18 August 2016
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Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Neupro

rotigotine

Procedure no: EMEA/H/C/000626/P46/046

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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London, 18 August 2016
Committee for Medicinal Products for Human Use (CHMP)

Preliminary assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Neupro

International non-proprietary name: Rotigotine

Procedure no.: EMA/H/C/626/P46

Marketing authorisation holder (MAH): UCB Manufacturing Ireland Ltd.

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1. Introduction

On 07JUN2016, the MAH submitted a completed paediatric study for Neupro, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that An open-label, long-term follow-up study to determine the safety, tolerability, and efficacy of rotigotine transdermal system as monotherapy in adolescents with Restless Legs Syndrome - SP1005 is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

The rotigotine transdermal patch was supplied by the UCB Clinical Trial Supply group and was administered in the following doses and sizes: 0.2mg/24h (1cm2), 0.5mg/24h (2.5cm2), 1mg/24h (5cm2), 2mg/24h (10cm2), and 3mg/24h (15cm2).

The batch numbers of rotigotine in this study were as follows: (0.2mg/24h [1cm2]); (0.5mg/24h [2.5cm2]); (1mg/24h [5cm2]); (2mg/24h [10cm2]); (3mg/24h [15cm2]).

2.3. Clinical aspects

2.3.1. Introduction

MAH has submitted the results of the SP1005 study (an open-label, long-term follow-up study to determine the safety, tolerability, and efficacy of rotigotine transdermal system as monotherapy in adolescents with Restless Legs Syndrome) in accordance with Article 46 of Regulation (EC) No 1901/2006 (The Paediatric Regulation), which requires Sponsors to report new study results in paediatric subjects.

Investigational medicinal product: Rotigotine

The MAH submitted a final report for:

- SP1005 study (an open-label, long-term follow-up study to determine the safety, tolerability, and efficacy of rotigotine transdermal system as monotherapy in adolescents with Restless Legs Syndrome)

2.3.2. Clinical study

SP1005 study (an open-label, long-term follow-up study to determine the safety, tolerability, and efficacy of rotigotine transdermal system as monotherapy in adolescents with Restless Legs Syndrome)

Description

SP1005 was a Phase 2A, multicenter, open-label, single-arm, optimal dose, long-term follow-up study of monotherapy administration of the rotigotine transdermal patch. Subjects entering this study from a previous rotigotine pharmacokinetic (PK) study in adolescents with RLS (SP1004; filed to Article 46 at

the end of 2014) must have tolerated the first dose level of rotigotine in that study without meeting any of the withdrawal criteria.

Methods

Objective(s)

The primary objective of this study was to assess the long-term safety and tolerability of rotigotine treatment in adolescents with idiopathic Restless Legs Syndrome (RLS).

The secondary objective of this study was to assess the long-term efficacy of rotigotine treatment in adolescents with idiopathic RLS.

Study design

This was a Phase 2A, multicenter, open-label, single-arm, optimal dose, long-term follow-up (LTFU) study of monotherapy administration of the rotigotine transdermal patch. Subjects entering this study from a previous rotigotine study in adolescents with RLS (SP1004) must have tolerated the first dose level of rotigotine in that study without meeting the withdrawal criteria.

The study began with a Titration Period of up to 4 weeks with the aim of achieving the individually optimized dosage (with a maximum dose of 3mg/24h at Visit 4 of SP1005). During the Titration Period, the investigator should have determined whether the subject had reached his/her optimal dose prior to completing the scheduled assessments for that visit. Once a subject had reached his/her optimal dose, he/she should have proceeded to the Maintenance Period (Visit 5) and completed those assessments.

The Titration Period was followed by a Maintenance Period of up to 2 years. Dose adjustment of rotigotine was allowed at any time during the Maintenance Period, based on clinical judgment up to a maximum dose of 3mg/24h. At the End of the Maintenance Period (EOM), subjects entered a Taper Period lasting up to 6 days (de-escalation of study medication), followed by a 30-day Safety Follow-up (SFU) Period.

Study population /Sample size

No formal sample size calculation was performed for this study. A maximum of 24 subjects from SP1004 were expected to participate in SP1005, based on the assumption that all planned subjects from SP1004 rolled over into SP1005.

A total of 14 subjects from SP1004 were enrolled during the study, and 14 subjects were treated with study medication. Of these 14 subjects, 1 subject completed the study.

Treatments

The rotigotine transdermal patch was supplied by the UCB Clinical Trial Supply group and was administered in the following doses and sizes: 0.2mg/24h (1cm2), 0.5mg/24h (2.5cm2), 1mg/24h (5cm2), 2mg/24h (10cm2), and 3mg/24h (15cm2).

The study began with a Titration Period of up to 4 weeks with the aim of achieving the individually optimized dosage (with a maximum dose of 3mg/24h at Visit 4 of SP1005). The Titration Period was followed by a Maintenance Period of up to 2 years. At the EOM, subjects entered a Taper Period of up to 6 days, followed by a 30-day SFU Period.

The mean number of days of study medication exposure for the Safety Set (SS) was 245.2 days.

Outcomes/endpoints

Safety:

Primary safety variables included:

- Adverse events (AEs), treatment-emergent AEs (TEAEs), serious TEAEs, drug-related TEAEs, TEAEs leading to withdrawal, nonserious TEAEs, and fatal TEAEs

Other safety variables included:

- Changes from Baseline at Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, Visit 13, Visit 14, EOM, EOM/Early Discontinuation Visit (EOM/EDV), and the SFU Visit in 12-lead ECG parameters
- Changes from Baseline at Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, Visit 13, Visit 14, EOM, and EOM/EDV, and the SFU Visit in vital sign parameters
- Neurological examination findings at Visit 5, Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, Visit 13, Visit 14, EOM, EOM/EDV, and the SFU Visit for each parameter
- Skin tolerability at Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, Visit 13, Visit 14, EOM, and EOM/EDV
- Changes from Baseline at Visit 5, Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, Visit 13, Visit 14, EOM, and EOM/EDV in hormone status parameters
- Changes from Baseline at Visit 5, Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, Visit 13, Visit 14, EOM, EOM/EDV, and the SFU Visit in laboratory test parameters (hematology, blood chemistry, and urinalysis)
- Menstrual and sexual function at Visit 5, Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, Visit 13, Visit 14, EOM, EOM/EDV, and the SFU Visit
- Changes from Baseline at Visit 5, Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, Visit 13, Visit 14, EOM, and EOM/EDV in modified Minnesota Impulsive Disorders Interview (mMIDI)
- Changes from Baseline at Visit 5, Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, Visit 13, Visit 14, EOM, EOM/EDV, and the SFU Visit in body weight, height, and calculated body mass index (BMI)
- Tanner Stage assessment at Visit 5, Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, Visit 13, Visit 14, EOM, and EOM/EDV
- Clinical Global Impressions (CGI) Item 4 (Side Effects) at Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, Visit 13, Visit 14, EOM, and EOM/EDV
- Global subject rating of tolerability at EOM and EOM/EDV

Efficacy:

Efficacy variables included:

- Changes from Baseline at Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, Visit 13, Visit 14, EOM, and EOM/EDV in the ratio of average number of periodic limb movements (PLMs)/hour measured by ankle actimetry

- Changes from Baseline at Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, Visit 13, Visit 14, EOM, and EOM/EDV in International Restless Legs Syndrome Study Group Rating Scale© (IRLS©) sum score
- Changes from Baseline in CGI Item 1 (Severity of Illness) at Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, Visit 13, Visit 14, EOM, and EOM/EDV
- CGI Item 2 (Global Rating of Change of Condition) at Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, Visit 13, Visit 14, EOM, and EOM/EDV
- CGI Item 3 (Therapeutic Effect) at Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, Visit 13, Visit 14, EOM, and EOM/EDV
- Changes from Baseline at Visit 5, Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, Visit 13, Visit 14, EOM, and EOM/EDV in Restless Legs Syndrome-6 Rating Scales (RLS-6)
- Other variables included:
- Changes from Baseline at Visit 5, Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, Visit 13, Visit 14, EOM, and EOM/EDV in Attention Deficit Hyperactivity Disorder (ADHD) Rating Scale-IV
- Changes from Baseline at Visit 5, Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, Visit 13, Visit 14, EOM, and EOM/EDV in Cleveland Adolescent Sleepiness Questionnaire
- Changes from Baseline at Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, Visit 13, Visit 14, EOM, and EOM/EDV in sleep duration
- Patch adhesiveness at Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, Visit 13, Visit 14, EOM, and EOM/EDV

Pharmacokinetics (PK):

The PK variable included:

- Plasma concentration of unconjugated rotigotine at Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, and Visit 7

Statistical Methods

All statistical analyses were considered exploratory in nature. A complete set of data listings containing all documented data and all calculated data (eg, change from Baseline) were generated and were sorted by site, subject number, and visit (where applicable). Descriptive statistics were displayed to provide an overview of the safety, efficacy, and PK results. For categorical parameters, the number and percentages of subjects in each category were presented overall for all subjects, or by dose level or modal dose, as appropriate. The denominator for percentages was based on the number of subjects appropriate for the purpose of the analysis. For continuous parameters, descriptive statistics included number of subjects (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum and were presented by treatment. Summary statistics were presented overall and by modal dose.

Baseline for IRLS, RLS-6, CGI Items 1 through 4, safety variables (eg, laboratory data, ECG findings, vital signs), and other variables (ADHD Rating Scale-IV, Cleveland Adolescent Sleepiness Questionnaire, patch adhesiveness) was defined as the last nonmissing scheduled or unscheduled assessment prior to first rotigotine administration in SP1004, unless otherwise noted for a specific type of data. Baseline for PLMs and for sleep duration was defined as the average of the repeated assessments before first rotigotine administration in SP1004.

All enrolled subjects who signed informed consent for SP1005 were included in the Enrolled Set (ES). All safety and PK analyses were performed on the SS, which included all subjects in the ES who received at least 1 dose of study medication. All efficacy analyses were performed on the Full Analysis Set (FAS), which included all subjects in the SS who had at least 1 post-Baseline efficacy measurement.

The duration of rotigotine exposure overall for the entire study, during the Titration Period, Maintenance Period, and Taper Period, and by visit was summarized with quantitative statistics for the SS.

The safety of rotigotine was the primary endpoint in this study and was assessed via AEs, laboratory data, ECG parameters, vital signs, neurological examination findings, skin tolerability, hormone status, menstrual and sexual function, mMIDI results, body weight, height, BMI, Tanner Stage, and CGI Item 4.

Results

Recruitment / Number analysed

Subject disposition: A total of 14 subjects were enrolled in the study (signed informed consent) and were treated with study medication. Overall, of the 14 subjects, 1 subject (7.1%) completed the study, and 13 subjects (92.9%) discontinued the study. The most common reason for discontinuation from the study was consent withdrawn (5 subjects [35.7%]).

Of the 14 subjects who were enrolled in the study, 11 subjects (78.6%) completed all 4 titration steps. One subject (7.1%) attained the optimal dose of 0.5mg/24h, 2 subjects (14.3%) attained the optimal dose of 2mg/24h, and 11 subjects (78.6%) attained the optimal dose of 3mg/24h. No subjects attained the optimal dose of 1mg/24h.

Baseline data

Demographics summary (SS)

Variable	Statistics	All subjects N=14
Age (years)	Mean (SD)	15.4 (1.2)
	Median	15.0
	Min, max	14, 17
Age (years)		
14	n (%)	4 (28.6)
15		4 (28.6)
16		3 (21.4)
17		3 (21.4)
Gender		
Male	n (%)	4 (28.6)
Female		10 (71.4)
Racial group		
Black	n (%)	5 (35.7)
White		9 (64.3)
Ethnicity		
Not Hispanic or Latino	n (%)	12 (85.7)
Hispanic or Latino		2 (14.3)
Weight (kg)	Mean (SD)	66.34 (8.89)
	Median	65.85
	Min, max	52.4, 84.5
Height (cm)	Mean (SD)	166.33 (6.71)
	Median	167.46
	Min, max	153.7, 175.3
BMI (kg/m^2)	Mean (SD)	23.971 (2.816)
	Median	23.595
	Min, max	18.12, 29.18

BMI=body mass index; max=maximum; Min=minimum; SD=standard deviation; SS=Safety Set
Note: Age calculations were based on date of birth (integer[date of informed consent in SP1004-date of birth]/365.25). The BMI calculations were based on weight and height at Screening in SP1004 (weight[kg]/height[m]**2). At Screening, Weight in (lb) was converted to (kg), Height in (in) was converted to (cm).

Overall, the mean age of the 14 subjects treated with study medication was 15.4 years (range: 14 to 17 years). Of these 14 subjects, 4 of the subjects were 14 years of age, 4 of the subjects were 15 years of age, 3 of the subjects were 16 years of age, and 3 of the subjects were 17 years of age; no subjects were 13 years of age or 18 to <65 years of age. The majority of subjects were female (71.4%) and white (64.3%). No subjects were American Indian or Alaska native, Asian, Native Hawaiian or other Pacific Islander, or other/mixed. The mean height, weight, and BMI were 166.33cm, 66.34kg, and 23.971kg/m2, respectively.

A total of 13 subjects (92.9%) in the SS reported a history of any prior or concomitant condition (except RLS). The most common conditions by SOC were Nervous system disorders (57.1%); Injury, poisoning and procedural complications (42.9%); and Psychiatric disorders (42.9%).

Nine subjects (64.3%) in the SS reported concomitant medication use. The most common concomitant medications by level 1 anatomical therapeutic chemical class were nervous system medications (57.1%) and anti-infectives for systemic use, musculoskeletal system medications, and respiratory system medications (28.6% each).

The mean time since the first RLS symptoms for subjects in the SS was 4.9 years (range: 0 to 13 years), and the mean time since RLS diagnosis was 0.9 years (range: 0 to 3 years).

A summary of the descriptive statistics for compliance rate is presented in Table below:

Descriptive statistics for compliance rate (SS)

Time Period	**Statistic**	**All subjects N=14 n (%)**
Overall study		
Overall compliance (%)	n	14
	Mean (SD)	98.31 (9.21)
	Median	98.65
	Min, max	83.6, 119.4
Overall compliance		
<85%	n (%)	2 (14.3)
85% to 115%		11 (78.6)
>115%		1 (7.1)
Titration Period		
Titration Period compliance (%)	n	14
	Mean (SD)	102.28 (11.40)
	Median	100.00
	Min, max	75.9, 118.3
Titration Period compliance		
<85%	n (%)	1 (7.1)
85% to 115%		11 (78.6)
>115%		2 (14.3)

Mean compliance across visits was high (range: 88.50% to 107.80%). Mean compliance during the Titration and Maintenance Periods was 102.28% and 95.92%, respectively. The majority of subjects were 85% to 115% compliant at each study visit during the Titration and Maintenance Periods (Table 6.2).

Overall, 2 subjects (Subject and Subject) were <85% compliant and 1 subject (Subject) was >115% compliant during the study. During the Titration Period, Subject was <85% compliant and Subject and Subject were >115% compliant. During the Maintenance Period, Subject and Subject were <85% compliant and Subject was >115% compliant.

Efficacy results

Change from Baseline in periodic limb movements

The mean PLMI at Baseline was generally similar across all modal dose categories (mean range: 5.760/h to 16.585/h) (Table 12.1). The mean PLMI ratios relative to Baseline generally decreased across visits for all modal dose categories (mean range from Month 7 to EOM/EDV: 0.150/h to 0.840/h).

Change from Baseline in International Restless Legs Syndrome Study Group Rating Scale

A summary of the change from Baseline in IRLS by modal dose is presented below:

Change from Baseline in IRLS by modal dose (FAS)

Variable Visit	Statistic	Rotigotine		
		0.5mg/24h N=2	2mg/24h N=2	3mg/24h N=10
Baseline	n	2	2	10
	Mean (SD)	27.5 (3.5)	23.5 (4.9)	26.0 (5.1)
	Median (min, max)	15.5 (12, 19)	23.5 (20, 27)	23.0 (20, 36)
Change from Baseline				
Day 8	n	2	2	10
	Mean (SD)	-12.0 (8.5)	-7.0 (4.2)	-8.8 (4.3)
	Median (min, max)	-12.0 (-18, -6)	-7.0 (-10, -4)	-8.5 (-15, -1)
Day 15	n	1	2	10
	Mean (SD)	-19.0	-11.0 (2.8)	-11.2 (6.7)
	Median (min, max)	-19.0 (-19, -19)	-11.0 (-13, -9)	-11.0 (-20, -1)
Day 22	n	1	1	10
	Mean (SD)	-19.0	-11.0	-13.4 (5.7)
	Median (min, max)	-19.0 (-19, -19)	-11.0 (-11, -11)	-11.5 (-25, -8)
Month 1	n	--	2	10
	Mean (SD)	--	-19.5 (10.6)	-14.3 (6.9)
	Median (min, max)	--	-19.5 (-27, -12)	-14.0 (-28, -3)
Month 2	n	--	2	10
	Mean (SD)	--	-17.5 (13.4)	-14.8 (6.8)
	Median (min, max)	--	-17.5 (-27, -8)	-13.0 (-30, -5)
Month 3	n	--	2	10
	Mean (SD)	--	-19.5 (10.6)	-16.5 (6.5)
	Median (min, max)	--	-19.5 (-27, -12)	-15.5 (-29, -6)
Month 4	n	--	2	8
	Mean (SD)	--	-19.5 (10.6)	-19.0 (6.3)
	Median (min, max)	--	-19.5 (-27, -12)	-16.5 (-31, -12)
Month 7	n	--	1	7
	Mean (SD)	--	-27	-21.3 (7.7)
	Median (min, max)	--	-27.0 (-27, -27)	-22.0 (-32, -13)

Variable Visit	Statistic	Rotigotine		
		0.5mg/24h N=2	2mg/24h N=2	3mg/24h N=10
Month 10	n	--	1	6
	Mean (SD)	--	-27	-18.8 (8.4)
	Median (min, max)	--	-27.0 (-27, -27)	-18.0 (-32, -9)
Month 13	n	--	1	3
	Mean (SD)	--	-27	-17.7 (6.8)
	Median (min, max)	--	-27.0 (-27, -27)	-20.0 (-23, -10)
Month 16	n	--	1	1
	Mean (SD)	--	-27	-25.0
	Median (min, max)	--	-27.0 (-27, -27)	-25.0 (-25, -25)
Month 19	n	--	1	1
	Mean (SD)	--	-27	-32.0
	Median (min, max)	--	-27.0 (-27, -27)	-32.0 (-32, -32)
Month 22	n	--	--	1
	Mean (SD)	--	--	-32.0
	Median (min, max)	--	--	-32.0 (-32, -32)
EOM	n	--	--	1
	Mean (SD)	--	--	-30.0
	Median (min, max)	--	--	-30.0 (-30, -30)
EOM/EDV	n	2	2	9
	Mean (SD)	-12.5 (9.2)	-19.5 (10.6)	-18.0 (8.6)
	Median (min, max)	-12.5 (-19, -6)	-19.5 (-27, -12)	-14.0 (-32, -9)

EOM=End of Maintenance; EOM/EDV=End of Maintenance/Early Discontinuation Visit; FAS=Full Analysis Set; IRLS=International Restless Legs Syndrome Study Group Rating Scale; max=maximum; min=minimum; SD=standard deviation

Note: Baseline was defined as the last assessment before first dosing in SP1004.

Note: If at least 1 item from the IRLS Questionnaire was missing, the sum score was not calculated.

Note: Modal dose was calculated across all study days on or after the first dose of study medication and up to and including the day of the last dose of study medication. It was the most frequently taken daily dose during this period.

Note: Modal dose categories: 0.5mg/24h represents doses <1.0mg/24h, 1mg/24h represents doses from 1.0 to <2.0mg/24h, 2mg/24h represents doses from 2.0 to <3.0mg/24h, 3mg/24h represents doses equal to 3.0mg/24h.

Note: There were no subjects in the 1mg/24h modal dose category.

The severity of RLS at Baseline was similar across all modal dose categories based on the mean IRLS sum scores (mean range: 23.5 to 27.5 points).

Mean reductions in the IRLS sum score were observed across visits for all modal dose categories (mean range at EOM/EDV: -19.5 to -12.5 points), indicating a lower severity of RLS.

Change from Baseline in Clinical Global Impressions items

Change from Baseline in CGI Item 1 (severity of illness) by modal dose (FAS)

Variable Visit	Statistic	Rotigotine		
		0.5mg/24h N=2	2mg/24h N=2	3mg/24h N=10
Baseline	n	2	2	10
	Mean (SD)	5.0 (1.4)	4.0 (0.0)	4.5 (0.5)
	Median (min, max)	5.0 (4, 6)	4.0 (4, 4)	4.5 (4, 5)
Change from Baseline				
Day 8	n	2	2	10
	Mean (SD)	-2.5 (2.1)	-1.5 (2.1)	-1.0 (0.9)
	Median (min, max)	-2.5 (-4, -1)	-1.5 (-3, 0)	-1.0 (-2, 0)
Day 15	n	1	2	10
	Mean (SD)	-4.0	-2.0 (1.4)	-1.4 (1.3)
	Median (min, max)	-4.0 (-4, -4)	-2.0 (-3, -1)	-1.0 (-4, 0)
Day 22	n	1	1	10
	Mean (SD)	-4.0	-3.0	-1.8 (1.0)
	Median (min, max)	-4.0 (-4, -4)	-3.0 (-3, -3)	-2.0 (-3, 0)
Month 1	n	--	2	10
	Mean (SD)	--	-2.5 (0.7)	-2.0 (1.2)
	Median (min, max)	--	-2.5 (-3, -2)	-2.0 (-4, 0)
Month 2	n	--	2	10
	Mean (SD)	--	-2.5 (0.7)	-2.6 (0.8)
	Median (min, max)	--	-2.5 (-3, -2)	-2.0 (-4, -2)
Month 3	n	--	2	10
	Mean (SD)	--	-3.0 (0.0)	-2.6 (1.0)
	Median (min, max)	--	-3.0 (-3, -3)	-3.0 (-4, -1)
Month 4	n	--	2	8
	Mean (SD)	--	-2.0 (1.4)	-2.8 (0.7)
	Median (min, max)	--	-2.0 (-3, -1)	-3.0 (-4, -2)
Month 7	n	--	1	7
	Mean (SD)	--	-3.0	-2.9 (1.1)
	Median (min, max)	--	-3.0 (-3, -3)	-3.0 (-4, -1)

Variable Visit	Statistic	Rotigotine		
		0.5mg/24h N=2	2mg/24h N=2	3mg/24h N=10
Month 10	n	--	1	6
	Mean (SD)	--	-3.0	-3.0 (0.9)
	Median (min, max)	--	-3.0 (-3, -3)	-3.0 (-4, -2)
Month 13	n	--	1	3
	Mean (SD)	--	-3.0	-2.0 (0.0)
	Median (min, max)	--	-3.0 (-3, -3)	-2.0 (-2, -2)
Month 16	n	--	1	1
	Mean (SD)	--	-3.0	-2.0
	Median (min, max)	--	-3.0 (-3, -3)	-2.0 (-2, -2)
Month 19	n	--	1	1
	Mean (SD)	--	-3.0	-3.0
	Median (min, max)	--	-3.0 (-3, -3)	-3.0 (-3, -3)
Month 22	n	--	--	1
	Mean (SD)	--	--	-3.0
	Median (min, max)	--	--	-3.0 (-3, -3)
EOM	n	--	--	1
	Mean (SD)	--	--	-3.0
	Median (min, max)	--	--	-3.0 (-3, -3)
EOM/EDV	n	2	2	9
	Mean (SD)	-2.5 (2.1)	-2.0 (1.4)	-2.2 (1.0)
	Median (min, max)	-2.5 (-4, -1)	-2.0 (-3, -1)	-2.0 (-4, -1)

CGI=Clinical Global Impressions; EOM=End of Maintenance; EOM/EDV=End of Maintenance/Early Discontinuation Visit; FAS=Full Analysis Set; max=maximum; min=minimum; SD=standard deviation

Note: Baseline was defined as the last assessment before first dosing in SP1004.

Note: Modal dose was calculated across all study days on or after the first dose of study medication and up to and including the day of the last dose of study medication. It was the most frequently taken daily dose during this period.

Note: Modal dose categories: 0.5mg/24h represents doses <1.0mg/24h, 1mg/24h represents doses from 1.0 to <2.0mg/24h, 2mg/24h represents doses from 2.0 to <3.0mg/24h, 3mg/24h represents doses equal to 3.0mg/24h.

Note: There were no subjects in the 1mg/24h modal dose category.

Change from Baseline in Restless Legs Syndrome-6 Rating Scales

In general, the mean RLS-6 scores for individual items at Baseline were similar among the modal dose categories. For Items 1 through 6, mean reductions (indicating improvement) from Baseline were observed for all modal dose categories at all visits through the EOM/EDV, with the exception of Items 3, 4, and 5 (range: 0.0 to 1.0 points) for the rotigotine 0.5mg/24h modal dose category.

The mean change from Baseline value across all 6 items for all modal dose categories had the following ranges: -9.0 to 1.0 points.

Sleep duration

The derived sleep duration at Baseline was similar for all modal dose categories (mean range: 7.171h to 7.390h). Mean changes from Baseline in derived sleep duration were small at all visits for the rotigotine 2mg/24h and 3mg/24h modal dose categories (mean range across visits: -1.770h to 0.650h; no change from Baseline data exist for the rotigotine 0.5mg/24h modal dose category).

Pharmacokinetic results

As expected, mean plasma concentrations of unconjugated rotigotine generally increased in Mean plasma concentrations of unconjugated rotigotine normalized by body weight generally increased in parallel with dose for rotigotine 0.5mg/24h through 3mg/24hparallel with dose for rotigotine 0.5mg/24h through 3mg/24h.

Safety results

The mean number of days of study medication exposure for the SS was 245.2 days. Most subjects had a duration of exposure of >4 to ≤26 weeks (4 subjects [28.6%]) or >26 to ≤52 weeks (6 subjects [42.9%]). Two subjects (14.3%) had a duration of exposure of ≤4 weeks, and 1 subject (7.1%) had a duration of exposure of >104 weeks.

Overall summary of treatment-emergent adverse events by modal dose

Summaries of the incidence of TEAEs and nonserious TEAEs by modal dose for the SS are provided below. An overall summary of the incidence of TEAEs by modal dose for the SS is presented next:

Overall summary of TEAEs by modal dose (SS)

Category	Rotigotine			All subjects
	0.5mg/24h N=2 n (%)	2mg/24h N=2 n (%)	3mg/24h N=10 n (%)	N=14 n (%)
Any TEAEs	1 (50.0)	2 (100)	7 (70.0)	10 (71.4)
Serious TEAEs	0	0	0	0
Subject discontinuations due to TEAEs	1 (50.0)	1 (50.0)	1 (10.0)	3 (21.4)
Permanent withdrawal of study medication due to TEAEs	1 (50.0)	1 (50.0)	1 (10.0)	3 (21.4)
Drug-related TEAEs	1 (50.0)	1 (50.0)	3 (30.0)	5 (35.7)
Serious drug-related TEAEs	0	0	0	0
Severe TEAEs	0	0	0	0
All deaths	0	0	0	0
TEAEs leading to death	0	0	0	0

SFU=Safety Follow-Up; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: n=number of subjects reporting at least 1 TEAE in that category.
Note: All subjects included TEAEs from the Titration Period, Maintenance Period, Taper Period, and SFU Period.
Note: Modal dose was calculated across all study days on or after the first dose of study medication and up to and including the day of the last dose of study medication. It was the most frequently taken daily dose during this period.
Note: Modal dose categories: 0.5mg/24h represents doses <1.0mg/24h, 1mg/24h represents doses from 1.0 to <2.0mg/24h,2mg/24h represents doses from 2.0 to <3.0mg/24h, 3mg/24h represents doses equal to 3.0mg/24h.
Note: There were no subjects in the modal dose of 1mg/24h.

Overall, 10 subjects (71.4%) reported TEAEs, 3 subjects (21.4%) each reported discontinuations due to TEAEs and permanent withdrawal of study medication due to TEAEs, and 5 subjects (35.7%)

reported drug-related TEAEs. There were no serious TEAEs, serious drug-related TEAEs (per investigator assessment), severe TEAEs, or deaths during the study.

The most common TEAEs by PT (reported by ≥2 subjects in any treatment group) by modal dose (SS)

MedDRA (version 16.1) SOC PT	Rotigotine 0.5mg/24h N=2 n (%)	Rotigotine 2mg/24h N=2 n (%)	Rotigotine 3mg/24h N=10 n (%)	All subjects N=14 n (%)
Any TEAE	1 (50.0)	2 (100)	7 (70.0)	10 (71.4)
Gastrointestinal disorders	1 (50.0)	0	3 (30.0)	4 (28.6)
Nausea	1 (50.0)	0	3 (30.0)	4 (28.6)
Vomiting	1 (50.0)	0	2 (20.0)	3 (21.4)
Infections and infestations	0	1 (50.0)	4 (40.0)	5 (35.7)
Upper respiratory tract infection	0	1 (50.0)	2 (20.0)	3 (21.4)
Urinary tract infection	0	1 (50.0)	1 (10.0)	2 (14.3)

MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SFU=Safety Follow-Up; SOC=system organ class; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: N=number of subjects in that modal dose category; n=number of subjects reporting at least 1 TEAE within the SOC/PT; (%)=percentages are based on the number of subjects in the SS in that modal dose category.
Note: All subjects included TEAEs from the Titration Period, Maintenance Period, Taper Period, and SFU Period.
Note: Modal dose was calculated across all study days on or after the first dose of study medication and up to and including the day of the last dose of study medication. It was the most frequently taken daily dose during this period.
Note: Modal dose categories: 0.5mg/24h represents doses <1.0mg/24h, 1mg/24h represents doses from 1.0 to <2.0mg/24h,2mg/24h represents doses from 2.0 to <3.0mg/24h, 3mg/24h represents doses equal to 3.0mg/24h.
Note: There were no subjects in the modal dose of 1mg/24h.

Overall, the most frequently reported TEAEs were in the SOCs of Gastrointestinal disorders (4 subjects [28.6%]) and Infections and infestations (5 subjects [35.7%]) (Table 8–2). The most frequently reported TEAEs by PT overall were nausea (4 subjects [28.6%]), vomiting (3 subjects reported by >2 subjects.

The most frequently reported TEAEs (by PT) in the rotigotine 3mg/24h group were nausea (3 subjects [30.0%]), vomiting (2 subjects [20.0%]), and upper respiratory tract infection (2 subjects [20.0%]). No other TEAEs were reported by >1 subject within any modal dose category.

Treatment-emergent adverse events by intensity

All of the TEAEs in this study were mild or moderate in intensity (35.7% each); no severe TEAEs were reported

Deaths

No deaths occurred during this study.

Other serious adverse events

No serious TEAEs were reported during this study. One subject reported a posttreatment SAE of abortion spontaneous.

Clinical laboratory evaluation

Individual clinically relevant abnormalities

One subject had a clinical chemistry-related TEAE during the study: Subject, a 17-year-old white male, experienced a TEAE of blood sodium increased 166 days after the first dose of study medication; the subject was taking rotigotine 1mg/24h at TEAE onset. The TEAE was mild in intensity, not considered to be drug related, and resolved within 6 days. On the day of the TEAE onset (EOM/EDV), the subject had a high sodium value of 167mmol/L (normal range: 132 to 147mmol/L). At an unscheduled EOM/EDV.2, the subject had a normal sodium value of 145mmol/L. The subject also had a high sodium value at Month 1, Month 3, and the SFU Visit, which ranged from 149 to 155mmol/L.

One subject had a urinalysis-related TEAE during the study. Subject, a 16-year-old white female, experienced a TEAE of hematuria 23 day after removal of the last rotigotine patch. The TEAE was moderate in intensity, not considered to be drug related, and resolved within 9 days (Listing 6.2). On the day of TEAE onset (SFU Visit), the subject had occult blood results of 3+ (first result) and trace (second result), an amorphous crystal result of 4+, a bacteria result of 4+, and specimen appearance results of clear (first result) and turbid (second result). All other results for this subject were not clinically relevant (ie, findings of normal, negative, or trace) during the study.

Two subjects reported ECG-related TEAEs during the study. Subject, a 17-year-old white female, experienced a TEAE of ECG QTc prolonged 57 days after the first dose of study medication (ie, at Month 2); the subject was taking rotigotine 3mg/24h at the TEAE onset (Listing 6.2). The TEAE was mild in intensity, not considered to be drug related, and resolved within 28 days. The details of this subject's TEAE are included in the medical monitor review forms, located in the study files, based on the discussions between the medical monitor and site personnel. Subject, a 14-year-old white female, experienced a TEAE of sinus tachycardia 523 days after the first dose of study medication; the subject was taking rotigotine 2mg/24h at the TEAE onset (Listing 6.2). The TEAE was moderate in intensity, considered to be drug-related, and resolved within 1 day. The onset of the TEAE did not correspond to ECG results collected at a specified visit. The subject's heart rate was 78bpm at Baseline and ranged from 63 to 93bpm during the study.

Vital sign measurements

Five subjects had decreases in BP that was determined to be evidence of orthostatic hypotension by the investigator (ie, drop in SBP of ≥20mmHg and/or drop in DBP of ≥10mmHg at 1 and/or 3 minutes upon standing after remaining supine for 5 minutes). These events were considered to be asymptomatic orthostatic hypotension that was not clinically relevant for 4 of these subjects. One subject (Subject) experienced symptomatic orthostatic hypotension at Month 1 that was captured as a TEAE.

No clinically relevant changes from Baseline in BMI were observed for all subjects during the study. No weight-related TEAEs were reported during the study.

Skin tolerability

Most subjects (range: 50% to 100%) at each modal dose had no evidence of dermal irritation at the study medication application site at any visit. Five subjects (Subject, Subject, Subject, Subject, and Subject) had minimal erythema at any visit during the study. No subjects had evidence of definite erythema, any edema or papules, vesicular eruption, or strong reactions spreading beyond the study medication application site.

The majority of subjects (range: 75.0% to 100%) at each modal dose had no other effects at the study medication application site at any visit; 1 subject in the rotigotine 3mg/24h group had a slight glazed appearance at the study medication application site at Month 1, Month 7, and Month 10. No subjects had marked glazing, glazing with peeling and cracking, glazing with fissures, film of dried

serious exudate covering all or part of the study medication application site, or small petechial erosions and/or scabs.

Subject, a 17-year-old Black or African American female, experienced a TEAE of application site pruritus 111 days after the first dose of study medication; the subject was taking rotigotine 3mg/24h at the TEAE onset. The TEAE was mild in intensity, considered to be drug related, and resolved within 103 days. This TEAE was not associated with any evidence of dermal response or other effects at any visit.

Tanner Stage assessment and menstrual/sexual function

The majority of subjects (range: 80.0% to 100%) were Tanner Stage 5 at each modal dose during the study (Table 11.4). One subject in the rotigotine 3mg/24h group was Tanner Stage 3 at all visits, including Baseline, and 1 subject in the rotigotine 3mg/24h group was Tanner Stage 4 at Baseline and Month 1. No subjects were Tanner Stage 1 or 2 at any time point.

Three subjects reported changes in menstrual functioning as follows: Subject reported changes at Months 4, 7, and 10; Subject reported changes at the EOM/EDV; and Subject reported changes at the SFU Visit.

Subject reported a TEAE of dysmenorrhea 61 days after the first dose of study medication (ie, prior to Month 3); this TEAE was mild in intensity, was not considered to be drug related, and resolved within 231 days.

2.3.3. Discussion on clinical aspects

This was a Phase 2A, multicenter, open-label, single-arm, optimal dose, LTFU study of monotherapy administration of the rotigotine transdermal patch in adolescents with RLS. Subjects entering this study from a previous rotigotine study in adolescents with RLS (SP1004) must have tolerated the first dose level of rotigotine in that study without meeting the withdrawal criteria. The primary objective of this study was to assess the long-term safety and tolerability of rotigotine treatment in adolescents with idiopathic RLS. The secondary objective of this study was to assess the long-term efficacy of rotigotine treatment.

Fourteen subjects were enrolled and treated with study medication. The mean number of days of study medication exposure for treated subjects was 245.2 days. Of the 14 subjects, 1 subject completed the study. For the 13 subjects who discontinued the study, the most common reason for discontinuation from the study was consent withdrawn. Of the 14 enrolled subjects, 11 of these subjects attained an optimal dose of the rotigotine transdermal system of 3mg/24h. The subject demographics and Baseline characteristics of disease severity were representative of adolescent patients with idiopathic RLS who require pharmacologic treatment. The majority of subjects were Tanner Stage 5 at Baseline, indicating that the development of their external sex characteristics was that of an adult.

The results of this study demonstrated that the rotigotine transdermal system was well tolerated at doses up to 3mg/24h in adolescent subjects with idiopathic RLS. No safety issues were identified, and there were no deaths or serious TEAEs. The most commonly reported TEAEs were nausea, vomiting, and upper respiratory tract infection. The most frequently reported drug-related TEAEs by PT were nausea and vomiting and were consistent with the stimulation of dopamine receptors and the use of a transdermal patch. One subject in each dose group reported discontinuations due to TEAEs (nausea, vomiting, and drug screen positive). One posttreatment SAE of abortion spontaneous was reported; this SAE was severe in intensity, not considered to be drug related, and resolved within 1 day.

No consistent or clinically relevant changes from Baseline in hematology, clinical chemistry, urinalysis, or hormone status (for males or females) values across modal dose categories were observed. One subject had a TEAE of blood sodium increased, which was mild in intensity, and 1 subject had a TEAE of hematuria, which was moderate in intensity; both TEAEs were not considered to be drug related and resolved.

No consistent or clinically relevant changes in 12-lead ECG results or vital signs were observed for all subjects during the study. The TEAEs of ECG QTc prolonged and palpitations were reported by 1 subject each; both TEAEs were mild in intensity, not considered to be drug related, and resolved. One subject had a TEAE of sinus tachycardia and 1 subject had TEAEs of syncope, orthostatic hypotension, and presyncope, all of which were moderate in intensity and resolved; only the TEAE of sinus tachycardia was considered to be drug related.

The majority of subjects had no evidence of dermal irritation at the study medication application site and reported no side effects during the study on CGI Item 4. No subjects had a positive response, which would indicate the presence of compulsive behaviors, at Baseline or at the end of the study in any of the mMIDI modules.

Improvements at each modal dose were generally observed for most efficacy parameters including the IRLS, CGI Items 1 through 3, and select individual items of the RLS-6, indicating improvements in RLS symptoms and sleep. Mean reductions from Baseline in the ADHD Rating Scale-IV score and Cleveland Adolescent Sleepiness Questionnaire score were generally observed at all visits through the EOM/EDV for all modal dose categories, indicating improvements in attention and a lessening of sleepiness, respectively, in these subjects. Small decreases in derived sleep duration were observed for all modal dose categories. The majority of subjects had ≥75% patch adhesiveness for each modal dose category, and patch detachment was reported by no more than 1 subject at any visit.

Mean plasma concentrations of unconjugated rotigotine generally increased in parallel with dose for rotigotine 0.5mg/24h through 3mg/24h and were in the range of results from earlier studies both in adolescents and adults.

The results of this study suggest that the rotigotine transdermal system is safe and effective in adolescent subjects (14 to 17 years of age at Baseline) with idiopathic RLS. However, due to the small number of subjects, and the open-label design, the findings of this study should be interpreted with caution.

Safety

From the results obtained, the rotigotine transdermal system was well tolerated at doses up to and including 3mg/24h in adolescent subjects (14 to <18 years of age) with idiopathic RLS:

- Overall, the majority of TEAEs were consistent with the stimulation of dopamine receptors and the use of a transdermal patch.
- Overall, 10 subjects (71.4%) reported TEAEs and of these, 1, 2, and 7 subjects were in the rotigotine 0.5mg/24h, 2mg/24h, and 3mg/24h groups, respectively. The most frequently reported TEAEs by PT overall were nausea (4 subjects [28.6%]), vomiting (3 subjects [21.4%]) and upper respiratory tract infection (3 subjects [21.4%]). No other TEAEs were reported by >2 subjects.
- One subject each in the rotigotine 0.5mg/24h and 2mg/24h groups, and 3 subjects in the rotigotine 3mg/24h group reported drug-related TEAEs (per the investigator's assessment). The most frequently reported drug-related TEAEs by PT were nausea (21.4%) and vomiting (14.3%). No other drug-related TEAEs were reported by >1 subject.

- All of the TEAEs in this study were mild or moderate in intensity. One posttreatment SAE (abortion spontaneous) was severe in intensity.
- No deaths or serious TEAEs were reported during the study.
- One subject in each dose group reported discontinuations due to TEAEs (nausea, vomiting, and drug screen positive), which were mild or moderate in intensity and considered to be drug related.
- Eight subjects reported TEAEs that led to intervention. With the exception of 1 TEAE of nausea that led to withdrawal of study medication, none of the TEAEs leading to an intervention led to a change in the dose of the study medication. The majority of TEAEs resulted in the subject being administered a concomitant medication and were not drug related. □ In general, mean values for hematology, clinical chemistry, and hormone status (for males and females) parameters were within the normal ranges for subjects in all modal dose categories. Overall, no notable differences in hematology, clinical chemistry, or hormone status (for males or females) values across modal dose categories and no consistent or clinically relevant changes from Baseline were observed. No clinically relevant changes in urinalysis parameters were observed for any modal dose during the study.
- One subject had a TEAE of blood sodium increased, which was mild in intensity, and 1 subject had a TEAE of hematuria, which was moderate in intensity. Both TEAEs were not considered to be drug related and resolved. No other laboratory-related TEAEs were reported during the study.
- No clinically relevant changes in 12-lead ECG results, vital signs, or BMI were observed for all subjects during the study. None of the abnormal vital signs or 12-lead ECG results was considered to be clinically relevant by the investigator. No clinically relevant physical abnormalities were reported during the study.
- The TEAEs of ECG QTc prolonged and palpitations were reported by 1 subject each; both TEAEs were mild in intensity, not considered to be drug related, and resolved. One subject had a TEAE of sinus tachycardia and 1 subject had TEAEs of syncope, orthostatic hypotension, and presyncope, all of which were moderate in intensity and resolved; only the TEAE of sinus tachycardia was considered to be drug related.
- Most subjects (range: 50% to 100%) at each modal dose had no evidence of dermal irritation at the study medication application site at any visit. Five subjects had minimal erythema at any visit during the study. The majority of subjects (range: 75.0% to 100%) at each modal dose had no other effects at the study medication application site at any visit; 1 subject in the rotigotine 3mg/24h group had a slight glazed appearance at the study medication application site. One subject had a mild, drug-related TEAE of application site pruritus that resolved.
- No subjects had positive responses in any of the mMIDI modules during the study, indicating that no subjects reported compulsive behaviors. As a result, no subjects had a change from Baseline in their mMIDI response during the study.
- The majority of subjects were Tanner Stage 5 at each modal dose (range: 80.0% to 100%) during the study, indicating that the development of their external sex characteristics was that of an adult. Three subjects reported changes in menstrual functioning; 1 of these subjects reported a TEAE of dysmenorrhea that was mild in intensity, was not considered to be drug related, and resolved. No subjects reported changes in sexual function during the study.

- The majority of subjects (range: 70.0% to 100%) reported no side effects at all time points on CGI Item 4. Three subjects reported side effects that significantly interfered with the subjects' functioning or that outweighed therapeutic efficacy across visits. Moderate, drug-related TEAEs of sudden onset of sleep, nausea, and nausea and vomiting were reported by 1 subject each; all of these TEAEs resolved.
- One subject (100%) at EOM and 10 subjects (76.9%) at EOM/EDV reported their overall tolerability of the treatment as very good. Overall tolerability of treatment was reported as good, neither good nor bad, or bad at EOM/EDV by 1 subject (7.7%) each.
- No subjects reported that they had suicidal ideation or suicidal behavior during the study.

Efficacy

Due to the small number of subjects, as well as the open-label design of the study, the efficacy observations of this study should be interpreted with caution. The efficacy observations were as follows:

- The mean PLMI at Baseline was generally similar across all modal dose categories (mean range: 5.760/h to 16.585/h). The mean PLMI ratios relative to Baseline generally decreased across visits for all modal dose categories (mean range from Month 7 to EOM/EDV: 0.150/h to 0.840/h).
- The severity of RLS at Baseline was similar across all modal dose categories based on the mean IRLS sum scores (mean range: 23.5 to 27.5 points). Mean reductions in the IRLS sum score were observed across visits for all modal dose categories (mean range at EOM/EDV: -19.5 to -12.5 points), indicating a lower severity of RLS.
- The mean CGI Item 1 score at Baseline was similar across all modal dose categories (mean range: 4.0 to 5.0 points). The mean change from Baseline in CGI Item 1 score was generally similar across visits for all modal dose categories (mean range at EOM/EDV: -2.5 to -2.0 points).
- Most subjects reported improvements in their condition (CGI Item 2) and very good therapeutic efficacy of study medication (CGI Item 3) during the study.
- In general, mean reductions (indicating improvement) from Baseline were observed for RLS Items 1 through 6, ADHD Rating Scale-IV score, and Cleveland Adolescent Sleepiness Questionnaire score for all modal dose categories at all visits through the EOM/EDV.
- The derived sleep duration at Baseline was similar for all modal dose categories (mean range: 7.171h to 7.390h). Mean changes from Baseline in derived sleep duration were small visits: -1.770h to 0.650h; no change from Baseline data exist for the rotigotine 0.5 mg/24h modal dose category).
- Most subjects had ≥75% patch adhesiveness for each modal dose category; patch detachment was reported by no more than 1 subject at any visit. In addition, the percentage of subjects with ≥90% patch adhesiveness at the EOM/EDV was 75.0% (range: 50.0% to 100% across modal dose categories).

Conclusions

- The results of this study showed that the rotigotine transdermal system was rather well tolerated at doses up to and including 3mg/24h in adolescent subjects with idiopathic RLS. No safety issues were identified, and there were no deaths or serious TEAEs. All of the TEAEs were

mild or moderate in intensity; 1 severe posttreatment SAE that was not drug related (as per the investigator's assessment) was reported.

- Overall, the majority of TEAEs were consistent with the stimulation of dopamine receptors and the use of a transdermal patch. The most frequently reported TEAEs overall were nausea, vomiting, and upper respiratory tract infection, and the most frequently reported drug-related TEAEs were nausea and vomiting.
- Improvements at each modal dose category were observed in most efficacy parameters, including the IRLS, CGI Items 1 through 3, and select individual items of the RLS-6, indicating improvements in RLS symptoms and sleep.
- Mean plasma concentrations of unconjugated rotigotine were within expected values and generally increased in parallel with dose for rotigotine 0.5mg/24h to 3mg/24h.
- Based on the results of this long-term extension study, the rotigotine transdermal system appears to be safe and effective for adolescent subjects (14 to 17 years of age at Baseline) with idiopathic RLS. However, due to the small number of subjects, and the open-label design, the findings of this study should be interpreted with caution.

3. Rapporteur's CHMP overall conclusion and recommendation

Paediatric RLS is a rare disorder and may be self limited if related to a transient comorbidity such as iron deficiency. Therefore it is understood the low number of subjects being enrolled, and possibly the fact that most have withdrawn the consent to remain in study, as many might have improved spontaneously, without the need to be kept under treatment. Being an open label study, the true magnitude of efficacy cannot be ascertained. As such, we do not agree with MAH when they state that the drug appears to be efficacious in paediatric RLS, because we simply do not now.

Regarding safety, based on the results of SP1005 (ie, the long-term extension study to SP1004), the rotigotine transdermal system appears to be safe for adolescent subjects (14 to 17 years of age at Baseline) with idiopathic RLS when administered at doses up to and including 3mg/24h. No new safety concerns were identified in this study. However, due to the small number of subjects and the open-label design, the findings of this study should be interpreted with caution.

No changes to the approved EU Product Information for Neupro are proposed following the completion of this study. UCB is submitting this study in accordance with Article 46 of the Paediatric Regulation. The information is too scarce to deserve a listing in section 5.1 of SmPC.

☒ Fulfilled:

No regulatory action required.