Clinical trial results:
A Multicenter, Multinational, Double-Blind, Placebo-Controlled, 3-Arm, Phase 4 Study To Evaluate The Efficacy Of Rotigotine On Parkinson's Disease-Associated Apathy, Motor Symptoms, And Mood

Summary

EudraCT number	2012-002840-26
Trial protocol	AT ES HU IT BG SI RO SK
Global end of trial date	04 March 2014

Results information

Result version number	v1 (current)
This version publication date	30 June 2016
First version publication date	25 June 2015

Trial information

Trial identification

Sponsor protocol code	PD0005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01782222
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB BIOSCIENCES GmbH
Sponsor organisation address	Alfred-Nobel-Str.10, Monheim, Germany, 40789
Public contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, 0049 2173 48 15 15, clinicaltrials@ucb.com
Scientific contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, 0049 2173 48 15 15, clinicaltrials@ucb.com

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	08 September 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to assess the effects of rotigotine over placebo on improvement of apathy and motor symptoms in subjects with early-stage and advanced-stage idiopathic Parkinson's disease.

Protection of trial subjects:

Close monitoring of subjects safety status, including checks of mental health e.g. by CSSR-S questionnaire.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	05 February 2013
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	Austria: 3
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Poland: 21
Country: Number of subjects enrolled	Slovakia: 30
Country: Number of subjects enrolled	United States: 66
Worldwide total number of subjects	122
EEA total number of subjects	56

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)	43
From 65 to 84 years	72
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

This study was planned to be conducted globally with 480 subjects (160 subjects per treatment group for the Full Analysis Set). Approx. 600 subjects
were planned for enrollment in order to obtain 504 subjects for randomization. Subjects were randomized in a 1:1:1 ratio to either Rotigotine low dose, Rotigotine high dose or Placebo.

Pre-assignment

Screening details:

The Participant Flow refers to the Randomized Set (RS). The RS included all subjects who were randomized.
The outcome of the Interim Analysis was to stop the study, i.e. no more subjects were enrolled into the study and all included subjects completed the study as planned.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo, matching transdermal patches
Duration: up to 21 weeks (including de-escalation)

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	Placebo
Other name	Placebo
Pharmaceutical forms	Transdermal patch
Routes of administration	Transdermal use

Dosage and administration details:

Matching Placebo to Rotigotine.

Arm title	Rotigotine, low dose

Arm description:

Rotigotine, transdermal patches, optimal dose, maximal 8 mg / 24 hours for patients with advanced Parkinson’s Disease and 6 mg / 24 hours for those with early Parkinson’s DiseaseRotigotine: Rotigotine, transdermal patches:10 cm^2 (2 mg / 24 hours); 20 cm^2 (4 mg / 24 hours); 30 cm^2 (6 mg / 24 hours);40 cm^2 (8 mg / 24 hours) Optimal dosage:The maximum Rotigotine dose allowed was 8 mg / 24 hours or 16 mg / 24 hours for patients with advanced Parkinson's Disease and 6 mg / 24 hours or 8 mg / 24 hours for those with early Parkinson's Disease Duration: up to 21 weeks (including de-escalation)

Arm type	Experimental
Investigational medicinal product name	Rotigotine
Investigational medicinal product code	Neupro
Other name	Neupro
Pharmaceutical forms	Transdermal patch
Routes of administration	Transdermal use

Dosage and administration details:

Rotigotine, transdermal patches:

10 cm^2 (2 mg / 24 hours); 20 cm^2 (4 mg / 24 hours); 30 cm^2 (6 mg / 24 hours); 40 cm^2 (8 mg / 24 hours)

The maximum Rotigotine dose allowed is 8 mg / 24 hours or 16 mg / 24 hours for patients with advanced Parkinson's Disease and 6 mg / 24 hours or 8 mg / 24 hours for those with early Parkinson's Disease Duration: up to 21 weeks (including de-escalation)

Other Name: (6S)-6-propyl-[2 (2 thienyl)ethyl]amino-5,6,7,8-tetrahydro-1-naphthalenol

Arm title	Rotigotine, high dose

Arm description:

Rotigotine, transdermal patches, maximal 16 mg / 24 hours for patients with advanced Parkinson's Disease and 8 mg / 24 hours for those with early Parkinson's DiseaseRotigotine: Rotigotine, transdermal patches:10 cm^2 (2 mg / 24 hours); 20 cm^2 (4 mg / 24 hours); 30 cm^2 (6 mg / 24 hours);40 cm^2 (8 mg / 24 hours) Optimal dosage:The maximum Rotigotine dose allowed was 8 mg / 24 hours or 16 mg / 24 hours for patients with advanced Parkinson's Disease and 6 mg / 24 hours or 8 mg / 24 hours for those with early Parkinson's Disease Duration: up to 21 weeks (including de-escalation)

Arm type	Experimental
Investigational medicinal product name	Rotigotine
Investigational medicinal product code	Neupro
Other name	Neupro
Pharmaceutical forms	Transdermal patch
Routes of administration	Transdermal use

Dosage and administration details:

Rotigotine, transdermal patches:

10 cm^2 (2 mg / 24 hours); 20 cm^2 (4 mg / 24 hours); 30 cm^2 (6 mg / 24 hours); 40 cm^2 (8 mg / 24 hours)

The maximum Rotigotine dose allowed is 8 mg / 24 hours or 16 mg / 24 hours for patients with advanced Parkinson's Disease and 6 mg / 24 hours or 8 mg / 24 hours for those with early Parkinson's Disease Duration: up to 21 weeks (including de-escalation)

Other Name: (6S)-6-propyl-[2 (2 thienyl)ethyl]amino-5,6,7,8-tetrahydro-1-naphthalenol

Number of subjects in period 1	Placebo	Rotigotine, low dose	Rotigotine, high dose
Started	40	41	41
Completed	32	30	37
Not completed	8	11	4
Consent withdrawn by subject	1	4	1
'Moved to other state '	-	1	-
AE, non-serious non-fatal	3	5	3
SAE, non-fatal	1	-	-
Lack of efficacy	2	1	-
Protocol deviation	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo, matching transdermal patches Duration: up to 21 weeks (including de-escalation)	
Reporting group title	Rotigotine, low dose
Reporting group description:	
Rotigotine, transdermal patches, optimal dose, maximal 8 mg / 24 hours for patients with advanced Parkinson's Disease and 6 mg / 24 hours for those with early Parkinson's DiseaseRotigotine: Rotigotine, transdermal patches:10 cm^2 (2 mg / 24 hours); 20 cm^2 (4 mg / 24 hours); 30 cm^2 (6 mg / 24 hours);40 cm^2 (8 mg / 24 hours) Optimal dosage:The maximum Rotigotine dose allowed was 8 mg / 24 hours or 16 mg / 24 hours for patients with advanced Parkinson's Disease and 6 mg / 24 hours or 8 mg / 24 hours for those with early Parkinson's Disease Duration: up to 21 weeks (including de-escalation)	
Reporting group title	Rotigotine, high dose
Reporting group description:	
Rotigotine, transdermal patches, maximal 16 mg / 24 hours for patients with advanced Parkinson's Disease and 8 mg / 24 hours for those with early Parkinson's DiseaseRotigotine: Rotigotine, transdermal patches:10 cm^2 (2 mg / 24 hours); 20 cm^2 (4 mg / 24 hours); 30 cm^2 (6 mg / 24 hours);40 cm^2 (8 mg / 24 hours) Optimal dosage:The maximum Rotigotine dose allowed was 8 mg / 24 hours or 16 mg / 24 hours for patients with advanced Parkinson's Disease and 6 mg / 24 hours or 8 mg / 24 hours for those with early Parkinson's Disease Duration: up to 21 weeks (including de-escalation)	

Reporting group values	Placebo	Rotigotine, low dose	Rotigotine, high dose
Number of subjects	40	41	41
Age categorical Units: Subjects			
>18 - < 65 years	14	17	12
≥ 65 years	26	24	29
Age Continuous Units: years			
arithmetic mean	69	68.1	70.2
standard deviation	± 11.7	± 10.5	± 8
Gender Categorical Units: Subjects			
Female	18	14	14
Male	22	27	27
Race/Ethnicity, Customized Units: Subjects			
Black	1	2	1
White	38	39	40
Other/mixed	1	0	0
Weight Units: kilograms			
arithmetic mean	79.59	77.34	78.96
standard deviation	± 14.73	± 17.93	± 15.96
Height Units: centimeters			
arithmetic mean	167.16	169.25	170.88
standard deviation	± 10.34	± 10.76	± 10.94

Body Mass Index (BMI)			
Units: kilogram per square meter			
arithmetic mean	28.525	26.859	26.9
standard deviation	± 4.792	± 4.887	± 3.859

Reporting group values	Total		
Number of subjects	122		
Age categorical			
Units: Subjects			
>18 - < 65 years	43		
≥ 65 years	79		
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender Categorical			
Units: Subjects			
Female	46		
Male	76		
Race/Ethnicity, Customized			
Units: Subjects			
Black	4		
White	117		
Other/mixed	1		
Weight			
Units: kilograms			
arithmetic mean			
standard deviation	-		
Height			
Units: centimeters			
arithmetic mean			
standard deviation	-		
Body Mass Index (BMI)			
Units: kilogram per square meter			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo, matching transdermal patches Duration: up to 21 weeks (including de-escalation)	
Reporting group title	Rotigotine, low dose
Reporting group description:	
Rotigotine, transdermal patches, optimal dose, maximal 8 mg / 24 hours for patients with advanced Parkinson’s Disease and 6 mg / 24 hours for those with early Parkinson’s DiseaseRotigotine: Rotigotine, transdermal patches:10 cm^2 (2 mg / 24 hours); 20 cm^2 (4 mg / 24 hours); 30 cm^2 (6 mg / 24 hours);40 cm^2 (8 mg / 24 hours) Optimal dosage:The maximum Rotigotine dose allowed was 8 mg / 24 hours or 16 mg / 24 hours for patients with advanced Parkinson's Disease and 6 mg / 24 hours or 8 mg / 24 hours for those with early Parkinson's Disease Duration: up to 21 weeks (including de-escalation)	
Reporting group title	Rotigotine, high dose
Reporting group description:	
Rotigotine, transdermal patches, maximal 16 mg / 24 hours for patients with advanced Parkinson's Disease and 8 mg / 24 hours for those with early Parkinson's DiseaseRotigotine: Rotigotine, transdermal patches:10 cm^2 (2 mg / 24 hours); 20 cm^2 (4 mg / 24 hours); 30 cm^2 (6 mg / 24 hours);40 cm^2 (8 mg / 24 hours) Optimal dosage:The maximum Rotigotine dose allowed was 8 mg / 24 hours or 16 mg / 24 hours for patients with advanced Parkinson's Disease and 6 mg / 24 hours or 8 mg / 24 hours for those with early Parkinson's Disease Duration: up to 21 weeks (including de-escalation)	

Primary: Change from Baseline to the End of the Maintenance Period in the score of the Apathy Evaluation Scale (AS) rated by the patient

End point title	Change from Baseline to the End of the Maintenance Period in the score of the Apathy Evaluation Scale (AS) rated by the patient
End point description:	
The Apathy Scale (AS) is an abbreviated version of the Apathy Evaluation Scale. The AS (Starkstein et al, 1992) consists of 14 items phrased as questions by the examiner that are to be answered on a 4-point Likert scale. It was developed specifically for subjects with Parkinson’s disease because the Apathy Evaluation Scale was considered too demanding. The questions comprising the AS were answered by the subject. The total scores for Apathy Evaluation Scale ranges from 0 (best possible outcome) to 42 (worst possible outcome).	
End point type	Primary
End point timeframe:	
Baseline (Visit 2) until End of the Maintenance Period / Early Withdrawal (up to 19 weeks after Baseline)	

End point values	Placebo	Rotigotine, low dose	Rotigotine, high dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	36	40	
Units: scores on a scale				
arithmetic mean (standard deviation)				
mean (standard deviation)	-4.4 (± 4.9)	-4.6 (± 6.7)	-4.9 (± 5.9)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

ANCOVA model for the change from Baseline to End of Maintenance containing treatment and disease stage as factors, and Baseline value as covariate.

Comparison groups	Rotigotine, low dose v Placebo
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.977
Method	ANCOVA
Parameter estimate	Least Square Mean
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.42
upper limit	2.5
Variability estimate	Standard error of the mean
Dispersion value	1.24

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

ANCOVA model for the change from Baseline to End of Maintenance containing treatment and disease stage as factors, and Baseline value as covariate.

Comparison groups	Placebo v Rotigotine, high dose
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.859
Method	ANCOVA
Parameter estimate	Least Square Mean
Point estimate	-0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.61
upper limit	2.18
Variability estimate	Standard error of the mean
Dispersion value	1.21

Primary: Change from Baseline to the End of the Maintenance Period in the total score of the Unified Parkinson's Disease Rating Scale (UPDRS) Parts II (activities of daily living) + III (motor symptoms)

End point title	Change from Baseline to the End of the Maintenance Period in the total score of the Unified Parkinson's Disease Rating Scale (UPDRS) Parts II (activities of daily living) + III (motor symptoms)

End point description:

Part II of the Unified Parkinson's Disease Rating Scale (UPDRS) assesses the subject's activities of daily living. Part III assesses motor function. The UPDRS is completed by questioning the subject about his/her general state in conjunction with any observations made by the investigator (or designee) since the previous visit. Part II is subject-rated and Part III is physician-rated. The UPDRS Part II (Activities of Daily Living) consists of 13 items scored between 0 and 4. The sum score was calculated as the sum of these 13 individual scores. The UPDRS Part III (motor subscale) consists of 27 items and sub items scored between 0 and 4. The sum score was calculated as sum of these 27 individual scores. The sum score of UPDRS Parts II and III is the sum of the corresponding single sum scores. A negative value indicates an improvement.

End point type	Primary

End point timeframe:

Baseline (Visit 2) until End of the Maintenance Period / Early Withdrawal (up to 19 weeks after Baseline)

End point values	Placebo	Rotigotine, low dose	Rotigotine, high dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	36	40	
Units: scores on a scale				
arithmetic mean (standard deviation)				
mean (standard deviation)	-4.8 (± 10.4)	-12.4 (± 14)	-10.7 (± 8.4)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

ANCOVA model for the change from Baseline to End of Maintenance containing treatment and disease stage as factors, and Baseline value as covariate.

Comparison groups	Placebo v Rotigotine, low dose
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	ANCOVA
Parameter estimate	Least Square Mean
Point estimate	-7.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.3
upper limit	-2.28
Variability estimate	Standard error of the mean
Dispersion value	2.53

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

ANCOVA model for the change from Baseline to End of Maintenance containing treatment and disease

stage as factors, and Baseline value as covariate.

Comparison groups	Placebo v Rotigotine, high dose
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015
Method	ANCOVA
Parameter estimate	Least Square Mean
Point estimate	-6.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.9
upper limit	-1.21
Variability estimate	Standard error of the mean
Dispersion value	2.45

Secondary: Change from Baseline to the End of the Maintenance Period in the score of the Apathy Evaluation Scale (AS) rated by the caregiver (where available)

End point title	Change from Baseline to the End of the Maintenance Period in the score of the Apathy Evaluation Scale (AS) rated by the caregiver (where available)

End point description:

The Apathy Scale (AS) is an abbreviated version of the Apathy Evaluation Scale. The AS (Starkstein et al, 1992) consists of 14 items phrased as questions by the examiner that are to be answered on a 4-point Likert scale. It was developed specifically for subjects with Parkinson's disease because the Apathy Evaluation Scale was considered too demanding.
The questions comprising the AS were answered by the caregiver. The questions were asked in a structured interview format. The caregiver was interviewed by appropriate medical staff and asked questions about the subject in the third person.The total scores for Apathy Evaluation Scale ranges from 0 (best possible outcome) to 42 (worst possible outcome).

End point type	Secondary

End point timeframe:

Baseline (Visit 2) until End of the Maintenance Period / Early Withdrawal (up to 19 weeks after Baseline)

End point values	Placebo	Rotigotine, low dose	Rotigotine, high dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	16	13	
Units: scores on a scale				
arithmetic mean (standard deviation)				
mean (standard deviation)	-1.5 (± 7)	-4.8 (± 8)	-5.5 (± 6.1)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

ANCOVA model for the change from Baseline to End of Maintenance containing treatment and disease stage as factors, and Baseline value as covariate.

Comparison groups	Placebo v Rotigotine, low dose
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2
Method	ANCOVA
Parameter estimate	Least Square Mean
Point estimate	-3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.17
upper limit	1.76
Variability estimate	Standard error of the mean
Dispersion value	2.46

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

ANCOVA model for the change from Baseline to End of Maintenance containing treatment and disease stage as factors, and Baseline value as covariate.

Comparison groups	Placebo v Rotigotine, high dose
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.239
Method	ANCOVA
Parameter estimate	Least Square Mean
Point estimate	-3.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.19
upper limit	2.1
Variability estimate	Standard error of the mean
Dispersion value	2.55

Secondary: Change from Baseline to the End of the Maintenance Period in the sum score of the 8-item Parkinson's Disease Questionnaire (PDQ-8)

End point title	Change from Baseline to the End of the Maintenance Period in the sum score of the 8-item Parkinson's Disease Questionnaire (PDQ-8)

End point description:

The 8-Item Parkinson's Disease Questionnaire (PDQ-8) (Peto et al, 1998) is a self-administered questionnaire that provides a reliable measure of overall health status. The PDQ-8 collects 8 items with 5 categories each (0=never, 1=occasionally, 2=sometimes, 3=often, 4=always or cannot do at all). The total score was calculated by summing the scores of all applicable questions and convert the resulting

sum to a summary index score between 0 and 100 by multiplying with 100/32. A negative value indicates an improvement.

End point type	Secondary

End point timeframe:

Baseline (Visit 2) until End of the Maintenance Period / Early Withdrawal (up to 19 weeks after Baseline)

End point values	Placebo	Rotigotine, low dose	Rotigotine, high dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	36	40	
Units: scores on a scale				
arithmetic mean (standard deviation)				
mean (standard deviation)	-3.8 (± 14)	-5.1 (± 20.4)	-10 (± 15)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

ANCOVA model for the change from Baseline to End of Maintenance containing treatment and disease stage as factors, and Baseline value as covariate.

Comparison groups	Placebo v Rotigotine, low dose
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.519
Method	ANCOVA
Parameter estimate	Least Square Mean
Point estimate	-2.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.48
upper limit	4.31
Variability estimate	Standard error of the mean
Dispersion value	3.23

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

ANCOVA model for the change from Baseline to End of Maintenance containing treatment and disease stage as factors, and Baseline value as covariate.

Comparison groups	Placebo v Rotigotine, high dose

Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.111
Method	ANCOVA
Parameter estimate	Least Square Mean
Point estimate	-5.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.29
upper limit	1.17
Variability estimate	Standard error of the mean
Dispersion value	3.15

Secondary: Change from Baseline to the End of the Maintenance Period in the sum score of the mood / cognition domain of the Nonmotor Symptom Assessment Scale (NMSS)

End point title	Change from Baseline to the End of the Maintenance Period in the sum score of the mood / cognition domain of the Nonmotor Symptom Assessment Scale (NMSS)

End point description:

Nonmotor performance was assessed via the Nonmotor Symptom Assessment Scale (NMSS), an accepted scale that has been validated in an international study (Naidu et al, 2006; Chaudhuri et al, 2007), at the Baseline Visit as well as at the end of the Maintenance Period. The severity and frequency of the subject's nonmotor symptoms were assessed by the investigator (or designee) in the following 9 domain categories: cardiovascular, including falls; sleep/fatigue; mood/cognition; perceptual problems/hallucinations; attention/memory; gastrointestinal tract; urinary; sexual function; and miscellaneous.

Items are scored for severity (from 0 (none) to 3 (severe)) and frequency (from 1 (rarely) to 4 (very frequent)). The score was calculated as severity x frequency. The theoretical minimum is 0 (best possible outcome) and maximum total score is 360 points (worst possible outcome).

End point type	Secondary

End point timeframe:

Baseline (Visit 2) until End of the Maintenance Period / Early Withdrawal (up to 19 weeks after Baseline)

End point values	Placebo	Rotigotine, low dose	Rotigotine, high dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	32	39	
Units: scores on a scale				
arithmetic mean (standard deviation)				
mean (standard deviation)	-4.6 (± 7.9)	-9.8 (± 12.1)	-9.8 (± 10.7)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

ANCOVA model for the change from Baseline to End of Treatment containing treatment and disease stage as factors, and Baseline value as covariate.

Comparison groups	Placebo v Rotigotine, low dose
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.06
Method	ANCOVA
Parameter estimate	Least Square Mean
Point estimate	-3.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.39
upper limit	0.15
Variability estimate	Standard error of the mean
Dispersion value	1.9

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

ANCOVA model for the change from Baseline to End of Treatment containing treatment and disease stage as factors, and Baseline value as covariate.

Comparison groups	Placebo v Rotigotine, high dose
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.034
Method	ANCOVA
Parameter estimate	Least Square Mean
Point estimate	-3.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.46
upper limit	-0.3
Variability estimate	Standard error of the mean
Dispersion value	1.8

Secondary: Change from Baseline to the End of the Maintenance Period in the sum score of the Snaith Hamilton Pleasure Scale (SHAPS)

End point title	Change from Baseline to the End of the Maintenance Period in the sum score of the Snaith Hamilton Pleasure Scale (SHAPS)

End point description:

The Snaith Hamilton Pleasure Scale (SHAPS) (Snaith et al, 1995) is a self-report instrument developed for the assessment of hedonic capacity. The sum of the 14 items scores range from 0 to 14. A higher

score represents more anhedonic symptoms.

End point type	Secondary

End point timeframe:

Baseline (Visit 2) until End of the Maintenance Period / Early Withdrawal (up to 19 weeks after Baseline)

End point values	Placebo	Rotigotine, low dose	Rotigotine, high dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	36	40	
Units: scores on a scale				
arithmetic mean (standard deviation)				
mean (standard deviation)	-0.5 (± 2.5)	-1.3 (± 2.2)	-0.9 (± 2.8)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

ANCOVA model for the change from Baseline to End of Maintenance containing treatment and disease stage as factors, and Baseline value as covariate.

Comparison groups	Placebo v Rotigotine, low dose
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.334
Method	ANCOVA
Parameter estimate	Least Square Mean
Point estimate	-0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.16
upper limit	0.4
Variability estimate	Standard error of the mean
Dispersion value	0.39

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

ANCOVA model for the change from Baseline to End of Maintenance containing treatment and disease stage as factors, and Baseline value as covariate.

Comparison groups	Placebo v Rotigotine, high dose

Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.968
Method	ANCOVA
Parameter estimate	Least Square Mean
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.74
upper limit	0.77
Variability estimate	Standard error of the mean
Dispersion value	0.38

Secondary: Change from Baseline to the End of the Maintenance Period in the sum score of the Beck Depression Inventory Second Edition (BDI-II)

End point title	Change from Baseline to the End of the Maintenance Period in the sum score of the Beck Depression Inventory Second Edition (BDI-II)

End point description:

The Beck Depression Inventory (BDI) is a self-report instrument to measure depression symptoms and severity (Beck et al, 1961). The BDI-II is a revised version of the scale in order to be more consistent with the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for depression (Beck et al, 1996). There are 21 items in the BDI-II, classified as cognitive-affective (Items 1-13) and somatic-performance (Items 14-21) subscales. The degree of severity is indicated on a 4-point scale; items are rated from 0 (not at all) to 3 (extreme form of each symptom). Scores of 0-13 indicate minimal depression, 14-19 indicate mild depression, 20-28 indicate moderate depression, and 29-63 indicate severe depression.

End point type	Secondary

End point timeframe:

Baseline (Visit 2) until End of the Maintenance Period / Early Withdrawal (up to 19 weeks after Baseline)

End point values	Placebo	Rotigotine, low dose	Rotigotine, high dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	31	39	
Units: scores on a scale				
arithmetic mean (standard deviation)				
mean (standard deviation)	-3.3 (± 7)	-2.9 (± 5.9)	-3.7 (± 5.3)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

ANCOVA model for the change from Baseline to End of Maintenance containing treatment and disease stage as factors, and Baseline value as covariate.

Comparison groups	Placebo v Rotigotine, low dose
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.899
Method	ANCOVA
Parameter estimate	Least Square Mean
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.34
upper limit	2.66
Variability estimate	Standard error of the mean
Dispersion value	1.26

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

ANCOVA model for the change from Baseline to End of Treatment containing treatment and disease stage as factors, and Baseline value as covariate.

Comparison groups	Placebo v Rotigotine, high dose
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.785
Method	ANCOVA
Parameter estimate	Least Square Mean
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.68
upper limit	2.03
Variability estimate	Standard error of the mean
Dispersion value	1.19

Secondary: Change from Baseline to the End of the Maintenance Period in the sum score of the Unified Parkinson's Disease Rating Scale (UPDRS) Part III (motor subscale) in 'on' state

End point title	Change from Baseline to the End of the Maintenance Period in the sum score of the Unified Parkinson's Disease Rating Scale (UPDRS) Part III (motor subscale) in 'on' state

End point description:

Part III of the Unified Parkinson's Disease Rating Scale (UPDRS) assesses motor function. The UPDRS is completed by questioning the subject about his/her general state in conjunction with any observations made by the investigator (or designee) since the previous visit.

The UPDRS Part III (motor subscale) had to be measured in the “on” state and consisted of 27 items and sub items scored between 0 and 4. The sum score ranged between 0 and 108 and was calculated as

sum of the 27 individual scores. If 1 or more items were missing and could not be substituted with a previous post-Baseline value, the sum score was also missing.
A negative value indicates an improvement.

End point type	Secondary

End point timeframe:

Baseline (Visit 2) until End of the Maintenance Period / Early Withdrawal (up to 19 weeks after Baseline)

End point values	Placebo	Rotigotine, low dose	Rotigotine, high dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	36	40	
Units: scores on a scale				
arithmetic mean (standard deviation)				
mean (standard deviation)	-3.4 (± 8.2)	-8.9 (± 10.4)	-8.1 (± 7.3)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

ANCOVA model for the change from Baseline to End of Maintenance containing treatment and disease stage as factors, and Baseline value as covariate.

Comparison groups	Placebo v Rotigotine, low dose
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.014
Method	ANCOVA
Parameter estimate	Least Square Mean
Point estimate	-4.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.91
upper limit	-1.01
Variability estimate	Standard error of the mean
Dispersion value	1.99

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

ANCOVA model for the change from Baseline to End of Maintenance containing treatment and disease stage as factors, and Baseline value as covariate.

Comparison groups	Rotigotine, high dose v Placebo

Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	ANCOVA
Parameter estimate	Least Square Mean
Point estimate	-4.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.63
upper limit	-1.03
Variability estimate	Standard error of the mean
Dispersion value	1.92

Secondary: Change from Baseline to the End of the Maintenance Period in the score of the Clinical Global Impression Scale (CGI) Item I (Severity of Illness)

End point title	Change from Baseline to the End of the Maintenance Period in the score of the Clinical Global Impression Scale (CGI) Item I (Severity of Illness)

End point description:

The Clinical Global Impression (CGI) scales (Guy and Bonato, 1970) were initially developed for a risk-benefit estimation within the treatment of mentally ill patients. The 4 global scales (severity of illness, change in severity from Baseline, therapeutic efficacy, and tolerability of treatment) are used as different measures of treatment outcome in different kinds of pharmacological studies.
The CGI Item 1 (severity of illness) collected 1 answer out of 8 categories (0-'Not assessed', 1-'Normal, not at all ill', 2-'Borderline ill', 3-'Mildly ill', 4-'Moderately ill', 5-'Markedly ill', 6-'Severely ill', and 7-'Among the most extremely ill patients') at each assessment. The category 0-'Not assessed' was considered as missing and therefore used neither for calculation nor for display purposes.

End point type	Secondary

End point timeframe:

Baseline (Visit 2) until End of the Maintenance Period/Early Withdrawal (up to 19 weeks after Baseline)

End point values	Placebo	Rotigotine, low dose	Rotigotine, high dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	36	40	
Units: participants				
number (not applicable)				
Normal, not ill at all	1	1	2	
Borderline ill	6	2	3	
Mildly ill	19	16	21	
Moderately ill	9	10	12	
Markedly ill	2	1	1	
Severely ill	1	1	0	
Amongst the most extremely ill subjects	0	0	0	
Missing	2	5	1	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment Emergent Adverse Events (TEAEs) were reported from Baseline up to the Safety Follow-up Visit (approximately during 19 weeks).

Adverse event reporting additional description:

The Baseline Analysis Population refers to the Safety Set (SS). The SS includes all randomized subjects who received at least 1 dose of study medication.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo: Placebo, matching transdermal patches

Duration: up to 21 weeks (including de-escalation)

Reporting group title	Rotigotine, low dose

Reporting group description:

Rotigotine, transdermal patches, optimal dose, maximal 8 mg / 24 hours for patients with advanced Parkinson’s Disease and 6 mg / 24 hours for those with early Parkinson’s Disease

Rotigotine: Rotigotine, transdermal patches:
10 cm^2 (2 mg / 24 hours);
20 cm^2 (4 mg / 24 hours);
30 cm^2 (6 mg / 24 hours);
40 cm^2 (8 mg / 24 hours)

Optimal dosage:
The maximum Rotigotine dose allowed was 8 mg / 24 hours or 16 mg / 24 hours for patients with advanced Parkinson's Disease and 6 mg / 24 hours or 8 mg / 24 hours for those with early Parkinson's Disease
Duration: up to 21 weeks (including de-escalation)

Reporting group title	Rotigotine, high dose

Reporting group description:

Rotigotine, transdermal patches, maximal 16 mg / 24 hours for patients with advanced Parkinson's Disease and 8 mg / 24 hours for those with early Parkinson's Disease

Rotigotine: Rotigotine, transdermal patches:
10 cm^2 (2 mg / 24 hours);
20 cm^2 (4 mg / 24 hours);
30 cm^2 (6 mg / 24 hours);
40 cm^2 (8 mg / 24 hours)

Optimal dosage:
The maximum Rotigotine dose allowed was 8 mg / 24 hours or 16 mg / 24 hours for patients with advanced Parkinson's Disease and 6 mg / 24 hours or 8 mg / 24 hours for those with early Parkinson's Disease
Duration: up to 21 weeks (including de-escalation)

Serious adverse events	Placebo	Rotigotine, low dose	Rotigotine, high dose
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 40 (10.00%)	2 / 41 (4.88%)	1 / 41 (2.44%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Cerebral haematoma			
subjects affected / exposed	0 / 40 (0.00%)	0 / 41 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 40 (2.50%)	0 / 41 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 40 (2.50%)	0 / 41 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Small intestinal obstruction			
subjects affected / exposed	0 / 40 (0.00%)	1 / 41 (2.44%)	0 / 41 (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
Abdominal pain			
subjects affected / exposed	1 / 40 (2.50%)	0 / 41 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 40 (0.00%)	1 / 41 (2.44%)	0 / 41 (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
Infections and infestations			
Abscess			

subjects affected / exposed	0 / 40 (0.00%)	1 / 41 (2.44%)	0 / 41 (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
Sepsis			
subjects affected / exposed	1 / 40 (2.50%)	0 / 41 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	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	Placebo	Rotigotine, low dose	Rotigotine, high dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 40 (45.00%)	17 / 41 (41.46%)	15 / 41 (36.59%)
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 40 (5.00%)	3 / 41 (7.32%)	2 / 41 (4.88%)
occurrences (all)	3	3	2
Nervous system disorders			
Somnolence			
subjects affected / exposed	3 / 40 (7.50%)	2 / 41 (4.88%)	4 / 41 (9.76%)
occurrences (all)	3	2	5
Dyskinesia			
subjects affected / exposed	2 / 40 (5.00%)	3 / 41 (7.32%)	1 / 41 (2.44%)
occurrences (all)	3	3	1
Headache			
subjects affected / exposed	4 / 40 (10.00%)	1 / 41 (2.44%)	3 / 41 (7.32%)
occurrences (all)	6	1	6
General disorders and administration site conditions			
Application site pruritus			
subjects affected / exposed	2 / 40 (5.00%)	4 / 41 (9.76%)	1 / 41 (2.44%)
occurrences (all)	2	4	2
Oedema peripheral			
subjects affected / exposed	1 / 40 (2.50%)	2 / 41 (4.88%)	3 / 41 (7.32%)
occurrences (all)	1	2	3
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	1 / 40 (2.50%)	2 / 41 (4.88%)	3 / 41 (7.32%)
occurrences (all)	1	2	3
Nausea			
subjects affected / exposed	4 / 40 (10.00%)	4 / 41 (9.76%)	2 / 41 (4.88%)
occurrences (all)	5	5	2
Dry mouth			
subjects affected / exposed	0 / 40 (0.00%)	0 / 41 (0.00%)	3 / 41 (7.32%)
occurrences (all)	0	0	3
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 40 (5.00%)	4 / 41 (9.76%)	1 / 41 (2.44%)
occurrences (all)	2	4	1
Insomnia			
subjects affected / exposed	6 / 40 (15.00%)	1 / 41 (2.44%)	2 / 41 (4.88%)
occurrences (all)	6	1	2
Suicidal ideation			
subjects affected / exposed	3 / 40 (7.50%)	1 / 41 (2.44%)	0 / 41 (0.00%)
occurrences (all)	3	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 August 2013	- A description and rationale of the interim analysis to be performed was added. - The approximate number of participating investigational sites was increased to 120. - Inclusion Criterion 7 was modified to add "200 mg/day" as the minimum allowed stable dose of levodopa for consistency with the concomitant levodopa section. - Tables with the study medication administration schedule and De-Escalation Period for subjects with advanced-stage Parkinson's disease were corrected. - Wording regarding packaging was updated to remove references to cartons for the de-escalation kits. - Wording regarding the NMSS was updated to indicate that it could also be assessed by an investigator's designee. - The analysis sets to be used for the analyses of efficacy variables were revised. - The estimated screening failure rate was corrected. - The references list was updated. - The Snaith-Hamilton Pleasure Scale (SHAPS) was updated to reflect the version provided to the subjects. - Additionally, administrative, typographical, and editorial changes were made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported