



## Clinical trial results:

### A Multicenter, Open-Label, 2-Group, Dose Escalation Study of Monotherapy Administration of Rotigotine in Pediatric Subjects With Idiopathic Restless Legs Syndrome

#### Summary

EudraCT number	2014-004383-37
Trial protocol	Outside EU/EEA
Global end of trial date	30 April 2014

#### Results information

Result version number	v1 (current)
This version publication date	30 June 2016
First version publication date	03 July 2015

#### Trial information

##### Trial identification

Sponsor protocol code	SP1004
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01495793
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	UCB Biosciences Inc.
Sponsor organisation address	8010 Arco Corporate Drive, Raleigh, United States, NC 27617
Public contact	CTRRD, UCB Biosciences GmbH, +49 2173481515, clinicaltrials@ucb.com
Scientific contact	CTRRD, UCB Biosciences GmbH, +49 2173481515, 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?	Yes

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 August 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 April 2014
Global end of trial reached?	Yes
Global end of trial date	30 April 2014
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to determine the pharmacokinetic (PK) properties of rotigotine in adolescents with idiopathic restless legs syndrome (RLS) after multiple patch administrations.

Protection of trial subjects:

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

Background therapy:

If nausea or vomiting occurred during the study, antiemetic therapy with ondansetron was allowed. Ondansetron was not to be used prophylactically. Use of a topical anesthetic was permitted to treat the venous puncture or indwelling venous catheter site prior to the needle stick. If medication is medically indicated, the subject must inform the investigator immediately. All concomitant medication and treatment was recorded in the appropriate study documents (i.e. eCRF and source document).

Evidence for comparator:

Not applicable

Actual start date of recruitment	01 December 2011
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	United States: 24
Worldwide total number of subjects	24
EEA total number of subjects	0

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)	24
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

This was a multicenter study in which 42 subjects were enrolled and 24 treated at 8 sites in the USA.

### Pre-assignment

Screening details:

In total 42 subjects signed the informed consent and were enrolled into the study (Enrolled Set). 24 of these subjects were treated with medication. The sample size of 24 subjects was sufficient to target a 95% confidence interval and the calculation was based on a previous study. Participant Flow refers to the 24 treated subjects (Safety Set).

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Arm title	Rotigotine
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Arm description:

In the Titration Period a subject received the first dose of rotigotine then the dose was increased weekly by a dose step over 4 weeks.

Arm type	Experimental
Investigational medicinal product name	Neupro 0.5 mg/24 h
Investigational medicinal product code	Prod 1
Other name	
Pharmaceutical forms	Transdermal patch
Routes of administration	Transdermal use

Dosage and administration details:

In the Titration Period a subject received the first dose of rotigotine then the dose was increased weekly by a dose step over 4 weeks.

Dose (size): 0.5 mg/24 h (2.5 cm<sup>2</sup>)

The patch has to be applied continuously for 24h. After 24h, the patch has to be removed and a new one applied.

Investigational medicinal product name	Neupro 1 mg/24 h
Investigational medicinal product code	Prod 2
Other name	
Pharmaceutical forms	Transdermal patch
Routes of administration	Transdermal use

Dosage and administration details:

In the Titration Period a subject received the first dose of rotigotine then the dose was increased weekly by a dose step over 4 weeks.

Dose (size): 1 mg/24 h (5 cm<sup>2</sup>)

The patch has to be worn continuously for 24h. After 24h, the patch has to be removed and a new one applied.

Investigational medicinal product name	Neupro 3 mg/24 h
Investigational medicinal product code	Prod 4
Other name	
Pharmaceutical forms	Transdermal patch
Routes of administration	Transdermal use

Dosage and administration details:

In the Titration Period a subject received the first dose of rotigotine then the dose was increased weekly by a dose step over 4 weeks.

Dose (size): 3 mg/24 h (15 cm<sup>2</sup>)

The patch has to be worn continuously for 24h. After 24h, the patch has to be removed and a new one applied.

Investigational medicinal product name	Neupro 2 mg/24 h
Investigational medicinal product code	Prod 3
Other name	
Pharmaceutical forms	Transdermal patch
Routes of administration	Transdermal use

Dosage and administration details:

In the Titration Period a subject received the first dose of rotigotine than the dose was increased weekly by a dose step over 4 weeks.

Dose (size): 2 mg/24 h (10 cm<sup>2</sup>)

The patch has to be worn continuously for 24h. After 24h, the patch has to be removed and a new one applied.

<b>Number of subjects in period 1</b>	Rotigotine
Started	24
Completed	22
Not completed	2
Lost to follow-up	1
Violation of inclusion criteria	1

## Baseline characteristics

### Reporting groups

Reporting group title	Rotigotine
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Reporting group description:

In the Titration Period a subject received the first dose of rotigotine then the dose was increased weekly by a dose step over 4 weeks.

Reporting group values	Rotigotine	Total	
Number of subjects	24	24	
Age categorical			
Units: Subjects			
13 years	2	2	
14 years	6	6	
15 years	6	6	
16 years	4	4	
17 years	6	6	
Age Continuous			
Units: years			
arithmetic mean	15.3		
standard deviation	± 1.3	-	
Gender Categorical			
Units: Subjects			
Male	9	9	
Female	15	15	
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Black or African American	8	8	
Native Hawaiian or Other Pacific Islander	0	0	
White	16	16	
More than one race	0	0	
Unknown or Not Reported	0	0	
Ethnicity (NIH/OMB)			
Units: Subjects			
Not Hispanic or Latino	20	20	
Hispanic or Latino	4	4	
Unknown or Not Reported	0	0	
Height			
Units: cm			
arithmetic mean	167.39		
standard deviation	± 6.89	-	
Weight			
Units: kg			
arithmetic mean	65.7		
standard deviation	± 10.72	-	
BMI (Body Mass Index)			

Units: kg/m <sup>2</sup>			
arithmetic mean	23.388		
standard deviation	± 3.133	-	

## End points

### End points reporting groups

Reporting group title	Rotigotine
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Reporting group description:

In the Titration Period a subject received the first dose of rotigotine then the dose was increased weekly by a dose step over 4 weeks.

Subject analysis set title	Rotigotine (PKPPS)
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Subject analysis set type	Per protocol
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Subject analysis set description:

The Pharmacokinetic Per Protocol Set (PKPPS) includes all enrolled subjects who were included in the Safety Set, who had no protocol deviations that were considered to impact the subject's validity for analysis of the primary study objective and who for at least 1 dose step fulfilled specific predefined conditions.

### Primary: Apparent Total Body Clearance (Cl/f) of unconjugated rotigotine 0.5 mg/24 h (2.5 cm<sup>2</sup>)

End point title	Apparent Total Body Clearance (Cl/f) of unconjugated rotigotine 0.5 mg/24 h (2.5 cm <sup>2</sup> ) <sup>[1]</sup>
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End point description:

CL/f was calculated for each subject treated with rotigotine derived from the concentrations of unconjugated rotigotine measured in plasma.

For the primary variables the parametric point estimator for each dose step and the 95% CI was calculated using the least-squares (LS) means and the root mean square of error from the ANOVA of the log-transformed data with subsequent exponential transformation.

End point type	Primary
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End point timeframe:

0 h (predose), 1 h, 2 h, 7-12 h and 22-24 h on Day 7, 14, 21 and 28

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized in tables as descriptive statistics only.

End point values	Rotigotine (PKPPS)			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: L/h (liter per hour)				
least squares mean (confidence interval 95%)				
Apparent Total Body Clearance	676.86 (408.5 to 1121.51)			

### Statistical analyses

No statistical analyses for this end point

### Primary: Apparent Total Body Clearance (Cl/f) of unconjugated rotigotine 1 mg/24 h (5 cm<sup>2</sup>)

End point title	Apparent Total Body Clearance (Cl/f) of unconjugated rotigotine 1 mg/24 h (5 cm <sup>2</sup> ) <sup>[2]</sup>
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End point description:

CL/f was calculated for each subject treated with rotigotine derived from the concentrations of unconjugated rotigotine measured in plasma.  
For the primary variables the parametric point estimator for each dose step and the 95% CI was calculated using the least-squares (LS) means and the root mean square of error from the ANOVA of the log-transformed data with subsequent exponential transformation.

End point type	Primary
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End point timeframe:

0 h (predose), 1 h, 2 h, 7-12 h and 22-24 h on Day 7, 14, 21 and 28

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized in tables as descriptive statistics only.

End point values	Rotigotine (PKPPS)			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: L/h (Liter per hour)				
least squares mean (confidence interval 95%)				
Apparent Total Body Clearance	671.72 (459.11 to 982.8)			

## Statistical analyses

No statistical analyses for this end point

### Primary: Apparent Total Body Clearance (CL/f) of unconjugated rotigotine 2 mg/24 h (10 cm<sup>2</sup>)

End point title	Apparent Total Body Clearance (CL/f) of unconjugated rotigotine 2 mg/24 h (10 cm <sup>2</sup> ) <sup>[3]</sup>
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End point description:

CL/f was calculated for each subject treated with rotigotine derived from the concentrations of unconjugated rotigotine measured in plasma.  
For the primary variables the parametric point estimator for each dose step and the 95% CI was calculated using the least-squares (LS) means and the root mean square of error from the ANOVA of the log-transformed data with subsequent exponential transformation.

End point type	Primary
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End point timeframe:

0 h (predose), 1 h, 2 h, 7-12 h and 22-24 h on Day 7, 14, 21 and 28

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized in tables as descriptive statistics only.

End point values	Rotigotine (PKPPS)			
Subject group type	Subject analysis set			
Number of subjects analysed	11			
Units: L/h (Liter per hour)				
least squares mean (confidence interval 95%)				
Apparent Total Body Clearance	937.56 (658.5 to 1334.89)			

## Statistical analyses

No statistical analyses for this end point

### Primary: Apparent Total Body Clearance (Cl/f) of unconjugated rotigotine 3 mg/24 h (15 cm<sup>2</sup>)

End point title	Apparent Total Body Clearance (Cl/f) of unconjugated rotigotine 3 mg/24 h (15 cm <sup>2</sup> ) <sup>[4]</sup>
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End point description:

CL/f was calculated for each subject treated with rotigotine derived from the concentrations of unconjugated rotigotine measured in plasma.

For the primary variables the parametric point estimator for each dose step and the 95% CI was calculated using the least-squares (LS) means and the root mean square of error from the ANOVA of the log-transformed data with subsequent exponential transformation.

End point type	Primary
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End point timeframe:

0 h (predose), 1 h, 2 h, 7-12 h and 22-24 h on Day 7, 14, 21 and 28

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized in tables as descriptive statistics only.

End point values	Rotigotine (PKPPS)			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: L/h (Liter per hour)				
least squares mean (confidence interval 95%)				
Apparent Total Body Clearance	1088.77 (723.47 to 1638.53)			

## Statistical analyses

No statistical analyses for this end point

### Primary: Volume of Distribution at steady state (VSS/f) of unconjugated rotigotine 0.5 mg/24 h (2.5 cm<sup>2</sup>)

End point title	Volume of Distribution at steady state (VSS/f) of unconjugated rotigotine 0.5 mg/24 h (2.5 cm <sup>2</sup> ) <sup>[5]</sup>
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End point description:

VSS/f was calculated for each subject treated with rotigotine derived from the concentrations of unconjugated rotigotine measured in plasma.

For the primary variables the parametric point estimator for each dose step and the 95% CI was calculated using the least-squares (LS) means and the root mean square of error from the ANOVA of the log-transformed data with subsequent exponential transformation.

End point type	Primary
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End point timeframe:

0 h (predose), 1 h, 2 h, 7-12 h and 22-24 h on Day 7, 14, 21 and 28

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized in tables as descriptive statistics only.

End point values	Rotigotine (PKPPS)			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: L (Liter)				
least squares mean (confidence interval 95%)				
Volume of Distribution at steady state	5403.16 (2850.67 to 10241.17)			

## Statistical analyses

No statistical analyses for this end point

### Primary: Volume of Distribution at steady state (VSS/f) of unconjugated rotigotine 1 mg/24 h (5 cm<sup>2</sup>)

End point title	Volume of Distribution at steady state (VSS/f) of unconjugated rotigotine 1 mg/24 h (5 cm <sup>2</sup> ) <sup>[6]</sup>
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End point description:

VSS/f was calculated for each subject treated with rotigotine derived from the concentrations of unconjugated rotigotine measured in plasma.

For the primary variables the parametric point estimator for each dose step and the 95% CI was calculated using the least-squares (LS) means and the root mean square of error from the ANOVA of the log-transformed data with subsequent exponential transformation.

End point type	Primary
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End point timeframe:

0 h (predose), 1 h, 2 h, 7-12 h and 22-24 h on Day 7, 14, 21 and 28

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized in tables as descriptive statistics only.

End point values	Rotigotine (PKPPS)			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: L (Liter)				
least squares mean (confidence interval 95%)				
Volume of Distribution at steady state	6220.79 (3842.05 to 10072.28)			

## Statistical analyses

No statistical analyses for this end point

### Primary: Volume of Distribution at steady state (VSS/f) of unconjugated rotigotine 2 mg/24 h (10 cm<sup>2</sup>)

End point title	Volume of Distribution at steady state (VSS/f) of unconjugated rotigotine 2 mg/24 h (10 cm <sup>2</sup> ) <sup>[7]</sup>
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End point description:

VSS/f was calculated for each subject treated with rotigotine derived from the concentrations of unconjugated rotigotine measured in plasma.

For the primary variables the parametric point estimator for each dose step and the 95% CI was calculated using the least-squares (LS) means and the root mean square of error from the ANOVA of the log-transformed data with subsequent exponential transformation.

End point type	Primary
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End point timeframe:

0 h (predose), 1 h, 2 h, 7-12 h and 22-24 h on Day 7, 14, 21 and 28

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized in tables as descriptive statistics only.

End point values	Rotigotine (PKPPS)			
Subject group type	Subject analysis set			
Number of subjects analysed	11			
Units: L (Liter)				
least squares mean (confidence interval 95%)				
Volume of Distribution at steady state	7114.01 (4547.88 to 11128.07)			

## Statistical analyses

No statistical analyses for this end point

### Primary: Volume of Distribution at steady state (VSS/f) of unconjugated rotigotine 3 mg/24 h (15 cm<sup>2</sup>)

End point title	Volume of Distribution at steady state (VSS/f) of unconjugated
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**End point description:**

VSS/f was calculated for each subject treated with rotigotine derived from the concentrations of unconjugated rotigotine measured in plasma.

For the primary variables the parametric point estimator for each dose step and the 95% CI was calculated using the least-squares (LS) means and the root mean square of error from the ANOVA of the log-transformed data with subsequent exponential transformation.

**End point type**

Primary

**End point timeframe:**

0 h (predose), 1 h, 2 h, 7-12 h and 22-24 h on Day 7, 14, 21 and 28

**Notes:**

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized in tables as descriptive statistics only.

<b>End point values</b>	Rotigotine (PKPPS)			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: L (Liter)				
least squares mean (confidence interval 95%)				
Volume of Distribution at steady state	6037.92 (3598.36 to 10131.41)			

**Statistical analyses**

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

This summary includes TEAEs from the Titration period, Taper period and Safety Follow-up (Day 1 up to 69 days).

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	9.1
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### Reporting groups

Reporting group title	Rotigotine
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Reporting group description:

In the Titration Period a subject received the first dose of rotigotine then the dose was increased weekly by a dose step over 4 weeks.

Serious adverse events	Rotigotine		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Rotigotine		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 24 (62.50%)		
Investigations			
Blood bilirubin increased			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Stress fracture			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Animal bite			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		

Road traffic accident subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Wound subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Nervous system disorders			
Somnolence subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Syncope subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Headache subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		
Migraine subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Dizzines subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		
Sudden onset of sleep subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 2		
General disorders and administration site conditions			
Application site pruritus subjects affected / exposed occurrences (all)	4 / 24 (16.67%) 4		
Application site irritation subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Irritability subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Immune system disorders			

Allergy to arthropod sting subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Food allergy subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Nausea subjects affected / exposed occurrences (all)	7 / 24 (29.17%) 11		
Vomiting subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		
Reproductive system and breast disorders			
Dysmenorrhoea subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Skin and subcutaneous tissue disorders			
Acne subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Urticaria subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Muscular weakness subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Musculoskeletal chest pain			



subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Muscukoseletal pain			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Fungal infection			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	3		
Pharyngitis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Increased appetite			

subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 March 2011	<p>The main purpose of this substantial amendment was to include the suicidality risk assessment (Columbia-Suicide Severity Rating Scale [C-SSRS]). In accordance with the FDA draft Guidance for Industry, which went into effect on 29 Oct 2010. In addition, a list of anticipated serious adverse events (SAEs) was included in this amendment in compliance with the recent FDA guidance on safety reporting requirements for studies conducted under an open Investigational New Drug Application. The Beck Depression Inventory II and the Beck Anxiety Inventory were removed from the study assessments.</p> <p>Other changes included in this amendment were as follows:</p> <ul style="list-style-type: none"><li>- Procedures for subjects wishing to enter the open-label, LTFU study (SP1005) following dose de-escalation but prior to the SFU Visit were added.</li><li>- Definition of clinically relevant renal dysfunction at Visit 1/Screening Period as an exclusion criterion was increased from serum creatinine &gt;1.0mg/dL to &gt;1.5mg/dL since the previous serum creatinine level &gt;1.0mg/dL was within the central laboratory's normal range.</li><li>- Physical examination was removed as a safety variable.</li><li>- The version number of the Attention Deficit Hyperactivity Disorder (ADHD) Rating Scale was added.</li><li>- For clarity, a dose de-escalation table (Table 3-3) was added.</li><li>- Storage requirements for the rotigotine patch were updated.</li><li>- Use of a topical anesthetic prior to the needle stick was permitted.</li><li>- Corrections were made to the definitions of some PK parameters, as well as the preparation and handling of the blood and saliva PK samples.</li><li>- Reference to patch size was removed from all sections, except Section 7.1 of the protocol, Description of investigational medicinal product (IMP).</li><li>- Vital sign parameters to be measured were specified as pulse rate, SBP, DBP, and orthostatic hypertension assessments.</li><li>- Sponsor Clinical Project Manager contact information was updated.</li><li>- Typographic errors and changes of an editorial nature were made.</li></ul>
19 September 2011	<p>The purpose of this substantial amendment was to increase the minimum weight for enrollment in the study from 30kg to 40kg.</p> <p>An additional change clarifying that subjects must tolerate the first dose step to be able to transition into the open-label, LTFU study was also made.</p>
02 May 2012	<p>The main purpose of this substantial amendment was to ensure consistency between the protocol and the FDA Pediatric Development Plan for the RLS indication in subjects 13 to &lt;18 years of age. Since the subject's dosing was no longer dependent on body weight, the dosing schedules for each study period were revised. The primary PK variables were changed to reflect those that were requested by the FDA for the revised sample size calculation. In addition, PK saliva sampling was removed from the study. Data from a recently completed PK study (RL0002) suggest that saliva concentrations of rotigotine cannot be used as a surrogate for plasma concentrations of rotigotine.</p> <p>Other changes included in this amendment were as follows:</p> <ul style="list-style-type: none"><li>- Updated contact information for SAE reporting and procedures for reporting SAEs to be consistent with the current protocol template.</li><li>- Updated the regulatory status of rotigotine for the treatment of RLS in adults in the US.</li><li>- Removed the requirement for the PK blood samples to be centrifuged at a controlled temperature.</li><li>- Corrected typographic errors and minor inconsistencies of an editorial nature.</li></ul>

Notes:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported