EU Clinical Trials Register

Clinical trial results:
A fixed dose, dose-response study of ropinirole prolonged release (PR) as adjunctive treatment to L-dopa in patients with advanced Parkinson's disease.

Summary

EudraCT number	2011-002828-41
Trial protocol	EE SK
Global end of trial date	18 November 2014

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	29 July 2015

Trial information

Trial identification

Sponsor protocol code	ROP111569

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01494532
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	30 June 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To characterise the dose response for ropinirole PR as adjunctive treatment to L-dopa in patients with advanced Parkinson's disease.
Study participation will last up to a maximum of 33 weeks: 1-2 weeks for screening, an 13-21 week up-titration period, a 4-7 week maintenance period, 1 week down titration and a 1-2 week follow up period after the last dose of study medication.

Protection of trial subjects:

All subjects signed an Informed Consent form to participate in the study. If a subject experienced poor tolerability and the Investigator believed that the tolerability symptoms would not subside, dose adjustments could be made involving L-dopa initially with no change to the study medication dose level. Only after all available L-dopa dosing strategies had been employed could the investigator consider adjustment in the dose level of study medication. Only L-dopa adjustments could be made in titration stage 1. The duration of the titration period was extended for dose adjustments required due to tolerability issues. Otherwise, the subject continued on the visit schedule until the subject either reached the target dose level or highest tolerated dose.

Background therapy:

All subjects were required to be taking L-dopa.

Evidence for comparator: -

Actual start date of recruitment	02 April 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	Argentina: 67
Country: Number of subjects enrolled	Chile: 42
Country: Number of subjects enrolled	Estonia: 5
Country: Number of subjects enrolled	Korea, Republic of: 22
Country: Number of subjects enrolled	Russian Federation: 143
Country: Number of subjects enrolled	Slovakia: 26
Country: Number of subjects enrolled	United States: 47
Worldwide total number of subjects	352
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)	171
From 65 to 84 years	180
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Eligible participants(par) were diagnosed with advanced stage idiopathic Parkinson's Disease (PD), demonstrated lack of control with Levo(L)-dopa therapy, and on a stable dose of L-dopa for a minimum of 4 weeks prior to screening. Par were randomized 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 and continued on their target dose for a 4 Week Maintenance Period up to Week 17. All par underwent a 1 Week down-titration period and then a follow-up visit 2 Weeks after receiving the last dose of study medication.

Period 1

Period 1 title	Overall Study Period (Up to 33 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
Arm title	Treatment Group A: Placebo

Arm description:

Participants (par) were administered matching prolonged release (PR) placebo tablet once daily (OD) for up to 17 Weeks followed by down titration with placebo over 1 week. 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, 12.62 millimeter(mm) 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.

Arm title	Treatment Group B: 4 mg/day

Arm description:

Par were administered a ropinirole PR tablet totalling 2 milligrams per day (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 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

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.

Arm title	Treatment Group C: 8 mg/day

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, 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 switched to ropinirole PR 6.0 mg/day for 4 days then 4.0 mg/day 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.

Arm title	Treatment Group D: 12 mg/day

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 switched to ropinirole PR 8.0 mg/day for 4 days then 4.0 mg/day 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.

Arm title	Treatment Group E: 16 mg/day

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 and 16 mg/day at Week 8. Par continued this dose up to study Week 17. Par reaching their target dose and completing the Maintenance Period or withdrawing prematurely were switched to ropinirole PR 12.0 mg/day for 4 days then 6.0 mg/day 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.

Arm title	Treatment Group F: 24 mg/day

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 switched to ropinirole PR 16.0 mg/day for 4 days then 8.0 mg/day 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.

Number of subjects in period 1	Treatment Group A: Placebo	Treatment Group B: 4 mg/day	Treatment Group C: 8 mg/day
Started	75	25	76
Completed	65	21	59
Not completed	10	4	17
Consent withdrawn by subject	3	1	4
Physician decision	-	1	1

Subject reached protocol-defined stopping criteria	-	-	1
Adverse event, non-fatal	4	1	8
Lost to follow-up	1	-	-
Protocol deviation	2	1	3
Lack of efficacy	-	-	-

Number of subjects in period 1	Treatment Group D: 12 mg/day	Treatment Group E: 16 mg/day	Treatment Group F: 24 mg/day
Started	75	76	25
Completed	60	64	25
Not completed	15	12	0
Consent withdrawn by subject	3	2	-
Physician decision	2	-	-
Subject reached protocol-defined stopping criteria	-	-	-
Adverse event, non-fatal	6	5	-
Lost to follow-up	2	-	-
Protocol deviation	2	3	-
Lack of efficacy	-	2	-

Baseline characteristics

Reporting groups

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

Participants (par) were administered matching prolonged release (PR) placebo tablet once daily (OD) for up to 17 Weeks followed by down titration with placebo over 1 week. Par completed a follow-up visit 2 weeks after receiving the last dose of study medication.

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

Par were administered a ropinirole PR tablet totalling 2 milligrams per day (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 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: 8 mg/day
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 switched to ropinirole PR 6.0 mg/day for 4 days then 4.0 mg/day 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: 12 mg/day
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 switched to ropinirole PR 8.0 mg/day for 4 days then 4.0 mg/day 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 E: 16 mg/day
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 and 16 mg/day at Week 8. Par continued this dose up to study Week 17. Par reaching their target dose and completing the Maintenance Period or withdrawing prematurely were switched to ropinirole PR 12.0 mg/day for 4 days then 6.0 mg/day 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 F: 24 mg/day
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 switched to ropinirole PR 16.0 mg/day for 4 days then 8.0 mg/day for 3 days for down-titration 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: 4 mg/day	Treatment Group C: 8 mg/day
Number of subjects	75	25	76
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	63.7	66.5	65.6

standard deviation	± 9.98	± 7.45	± 9.19

Gender categorical			
Units: Subjects			
Female	42	12	33
Male	33	13	43

Race, customized			
Units: Subjects			
African American/African Heritage	2	0	0
American Indian or Alaskan Native	0	0	0
Asian - East Asian Heritage	3	3	3
Asian - Japanese Heritage	0	0	0
Asian - South East Asian Heritage	0	1	0
White - White/Caucasian/European Heritage	70	21	73

Reporting group values	Treatment Group D: 12 mg/day	Treatment Group E: 16 mg/day	Treatment Group F: 24 mg/day
Number of subjects	75	76	25
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	65.2	63.7	66.9
standard deviation	± 9.62	± 9.13	± 7.94
Gender categorical			
Units: Subjects			
Female	33	38	10
Male	42	38	15
Race, customized			
Units: Subjects			
African American/African Heritage	0	0	0
American Indian or Alaskan Native	1	0	0
Asian - East Asian Heritage	4	6	1
Asian - Japanese Heritage	1	0	0
Asian - South East Asian Heritage	1	1	0
White - White/Caucasian/European Heritage	68	69	24

Reporting group values	Total		
Number of subjects	352		
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		

Gender categorical Units: Subjects			
Female	168		
Male	184		
Race, customized Units: Subjects			
African American/African Heritage	2		
American Indian or Alaskan Native	1		
Asian - East Asian Heritage	20		
Asian - Japanese Heritage	1		
Asian - South East Asian Heritage	3		
White - White/Caucasian/European Heritage	325		

End points

End points reporting groups

Reporting group title	Treatment Group A: Placebo

Reporting group description:

Participants (par) were administered matching prolonged release (PR) placebo tablet once daily (OD) for up to 17 Weeks followed by down titration with placebo over 1 week. Par completed a follow-up visit 2 weeks after receiving the last dose of study medication.

Reporting group title	Treatment Group B: 4 mg/day

Reporting group description:

Par were administered a ropinirole PR tablet totalling 2 milligrams per day (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 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: 8 mg/day

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 switched to ropinirole PR 6.0 mg/day for 4 days then 4.0 mg/day 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: 12 mg/day

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 switched to ropinirole PR 8.0 mg/day for 4 days then 4.0 mg/day 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 E: 16 mg/day

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 and 16 mg/day at Week 8. Par continued this dose up to study Week 17. Par reaching their target dose and completing the Maintenance Period or withdrawing prematurely were switched to ropinirole PR 12.0 mg/day for 4 days then 6.0 mg/day 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 F: 24 mg/day

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 switched to ropinirole PR 16.0 mg/day for 4 days then 8.0 mg/day for 3 days for down-titration before completing a follow-up visit 2 weeks after receiving the last dose of study medication.

Primary: Change from Baseline (BL) in total awake time spent "off" (Hours [hr]) at Week 4 of Maintenance Period (MP)

End point title	Change from Baseline (BL) in total awake time spent "off" (Hours [hr]) at Week 4 of Maintenance Period (MP)

End point description:

"Off" time is defined as the state in which the participants(par) symptoms include lack of mobility(bradykinesia) with or without additional features such as tremor or rigidity. Par were asked to record awake time "off", awake time "on", troublesome dyskinesias(TD) during awake time "on", or time asleep for 30 minute intervals in 24 hr diary cards for 2 days preceding visits. Total number of awake hrs spent "off" per 24-hr period was the average of the 2 diary cards of the sum of awake hours

"off" in each 24-hr diary card. BL is the last non-missing assessment measured on or before the first dose, change from BL was calculated by subtracting the BL values from the MP Week 4 values. The Intent to Treat(ITT) Population included all randomized par who received at least one dose of study medication, had a BL efficacy assessment for the outcome, and at least one respective Post-BL efficacy assessment. MMRM model used BL total awake time 'Off', treatment, visit and treatment by visit

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

End point values	Treatment Group A: Placebo	Treatment Group B: 4 mg/day	Treatment Group C: 8 mg/day	Treatment Group D: 12 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65[1]	21[2]	60[3]	61[4]
Units: Hours				
least squares mean (confidence interval 95%)	-1.91 (-2.46 to -1.35)	-2.04 (-3.02 to -1.06)	-2.92 (-3.5 to -2.34)	-2.34 (-2.91 to -1.76)

Notes:

[1] - Par with a non-missing efficacy observation at BL and during the maintenance period are included

[2] - Par with a non-missing efficacy observation at BL and during the maintenance period are included

[3] - Par with a non-missing efficacy observation at BL and during the maintenance period are included

[4] - Par with a non-missing efficacy observation at BL and during the maintenance period are included

End point values	Treatment Group E: 16 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[5]	25[6]		
Units: Hours				
least squares mean (confidence interval 95%)	-2.8 (-3.36 to -2.24)	-2.37 (-3.26 to -1.47)		

Notes:

[5] - Par with a non-missing efficacy observation at BL and during the maintenance period are included

[6] - Par with a non-missing efficacy observation at BL and during the maintenance period are included

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
4mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group B: 4 mg/day
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.814 [7]
Method	Mixed models analysis

Notes:

[7] - P-values are from a Mixed Model Repeated Measures (MMRM).

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
8mg/day vs Placebo	

Comparison groups	Treatment Group A: Placebo v Treatment Group C: 8 mg/day
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.013 [8]
Method	Mixed models analysis

Notes:

[8] - P-values are from a Mixed Model Repeated Measures (MMRM).

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

12mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group D: 12 mg/day
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.287 [9]
Method	Mixed models analysis

Notes:

[9] - P-values are from a Mixed Model Repeated Measures (MMRM).

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

16mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group E: 16 mg/day
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.027 [10]
Method	Mixed models analysis

Notes:

[10] - P-values are from a Mixed Model Repeated Measures (MMRM).

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

24mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.39 [11]
Method	Mixed models analysis

Notes:

[11] - P-values are from a Mixed Model Repeated Measures (MMRM).

Statistical analysis title	Statistical analysis 6

Statistical analysis description:

4mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group B: 4 mg/day

Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.844 [12]
Method	ANCOVA

Notes:

[12] - P-values are from a nonparametric rank ANCOVA.

Statistical analysis title	Statistical analysis 7
Statistical analysis description:	
8mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group C: 8 mg/day
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.03 [13]
Method	ANCOVA

Notes:

[13] - P-values are from a nonparametric rank ANCOVA.

Statistical analysis title	Statistical analysis 8
Statistical analysis description:	
12mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group D: 12 mg/day
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.437 [14]
Method	ANCOVA

Notes:

[14] - P-values are from a nonparametric rank ANCOVA.

Statistical analysis title	Statistical analysis 9
Statistical analysis description:	
16mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group E: 16 mg/day
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.034 [15]
Method	ANCOVA

Notes:

[15] - P-values are from a nonparametric rank ANCOVA.

Statistical analysis title	Statistical analysis 10
Statistical analysis description:	
24mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day

Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.808 [16]
Method	ANCOVA

Notes:

[16] - P-values are from a nonparametric rank ANCOVA.

Secondary: Responder rate defined as the percentage of participants with a 20% reduction in Baseline (BL) "off" time at Week-4 of Maintenance Period

End point title	Responder rate defined as the percentage of participants with a 20% reduction in Baseline (BL) "off" time at Week-4 of Maintenance Period

End point description:

The responder rate was defined as the percentage of par with greater than or equal to (>=) 20 percent (%) reduction in their individual BL "off" time at Week 4 of the Maintenance Period. The "off" time is defined as the state in which the participants' symptoms include lack of mobility (bradykinesia) with or without additional features such as tremor or rigidity. BL is defined as the last non-missing assessment measured on or before the first dose date. Responder Rate (Least Squares [LS] means on inverse linked scale), odds ratio with 95% CI and p-value comparing against placebo were estimated by Generalized Estimating Equations (GEE) model. Baseline total awake time 'Off', treatment, visit and treatment*visit are included in the model. 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)

End point values	Treatment Group A: Placebo	Treatment Group B: 4 mg/day	Treatment Group C: 8 mg/day	Treatment Group D: 12 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65[17]	21[18]	60[19]	61[20]
Units: percentage of participants				
least squares mean (confidence interval 95%)	65.4 (52.4 to 76.4)	68 (46.6 to 83.8)	75.4 (63 to 84.6)	64.3 (50.8 to 75.8)

Notes:

[17] - ITT Population

[18] - ITT Population

[19] - ITT Population

[20] - ITT Population

End point values	Treatment Group E: 16 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[21]	25[22]		
Units: percentage of participants				
least squares mean (confidence interval 95%)	77.9 (66 to 86.5)	72 (51.1 to 86.4)		

Notes:

[21] - ITT Population

[22] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: 4mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group B: 4 mg/day
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.826
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	1.123
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.398
upper limit	3.166

Statistical analysis title	Statistical analysis 2
Statistical analysis description: 8mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group C: 8 mg/day
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.233
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	1.622
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.732
upper limit	3.593

Statistical analysis title	Statistical analysis 3
Statistical analysis description: 12mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group D: 12 mg/day
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.902
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	0.953

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.439
upper limit	2.065

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

16mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group E: 16 mg/day
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.127
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	1.866
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.837
upper limit	4.158

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

24mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.564
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	1.362
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.477
upper limit	3.888

Secondary: Percentage of participants with a >=1 hour reduction in Baseline "off" time at Week 4 of the Maintenance Period

End point title	Percentage of participants with a >=1 hour reduction in Baseline "off" time at Week 4 of the Maintenance Period

End point description:

The "off" time is defined as the state in which the participants' symptoms include lack of mobility (bradykinesia) with or without additional features such as tremor or rigidity. BL is defined as the last non-missing assessment measured on or before the first dose date. The percent change from BL was calculated by subtracting the BL values from the Maintenance Period Week 4 values. Percentage of participants meeting the criterion (LS mean on inverse linked scale), odds ratio with 95% CI and p-value comparing against placebo were estimated by Generalized Estimating Equations (GEE) model. Baseline 'off-time', treatment, visit and treatment*visit are included in the model. 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: 4 mg/day	Treatment Group C: 8 mg/day	Treatment Group D: 12 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65[23]	21[24]	60[25]	61[26]
Units: percentage of participants				
least squares mean (confidence interval 95%)	72.1 (59.5 to 82)	70.1 (48.6 to 85.4)	80.6 (68.7 to 88.7)	73.5 (59.6 to 83.9)

Notes:

[23] - ITT Population

[24] - ITT Population

[25] - ITT Population

[26] - ITT Population

End point values	Treatment Group E: 16 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[27]	25[28]		
Units: percentage of participants				
least squares mean (confidence interval 95%)	83.2 (72.1 to 90.5)	81.4 (62.3 to 92)		

Notes:

[27] - ITT Population

[28] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

4 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group B: 4 mg/day
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.861
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	0.908

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	2.659

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
8 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group C: 8 mg/day
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.277
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	1.608
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.684
upper limit	3.782

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
12 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group D: 12 mg/day
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.869
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	1.074
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.461
upper limit	2.5

Statistical analysis title	Statistical analysis 4
Statistical analysis description:	
16 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group E: 16 mg/day

Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.14
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	1.916
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.808
upper limit	4.545

Statistical analysis title	Statistical analysis 5
Statistical analysis description:	
24 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.362
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	1.689
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.547
upper limit	5.218

Secondary: Percentage of participants with a >=2 hours reduction in Baseline "off" time at Week 4 of the Maintenance Period

End point title	Percentage of participants with a >=2 hours reduction in Baseline "off" time at Week 4 of the Maintenance Period

End point description:

The "off" time is defined as the state in which the participants' symptoms include lack of mobility (bradykinesia) with or without additional features such as tremor or rigidity. BL is defined as the last non-missing assessment measured on or before the first dose date. The percent change from BL was calculated by subtracting the BL values from the Maintenance Period Week 4 values. Percentage of participants meeting the criterion (LS mean on inverse linked scale), odds ratio with 95% CI and p-value comparing against placebo were estimated by Generalized Estimating Equations (GEE) model. Baseline 'off-time', treatment, visit and treatment*visit are included in the model. 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: 4 mg/day	Treatment Group C: 8 mg/day	Treatment Group D: 12 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65[29]	21[30]	60[31]	61[32]
Units: percentage of participants				
least squares mean (confidence interval 95%)	53.7 (39.8 to 67.1)	45.6 (26.8 to 65.8)	68.2 (54.8 to 79.2)	53.6 (39.3 to 67.3)

Notes:

[29] - ITT Population

[30] - ITT Population

[31] - ITT Population

[32] - ITT Population

End point values	Treatment Group E: 16 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[33]	25[34]		
Units: percentage of participants				
least squares mean (confidence interval 95%)	63.2 (49.6 to 75)	51.3 (30.1 to 72)		

Notes:

[33] - ITT Population

[34] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
4 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group B: 4 mg/day
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.525
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	0.723
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.266
upper limit	1.965

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
8 mg/day vs Placebo	

Comparison groups	Treatment Group A: Placebo v Treatment Group C: 8 mg/day
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.13
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	1.851
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.834
upper limit	4.109

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
12 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group D: 12 mg/day
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.992
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	0.996
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.444
upper limit	2.232

Statistical analysis title	Statistical analysis 4
Statistical analysis description:	
16 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group E: 16 mg/day
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.329
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	1.48

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.674
upper limit	3.248

Statistical analysis title	Statistical analysis 5
Statistical analysis description:	

24 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.856
Method	Generalized Estimating Equations model
Parameter estimate	Odds ratio (OR)
Point estimate	0.907
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.315
upper limit	2.61

Secondary: Responder rate according to the clinical global impression–global improvement (CGI-I) scale at Week 4 of the Maintenance Period

End point title	Responder rate according to the clinical global impression-global improvement (CGI-I) scale at Week 4 of the Maintenance Period

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. The Generalized Estimating Equations (GEE) model was used to determine CGI responder rate with treatment, visit, and treatment by visit interaction included in the model. Only scheduled visits were included. 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)

End point values	Treatment Group A: Placebo	Treatment Group B: 4 mg/day	Treatment Group C: 8 mg/day	Treatment Group D: 12 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65[35]	21[36]	60[37]	61[38]
Units: Percentage of participants				
number (not applicable)	35	28	39	42

Notes:

[35] - ITT Population

[36] - ITT Population

[37] - ITT Population

[38] - ITT Population

End point values	Treatment Group E: 16 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[39]	25[40]		
Units: Percentage of participants				
number (not applicable)	46	56		

Notes:

[39] - ITT Population

[40] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in absolute awake time spent "on" without troublesome dyskinesia (TD) at Week 4 of the Maintenance Period

End point title	Change from Baseline in absolute awake time spent "on" without troublesome dyskinesia (TD) at Week 4 of the Maintenance Period

End point description:

Dyskinesias are involuntary twisting, turning movements caused by medication during "on" time in Parkinson's Disease (PD). TD is defined as those movements that interfere with function and cause meaningful discomfort. Par were asked to record awake time "off", awake time "on", TD during awake time "on", or time asleep for all 30 minute time intervals in 24 hour diary cards for the 2 days preceding each visit. The total number of awake hours spent "on" without TD per 24-hour period was the average across the 2 diary cards of the sum of awake hours spent "on" without TD in each 24 hour diary card. The change from BL was calculated by subtracting the BL values from the MP Week 4 values. LS means, 95% CIs and P-values were estimated from Mixed Model Repeated Measures (MMRM). Par with a non-missing efficacy observation at BL and during the MP were analyzed.

End point type	Secondary

End point timeframe:

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

End point values	Treatment Group A: Placebo	Treatment Group B: 4 mg/day	Treatment Group C: 8 mg/day	Treatment Group D: 12 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65[41]	21[42]	60[43]	61[44]
Units: Hours				
least squares mean (confidence interval	1.76 (1.15 to	1.21 (0.15 to	2.69 (2.06 to	2.16 (1.54 to

95%)	2.36)	2.27)	3.31)	2.78)

Notes:

[41] - ITT Population

[42] - ITT Population

[43] - ITT Population

[44] - ITT Population

End point values	Treatment Group E: 16 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[45]	25[46]		
Units: Hours				
least squares mean (confidence interval 95%)	2.49 (1.89 to 3.1)	2.24 (1.27 to 3.21)		

Notes:

[45] - ITT Population

[46] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
4 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group B: 4 mg/day
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.376 [47]
Method	Mixed models analysis

Notes:

[47] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
8 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group C: 8 mg/day
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.036 [48]
Method	Mixed models analysis

Notes:

[48] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
12 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group D: 12 mg/day

Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.362 [49]
Method	Mixed models analysis

Notes:

[49] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

16 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group E: 16 mg/day
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.089 [50]
Method	Mixed models analysis

Notes:

[50] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

24 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.403 [51]
Method	Mixed models analysis

Notes:

[51] - Mixed Model Repeated Measures

Secondary: Change from Baseline in absolute awake time spent "on" at Week 4 of the Maintenance Period

End point title	Change from Baseline in absolute awake time spent "on" at Week 4 of the Maintenance Period

End point description:

Par were asked to record awake time "off", awake time "on", TD during awake time "on", or time asleep for all 30 minute time intervals in 24 hour diary cards for the 2 days preceding each visit of the study. The total number of awake hours spent "on" per 24-hour period was the average across the 2 diary cards of the sum of the awake hours spent "on" in each 24 hour diary card. BL is defined as the last non-missing assessment measured on or before the first dose date. The change from BL was calculated by subtracting the BL values from the Maintenance Period Week 4 values. LS means, 95% CIs and P-values were estimated from MMRM. 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: 4 mg/day	Treatment Group C: 8 mg/day	Treatment Group D: 12 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65[52]	21[53]	60[54]	61[55]
Units: Hours				
least squares mean (confidence interval 95%)	1.7 (1.1 to 2.3)	1.2 (0.14 to 2.25)	2.69 (2.06 to 3.31)	2.23 (1.61 to 2.85)

Notes:

[52] - ITT Population

[53] - ITT Population

[54] - ITT Population

[55] - ITT Population

End point values	Treatment Group E: 16 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[56]	25[57]		
Units: Hours				
least squares mean (confidence interval 95%)	2.62 (2.02 to 3.23)	2.34 (1.38 to 3.31)		

Notes:

[56] - ITT Population

[57] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
4 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group B: 4 mg/day
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.419 [58]
Method	Mixed models analysis

Notes:

[58] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
8 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group C: 8 mg/day
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.026 [59]
Method	Mixed models analysis

Notes:

[59] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

12 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group D: 12 mg/day
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.23 [60]
Method	Mixed models analysis

Notes:

[60] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

16 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group E: 16 mg/day
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.033 [61]
Method	Mixed models analysis

Notes:

[61] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

24 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.266 [62]
Method	Mixed models analysis

Notes:

[62] - Mixed Model Repeated Measures

Secondary: Change from Baseline for total sleep time during the night time hours of sleep at Week 4 of the Maintenance Period

End point title	Change from Baseline for total sleep time during the night time hours of sleep at Week 4 of the Maintenance Period

End point description:

Par. were asked to record awake time "off", awake time "on", TD during awake time "on", or time asleep for all 30 minute time intervals in 24 hour diary cards for the 2 days preceding each visit of the study. The total sleep hours during the night time hours of sleep was the average across the 2 diary cards of the sum of time (hours) asleep during night time in each 24-hour diary card. BL is defined as the last non-missing assessment measured on or before the first dose date. The change from BL was calculated by subtracting the BL values from the Maintenance Period Week 4 values. LS means, 95% CIs and P-values were estimated from MMRM. 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: 4 mg/day	Treatment Group C: 8 mg/day	Treatment Group D: 12 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65[63]	21[64]	60[65]	61[66]
Units: Hours				
least squares mean (confidence interval 95%)	0.22 (-0.13 to 0.56)	0.86 (0.25 to 1.46)	0.22 (-0.14 to 0.58)	0.15 (-0.21 to 0.51)

Notes:

[63] - ITT Population

[64] - ITT Population

[65] - ITT Population

[66] - ITT Population

End point values	Treatment Group E: 16 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[67]	25[68]		
Units: Hours				
least squares mean (confidence interval 95%)	0.14 (-0.21 to 0.49)	0.04 (-0.51 to 0.6)		

Notes:

[67] - ITT Population

[68] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
4 mg/day vs Placebo	
Comparison groups	Treatment Group B: 4 mg/day v Treatment Group A: Placebo
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.073 [69]
Method	Mixed models analysis

Notes:

[69] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
8 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group C: 8 mg/day

Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.996 [70]
Method	Mixed models analysis

Notes:

[70] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

12 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group D: 12 mg/day
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.791 [71]
Method	Mixed models analysis

Notes:

[71] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

16 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group E: 16 mg/day
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.747 [72]
Method	Mixed models analysis

Notes:

[72] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

24 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6 [73]
Method	Mixed models analysis

Notes:

[73] - Mixed Model Repeated Measures

Secondary: Percent change from Baseline in awake time spent "off" at Week 4 of the Maintenance Period	
End point title	Percent change from Baseline in awake time spent "off" at Week 4 of the Maintenance Period

End point description:

The "off" state is defined as the state in which the participants' symptoms include lack of mobility (bradykinesia), with or without additional features such as tremor or rigidity. Par. were asked to record awake time "off", awake time "on", TD during awake time "on", or time asleep for all 30 minute time intervals in 24 hour diary cards for the 2 days preceding each visit of the study. The total number of awake hours spent "off" per 24-hour period was the average across the 2 diary cards of the sum of awake hours spent "off" in each 24-hour diary card. The percent change from BL was calculated by subtracting the BL values from the Maintenance Period Week 4 values divided by BL values multiplied (×) the results with 100. LS means, 95% CIs and P-values were estimated from MMRM. 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: 4 mg/day	Treatment Group C: 8 mg/day	Treatment Group D: 12 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65[74]	21[75]	60[76]	61[77]
Units: Percentage of "off" time in hours				
least squares mean (confidence interval 95%)	-30.44 (-39.67 to -21.21)	-30.47 (-46.69 to -14.24)	-46.65 (-56.27 to -37.03)	-37.26 (-46.81 to -27.71)

Notes:

[74] - ITT Population

[75] - ITT Population

[76] - ITT Population

[77] - ITT Population

End point values	Treatment Group E: 16 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[78]	25[79]		
Units: Percentage of "off" time in hours				
least squares mean (confidence interval 95%)	-48.36 (-57.64 to -39.08)	-34.37 (-49.23 to -19.5)		

Notes:

[78] - ITT Population

[79] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

4 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group B: 4 mg/day
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.998 [80]
Method	Mixed models analysis

Notes:

[80] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
8 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group C: 8 mg/day
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.017 [81]
Method	Mixed models analysis

Notes:

[81] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
12 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group D: 12 mg/day
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.312 [82]
Method	Mixed models analysis

Notes:

[82] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 4
Statistical analysis description:	
16 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group E: 16 mg/day
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.008 [83]
Method	Mixed models analysis

Notes:

[83] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 5
Statistical analysis description:	
24 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day

Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.659 [84]
Method	Mixed models analysis

Notes:

[84] - Mixed Model Repeated Measures

Secondary: Percent change from Baseline in awake time spent "on" without TD at Week 4 of the Maintenance Period

End point title	Percent change from Baseline in awake time spent "on" without TD at Week 4 of the Maintenance Period

End point description:

Dyskinesias are involuntary twisting, turning movements caused by medication during "on" time in PD. TD is defined as those movements that interfere with function and cause meaningful discomfort. Par. were asked to record awake time "off", awake time "on", TD during awake time "on", or time asleep for all 30 minute time intervals in 24 hour diary cards for the 2 days preceding each visit of the study. The total number of awake hours spent "on" without TD per 24-hour period was the average across the 2 diary cards of the sum of awake hours spent "on" without TD in each 24-hour diary card. The percent change from BL was calculated by subtracting the BL values from the Maintenance Period Week 4 values divided by BL values × 100. LS means, 95% CIs and P-values were estimated from MMRM. 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: 4 mg/day	Treatment Group C: 8 mg/day	Treatment Group D: 12 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65[85]	21[86]	60[87]	61[88]
Units: Percentage of "on" time in hours				
least squares mean (confidence interval 95%)	24.55 (15.05 to 34.04)	15.2 (-1.37 to 31.78)	35.2 (25.38 to 45.02)	32.02 (22.2 to 41.84)

Notes:

[85] - ITT Population

[86] - ITT Population

[87] - ITT Population

[88] - ITT Population

End point values	Treatment Group E: 16 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[89]	25[90]		
Units: Percentage of "on" time in hours				
least squares mean (confidence interval 95%)	34.45 (24.94 to 43.97)	29.58 (14.39 to 44.76)		

Notes:

[89] - ITT Population

[90] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
4 mg/day vs Placebo	
Comparison groups	Treatment Group B: 4 mg/day v Treatment Group A: Placebo
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.337 [91]
Method	Mixed models analysis
Notes:	
[91] - Mixed Model Repeated Measures	

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
8 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group C: 8 mg/day
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.126 [92]
Method	Mixed models analysis
Notes:	
[92] - Mixed Model Repeated Measures	

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
12 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group D: 12 mg/day
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.283 [93]
Method	Mixed models analysis
Notes:	
[93] - Mixed Model Repeated Measures	

Statistical analysis title	Statistical analysis 4
Statistical analysis description:	
16 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group E: 16 mg/day
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.148 [94]
Method	Mixed models analysis
Notes:	
[94] - Mixed Model Repeated Measures	

Statistical analysis title	Statistical analysis 5

Statistical analysis description:	
24 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.581 [95]
Method	Mixed models analysis

Notes:

[95] - Mixed Model Repeated Measures

Secondary: Percent change from Baseline in awake time spent "on" at Week 4 of the Maintenance Period

End point title	Percent change from Baseline in awake time spent "on" at Week 4 of the Maintenance Period

End point description:

Par. were asked to recordawake time "off", awake time "on", TD during awake time "on", or time asleep for all 30 minute time intervals in 24 hour diary cards for the 2 days preceding each visit of the study. The total number of awake hours spent "on" per 24-hour period was the average across the 2 diary cards of the sum of awake hours spent "on" in each 24-hour diary card. The percent change from BL was calculated by subtracting the BL values from the Maintenance Period Week 4 values divided by BL values × 100. LS means, 95% CIs and P-values were estimated from MMRM. 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: 4 mg/day	Treatment Group C: 8 mg/day	Treatment Group D: 12 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65[96]	21[97]	60[98]	61[99]
Units: Percentage of "on" time in hours				
least squares mean (confidence interval 95%)	21.31 (12.53 to 30.09)	15.05 (-0.28 to 30.38)	35.68 (26.6 to 44.77)	31.28 (22.19 to 40.36)

Notes:

[96] - ITT Population

[97] - ITT Population

[98] - ITT Population

[99] - ITT Population

End point values	Treatment Group E: 16 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[100]	25[101]		
Units: Percentage of "on" time in hours				
least squares mean (confidence interval 95%)	32.34 (23.6 to 41.08)	32.43 (18.39 to 46.48)		

Notes:

[100] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
4 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group B: 4 mg/day
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.486 [102]
Method	Mixed models analysis

Notes:

[102] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
8 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group C: 8 mg/day
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.026 [103]
Method	Mixed models analysis

Notes:

[103] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
12 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group D: 12 mg/day
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.121 [104]
Method	Mixed models analysis

Notes:

[104] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 4
Statistical analysis description:	
16 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group E: 16 mg/day

Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.081 [105]
Method	Mixed models analysis

Notes:

[105] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

24 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.187 [106]
Method	Mixed models analysis

Notes:

[106] - Mixed Model Repeated Measures

Secondary: Percent change from Baseline in total sleep time during the night time hours of sleep, at Week 4 of the Maintenance Period

End point title	Percent change from Baseline in total sleep time during the night time hours of sleep, at Week 4 of the Maintenance Period

End point description:

Par. were asked to record awake time "off", awake time "on", TD during awake time "on", or time asleep for all 30 minute time intervals in 24 hour diary cards for the 2 days preceding each visit of the study. The total sleep hours during the night time hours of sleep was the average across the 2 diary cards of the sum of time (hours) asleep during night time in each 24-hour diary card. BL is defined as the last non-missing assessment measured on or before the first dose date. The percent change from BL was calculated by subtracting the BL values from the Maintenance Period Week 4 values divided by BL value × 100. LS means, 95% CIs and P-values were estimated from MMRM. 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: 4 mg/day	Treatment Group C: 8 mg/day	Treatment Group D: 12 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65[107]	21[108]	60[109]	61[110]
Units: Percentage of total sleep time in hours				
least squares mean (confidence interval 95%)	3.99 (-0.42 to 8.39)	10.79 (3.04 to 18.54)	4.94 (0.34 to 9.54)	3.41 (-1.15 to 7.98)

Notes:

[107] - ITT Population

[108] - ITT Population

[109] - ITT Population

End point values	Treatment Group E: 16 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[111]	25[112]		
Units: Percentage of total sleep time in hours				
least squares mean (confidence interval 95%)	3.6 (-0.83 to 8.03)	0.91 (-6.19 to 8.01)		

Notes:

[111] - ITT Population

[112] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
4 mg/day vs Placebo	
Comparison groups	Treatment Group B: 4 mg/day v Treatment Group A: Placebo
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.134 [113]
Method	Mixed models analysis

Notes:

[113] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
8 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group C: 8 mg/day
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.768 [114]
Method	Mixed models analysis

Notes:

[114] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
12 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group D: 12 mg/day

Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.859 [115]
Method	Mixed models analysis

Notes:

[115] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

16 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group E: 16 mg/day
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.903 [116]
Method	Mixed models analysis

Notes:

[116] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

24 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.47 [117]
Method	Mixed models analysis

Notes:

[117] - Mixed Model Repeated Measures

Secondary: Change from Baseline in the percent awake time spent "off" at Week 4 of the Maintenance Period

End point title	Change from Baseline in the percent awake time spent "off" at Week 4 of the Maintenance Period

End point description:

The "off" state is defined as the state in which the participants' symptoms include lack of mobility(bradykinesia), with or without additional features such as tremor or rigidity. Par were asked to record awake time "off", awake time "on", TD during awake time "on", or time asleep for all 30 minute time intervals in 24 hour diary cards for the 2 days preceding each visit of the study. The total number of awake hours spent "off" per 24-hour period was the average across the 2 diary cards of the sum of awake hours spent "off" in each 24-hour diary card. The percentage of awake time spent "off"= Awake time spent "off" divided by (Awake time spent "off" + Awake time spent "on") × 100. BL is defined as the last non-missing assessment measured on or before the first dose date. The change from BL was calculated by subtracting the BL values from the MP Week 4 values. LS means, 95% CIs and P-values were estimated from MMRM. Par with a non-missing efficacy observation at BL and MP were analyzed

End point type	Secondary

End point timeframe:

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

End point values	Treatment Group A: Placebo	Treatment Group B: 4 mg/day	Treatment Group C: 8 mg/day	Treatment Group D: 12 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65[118]	21[119]	60[120]	61[121]
Units: Percentage of "off" time in hours				
least squares mean (confidence interval 95%)	-12.43 (-16.03 to -8.84)	-11.6 (-17.93 to -5.27)	-18.41 (-22.16 to -14.66)	-15.36 (-19.08 to -11.64)

Notes:

[118] - ITT Population

[119] - ITT Population

[120] - ITT Population

[121] - ITT Population

End point values	Treatment Group E: 16 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[122]	25[123]		
Units: Percentage of "off" time in hours				
least squares mean (confidence interval 95%)	-17.81 (-21.43 to -14.2)	-15.01 (-20.81 to -9.22)		

Notes:

[122] - ITT Population

[123] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
4 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group B: 4 mg/day
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.822 [124]
Method	Mixed models analysis

Notes:

[124] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
8 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group C: 8 mg/day

Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.025 [125]
Method	Mixed models analysis

Notes:

[125] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

12 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group D: 12 mg/day
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.267 [126]
Method	Mixed models analysis

Notes:

[126] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

16 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group E: 16 mg/day
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.039 [127]
Method	Mixed models analysis

Notes:

[127] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

24 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.458 [128]
Method	Mixed models analysis

Notes:

[128] - Mixed Model Repeated Measures

Secondary: Change from Baseline in the percent awake time spent "on" in hours (hr) without TD at Week 4 of the Maintenance Period

End point title	Change from Baseline in the percent awake time spent "on" in hours (hr) without TD at Week 4 of the Maintenance Period

End point description:

Dyskinesias are involuntary twisting, turning movements caused by medication during "on" time in PD. TD is defined as those movements that interfere with function and cause meaningful discomfort. Par were asked to record awake time "off", awake time "on", TD during awake time "on", or time asleep for all 30 minute time intervals in 24 hr diary cards for the 2 days preceding each visit of the study. The total number of awake hr spent "on" without TD per 24-hr period was the average across the 2 diary cards of the sum of awake hr spent "on" without TD in each 24-hr diary card. Percentage of awake time spent "on"without TD= Awake time spent "on" without TD divided by(Awake time spent "on" + Awake time spent "off") × 100. BL is defined as the last non-missing assessment measured on or before the first dose date, change from BL was calculated by subtracting BL values from MP Week 4 values. LS means, 95% CIs and P-values were estimated from MMRM.

End point type	Secondary

End point timeframe:

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

End point values	Treatment Group A: Placebo	Treatment Group B: 4 mg/day	Treatment Group C: 8 mg/day	Treatment Group D: 12 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65[129]	21[130]	60[131]	61[132]
Units: Percentage of "on" time in hours				
least squares mean (confidence interval 95%)	12.89 (9.15 to 16.62)	11.58 (5.01 to 18.15)	18.34 (14.44 to 22.24)	14.99 (11.12 to 18.85)

Notes:

[129] - ITT Population, Par with non-missing efficacy observation at BL and during the MP were analyzed.

[130] - ITT Population, Par with non-missing efficacy observation at BL and during the MP were analyzed.

[131] - ITT Population, Par with non-missing efficacy observation at BL and during the MP were analyzed.

[132] - ITT Population, Par with non-missing efficacy observation at BL and during the MP were analyzed.

End point values	Treatment Group E: 16 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[133]	25[134]		
Units: Percentage of "on" time in hours				
least squares mean (confidence interval 95%)	17.05 (13.3 to 20.8)	14.56 (8.54 to 20.59)		

Notes:

[133] - ITT Population, Par with non-missing efficacy observation at BL and during the MP were analyzed.

[134] - ITT Population, Par with non-missing efficacy observation at BL and during the MP were analyzed.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

4 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group B: 4 mg/day

Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.734 [135]
Method	Mixed models analysis

Notes:

[135] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

8 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group C: 8 mg/day
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.048 [136]
Method	Mixed models analysis

Notes:

[136] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

12 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group D: 12 mg/day
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.443 [137]
Method	Mixed models analysis

Notes:

[137] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

16 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group E: 16 mg/day
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.123 [138]
Method	Mixed models analysis

Notes:

[138] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

24 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day

Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.641 [139]
Method	Mixed models analysis

Notes:

[139] - Mixed Model Repeated Measures

Secondary: Change from Baseline in the percent awake time spent "on" at Week 4 of the Maintenance Period

End point title	Change from Baseline in the percent awake time spent "on" at Week 4 of the Maintenance Period

End point description:

Par. were asked to record awake time "off", awake time "on", TD during awake time "on", or time asleep for all 30 minute time intervals in 24 hour diary cards for the 2 days preceding each visit of the study. The total number of awake hours spent "on" per 24-hour period was the average across the 2 diary cards of the sum of awake hours spent "on" in each 24-hour diary card. The percentage of awake time spent "on"= Awake time spent "on" divided by (Awake time spent "on" + Awake time spent "off") × 100. BL is defined as the last non-missing assessment measured on or before the first dose date. The change from BL was calculated by subtracting the BL values from the Maintenance Period Week 4 values. LS means, 95% CIs and P-values were estimated from MMRM. 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: 4 mg/day	Treatment Group C: 8 mg/day	Treatment Group D: 12 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65[140]	21[141]	60[142]	61[143]
Units: Percentage of "on" time in hours				
least squares mean (confidence interval 95%)	12.43 (8.84 to 16.03)	11.6 (5.27 to 17.93)	18.41 (14.66 to 22.16)	15.36 (11.64 to 19.08)

Notes:

[140] - ITT Population.

[141] - ITT Population.

[142] - ITT Population.

[143] - ITT Population.

End point values	Treatment Group E: 16 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[144]	25[145]		
Units: Percentage of "on" time in hours				
least squares mean (confidence interval 95%)	17.81 (14.2 to 21.43)	15.01 (9.22 to 20.81)		

Notes:

[144] - ITT Population.

[145] - ITT Population.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
4 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group B: 4 mg/day
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.822 [146]
Method	Mixed models analysis

Notes:

[146] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
8 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group C: 8 mg/day
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.025 [147]
Method	Mixed models analysis

Notes:

[147] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
12 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group D: 12 mg/day
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.267 [148]
Method	Mixed models analysis

Notes:

[148] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 4
Statistical analysis description:	
16 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group E: 16 mg/day
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.039 [149]
Method	Mixed models analysis

Notes:

[149] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 5

Statistical analysis description:	
24 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.458 [150]
Method	Mixed models analysis

Notes:

[150] - Mixed Model Repeated Measures

Secondary: Change from Baseline in the percent of a 24-hour day spent "off" at Week 4 of the Maintenance Period

End point title	Change from Baseline in the percent of a 24-hour day spent "off" at Week 4 of the Maintenance Period

End point description:

The "off" state is defined as the state in which the participants' symptoms include lack of mobility (bradykinesia), with or without additional features such as tremor or rigidity. Par were asked to record awake time "off", awake time "on", TD during awake time "on", or time asleep for all 30 minute time intervals in 24 hour diary cards for the 2 days preceding each visit of the study. The total number of day awake hours spent "off" per 24-hour period was the average across the 2 diary cards of the sum of awake hours spent "off" in each 24-hour diary card. The percentage of 24 hour day spent "off"= awake time spent "off" divided by 24 x 100. BL is defined as the last non-missing assessment measured on or before the first dose date. The change from BL was calculated by subtracting the BL values from the MP Week 4 values. LS means, 95% CIs and P-values were estimated from MMRM. Par with a non-missing efficacy observation at BL and during the MP were analyzed.

End point type	Secondary

End point timeframe:

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

End point values	Treatment Group A: Placebo	Treatment Group B: 4 mg/day	Treatment Group C: 8 mg/day	Treatment Group D: 12 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65[151]	21[152]	60[153]	61[154]
Units: Percentage of "off" time in hours				
least squares mean (confidence interval 95%)	-7.94 (-10.26 to -5.62)	-8.5 (-12.57 to -4.43)	-12.17 (-14.59 to -9.76)	-9.75 (-12.14 to -7.35)

Notes:

[151] - ITT Population

[152] - ITT Population

[153] - ITT Population

[154] - ITT Population

End point values	Treatment Group E: 16 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[155]	25[156]		
Units: Percentage of "off" time in hours				
least squares mean (confidence interval 95%)	-11.65 (-13.98 to -9.32)	-9.86 (-13.59 to -6.13)		

Notes:

[155] - ITT Population

[156] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
4 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group B: 4 mg/day
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.814 [157]
Method	Mixed models analysis

Notes:

[157] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
8 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group C: 8 mg/day
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.013 [158]
Method	Mixed models analysis

Notes:

[158] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
12 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group D: 12 mg/day
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.287 [159]
Method	Mixed models analysis

Notes:

[159] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 4
Statistical analysis description:	
16 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group E: 16 mg/day

Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.027 [160]
Method	Mixed models analysis

Notes:

[160] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

24 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.39 [161]
Method	Mixed models analysis

Notes:

[161] - Mixed Model Repeated Measures

Secondary: Change from Baseline in the percent of a 24- hour (hr) day spent "on" without TD at Week 4 of the Maintenance Period

End point title	Change from Baseline in the percent of a 24- hour (hr) day spent "on" without TD at Week 4 of the Maintenance Period

End point description:

Dyskinesias are involuntary twisting, turning movements caused by medication during "on" time in PD. TD is defined as those movements that interfere with function and cause meaningful discomfort. Par were asked to record awake time "off", awake time "on", TD during awake time "on", or time asleep for all 30 minute time intervals in 24 hr diary cards for the 2 days preceding each visit. The total number of day awake hr spent "on" without TD per 24-hr period was the average across the 2 diary cards of the sum of awake hours spent "on" without TD in each 24-hour diary card. The percentage of 24 hr day spent "on" without TD= awake time spent "on" without TD divided by 24 × 100. BL is defined as the last non-missing assessment measured on or before the first dose date, change from BL was calculated by subtracting the BL values from the MP Week 4 values. LS means, 95% CIs and P-values were estimated from MMRM. Par with non-missing efficacy observation at BL and during the MP were analyzed.

End point type	Secondary

End point timeframe:

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

End point values	Treatment Group A: Placebo	Treatment Group B: 4 mg/day	Treatment Group C: 8 mg/day	Treatment Group D: 12 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65[162]	21[163]	60[164]	61[165]
Units: Percentage of "on" time in hours				
least squares mean (confidence interval 95%)	7.32 (4.81 to 9.83)	5.03 (0.62 to 9.44)	11.19 (8.57 to 13.81)	8.99 (6.4 to 11.59)

Notes:

[162] - ITT Population

[163] - ITT Population

End point values	Treatment Group E: 16 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[166]	25[167]		
Units: Percentage of "on" time in hours				
least squares mean (confidence interval 95%)	10.4 (7.88 to 12.91)	9.34 (5.3 to 13.38)		

Notes:

[166] - ITT Population

[167] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
4 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group B: 4 mg/day
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.376 [168]
Method	Mixed models analysis

Notes:

[168] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
8 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group C: 8 mg/day
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.036 [169]
Method	Mixed models analysis

Notes:

[169] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
12 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group D: 12 mg/day

Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.362 [170]
Method	Mixed models analysis

Notes:

[170] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

16 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group E: 16 mg/day
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.089 [171]
Method	Mixed models analysis

Notes:

[171] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

24 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.403 [172]
Method	Mixed models analysis

Notes:

[172] - Mixed Model Repeated Measures

Secondary: Change from Baseline in the percent of a 24-hour day spent "on" at Week 4 of the Maintenance Period

End point title	Change from Baseline in the percent of a 24-hour day spent "on" at Week 4 of the Maintenance Period

End point description:

Par. were asked to record awake time "off", awake time "on", TD during awake time "on", or time asleep for all 30 minute time intervals in 24 hour diary cards for the 2 days preceding each visit of the study. The total number of day awake hours spent "on" per 24-hour period was the average across the 2 diary cards of the sum of awake hours spent "on" in each 24-hour diary card. The percentage of a 24-hour day spent "on" = Awake time spent "on" divided by 24 × 100. BL is defined as the last non-missing assessment measured on or before the first dose date. The change from BL was calculated by subtracting the BL values from the Maintenance Period Week 4 values. LS means, 95% CIs and P-values were estimated from MMRM. 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: 4 mg/day	Treatment Group C: 8 mg/day	Treatment Group D: 12 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65[173]	21[174]	60[175]	61[176]
Units: Percentage of "on" time in hours				
least squares mean (confidence interval 95%)	7.08 (4.57 to 9.58)	4.99 (0.59 to 9.39)	11.2 (8.59 to 13.81)	9.28 (6.69 to 11.87)

Notes:

[173] - ITT Population

[174] - ITT Population

[175] - ITT Population

[176] - ITT Population

End point values	Treatment Group E: 16 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[177]	25[178]		
Units: Percentage of "on" time in hours				
least squares mean (confidence interval 95%)	10.94 (8.42 to 13.45)	9.76 (5.73 to 13.8)		

Notes:

[177] - ITT Population

[178] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
4 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group B: 4 mg/day
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.419 [179]
Method	Mixed models analysis

Notes:

[179] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
8 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group C: 8 mg/day
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.026 [180]
Method	Mixed models analysis

Notes:

[180] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

12 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group D: 12 mg/day
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.23 [181]
Method	Mixed models analysis

Notes:

[181] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

16 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group E: 16 mg/day
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.033 [182]
Method	Mixed models analysis

Notes:

[182] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

24 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.266 [183]
Method	Mixed models analysis

Notes:

[183] - Mixed Model Repeated Measures

Secondary: Change from Baseline in total sleep time during the night time hours of sleep as a percentage of a 24-hour day, at Week 4 of the Maintenance Period

End point title	Change from Baseline in total sleep time during the night time hours of sleep as a percentage of a 24-hour day, at Week 4 of the Maintenance Period

End point description:

Par were asked to record awake time "off", awake time "on", TD during awake time "on", or time asleep for all 30 minute time intervals in 24 hour diary cards for the 2 days preceding each visit of the study. The total sleep hours during the night time hours of sleep was the average across the 2 diary cards of the sum of time (hours) asleep during night time in each 24-hour diary card. The percentage of a 24-hour day spent asleep during the night time hours = Total sleep hours during the night time hours of sleep divided by 24 × 100. BL is defined as the last non-missing assessment measured on or before the first dose date. The change from BL was calculated by subtracting the BL values from the Maintenance Period Week 4 values. LS means, 95% CIs and P-values were estimated from MMRM. 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: 4 mg/day	Treatment Group C: 8 mg/day	Treatment Group D: 12 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65[184]	21[185]	60[186]	61[187]
Units: Percentage of time in hours				
least squares mean (confidence interval 95%)	0.91 (-0.53 to 2.35)	3.57 (1.04 to 6.1)	0.92 (-0.59 to 2.42)	0.63 (-0.86 to 2.12)

Notes:

[184] - ITT Population

[185] - ITT Population

[186] - ITT Population

[187] - ITT Population

End point values	Treatment Group E: 16 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[188]	25[189]		
Units: Percentage of time in hours				
least squares mean (confidence interval 95%)	0.58 (-0.87 to 2.02)	0.18 (-2.14 to 2.5)		

Notes:

[188] - ITT Population

[189] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
4 mg/day vs Placebo	
Comparison groups	Treatment Group B: 4 mg/day v Treatment Group A: Placebo
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.073 [190]
Method	Mixed models analysis

Notes:

[190] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
8 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group C: 8 mg/day

Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.996 [191]
Method	Mixed models analysis

Notes:

[191] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

12 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group D: 12 mg/day
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.791 [192]
Method	Mixed models analysis

Notes:

[192] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

16 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group E: 16 mg/day
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.747 [193]
Method	Mixed models analysis

Notes:

[193] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

24 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6 [194]
Method	Mixed models analysis

Notes:

[194] - Mixed Model Repeated Measures

Secondary: Change from Baseline in Unified Parkinson Disease Rating Scale (UPDRS) motor score with participants in an "on" state, at Week 4 of the Maintenance Period

End point title	Change from Baseline in Unified Parkinson Disease Rating Scale (UPDRS) motor score with participants in an "on" state, at Week 4 of the Maintenance Period

End point description:

The UPDRS is a clinician based rating scale used to measure motor impairments and disability. The UPDRS assesses six features of PD impairment. These are evaluated using a combination of data collected by interview and examination of the par.. One of the six features include the Part III-motor examination where scores can range 0 to 108 with par. in an "on" state where the maximum score indicates the worse condition. BL is defined as the last non-missing assessment measured on or before the first dose date. The change from BL was calculated by subtracting the BL values from the Maintenance Period Week 4 values. LS means, 95% CIs and P-values were estimated from MMRM. 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: 4 mg/day	Treatment Group C: 8 mg/day	Treatment Group D: 12 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	64[195]	21[196]	59[197]	60[198]
Units: Score on scale				
least squares mean (confidence interval 95%)	-4.75 (-6.78 to -2.72)	-10.38 (-13.94 to -6.82)	-8.43 (-10.54 to -6.32)	-8.34 (-10.43 to -6.24)

Notes:

[195] - ITT Population

[196] - ITT Population

[197] - ITT Population

[198] - ITT Population

End point values	Treatment Group E: 16 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[199]	24[200]		
Units: Score on scale				
least squares mean (confidence interval 95%)	-8.86 (-10.88 to -6.85)	-10.06 (-13.37 to -6.75)		

Notes:

[199] - ITT Population

[200] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

4 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group B: 4 mg/day
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.007 [201]
Method	Mixed models analysis

Notes:

[201] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
8 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group C: 8 mg/day
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.014 [202]
Method	Mixed models analysis

Notes:

[202] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
12 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group D: 12 mg/day
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.016 [203]
Method	Mixed models analysis

Notes:

[203] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 4
Statistical analysis description:	
16 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group E: 16 mg/day
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.005 [204]
Method	Mixed models analysis

Notes:

[204] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 5
Statistical analysis description:	
24 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day

Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.008 [205]
Method	Mixed models analysis

Notes:

[205] - Mixed Model Repeated Measures

Secondary: Change from Baseline in UPDRS Activities of Daily Living (ADL) score with participants in an "on" state, at Week 4 of the Maintenance Period

End point title	Change from Baseline in UPDRS Activities of Daily Living (ADL) score with participants in an "on" state, at Week 4 of the Maintenance Period

End point description:

The UPDRS Part II is the ADL score and can range from 0 to 52 as determined by the physician. The higher score indicates the worse condition. Test were performed when the par. is in the "on" state of PD. BL is defined as the last non-missing assessment measured on or before the first dose date. The change from BL was calculated by subtracting the BL values from the Maintenance Period Week 4 values. LS means, 95% CIs and P-values were estimated from MMRM. 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: 4 mg/day	Treatment Group C: 8 mg/day	Treatment Group D: 12 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65[206]	20[207]	60[208]	58[209]
Units: Score on scale				
least squares mean (confidence interval 95%)	-1.32 (-2.17 to -0.47)	-3.08 (-4.61 to -1.56)	-3.06 (-3.94 to -2.18)	-2.18 (-3.07 to -1.28)

Notes:

[206] - ITT Population

[207] - ITT Population

[208] - ITT Population

[209] - ITT Population

End point values	Treatment Group E: 16 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63[210]	24[211]		
Units: Score on scale				
least squares mean (confidence interval 95%)	-2.63 (-3.49 to -1.77)	-3.04 (-4.43 to -1.65)		

Notes:

[210] - ITT Population

[211] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
4 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group B: 4 mg/day
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.047 [212]
Method	Mixed models analysis
Notes:	

[212] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
8 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group C: 8 mg/day
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.005 [213]
Method	Mixed models analysis
Notes:	

[213] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
12 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group D: 12 mg/day
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.172 [214]
Method	Mixed models analysis
Notes:	

[214] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 4
Statistical analysis description:	
16 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group E: 16 mg/day
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.034 [215]
Method	Mixed models analysis
Notes:	

[215] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 5

Statistical analysis description:	
24 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.039 [216]
Method	Mixed models analysis

Notes:

[216] - Mixed Model Repeated Measures

Secondary: Change from Baseline in UPDRS ADL score with participants in an "off" state, at Week 4 of the Maintenance Period

End point title	Change from Baseline in UPDRS ADL score with participants in an "off" state, at Week 4 of the Maintenance Period

End point description:

The UPDRS Part II is the ADL score and can range from 0 to 52 as determined by the physician. The higher score indicates the worse condition. Test was performed when the par is in the "off" state of PD. The "off" time is defined as the state in which the participants' symptoms include lack of mobility (bradykinesia) with or without additional features such as tremor or rigidity. BL is defined as the last non-missing assessment measured on or before the first dose date. The change from BL was calculated by subtracting the BL values from the Maintenance Period Week 4 values. LS means, 95% CIs and P-values were estimated from MMRM. 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: 4 mg/day	Treatment Group C: 8 mg/day	Treatment Group D: 12 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62[217]	15[218]	52[219]	50[220]
Units: Score on scale				
least squares mean (confidence interval 95%)	-2.94 (-4.23 to -1.65)	-4.5 (-7.12 to -1.88)	-4.72 (-6.13 to -3.31)	-4.29 (-5.74 to -2.84)

Notes:

[217] - ITT Population.

[218] - ITT Population.

[219] - ITT Population.

[220] - ITT Population.

End point values	Treatment Group E: 16 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57[221]	22[222]		
Units: Score on scale				
least squares mean (confidence interval 95%)	-5.76 (-7.11 to -4.41)	-4.77 (-6.94 to -2.61)		

Notes:

[221] - ITT Population.

[222] - ITT Population.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
4 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group B: 4 mg/day
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.292 [223]
Method	Mixed models analysis

Notes:

[223] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
8 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group C: 8 mg/day
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.068 [224]
Method	Mixed models analysis

Notes:

[224] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
12 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group D: 12 mg/day
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.17 [225]
Method	Mixed models analysis

Notes:

[225] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 4
Statistical analysis description:	
16 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group E: 16 mg/day

Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.003 [226]
Method	Mixed models analysis

Notes:

[226] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

24 mg/day vs Placebo

Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.153 [227]
Method	Mixed models analysis

Notes:

[227] - Mixed Model Repeated Measures

Secondary: Change from Baseline in UPDRS Part I at Week 4 of the Maintenance Period

End point title	Change from Baseline in UPDRS Part I at Week 4 of the Maintenance Period

End point description:

The UPDRS Part I scores mentation, behavior and mood as determined by a physician and par. were tested during the "on" phase of PD. This component of the UPDRS is the total score for 4 items (the items 1 to 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. The higher score (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 would also be missing. BL is defined as the last non-missing assessment measured on or before the first dose date. The change from BL was calculated by subtracting the BL values from the individual post-randomization values. LS means, 95% CIs and P-values were estimated from MMRM.   Participants with a non-missing efficacy observation at Baseline and during the maintenance period were analyzed.

End point type	Secondary

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: 4 mg/day	Treatment Group C: 8 mg/day	Treatment Group D: 12 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65[228]	21[229]	60[230]	61[231]
Units: Score on scale				
least squares mean (confidence interval 95%)	-0.24 (-0.47 to -0.01)	-0.44 (-0.84 to -0.03)	-0.33 (-0.57 to -0.09)	-0.24 (-0.48 to 0)

Notes:

[228] - ITT Population.

[229] - ITT Population.

[230] - ITT Population.

[231] - ITT Population.

End point values	Treatment Group E: 16 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[232]	25[233]		
Units: Score on scale				
least squares mean (confidence interval 95%)	-0.47 (-0.7 to -0.24)	-0.45 (-0.82 to -0.08)		

Notes:

[232] - ITT Population.

[233] - ITT Population.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
4 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group B: 4 mg/day
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.409 [234]
Method	Mixed models analysis

Notes:

[234] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
8 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group C: 8 mg/day
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.598 [235]
Method	Mixed models analysis

Notes:

[235] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
12 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group D: 12 mg/day

Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.992 [236]
Method	Mixed models analysis

Notes:

[236] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 4
Statistical analysis description:	
16 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group E: 16 mg/day
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.169 [237]
Method	Mixed models analysis

Notes:

[237] - Mixed Model Repeated Measures

Statistical analysis title	Statistical analysis 5
Statistical analysis description:	
24 mg/day vs Placebo	
Comparison groups	Treatment Group A: Placebo v Treatment Group F: 24 mg/day
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.348 [238]
Method	Mixed models analysis

Notes:

[238] - Mixed Model Repeated Measures

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

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 at least one post-Baseline efficacy assessment at any time during the study were analyzed.

End point type	Secondary

End point timeframe:

From start of study treatment until end of treatment (assessed up to 18 weeks)

End point values	Treatment Group A: Placebo	Treatment Group B: 4 mg/day	Treatment Group C: 8 mg/day	Treatment Group D: 12 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	74[239]	25[240]	76[241]	73[242]
Units: Percentage of participants	0	0	0	0

Notes:

[239] - ITT Population

[240] - ITT Population

[241] - ITT Population

[242] - ITT Population

End point values	Treatment Group E: 16 mg/day	Treatment Group F: 24 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76[243]	25[244]		
Units: Percentage of participants	3	0		

Notes:

[243] - ITT Population

[244] - ITT Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

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 (up to 33 Weeks)

Adverse event reporting additional description:

On-treatment SAEs and non-serious AEs were reported for the Safety Population, comprised all participants exposed to at least one dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Treatment Group A: Placebo

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: 4 mg/day

Reporting group description:

Par were administered a ropinirole PR tablet totalling 2 milligrams per day (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 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: 8 mg/day

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 switched to ropinirole PR 6.0 mg/day for 4 days then 4.0 mg/day 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: 12 mg/day

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 switched to ropinirole PR 8.0 mg/day for 4 days then 4.0 mg/day 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 E: 16 mg/day

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 and 16 mg/day at Week 8. Par continued this dose up to study Week 17. Par. reaching their target dose and completing the Maintenance Period or withdrawing prematurely were switched to ropinirole PR 12.0 mg/day for 4 days then 6.0 mg/day 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 F: 24 mg/day

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 switched to ropinirole PR 16.0 mg/day for 4 days then 8.0 mg/day for 3 days for down-titration before completing a follow-up visit 2 weeks after receiving the last dose of study medication.

Serious adverse events	Treatment Group A: Placebo	Treatment Group B: 4 mg/day	Treatment Group C: 8 mg/day
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 75 (0.00%)	0 / 25 (0.00%)	3 / 76 (3.95%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	0 / 75 (0.00%)	0 / 25 (0.00%)	0 / 76 (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			
Hernia			
subjects affected / exposed	0 / 75 (0.00%)	0 / 25 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Rectal haemorrhage			
subjects affected / exposed	0 / 75 (0.00%)	0 / 25 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Impulsive behaviour			
subjects affected / exposed	0 / 75 (0.00%)	0 / 25 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Treatment Group D: 12 mg/day	Treatment Group E: 16 mg/day	Treatment Group F: 24 mg/day
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 75 (0.00%)	1 / 76 (1.32%)	0 / 25 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			

subjects affected / exposed	0 / 75 (0.00%)	1 / 76 (1.32%)	0 / 25 (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
General disorders and administration site conditions			
Hernia			
subjects affected / exposed	0 / 75 (0.00%)	0 / 76 (0.00%)	0 / 25 (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
Gastrointestinal disorders			
Rectal haemorrhage			
subjects affected / exposed	0 / 75 (0.00%)	0 / 76 (0.00%)	0 / 25 (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
Psychiatric disorders			
Impulsive behaviour			
subjects affected / exposed	0 / 75 (0.00%)	0 / 76 (0.00%)	0 / 25 (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: 5 %

Non-serious adverse events	Treatment Group A: Placebo	Treatment Group B: 4 mg/day	Treatment Group C: 8 mg/day
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 75 (45.33%)	12 / 25 (48.00%)	38 / 76 (50.00%)
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	4 / 75 (5.33%)	0 / 25 (0.00%)	1 / 76 (1.32%)
occurrences (all)	6	0	2
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 75 (1.33%)	2 / 25 (8.00%)	1 / 76 (1.32%)
occurrences (all)	1	2	1
Nervous system disorders			
Dizziness			

subjects affected / exposed	2 / 75 (2.67%)	2 / 25 (8.00%)	3 / 76 (3.95%)
occurrences (all)	3	3	3
Dyskinesia			
subjects affected / exposed	1 / 75 (1.33%)	1 / 25 (4.00%)	3 / 76 (3.95%)
occurrences (all)	1	1	3
Headache			
subjects affected / exposed	4 / 75 (5.33%)	0 / 25 (0.00%)	2 / 76 (2.63%)
occurrences (all)	4	0	2
Somnolence			
subjects affected / exposed	4 / 75 (5.33%)	1 / 25 (4.00%)	4 / 76 (5.26%)
occurrences (all)	4	1	4
Sudden onset of sleep			
subjects affected / exposed	2 / 75 (2.67%)	2 / 25 (8.00%)	4 / 76 (5.26%)
occurrences (all)	2	2	4
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	4 / 75 (5.33%)	0 / 25 (0.00%)	0 / 76 (0.00%)
occurrences (all)	4	0	0
Nausea			
subjects affected / exposed	8 / 75 (10.67%)	1 / 25 (4.00%)	5 / 76 (6.58%)
occurrences (all)	8	1	5
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 75 (0.00%)	0 / 25 (0.00%)	0 / 76 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 75 (0.00%)	0 / 25 (0.00%)	2 / 76 (2.63%)
occurrences (all)	0	0	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 25 (0.00%)	2 / 76 (2.63%)
occurrences (all)	1	0	2

Non-serious adverse events	Treatment Group D: 12 mg/day	Treatment Group E: 16 mg/day	Treatment Group F: 24 mg/day
Total subjects affected by non-serious adverse events			

subjects affected / exposed	40 / 75 (53.33%)	43 / 76 (56.58%)	12 / 25 (48.00%)

Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 75 (4.00%)	2 / 76 (2.63%)	0 / 25 (0.00%)
occurrences (all)	3	2	0

Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 75 (1.33%)	3 / 76 (3.95%)	2 / 25 (8.00%)
occurrences (all)	1	3	2

Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 75 (8.00%)	4 / 76 (5.26%)	1 / 25 (4.00%)
occurrences (all)	6	5	2
Dyskinesia			
subjects affected / exposed	5 / 75 (6.67%)	8 / 76 (10.53%)	1 / 25 (4.00%)
occurrences (all)	5	11	1
Headache			
subjects affected / exposed	3 / 75 (4.00%)	4 / 76 (5.26%)	1 / 25 (4.00%)
occurrences (all)	3	7	1
Somnolence			
subjects affected / exposed	9 / 75 (12.00%)	8 / 76 (10.53%)	0 / 25 (0.00%)
occurrences (all)	10	8	0
Sudden onset of sleep			
subjects affected / exposed	3 / 75 (4.00%)	1 / 76 (1.32%)	0 / 25 (0.00%)
occurrences (all)	3	1	0

Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 75 (0.00%)	0 / 76 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	8 / 75 (10.67%)	7 / 76 (9.21%)	2 / 25 (8.00%)
occurrences (all)	11	9	5

Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 75 (1.33%)	4 / 76 (5.26%)	0 / 25 (0.00%)
occurrences (all)	1	4	0

Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 75 (0.00%)	2 / 76 (2.63%)	2 / 25 (8.00%)
occurrences (all)	0	2	2
Infections and infestations Nasopharyngitis			
subjects affected / exposed	2 / 75 (2.67%)	0 / 76 (0.00%)	2 / 25 (8.00%)
occurrences (all)	2	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 February 2012	Additions of apomorphine and Deep Brain Stimulation to the list of prohibited treatments, addition of urinalysis to the Time and Events table, and various administrative corrections.
24 July 2014	Added updates and clarifications to the Secondary Endpoints and Data Analysis Plan descriptions

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported