparison groups	Treatment Group A: Placebo v Treatment Group B: 2 mg/day
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.733
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	0.769
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	3.49

<b>Statistical analysis title</b>	Statistical Analysis 2
Comparison groups	Treatment Group A: Placebo v Treatment Group C: 4 mg/day
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.519
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	1.411

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	4.02

<b>Statistical analysis title</b>	Statistical Analysis 3
Comparison groups	Treatment Group A: Placebo v Treatment Group D: 8 mg/day
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.008
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	4.204
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.46
upper limit	12.07

<b>Statistical analysis title</b>	Statistical Analysis 4
Comparison groups	Treatment Group A: Placebo v Treatment Group E: 12 mg/day
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.001
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	5.456
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.93
upper limit	15.46

<b>Statistical analysis title</b>	Statistical Analysis 5
Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day

Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.752
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	1.281
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	5.98

### Secondary: Percentage of participants withdrawn from the study due to lack of efficacy

End point title	Percentage of participants withdrawn from the study due to lack of efficacy
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End point description:

The percentage of participants who withdrew from the study due to lack of efficacy as defined by either the participant or the investigator is presented here. All participants with a non-missing efficacy observation at Baseline and during the maintenance period were analyzed.

End point type	Secondary
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End point timeframe:

Up to Week 4 of the Maintenance Period (Study Week 17)

<b>End point values</b>	Treatment Group A: Placebo	Treatment Group B: 2 mg/day	Treatment Group C: 4 mg/day	Treatment Group D: 8 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40 <sup>[91]</sup>	13 <sup>[92]</sup>	40 <sup>[93]</sup>	40 <sup>[94]</sup>
Units: Percentage of participants				
number (not applicable)	5	0	0	0

Notes:

[91] - ITT Population

[92] - ITT Population

[93] - ITT Population

[94] - ITT Population

<b>End point values</b>	Treatment Group E: 12 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39 <sup>[95]</sup>	13 <sup>[96]</sup>		
Units: Percentage of participants				
number (not applicable)	0	0		

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Notes:

[95] - ITT Population

[96] - ITT Population

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### **Statistical analyses**

No statistical analyses for this end point

## Adverse events

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### Adverse events information

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Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-serious AEs were collected from the initial dose of study treatment through the completion of the Follow-up Period

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Adverse event reporting additional description:

An AE is any untoward medical occurrence in a participant temporally associated with the use of a medicinal product, whether or not considered related to the study treatment. A SAE results in death, is life-threatening, requires hospitalization, results in disability or incapacity, or is a congenital anomaly or birth defect.

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Assessment type	Systematic
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### Dictionary used

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Dictionary name	MedDRA
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Dictionary version	17.1
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### Reporting groups

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Reporting group title	Treatment Group A: Placebo
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Reporting group description:

Participants (par.) were administered a matching Prolonged Release (PR) placebo tablet Once Daily (OD) for up to 17 weeks. Par. completed a Follow-up visit 2 weeks after receiving the last dose of study medication.

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Reporting group title	Treatment Group B: 2 mg/day
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Reporting group description:

Par. were administered a ropinirole PR tablet totalling 2 milligrams per day (mg/day), OD up to Study Week 17. Par. reaching their target dose and completing the maintenance period or withdrawing prematurely were switched to placebo for down-titration for 1 week before completing a Follow-up visit 2 weeks after receiving the last dose of study medication.

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Reporting group title	Treatment Group C: 4 mg/day
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Reporting group description:

Par. were administered a ropinirole PR tablet totalling 2 mg/day, OD for one week. Par. were up-titrated to 4 mg/day at Week 2 and continued this dose up to Study Week 17. Par. reaching their target dose and completing the maintenance period or withdrawing prematurely were down-titrated to 2 mg for 4 days and then switched to placebo for 3 days for down-titration before completing a Follow-up visit 2 weeks after receiving the last dose of study medication.

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Reporting group title	Treatment Group D: 8 mg/day
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Reporting group description:

ar. were administered a ropinirole PR tablet totalling 2 mg/day, OD for one week. Par. were up-titrated to 4 mg/day at Week 2, 6 mg/day at Week 3, and 8 mg/day at Week 4. Par. continued this dose up to Study Week 17. Par. reaching their target dose and completing the maintenance period or withdrawing prematurely were down-titrated for 1 week before completing a Follow-up visit 2 weeks after receiving the last dose of study medication.

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Reporting group title	Treatment Group E: 12 mg/day
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Reporting group description:

Par. were administered a ropinirole PR tablet totalling 2 mg/day, OD for one week. Par. were up-titrated to 4 mg/day at Week 2, 6 mg/day at Week 3, 8 mg/day at Week 4, and 12 mg/day at Week 6. Par. continued this dose up to Study Week 17. Par. reaching their target dose and completing the maintenance period or withdrawing prematurely were down-titrated for 1 week before completing a Follow-up visit 2 weeks after receiving the last dose of study medication.

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Reporting group title	Treatment Group F: 24 mg/day
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Reporting group description:

Par. were administered a ropinirole PR tablet totalling 2 mg/day, OD for one week. Par. were up-titrated to 4 mg/day at Week 2, 6 mg/day at Week 3, 8 mg/day at Week 4, 12 mg/day at Week 6, 16 mg/day at Week 8, 20 mg/day at Week 10, and 24 mg/day at Week 12. Par. continued this dose up to Study Week 17. Par. reaching their target dose and completing the maintenance or withdrawing prematurely were down-titrated for 1 week before completing a Follow-up visit 2 weeks after receiving the last dose of study medication.

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<b>Serious adverse events</b>	Treatment Group A: Placebo	Treatment Group B: 2 mg/day	Treatment Group C: 4 mg/day
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	1 / 41 (2.44%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

<b>Serious adverse events</b>	Treatment Group D: 8 mg/day	Treatment Group E: 12 mg/day	Treatment Group F: 24 mg/day
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 40 (0.00%)	2 / 39 (5.13%)	0 / 13 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral infarction			

subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>General disorders and administration site conditions</b>			
Chest pain			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

<b>Non-serious adverse events</b>	Treatment Group A: Placebo	Treatment Group B: 2 mg/day	Treatment Group C: 4 mg/day
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 40 (42.50%)	5 / 13 (38.46%)	18 / 41 (43.90%)
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>			
Basal cell carcinoma			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Dysplastic naevus			
subjects affected / exposed	0 / 40 (0.00%)	1 / 13 (7.69%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
<b>Vascular disorders</b>			
Hypertension			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	2 / 41 (4.88%)
occurrences (all)	0	0	3
Hypotension			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Labile blood pressure			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Orthostatic hypotension			
subjects affected / exposed	1 / 40 (2.50%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	2	0	0
<b>General disorders and administration</b>			

site conditions			
Asthenia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Feeling abnormal			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Ill-defined disorder			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Local swelling			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Peyronie's disease			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Hiccups			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	1 / 40 (2.50%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0

Upper-airway cough syndrome subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 13 (0.00%) 0	0 / 41 (0.00%) 0
Yawning subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 13 (0.00%) 0	0 / 41 (0.00%) 0
<b>Psychiatric disorders</b>			
Abnormal dreams subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2	0 / 13 (0.00%) 0	0 / 41 (0.00%) 0
Confusional state subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 13 (0.00%) 0	0 / 41 (0.00%) 0
Dissociation subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 13 (0.00%) 0	1 / 41 (2.44%) 1
Hallucination subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 13 (0.00%) 0	1 / 41 (2.44%) 1
Insomnia subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 13 (0.00%) 0	2 / 41 (4.88%) 3
Libido increased subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 13 (0.00%) 0	0 / 41 (0.00%) 0
Rapid eye movements sleep abnormal subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 13 (0.00%) 0	0 / 41 (0.00%) 0
<b>Investigations</b>			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 13 (0.00%) 0	1 / 41 (2.44%) 1
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 13 (0.00%) 0	1 / 41 (2.44%) 1
Blood creatinine increased			

subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Blood potassium increased			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Blood pressure increased			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram ST segment depression			
subjects affected / exposed	1 / 40 (2.50%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Heart rate increased			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Back injury			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Skeletal injury			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Somnolence			
subjects affected / exposed	2 / 40 (5.00%)	2 / 13 (15.38%)	5 / 41 (12.20%)
occurrences (all)	2	2	6

Headache			
subjects affected / exposed	1 / 40 (2.50%)	1 / 13 (7.69%)	4 / 41 (9.76%)
occurrences (all)	1	1	4
Dizziness			
subjects affected / exposed	2 / 40 (5.00%)	0 / 13 (0.00%)	2 / 41 (4.88%)
occurrences (all)	2	0	2
Sudden onset of sleep			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	2 / 41 (4.88%)
occurrences (all)	0	0	2
Hypoaesthesia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Tremor			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Dizziness postural			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Balance disorder			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Dyskinesia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Neuropathy peripheral			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Nystagmus			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Parkinson's disease			
subjects affected / exposed	1 / 40 (2.50%)	0 / 13 (0.00%)	1 / 41 (2.44%)
occurrences (all)	1	0	1

Parosmia subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 13 (0.00%) 0	0 / 41 (0.00%) 0
Restless legs syndrome subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 13 (0.00%) 0	1 / 41 (2.44%) 1
Tension headache subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 13 (0.00%) 0	0 / 41 (0.00%) 0
Blood and lymphatic system disorders Iron deficiency anaemia subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 13 (0.00%) 0	0 / 41 (0.00%) 0
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 13 (0.00%) 0	1 / 41 (2.44%) 1
Vertigo subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 13 (0.00%) 0	0 / 41 (0.00%) 0
Vertigo positional subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 13 (0.00%) 0	0 / 41 (0.00%) 0
Eye disorders Photopsia subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 13 (0.00%) 0	1 / 41 (2.44%) 1
Vision blurred subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 13 (0.00%) 0	2 / 41 (4.88%) 2
Visual impairment subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 13 (0.00%) 0	1 / 41 (2.44%) 1
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3	1 / 13 (7.69%) 1	6 / 41 (14.63%) 8

Diarrhoea			
subjects affected / exposed	1 / 40 (2.50%)	1 / 13 (7.69%)	0 / 41 (0.00%)
occurrences (all)	1	1	0
Dyspepsia			
subjects affected / exposed	2 / 40 (5.00%)	1 / 13 (7.69%)	1 / 41 (2.44%)
occurrences (all)	2	1	2
Vomiting			
subjects affected / exposed	2 / 40 (5.00%)	0 / 13 (0.00%)	2 / 41 (4.88%)
occurrences (all)	2	0	3
Constipation			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Abdominal discomfort			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	1 / 40 (2.50%)	0 / 13 (0.00%)	1 / 41 (2.44%)
occurrences (all)	1	0	1
Flatulence			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Irritable bowel syndrome			
subjects affected / exposed	1 / 40 (2.50%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Tooth disorder			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dermatitis allergic			

subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 13 (7.69%) 2	0 / 41 (0.00%) 0
Dermatitis contact subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 13 (0.00%) 0	1 / 41 (2.44%) 1
Renal and urinary disorders Micturition urgency subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 13 (0.00%) 0	0 / 41 (0.00%) 0
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 13 (0.00%) 0	2 / 41 (4.88%) 3
Muscle spasms subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 13 (0.00%) 0	0 / 41 (0.00%) 0
Arthralgia subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 13 (0.00%) 0	0 / 41 (0.00%) 0
Arthritis subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 13 (0.00%) 0	1 / 41 (2.44%) 1
Back disorder subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 13 (0.00%) 0	1 / 41 (2.44%) 1
Gouty arthritis subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 2	0 / 13 (0.00%) 0	0 / 41 (0.00%) 0
Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 13 (0.00%) 0	2 / 41 (4.88%) 2
Neck pain subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 13 (0.00%) 0	1 / 41 (2.44%) 1
Osteochondrosis			

subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
<b>Infections and infestations</b>			
<b>Nasopharyngitis</b>			
subjects affected / exposed	3 / 40 (7.50%)	0 / 13 (0.00%)	1 / 41 (2.44%)
occurrences (all)	3	0	1
<b>Pyelonephritis chronic</b>			
subjects affected / exposed	0 / 40 (0.00%)	1 / 13 (7.69%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
<b>Diverticulitis</b>			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
<b>Influenza</b>			
subjects affected / exposed	1 / 40 (2.50%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
<b>Upper respiratory tract infection</b>			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
<b>Urinary tract infection</b>			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
<b>Viral infection</b>			
subjects affected / exposed	1 / 40 (2.50%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
<b>Metabolism and nutrition disorders</b>			
<b>Decreased appetite</b>			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
<b>Dyslipidaemia</b>			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
<b>Glucose tolerance impaired</b>			

subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
<b>Gout</b>			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
<b>Hyperglycaemia</b>			
subjects affected / exposed	0 / 40 (0.00%)	1 / 13 (7.69%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
<b>Increased appetite</b>			
subjects affected / exposed	0 / 40 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0

<b>Non-serious adverse events</b>	Treatment Group D: 8 mg/day	Treatment Group E: 12 mg/day	Treatment Group F: 24 mg/day
<b>Total subjects affected by non-serious adverse events</b>			
subjects affected / exposed	24 / 40 (60.00%)	18 / 39 (46.15%)	7 / 13 (53.85%)
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>			
<b>Basal cell carcinoma</b>			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
<b>Dysplastic naevus</b>			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
<b>Vascular disorders</b>			
<b>Hypertension</b>			
subjects affected / exposed	2 / 40 (5.00%)	2 / 39 (5.13%)	2 / 13 (15.38%)
occurrences (all)	2	2	2
<b>Hypotension</b>			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
<b>Labile blood pressure</b>			
subjects affected / exposed	1 / 40 (2.50%)	1 / 39 (2.56%)	1 / 13 (7.69%)
occurrences (all)	1	1	1
<b>Orthostatic hypotension</b>			
subjects affected / exposed	0 / 40 (0.00%)	2 / 39 (5.13%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
<b>General disorders and administration site conditions</b>			

Asthenia			
subjects affected / exposed	2 / 40 (5.00%)	0 / 39 (0.00%)	1 / 13 (7.69%)
occurrences (all)	2	0	1
Fatigue			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Feeling abnormal			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Ill-defined disorder			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Local swelling			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Peyronie's disease			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Hiccups			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Upper-airway cough syndrome			

subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 39 (2.56%) 1	0 / 13 (0.00%) 0
Yawning subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 39 (2.56%) 1	0 / 13 (0.00%) 0
Psychiatric disorders			
Abnormal dreams subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 39 (0.00%) 0	0 / 13 (0.00%) 0
Confusional state subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 39 (0.00%) 0	1 / 13 (7.69%) 1
Dissociation subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 39 (0.00%) 0	0 / 13 (0.00%) 0
Hallucination subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 39 (0.00%) 0	0 / 13 (0.00%) 0
Insomnia subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 39 (0.00%) 0	0 / 13 (0.00%) 0
Libido increased subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 39 (0.00%) 0	1 / 13 (7.69%) 1
Rapid eye movements sleep abnormal subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 39 (2.56%) 1	0 / 13 (0.00%) 0
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 39 (0.00%) 0	0 / 13 (0.00%) 0
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2	1 / 39 (2.56%) 1	1 / 13 (7.69%) 1
Blood creatinine increased			

subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 39 (0.00%) 0	0 / 13 (0.00%) 0
Blood potassium increased subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 39 (0.00%) 0	0 / 13 (0.00%) 0
Blood pressure increased subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	1 / 39 (2.56%) 1	0 / 13 (0.00%) 0
Electrocardiogram ST segment depression subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 39 (0.00%) 0	0 / 13 (0.00%) 0
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 39 (0.00%) 0	0 / 13 (0.00%) 0
Heart rate increased subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 39 (0.00%) 0	0 / 13 (0.00%) 0
Injury, poisoning and procedural complications			
Arthropod bite subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 39 (0.00%) 0	0 / 13 (0.00%) 0
Back injury subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 39 (0.00%) 0	1 / 13 (7.69%) 1
Skeletal injury subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 39 (0.00%) 0	1 / 13 (7.69%) 1
Cardiac disorders			
Palpitations subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 39 (0.00%) 0	1 / 13 (7.69%) 1
Nervous system disorders			
Somnolence subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 5	3 / 39 (7.69%) 3	1 / 13 (7.69%) 1

Headache			
subjects affected / exposed	3 / 40 (7.50%)	2 / 39 (5.13%)	2 / 13 (15.38%)
occurrences (all)	7	2	3
Dizziness			
subjects affected / exposed	4 / 40 (10.00%)	3 / 39 (7.69%)	1 / 13 (7.69%)
occurrences (all)	5	3	1
Sudden onset of sleep			
subjects affected / exposed	0 / 40 (0.00%)	5 / 39 (12.82%)	1 / 13 (7.69%)
occurrences (all)	0	8	1
Hypoaesthesia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Tremor			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	1 / 13 (7.69%)
occurrences (all)	2	0	1
Dizziness postural			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Syncope			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Balance disorder			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Dyskinesia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Neuropathy peripheral			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Nystagmus			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Parkinson's disease			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	0 / 13 (0.00%)
occurrences (all)	0	1	0

Parosmia subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 39 (0.00%) 0	0 / 13 (0.00%) 0
Restless legs syndrome subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 39 (0.00%) 0	0 / 13 (0.00%) 0
Tension headache subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 39 (2.56%) 1	0 / 13 (0.00%) 0
Blood and lymphatic system disorders Iron deficiency anaemia subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 39 (2.56%) 1	0 / 13 (0.00%) 0
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 39 (0.00%) 0	0 / 13 (0.00%) 0
Vertigo subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	3 / 39 (7.69%) 3	1 / 13 (7.69%) 1
Vertigo positional subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 39 (0.00%) 0	0 / 13 (0.00%) 0
Eye disorders Photopsia subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 39 (0.00%) 0	0 / 13 (0.00%) 0
Vision blurred subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 39 (2.56%) 1	0 / 13 (0.00%) 0
Visual impairment subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 39 (0.00%) 0	0 / 13 (0.00%) 0
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	13 / 40 (32.50%) 16	4 / 39 (10.26%) 4	2 / 13 (15.38%) 3

Diarrhoea			
subjects affected / exposed	1 / 40 (2.50%)	1 / 39 (2.56%)	0 / 13 (0.00%)
occurrences (all)	3	3	0
Dyspepsia			
subjects affected / exposed	3 / 40 (7.50%)	0 / 39 (0.00%)	1 / 13 (7.69%)
occurrences (all)	4	0	1
Vomiting			
subjects affected / exposed	4 / 40 (10.00%)	0 / 39 (0.00%)	0 / 13 (0.00%)
occurrences (all)	5	0	0
Constipation			
subjects affected / exposed	2 / 40 (5.00%)	1 / 39 (2.56%)	0 / 13 (0.00%)
occurrences (all)	2	1	0
Abdominal discomfort			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Irritable bowel syndrome			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Tooth disorder			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Dermatitis allergic			

subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 39 (0.00%) 0	0 / 13 (0.00%) 0
Dermatitis contact subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 39 (0.00%) 0	0 / 13 (0.00%) 0
Renal and urinary disorders Micturition urgency subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 39 (2.56%) 1	0 / 13 (0.00%) 0
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	1 / 39 (2.56%) 1	2 / 13 (15.38%) 2
Muscle spasms subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 39 (0.00%) 0	1 / 13 (7.69%) 1
Arthralgia subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 39 (0.00%) 0	0 / 13 (0.00%) 0
Arthritis subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 39 (0.00%) 0	0 / 13 (0.00%) 0
Back disorder subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 39 (0.00%) 0	0 / 13 (0.00%) 0
Gouty arthritis subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 39 (0.00%) 0	0 / 13 (0.00%) 0
Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 39 (0.00%) 0	0 / 13 (0.00%) 0
Neck pain subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 39 (0.00%) 0	0 / 13 (0.00%) 0
Osteochondrosis			

subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 39 (2.56%) 1	0 / 13 (0.00%) 0
Pain in extremity subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 39 (0.00%) 0	0 / 13 (0.00%) 0
<b>Infections and infestations</b>			
<b>Nasopharyngitis</b> subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2	2 / 39 (5.13%) 2	0 / 13 (0.00%) 0
<b>Pyelonephritis chronic</b> subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 39 (0.00%) 0	0 / 13 (0.00%) 0
<b>Diverticulitis</b> subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 39 (0.00%) 0	0 / 13 (0.00%) 0
<b>Influenza</b> subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 39 (0.00%) 0	0 / 13 (0.00%) 0
<b>Upper respiratory tract infection</b> subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 39 (0.00%) 0	0 / 13 (0.00%) 0
<b>Urinary tract infection</b> subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 39 (2.56%) 1	0 / 13 (0.00%) 0
<b>Viral infection</b> subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 39 (0.00%) 0	0 / 13 (0.00%) 0
<b>Metabolism and nutrition disorders</b>			
<b>Decreased appetite</b> subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 39 (0.00%) 0	0 / 13 (0.00%) 0
<b>Dyslipidaemia</b> subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 39 (2.56%) 1	0 / 13 (0.00%) 0
<b>Glucose tolerance impaired</b>			

subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Gout			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Increased appetite			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 February 2012	Additions of MAO-B inhibitors, apomorphine and Deep Brain Stimulation to the list of prohibited treatments, addition of urinalysis to laboratory assessments, and various administrative corrections.
18 February 2013	Removed language referring to assessment of UPDRS motor score in the "on" state prior to study treatment, and added language clarifying how the UPDRS is to be administered during the study. A third ammendment, 24Jul2014, added updates and clarifications to the Data Analysis Plan descriptions

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported