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Human Medicines 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/P46/048

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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1. Introduction

On the 12th of September 2023, the MAH UCB submitted the results of the prematurely terminated paediatric study RL0007, an open-label, long-term follow-up study of monotherapy administration of the rotigotine transdermal system in adolescents (13 to 17 years of age) with idiopathic Restless Leg Syndrome (RLS), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

RL0007 was prematurely terminated by UCB because of unsatisfactory enrolment in the SP1006 parent study. Additionally, only 10 out of 18 study participants (56%) who completed this parent study were enrolled in study RL0007; 9 out of the 10 study participants (90%) who enrolled in study RL0007 received the investigational medicinal product (IMP). Despite extensive and diligent outreach efforts to increase enrolment in these studies, there appeared to be low interest from the population of adolescents with idiopathic RLS, which contributed to the insufficient enrolment.

A short critical expert overview was provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study RL0007, a Remote, 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, and study SP1006, are stand-alone studies.

2.2. Information on the pharmaceutical formulation used in the study<ies>

Rotigotine, a dopamine agonist, has been formulated as a transdermal delivery system and is designed to continuously provide rotigotine over a 24-hour period.

The rotigotine transdermal system has been approved in the EU for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease as monotherapy, and as adjunctive therapy in combination with levodopa over the course of the disease through to late stages, when the effect of levodopa wears off or becomes inconsistent and fluctuations of the therapeutic effect occur. In addition, the rotigotine transdermal system is approved for the symptomatic treatment of moderate-to-severe idiopathic RLS in adults in the EU. In the US, the rotigotine transdermal system is approved for the treatment of the signs and symptoms of early and advanced-stage idiopathic Parkinson's disease and for the treatment of moderate-to-severe primary RLS. In Japan, the rotigotine transdermal system is approved for the treatment of Parkinson's disease and for the symptomatic treatment of moderate-to-severe idiopathic RLS in adults.

Overall, UCB or licensed partners hold marketing authorizations for the rotigotine transdermal system in approximately 70 countries for the treatment of Parkinson's disease, and in approximately 40 countries for the treatment of RLS. The specific indication statement(s), approved formulation(s), and dosages for the rotigotine transdermal system may differ based on the country; thus, local labels should be consulted for further information.

In RL0007 study the rotigotine transdermal patch was administered in the following doses: 2mg/24h, and 3mg/24h.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for **RL007.**

2.3.2. Clinical study

RL007 - A Remote, 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

RL0007 was a Phase 3, remote, open-label, long-term follow-up study of monotherapy administration of the rotigotine transdermal system. Study participants who entered this study from the parent rotigotine study in adolescents (SP1006) must have tolerated the first dose level of rotigotine in that study without meeting the withdrawal criteria.

The total study duration per study participant was approximately 14 months after study entry or until the IMP development was stopped by the sponsor. The study included a titration period of up to 3 weeks (at maximum), a maintenance period of up to 1 year, a taper period up to a maximum of 4 days (de-escalation of IMP), and a 30-day safety Follow-Up (SFU) period.

Methods

Study participants

The study was conducted in adolescent, 13 to 17 years of age, with idiopathic RLS.

Treatments

Rotigotine transdermal system.

Objective(s)

In RL0007, the primary objective 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 in adolescents with idiopathic RLS.

Outcomes/endpoints

Safety variables

The primary safety variables were as follows:

- Occurrence of treatment-emergent adverse events (TEAEs)
- TEAEs leading to permanent withdrawal of investigational medicinal product (IMP)

The other safety variables were as follows:

- Changes from Baseline (Visit 1, SP1006) in 12-lead electrocardiograms (ECGs)
- Changes from Baseline (Visit 1, SP1006) in vital signs (including assessment of orthostasis)

- Changes from Baseline (Visit 1, SP1006) in hormone status
- Changes from Baseline (Visit 1, SP1006) in laboratory data (hematology, clinical chemistry, and urinalysis)
- Changes from Baseline in menstrual function for all female study participants
- Changes in Modified Minnesota Impulsive Disorder Interview (mMIDI)
- Changes from Baseline (Visit 1, SP1006) in body weight, height, and body mass index (BMI)

Efficacy variables

The secondary efficacy variables were as follows:

- Changes from Baseline in International Restless Legs Rating Scale (IRLS) sum score at Visit 9
- Changes from Baseline in Clinical Global Impressions (CGI) Item 1 at Visit 9
- Changes from Baseline in Restless Legs-6 Rating Scales (RLS-6) at Visit 9 Note: Visit 9 was the end of Maintenance (EoM) Visit.

The other efficacy variables were as follows:

- Changes from Baseline in IRLS sum score at all visits except Visit 9
- Changes from Baseline in CGI Item 1 at all visits except Visit 9
- Changes from Baseline in RLS-6 at all visits except Visit 9
- Restless Legs Syndrome-Quality of Life Questionnaire (RLS-QoL)

Pharmacokinetic variable

The pharmacokinetic (PK) variable was plasma concentrations of rotigotine.

Study design

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The total study duration per study participant was approximately 14 months after study entry or until the IMP development was stopped by the sponsor. The study included a titration period of up to 3 weeks (at maximum), a maintenance period of up to 1 year, a taper period up to a maximum of 4 days (de-escalation of IMP), and a 30-day safety Follow-Up (SFU) period.

RL0007 was conducted using a remote study model, which integrated telemedicine technology into the clinical research process and supported management of research activities, including data collection. Study visits were completed using the unique technology platform called Science 37 Platform (PLATFORM), a software interface that connected study participants/legal representatives to their investigator/study teams through a study-issued smartphone. Mobile study personnel visited study participants'/legal representatives' homes to complete certain study procedures (e.g., neurological exams, physical exams, ECGs, lab collections, and vital signs).

The study began with Visit 1/Screening, and assessments were performed on the same day as the final evaluation visit of the parent rotigotine study (Visit 9 of SP1006).

The titration period of 3 weeks (starting at Visit 2/Day 1 and ending at Visit 5/Day 22) had the aim of achieving the individually optimized rotigotine dosage. Study participants were initiated on rotigotine 1mg/24h and were up-titrated on a weekly basis by 1mg/24h at a time (up to a maximum dosage of rotigotine 3mg/24h) until the optimal dose was reached. At each visit during the Titration Period, the investigator determined whether the study participant had reached his or her optimal dose prior to completing the scheduled assessments. Once study participants reached their optimal rotigotine dose (with a minimum dose of rotigotine 1mg/24h and a maximum dose of rotigotine 3mg/24h), they maintained that dose and completed the Titration Period without titrating to the next higher dose.

The maintenance period followed the titration period and had a planned duration of up to 1 year (starting at Visit 5 and ending at Visit 9 [EoM]). Dose adjustment (up-titration and down-titration) of rotigotine was allowed at any time during the maintenance period, based on the investigator's assessment of efficacy/tolerability, up to a maximum dose of rotigotine 3mg/24h. At Visit 9 (EoM), study participants entered a 4-day Taper Period (de-escalation of IMP) followed by a 30-day SFU Period.

Visits were scheduled every week during the titration period, every 3 months during the maintenance period, and at the end of the SFU period.

Procedures for a withdrawal visit were the same as for the EoM visit (Visit 9/Month 12), and assessments to be performed at an unscheduled visit were at the investigator's discretion.

Results

Overall, 10 study participants from the SP1006 parent study enrolled in RL0007. One study participant was lost to follow up before starting IMP in RL0007; therefore, this study participant was not included in the Safety Set (SS), which consisted of all study participants who had at least 1 rotigotine patch applied.

A total of 9 study participants were included in the SS: 2 study participants in the rotigotine 2mg/24h group and 7 study participants in the rotigotine 3mg/24h group. No study participants had a final titrated or back-titrated dose of rotigotine 1mg/24h upon entering the maintenance period, and thus results are only presented for 2 rotigotine dose groups (rotigotine 2mg/24h and rotigotine 3mg/24h) for this study.

Among the study participants included in the SS, 3 study participants (33.3%) completed the study and 6 study participants (66.7%) discontinued the study. The most common primary reason for study discontinuation was other and occurred for 3 study participants (33.3%); all 3 were related to compliance. Other primary reasons for study discontinuation were withdrawal by parent/guardian (2 study participants [22.2%]) and protocol deviation (1 study participant [11.1%]).

Study participant demographics

Overall, the mean age of study participants was 15.7 years (range: 14 to 17 years), and the median age of participants was 15.0 years.

Four study participants (44.4%) were female, and 5 study participants (55.6%) were male. The 2 study participants in the rotigotine 2mg/24h group were female.

Eight out of the 9 study participants were white (88.9%), and 1 study participant was black or African American (11.1%). All of the study participants were not of Hispanic or Latino ethnicity.

The mean weight, height, and BMI were 77.04kg, 169.01cm, and 26.89kg/m2, respectively. Three out of the 9 study participants had BMIs ≥30kg/m2 recorded at Baseline.

Baseline data

Diagnosis of RLS at Screening, including information about primary disease, augmentation, movement, and RLS confirmation and family affected, was collected in the parent study, SP1006.

Efficacy results

Because of the study's premature termination, no statistical tests of efficacy data were performed; however, descriptive summaries of a subset of efficacy data were produced. No imputation rules for missing data were applied.

For all efficacy measurements (ie, IRLS, CGI Item 1, RLS-6, and RLS-QoL), higher scores indicate worse disease.

Because of the small number of study participants, no efficacy conclusions were reached.

Secondary efficacy variables

IRLS

Variable Visit	Statistic	Rotigotine 2mg/24h N=2	Rotigotine 3mg/24h N=7	All participants N=9
SP1006 Baseline	n	2	7	9
	Mean (SD)	NA	25.1 (5.8)	24.1 (5.7)
	Median	NA	24.0	24.0
	Min, max	17, 24	17, 36	17, 36
Change from Baseline				
Visit 5 (SoM)	n	2	7	9
	Mean (SD)	NA	-10.9 (7.2)	-11.4 (6.6)
	Median	NA	-8.0	-10.0
	Min, max	-17, -10	-24, -4	-24, -4
Visit 9 Month 12 (EoM)	n	2	2	4
	Mean (SD)	NA	NA	-16.3 (5.9)
	Median	NA	NA	-15.5
	Min, max	-24, -17	-14, -10	-24, -10

EoM=End of Maintenance; IRLS=International Restless Legs Rating Scale; max=maximum; min=minimum; NA=not applicable; SD=standard deviation; SoM=Start of Maintenance; SS=Safety Set

The Baseline mean IRLS sum score across all participants was 24.1.

The 4 study participants who completed the maintenance period had reductions in IRLS sum score (disease improvement) from SP1006 Baseline to RL0007 EoM. There was a mean change in score of -16.3 and a median change in score of -15.5 at Month 12 (EoM).

CGI Item 1

Variable Visit	Statistic	Rotigotine 2mg/24h N=2	Rotigotine 3mg/24h N=7	All participants N=9
SP1006 Baseline	n	2	7	9
	Mean (SD)	NA	4.4 (0.5)	4.4 (0.5)
	Median	NA	4.0	4.0
	Min, max	4, 5	4, 5	4, 5
Change from Baseline				
Visit 5 (SoM)	n	2	7	9
	Mean (SD)	NA	-1.1 (0.7)	-1.2 (0.7)
	Median	NA	-1.0	-1.0
	Min, max	-2, -1	-2, 0	-2, 0
Visit 9 Month 12 (EoM)	n	2	2	4
	Mean (SD)	NA	NA	-2.5 (1.3)
	Median	NA	NA	-2.5
	Min, max	-4, -3	-2, -1	-4, -1

CGI=Clinical Global Impressions; EoM=End of Maintenance; max=maximum; min=minimum; NA=not applicable; SD=standard deviation; SoM=Start of Maintenance; SS=Safety Set

The baseline mean CGI Item 1 score across all participants was 4.4.

The 4 study participants who completed the maintenance period had reductions in CGI Item 1 score (disease improvement) from SP1006 Baseline to RL0007 EoM. There were mean and median changes in score of -2.5 each at Month 12 (EoM).

RLS-6

The 4 study participants who completed the maintenance period had reductions in RLS-6 score (disease improvement) from SP1006 Baseline to RL0007 EoM across all 6 subscales.

Other efficacy variables

Seven out of 9 study participants had reductions in RLS-QoL total score (i.e., disease improvement) from SP1006 Baseline to RL0007 EoM or Early Withdrawal Visit.

For the remaining other efficacy variables, changes from Baseline by visit in IRLS sum score, CGI Item 1, and RLS-6, data are provided for the SS.

Safety results

Extent of exposure

Investigational medicinal product duration was calculated including 1 additional day after the final patch removal. Investigational medicinal product duration ranged from 125.0 to 378.0 days, not including IMP exposure from the SP1006 parent study. Of note, only 3 of 9 study participants completed the Treatment Period.

Adverse Events

Summary of all TEAEs

Category	Rotigotine 2mg/24h N=2 n (%)	Rotigotine 3mg/24h N=7 n (%)	All participants N=9 n (%)
Any TEAEs	2 (100)	6 (85.7)	8 (88.9)
Serious TEAEs	0	0	0
Discontinuations due to TEAEs	0	0	0
Permanent withdrawal of IMP due to TEAEs	0	0	0
IMP-related TEAEs	2 (100)	4 (57.1)	6 (66.7)
Severe TEAEs	0	0	0
All deaths	0	0	0

IMP=investigational medicinal product; SS=Safety Set; TEAE=treatment-emergent adverse event

Overall, 8 study participants (88.9%) reported TEAEs. Six study participants (66.7%) reported TEAEs that were considered IMP-related by the investigator (2 study participants [100%] in the rotigotine 2mg/24h group and 4 study participants [57.1%] in the rotigotine 3mg/24h group). No deaths, severe TEAEs, serious TEAEs, or TEAEs leading to discontinuation or permanent withdrawal of IMP were reported.

Most common TEAEs

MedDRA (version 25.1) SOC PT	Rotigotine 2mg/24h N=2 n (%)	Rotigotine 3mg/24h N=7 n (%)	All participants N=9 n (%)
Any TEAE	2 (100)	6 (85.7)	8 (88.9)
Gastrointestinal disorders	0	3 (42.9)	3 (33.3)
Nausea	0	3 (42.9)	3 (33.3)
General disorders and administration site conditions	2 (100)	2 (28.6)	4 (44.4)
Application site erythema	2 (100)	2 (28.6)	4 (44.4)
Infections and infestations	2 (100)	3 (42.9)	5 (55.6)
Upper respiratory tract infection	1 (50.0)	1 (14.3)	2 (22.2)
Skin and subcutaneous tissue disorders	1 (50.0)	4 (57.1)	5 (55.6)
Pruritus	1 (50.0)	1 (14.3)	2 (22.2)

MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; SS=Safety Set; TEAE=treatment-emergent adverse event

The most commonly reported TEAEs by PT were application site erythema (4 study participants [44.4%]) and nausea (3 study participants [33.3%]); no other TEAEs were reported by >2 study participants.

TEAEs by maximum intensity

No severe TEAEs were reported during the study.

IMP-related TEAEs

Six study participants (66.7%), 2 study participants (100%) in the rotigotine 2mg/24h group and 4 study participants (57.1%) in the rotigotine 3mg/24h group, reported IMP-related TEAEs. The most commonly reported IMP-related TEAEs were application site erythema (4 study participants [44.4%]),

pruritus (2 study participants [22.2%]), and nausea (2 study participants [22.2%]); all were mild in intensity. No other IMP-related TEAE was reported by >1 study participant.

Deaths

No deaths were reported during the study.

Other serious AEs

No serious TEAEs were reported during the study.

Discontinuation due to AEs

No study discontinuations due to TEAEs were reported during the study.

Clinical laboratory evaluation

Overall, there were no clinically relevant mean changes from Baseline or notable shift patterns observed for any of the haematology, endocrinology, or clinical chemistry parameters evaluated during the study for the SS. In addition, no clinically relevant changes in urinalysis parameters were observed for the SS

No study participants in the SS met the criteria for potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality.

Other observations related to safety

Overall, there were no clinically relevant findings related to ECGs, vital signs, physical and neurological examinations, mMIDI data, or menstrual function and libido assessment for the SS.

No suicidal ideation as assessed by the Columbia-Suicide Severity Rating Scale was reported for the SS.

2.3.3. Discussion on clinical aspects

Because of the small number of study participants, no efficacy conclusions were reached.

The safety profile was consistent with the previous studies of rotigotine transdermal system, and no new or unexpected safety concerns were observed. There were no deaths, severe TEAEs, serious TEAEs, or study discontinuations due to TEAEs reported. These safety data suggest that both rotigotine 2mg/24hr and rotigotine 3mg/24hr were well tolerated in adolescent study participants with idiopathic RLS.

The safety profile of the adolescent participants who received rotigotine transdermal system treatment was consistent with the established safety profile of the rotigotine transdermal system in adults. No new safety concerns were identified in these participants and the results of the study do not impact the current benefit-risk balance of the rotigotine transdermal system.

Because of the small number of study participants, the efficacy and safety results from this study should be interpreted with caution.

The results of RL0007 are being submitted in accordance with Article 46 of Regulation (EC) No 1901/2006 (The Paediatric Regulation). No changes to the approved EU Product Information (PI) for NEUPRO are being proposed based on RL0007 results.

3. CHMP overall conclusion and recommendation

Due to the small number of study participants, the efficacy and safety results from this study should be interpreted with caution.

Notwithstanding, the safety profile of the adolescent participants (13 to 17 years of age) who received rotigotine transdermal system treatment was consistent with the established safety profile of the rotigotine transdermal system in adults. No new safety concerns were identified in this study.

The results of RL0007 are being submitted in accordance with Article 46 of Regulation (EC) No 1901/2006 (The Paediatric Regulation). No changes to the approved EU PI for NEUPRO are being proposed based on RL0007 results.

☒ PAM Fulfilled

No regulatory action required