



## Clinical trial results:

**A multi-center, randomized, double-blind, placebo-controlled, parallel group, polysomnography study to investigate safety and efficacy of the rotigotine transdermal patch in subjects with Restless Legs Syndrome and End-Stage Renal Disease requiring hemodialysis**

### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2011-003486-15  |
| Trial protocol           | DE FI AT IT     |
| Global end of trial date | 29 October 2013 |

### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 30 June 2016  |
| First version publication date | 02 April 2015 |

### Trial information

#### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | SP0934 |
|-----------------------|--------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01537042 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | UCB BIOSCIENCES GmbH  |
| Sponsor organisation address | Alfred-Nobel-Strasse 10, Monheim, Germany, 40789  |
| Public contact               | Clinical Trial Registry & Results Disclosure, UCB BIOSCIENCES GmbH, 49 2173 48 1515, clinicaltrials@ucb.com |
| Scientific contact           | Clinical Trial Registry & Results Disclosure, UCB BIOSCIENCES GmbH, 49 2173 48 1515, clinicaltrials@ucb.com |

Notes:

### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

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**Results analysis stage**

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|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 27 November 2013 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 29 October 2013  |
| Was the trial ended prematurely?                     | No               |

Notes:

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**General information about the trial**

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Main objective of the trial:

The primary objective of this trial is to demonstrate superiority of rotigotine against placebo in subjects with Restless Legs Syndrome (RLS) and End Stage Renal Disease (ESRD) requiring hemodialysis.

Protection of trial subjects:

The study was conducted under the auspices of an IRB/IEC, as defined in local regulations, ICH-GCP, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

Subject's informed consent was obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Background therapy:

N/A

Evidence for comparator:

N/A

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 25 April 2012 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | No            |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Germany: 5        |
| Country: Number of subjects enrolled | France: 4         |
| Country: Number of subjects enrolled | Italy: 1          |
| Country: Number of subjects enrolled | Finland: 2        |
| Country: Number of subjects enrolled | United States: 18 |
| Worldwide total number of subjects   | 30                |
| EEA total number of subjects         | 12                |

Notes:

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**Subjects enrolled per age group**

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|   |   |
|---|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |

|  |    |
|--|----|
| Infants and toddlers (28 days-23 months) | 0  |
| Children (2-11 years)                    | 0  |
| Adolescents (12-17 years)                | 0  |
| Adults (18-64 years)                     | 23 |
| From 65 to 84 years                      | 7  |
| 85 years and over                        | 0  |

## Subject disposition

### Recruitment

Recruitment details:

The recruitment for the SP0934 study began in April 2012. It concluded in October 2013. This was a multicenter study with subjects enrolled by 9 sites across Europe and 6 sites across the United States. The subject disposition consists of the Randomized Set (RS), which is all subjects randomized into SP0934.

### Pre-assignment

Screening details:

The SP0934 study enrolled 49 patients. Out of the 49 patients, 19 were screen failures. Therefore, there were 30 patients randomized into the SP0934 study.

### Period 1

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

### Arms

|                              |            |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes        |
| <b>Arm title</b>             | Rotigotine |

Arm description:

Rotigotine Transdermal Patch

1 mg/24 h, 2 mg/24 h or 3 mg/24 h once daily depending on optimal dose; maximal dose is 3 mg/24 h.

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

Dosage and administration details:

Transdermal patch; Dose: 1 mg/24 h, 2 mg/24 h or 3 mg/24 h once daily depending on optimal dose; maximal dose is 3 mg/24 h.

Subjects start with a Rotigotine dose of 1 mg/24 h for 1 week. The dose can be increased weekly during Up-Titration Period until either the optimal or the maximal dose of 3 mg/24 h has been reached.

Subjects will maintain the optimal/maximal dose during the 2-week Maintenance Period. Following the Maintenance Period, subjects will be de-escalated from their optimal dose by decreasing the dose by 1 mg/24 h every other day during Taper Period until complete withdrawal.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

Transdermal patch; Patches matching to active treatment patches in size and appearance.

Up to 3 weeks of Titration, 2 weeks of Maintenance, up to 4 days of Taper Period.

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

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Dosage and administration details:

Transdermal patch; Patches matching to active treatment patches in size and appearance.

Up to 3 weeks of Titration, 2 weeks of Maintenance, up to 4 days of Taper Period.

| <b>Number of subjects in period 1</b> | Rotigotine | Placebo |
|---------------------------------------|------------|---------|
| Started                               | 20         | 10      |
| Completed                             | 15         | 10      |
| Not completed                         | 5          | 0       |
| Other                                 | 1          | -       |
| AE, non-serious non-fatal             | 1          | -       |
| SAE, non-fatal                        | 1          | -       |
| Lack of efficacy                      | 1          | -       |
| Protocol deviation                    | 1          | -       |

## Baseline characteristics

### Reporting groups

|   |            |
|---|------------|
| Reporting group title   | Rotigotine |
| Reporting group description:<br>Rotigotine Transdermal Patch  |            |
| 1 mg/24 h, 2 mg/24 h or 3 mg/24 h once daily depending on optimal dose; maximal dose is 3 mg/24 h.                      |            |
| Reporting group title   | Placebo    |
| Reporting group description:<br>Transdermal patch; Patches matching to active treatment patches in size and appearance. |            |
| Up to 3 weeks of Titration, 2 weeks of Maintenance, up to 4 days of Taper Period.                                       |            |

| Reporting group values   | Rotigotine | Placebo | Total |
|--|------------|---------|-------|
| Number of subjects   | 20         | 10      | 30    |
| Age categorical  |            |         |       |
| The baseline analysis population consisted of the Safety Set (SS), which is all subjects who were randomized and had at least 1 patch applied during the Treatment Period. |            |         |       |
| Units: Subjects  |            |         |       |
| Adults (18-64 years)   | 15         | 8       | 23    |
| From 65-84 years   | 5          | 2       | 7     |
| Age continuous   |            |         |       |
| The baseline analysis population consisted of the Safety Set (SS), which is all subjects who were randomized and had at least 1 patch applied during the Treatment Period. |            |         |       |
| Units: years   |            |         |       |
| arithmetic mean  | 50.7       | 57.2    |       |
| standard deviation   | ± 16.3     | ± 12.6  | -     |
| Gender categorical   |            |         |       |
| The baseline analysis population consisted of the Safety Set (SS), which is all subjects who were randomized and had at least 1 patch applied during the Treatment Period. |            |         |       |
| Units: Subjects  |            |         |       |
| Female   | 7          | 3       | 10    |
| Male   | 13         | 7       | 20    |
| Race Group   |            |         |       |
| The baseline analysis population consisted of the Safety Set (SS), which is all subjects who were randomized and had at least 1 patch applied during the Treatment Period. |            |         |       |
| Units: Subjects  |            |         |       |
| American Indian/ Alaska Native   | 0          | 0       | 0     |
| Asian  | 0          | 0       | 0     |
| Black  | 6          | 2       | 8     |
| Native Hawaiian or Other Pacific Islander  | 0          | 0       | 0     |
| White  | 13         | 4       | 17    |
| Other/mixed  | 0          | 1       | 1     |
| Missing  | 1          | 3       | 4     |
| Ethnicity  |            |         |       |
| The baseline analysis population consisted of the Safety Set (SS), which is all subjects who were randomized and had at least 1 patch applied during the Treatment Period. |            |         |       |
| Units: Subjects  |            |         |       |
| Hispanic or Latino   | 3          | 2       | 5     |
| Not Hispanic or Latino   | 16         | 5       | 21    |

|  |         |         |    |
|--|---------|---------|----|
| Missing  | 1       | 3       | 4  |
| Region   |         |         |    |
| The baseline analysis population consisted of the Safety Set (SS), which is all subjects who were randomized and had at least 1 patch applied during the Treatment Period. |         |         |    |
| Units: Subjects  |         |         |    |
| US   | 12      | 6       | 18 |
| EU   | 8       | 4       | 12 |
| Weight   |         |         |    |
| The baseline analysis population consisted of the Safety Set (SS), which is all subjects who were randomized and had at least 1 patch applied during the Treatment Period. |         |         |    |
| Units: kilogram(s)   |         |         |    |
| arithmetic mean  | 89.42   | 85.38   |    |
| standard deviation   | ± 15.34 | ± 20.99 | -  |
| Height   |         |         |    |
| The baseline analysis population consisted of the Safety Set (SS), which is all subjects who were randomized and had at least 1 patch applied during the Treatment Period. |         |         |    |
| Units: Centimeters   |         |         |    |
| arithmetic mean  | 171.5   | 171.77  |    |
| standard deviation   | ± 11.99 | ± 8.59  | -  |
| BMI  |         |         |    |
| The baseline analysis population consisted of the Safety Set (SS), which is all subjects who were randomized and had at least 1 patch applied during the Treatment Period. |         |         |    |
| Units: kilogram(s)/square meter  |         |         |    |
| arithmetic mean  | 30.405  | 28.85   |    |
| standard deviation   | ± 4.262 | ± 6.182 | -  |

## End points

### End points reporting groups

|   |            |
|---|------------|
| Reporting group title   | Rotigotine |
| Reporting group description:<br>Rotigotine Transdermal Patch  |            |
| 1 mg/24 h, 2 mg/24 h or 3 mg/24 h once daily depending on optimal dose; maximal dose is 3 mg/24 h.                      |            |
| Reporting group title   | Placebo    |
| Reporting group description:<br>Transdermal patch; Patches matching to active treatment patches in size and appearance. |            |
| Up to 3 weeks of Titration, 2 weeks of Maintenance, up to 4 days of Taper Period.                                       |            |

### Primary: Ratio from Baseline to the end of the 2-week Maintenance Period in Periodic Limb Movement Index (PLMI)

|   |  |
|---|--|
| End point title   | Ratio from Baseline to the end of the 2-week Maintenance Period in Periodic Limb Movement Index (PLMI) |
| End point description:<br>The PLMI is defined as Periodic Limb Movements (PLMs)/ total time in bed in hours. PLMs are measured by Polysomnography (PSG).<br>The reduction of the PLMI is reflected in terms of the ratio from Baseline to the end of the Maintenance Period and was calculated as [PLMI at end of Maintenance Period (MP)] / [PLMI at Baseline].<br>A PLMI Ratio <1 indicates an improvement from Baseline to the end of the 2-week MP. |  |
| End point type  | Primary  |
| End point timeframe:<br>From Baseline over the Up-Titration Period (up to 3 Weeks) to the end of the 2-Week Maintenance Period.   |  |

| End point values                             | Rotigotine         | Placebo             |  |  |
|--|--------------------|---------------------|--|--|
| Subject group type                           | Reporting group    | Reporting group     |  |  |
| Number of subjects analysed                  | 15                 | 10                  |  |  |
| Units: Ratio                                 |                    |                     |  |  |
| least squares mean (confidence interval 95%) | 0.51 (0.33 to 0.8) | 1.16 (0.68 to 1.99) |  |  |

### Statistical analyses

|                            |                                      |
|----------------------------|--------------------------------------|
| Statistical analysis title | Primary Outcome Statistical Analysis |
| Comparison groups          | Rotigotine v Placebo                 |



|   |                      |
|---|----------------------|
| Number of subjects included in analysis | 25                   |
| Analysis specification                  | Pre-specified        |
| Analysis type                           | other <sup>[1]</sup> |
| P-value                                 | = 0.0232             |
| Method                                  | ANCOVA               |
| Parameter estimate                      | Treatment Ratio      |
| Point estimate                          | 0.44                 |
| Confidence interval                     |                      |
| level                                   | 95 %                 |
| sides                                   | 2-sided              |
| lower limit                             | 0.22                 |
| upper limit                             | 0.88                 |

Notes:

[1] - An analysis of covariance (ANCOVA) was performed for the log-transformed PLMI ratio with treatment and region as factors and Baseline as a covariate.

### Secondary: Change from Baseline in the Periodic Limb Movements Index (PLMI) to the end of the Maintenance Period

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in the Periodic Limb Movements Index (PLMI) to the end of the Maintenance Period |
|-----------------|---|

End point description:

The PLMI is defined as Periodic Limb Movements (PLMs)/ total time in bed in hours. PLMs are measured by Polysomnography (PSG). A negative value in change from Baseline indicates an improvement from Baseline to the end of the Maintenance Period.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline over the Up-Titration Period (up to 3 Weeks) to the end of the 2-Week Maintenance Period.

| End point values                     | Rotigotine      | Placebo         |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 15              | 10              |  |  |
| Units: movement/ hour                |                 |                 |  |  |
| arithmetic mean (standard deviation) | -23.7 (± 38.7)  | 10.3 (± 21)     |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in the International Restless Legs Syndrome Study Group Rating Scale (IRLS) sum score to the end of the Maintenance Period

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in the International Restless Legs Syndrome Study Group Rating Scale (IRLS) sum score to the end of the Maintenance Period |
|-----------------|---|

End point description:

The IRLS is a subject based scale that consists of 10 items to evaluate the severity of major RLS symptoms and the impact of the disease on subjects' functioning in daytime activities. Each of the 10 items is measured on a scale that ranges from 0 (not present) to 4 (severe). A sum score between 0 (no RLS symptoms present at all) and 40 (maximum severity in all symptoms) across all 10 items will be calculated.

A negative value in Change from Baseline indicates an improvement from Baseline in IRLS.

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| From Baseline over the Up-Titration Period (up to 3 Weeks) to the end of the 2-Week Maintenance Period. |           |

| End point values                     | Rotigotine      | Placebo         |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 15              | 10              |  |  |
| Units: units on a scale              |                 |                 |  |  |
| arithmetic mean (standard deviation) | -15.9 (± 9.1)   | -8.6 (± 7.2)    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in the Restless Legs-6 (RLS-6) Rating Scale 1 to the end of the Maintenance Period

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in the Restless Legs-6 (RLS-6) Rating Scale 1 to the end of the Maintenance Period |
|-----------------|---|

End point description:

The RLS-6 consists of six scales of which four scales are designed to assess severity of RLS and two scales cover sleep and daytime tiredness.

Scale 1 measures satisfaction with sleep during the last seven nights on an 11-point scale that ranges between 0 (completely satisfied) to 10 (completely dissatisfied). The ratings are given by the subjects. A negative value in Change from Baseline indicates an improvement from Baseline.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline over the Up-Titration Period (up to 3 Weeks) to the end of the 2-Week Maintenance Period

| End point values                     | Rotigotine      | Placebo         |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 15              | 10              |  |  |
| Units: units on a scale              |                 |                 |  |  |
| arithmetic mean (standard deviation) | -2.8 (± 3.2)    | -1.1 (± 3.5)    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in the Restless Legs-6 (RLS-6) Rating Scale 2 to the end of the Maintenance Period

|   |   |
|---|---|
| End point title   | Change from Baseline in the Restless Legs-6 (RLS-6) Rating Scale 2 to the end of the Maintenance Period |
| End point description:<br>The RLS-6 consists of six scales of which four scales are designed to assess severity of RLS and two scales cover sleep and daytime tiredness.<br>Scale 2 measures the severity of RLS symptoms during the last 7 nights in the situation of falling asleep. This is measured on an 11-point scale that ranges between 0 (none) to 10 (very severe). The ratings are given by the subjects.<br>A negative value in Change from Baseline indicates an improvement from Baseline. |   |
| End point type  | Secondary   |
| End point timeframe:<br>From Baseline over the Up-Titration Period (up to 3 Weeks) to the end of the 2-Week Maintenance Period  |   |

| End point values                     | Rotigotine      | Placebo         |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 15              | 10              |  |  |
| Units: units on a scale              |                 |                 |  |  |
| arithmetic mean (standard deviation) | -4.4 (± 2.9)    | -2.8 (± 2.9)    |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in the Restless Legs-6 (RLS-6) Rating Scale 3 to the end of the Maintenance Period

|  |   |
|--|---|
| End point title  | Change from Baseline in the Restless Legs-6 (RLS-6) Rating Scale 3 to the end of the Maintenance Period |
| End point description:<br>The RLS-6 consists of six scales of which four scales are designed to assess severity of RLS and two scales cover sleep and daytime tiredness.<br>Scale 3 measures the severity of RLS symptoms during the last seven nights on an 11-point scale that ranges between 0 (none) to 10 (very severe). The ratings are given by the subjects.<br>A negative value in Change from Baseline indicates an improvement from Baseline. |   |
| End point type   | Secondary   |
| End point timeframe:<br>From Baseline over the Up-Titration Period (up to 3 Weeks) to the end of the 2-Week Maintenance Period   |   |

| End point values                     | Rotigotine      | Placebo         |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 15              | 10              |  |  |
| Units: units on a scale              |                 |                 |  |  |
| arithmetic mean (standard deviation) | -4.7 (± 3.1)    | -3.2 (± 2.6)    |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in the Restless Legs-6 (RLS-6) Rating Scale 4 to the end of the Maintenance Period

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in the Restless Legs-6 (RLS-6) Rating Scale 4 to the end of the Maintenance Period |
|-----------------|---|

End point description:

The RLS-6 consists of six scales of which four scales are designed to assess severity of RLS and two scales cover sleep and daytime tiredness.

Scale 4 measures the severity of RLS symptoms during the last seven days at rest on an 11-point scale that ranges between 0 (none) to 10 (very severe). The ratings are given by the subjects.

A negative value in Change from Baseline indicates an improvement from Baseline.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline over the Up-Titration Period (up to 3 Weeks) to the end of the 2-Week Maintenance Period

| End point values                     | Rotigotine      | Placebo         |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 15              | 10              |  |  |
| Units: units on a scale              |                 |                 |  |  |
| arithmetic mean (standard deviation) | -2.6 (± 2.2)    | -1.6 (± 3.2)    |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in the Restless Legs-6 (RLS-6) Rating Scale 5 to the end of the Maintenance Period

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in the Restless Legs-6 (RLS-6) Rating Scale 5 to the end of the Maintenance Period |
|-----------------|---|

End point description:

The RLS-6 consists of six scales of which four scales are designed to assess severity of RLS and two scales cover sleep and daytime tiredness.

Scale 5 measures the severity of RLS symptoms during the last seven days engaged in activities on an 11-point scale that ranges between 0 (none) to 10 (very severe). The ratings are given by the subjects.

A negative value in Change from Baseline indicates an improvement from Baseline.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline over the Up-Titration Period (up to 3 Weeks) to the end of the 2-Week Maintenance Period

| End point values                     | Rotigotine      | Placebo         |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 15              | 10              |  |  |
| Units: units on a scale              |                 |                 |  |  |
| arithmetic mean (standard deviation) | -1.6 (± 2.7)    | -1.6 (± 2.1)    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in the Restless Legs-6 (RLS-6) Rating Scale 6 to the end of the Maintenance Period

|  |   |
|--|---|
| End point title  | Change from Baseline in the Restless Legs-6 (RLS-6) Rating Scale 6 to the end of the Maintenance Period |
| End point description:<br>The RLS-6 consists of six scales of which four scales are designed to assess severity of RLS and two scales cover sleep and daytime tiredness.<br>Scale 6 measures the severity of daytime tiredness/ sleepiness on an 11-point scale that ranges between 0 (not at all) to 10 (very severe). The ratings are given by the subjects.<br>A negative value in Change from Baseline indicates an improvement from Baseline. |   |
| End point type   | Secondary   |
| End point timeframe:<br>From Baseline over the Up-Titration Period (up to 3 Weeks) to the end of the 2-Week Maintenance Period   |   |

| End point values                     | Rotigotine      | Placebo         |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 15              | 10              |  |  |
| Units: units on a scale              |                 |                 |  |  |
| arithmetic mean (standard deviation) | -3.4 (± 2.3)    | -1.6 (± 2)      |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in the Periodic Limb Movement during Sleep Arousal Index (PLMSAI) to the end of the Maintenance Period

|   |   |
|---|---|
| End point title   | Change from Baseline in the Periodic Limb Movement during Sleep Arousal Index (PLMSAI) to the end of the Maintenance Period |
| End point description:<br>The Periodic Limb Movement during Sleep Arousal Index (PLMSAI) reflects the influence of the PLM on |   |

subject's sleep. Arousal is defined as sudden change in the Electroencephalogram (EEG) activity and the index illustrates to what degree the PLMs contribute to arousal from sleep.

A negative value in Change from Baseline indicates an improvement from Baseline.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline over the Up-Titration Period (up to 3 Weeks) to the end of the 2-Week Maintenance Period

| End point values                     | Rotigotine             | Placebo              |  |  |
|--------------------------------------|------------------------|----------------------|--|--|
| Subject group type                   | Reporting group        | Reporting group      |  |  |
| Number of subjects analysed          | 15                     | 10                   |  |  |
| Units: movement per hour             |                        |                      |  |  |
| arithmetic mean (standard deviation) | -1.609 ( $\pm$ 14.412) | 4.634 ( $\pm$ 7.162) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in sleep efficiency to the end of the Maintenance Period

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in sleep efficiency to the end of the Maintenance Period |
|-----------------|---|

End point description:

Sleep stages and time spent in each sleep stage are determined from Electroencephalogram (EEG) readings. Sleep stage data will be used to calculate sleep efficiency. Sleep efficiency will be presented as percentages. Sleep efficiency is the percentage of time in bed spent asleep.

A positive value in Change from Baseline indicates an improvement from Baseline.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline over the Up-Titration Period (up to 3 Weeks) to the end of the 2-Week Maintenance Period

| End point values                     | Rotigotine            | Placebo               |  |  |
|--------------------------------------|-----------------------|-----------------------|--|--|
| Subject group type                   | Reporting group       | Reporting group       |  |  |
| Number of subjects analysed          | 15                    | 10                    |  |  |
| Units: sleep time/ total time in bed |                       |                       |  |  |
| arithmetic mean (standard deviation) | 7.668 ( $\pm$ 12.317) | -2.85 ( $\pm$ 10.347) |  |  |

### Statistical analyses

No statistical analyses for this end point

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**Secondary: Change from Baseline in the Restless Legs-Quality of Life (RLS-QoL) total score to the end of the Maintenance Period**

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|                 |  |
|-----------------|--|
| End point title | Change from Baseline in the Restless Legs-Quality of Life (RLS-QoL) total score to the end of the Maintenance Period |
|-----------------|--|

End point description:

The RLS-QoL is a disease-specific questionnaire to evaluate quality of life. It consists of 12 items. A total score will be calculated from all of the 12 items. The overall sum score can be from 0 (highest QoL) to 60 (lowest QoL).

A negative value in Change from Baseline indicates an improvement from Baseline.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline over the Up-Titration Period (up to 3 Weeks) to the end of the 2-Week Maintenance Period

---

| End point values                     | Rotigotine      | Placebo         |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 15              | 9               |  |  |
| Units: scores on a scale             |                 |                 |  |  |
| arithmetic mean (standard deviation) | -10.7 (± 10.9)  | -10.2 (± 10.8)  |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Change from Baseline in the Short-Form-36 (SF-36) item questionnaire Mental Component Summary (MCS) to the end of the Maintenance Period**

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|                 |  |
|-----------------|--|
| End point title | Change from Baseline in the Short-Form-36 (SF-36) item questionnaire Mental Component Summary (MCS) to the end of the Maintenance Period |
|-----------------|--|

End point description:

The SF-36 is a 36 item generic human research quality of life instrument that uses a recall period of 4 weeks. Items are grouped into 8 domains as follows: Physical Functioning (10 items), Role Physical (4 items), Bodily Pain (2 items), General Health (5 items), Vitality (4 items), Social Functioning (2 items), Role Emotional (3 items), Mental Health (5 items), and a further unscaled single item (question 2) for perceived stability or change in health (Health Transition) during the last year. The norm based scores (based on the US general population) were used for analysis. For the MCS, the lowest and highest possible scores are -9 and 82 (rounded).

The SF-36 domains (subscores) are scored so that a higher score indicates a better health state.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline over the Up-Titration Period (up to 3 Weeks) to the end of the 2-Week Maintenance Period

---

| End point values                     | Rotigotine        | Placebo          |  |  |
|--------------------------------------|-------------------|------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed          | 14                | 9                |  |  |
| Units: units on a scale              |                   |                  |  |  |
| arithmetic mean (standard deviation) | 2.2 ( $\pm$ 10.1) | 6.4 ( $\pm$ 6.6) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in the Short-Form-36 (SF-36) item questionnaire Physical Component Summary (PCS) to the end of the Maintenance Period

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in the Short-Form-36 (SF-36) item questionnaire Physical Component Summary (PCS) to the end of the Maintenance Period |
|-----------------|--|

End point description:

The SF-36 is a 36 item generic human research quality of life instrument that uses a recall period of 4 weeks. Items are grouped into 8 domains as follows: Physical Functioning (10 items), Role Physical (4 items), Bodily Pain (2 items), General Health (5 items), Vitality (4 items), Social Functioning (2 items), Role Emotional (3 items), Mental Health (5 items), and a further unscaled single item (question 2) for perceived stability or change in health (Health Transition) during the last year. The norm-based scores (based on the US general population) were used for analysis. For the PCS, the lowest and highest possible scores are 1 and 81 (rounded).

The SF-36 domains (subscores) are scored so that a higher score indicates a better health state.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline over the Up-Titration Period (up to 3 Weeks) to the end of the 2-Week Maintenance Period

| End point values                     | Rotigotine       | Placebo           |  |  |
|--------------------------------------|------------------|-------------------|--|--|
| Subject group type                   | Reporting group  | Reporting group   |  |  |
| Number of subjects analysed          | 14               | 9                 |  |  |
| Units: units on a scale              |                  |                   |  |  |
| arithmetic mean (standard deviation) | 3.8 ( $\pm$ 6.3) | -0.3 ( $\pm$ 8.7) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in Clinical Global Impressions (CGI) Item 1 score (Visit 2)

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in Clinical Global Impressions (CGI) Item 1 score (Visit 2) |
|-----------------|--|

End point description:

The CGI Item 1 score measures the severity of illness on a scale that ranges from 0 (Not assessed) to 7 (Among the most extremely ill).



|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Visit 2 (Baseline)   |           |

| End point values                      | Rotigotine      | Placebo         |  |  |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type                    | Reporting group | Reporting group |  |  |
| Number of subjects analysed           | 15              | 10              |  |  |
| Units: participants                   |                 |                 |  |  |
| Not assessed                          | 0               | 0               |  |  |
| Normal, not ill at all                | 0               | 0               |  |  |
| Borderline ill                        | 0               | 0               |  |  |
| Mildly ill                            | 0               | 0               |  |  |
| Moderately ill                        | 3               | 3               |  |  |
| Markedly ill                          | 5               | 9               |  |  |
| Severely ill                          | 2               | 2               |  |  |
| Among the most extremely ill subjects | 0               | 1               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in Clinical Global Impressions (CGI) Item 1 score (Visit 6)

|   |  |
|---|--|
| End point title   | Change from Baseline in Clinical Global Impressions (CGI) Item 1 score (Visit 6) |
| End point description:  |  |
| The CGI Item 1 score measures the severity of illness on a scale that ranges from 0 (Not assessed) to 7 (Among the most extremely ill). |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| Visit 6 (End of Maintenance Period)   |  |

| End point values                      | Rotigotine      | Placebo         |  |  |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type                    | Reporting group | Reporting group |  |  |
| Number of subjects analysed           | 15              | 10              |  |  |
| Units: participants                   |                 |                 |  |  |
| Not assessed                          | 0               | 0               |  |  |
| Normal, not ill at all                | 5               | 1               |  |  |
| Borderline ill                        | 4               | 1               |  |  |
| Mildly ill                            | 3               | 3               |  |  |
| Moderately ill                        | 1               | 5               |  |  |
| Markedly ill                          | 2               | 0               |  |  |
| Severely ill                          | 0               | 0               |  |  |
| Among the most extremely ill subjects | 0               | 0               |  |  |

## **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events were recorded during the course of the SP0934 study, which began in April 2012 and concluded in October 2013.

Adverse event reporting additional description:

Adverse Events reporting refers to the Safety Set (SS). All subjects who are randomized and have at least 1 patch applied during the Treatment Period were included in the SS.

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Rotigotine |
|-----------------------|------------|

Reporting group description:

Adverse Event, Non-Serious Adverse Event and Serious Adverse Event reporting refers to the Safety Set (SS). All subjects who are randomized and have at least 1 patch applied during the Treatment Period were included in the SS.

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Adverse Event, Non-Serious Adverse Event and Serious Adverse Event reporting refers to the Safety Set (SS). All subjects who are randomized and have at least 1 patch applied during the Treatment Period were included in the SS.

| Serious adverse events                               | Rotigotine      | Placebo         |  |
|--|-----------------|-----------------|--|
| Total subjects affected by serious adverse events    |                 |                 |  |
| subjects affected / exposed                          | 3 / 20 (15.00%) | 1 / 10 (10.00%) |  |
| number of deaths (all causes)                        | 0               | 0               |  |
| number of deaths resulting from adverse events       | 0               | 0               |  |
| Injury, poisoning and procedural complications       |                 |                 |  |
| Foot fracture  |                 |                 |  |
| subjects affected / exposed                          | 1 / 20 (5.00%)  | 0 / 10 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Chest pain   |                 |                 |  |
| subjects affected / exposed                          | 1 / 20 (5.00%)  | 0 / 10 (0.00%)  |  |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                           |                 |                 |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| Abdominal pain                                  |                |                 |  |
| subjects affected / exposed                     | 1 / 20 (5.00%) | 0 / 10 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                |                 |  |
| Dyspnoea  |                |                 |  |
| subjects affected / exposed                     | 1 / 20 (5.00%) | 0 / 10 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Psychiatric disorders                           |                |                 |  |
| Anxiety   |                |                 |  |
| subjects affected / exposed                     | 1 / 20 (5.00%) | 0 / 10 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Infections and infestations                     |                |                 |  |
| Gastrointestinal infection                      |                |                 |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 1 / 10 (10.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |

Frequency threshold for reporting non-serious adverse events: 5 %

| <b>Non-serious adverse events</b>                     | Rotigotine       | Placebo         |  |
|---|------------------|-----------------|--|
| Total subjects affected by non-serious adverse events |                  |                 |  |
| subjects affected / exposed                           | 12 / 20 (60.00%) | 4 / 10 (40.00%) |  |
| Investigations  |                  |                 |  |
| Electrocardiogram PR prolongation                     |                  |                 |  |
| subjects affected / exposed                           | 1 / 20 (5.00%)   | 0 / 10 (0.00%)  |  |
| occurrences (all)                                     | 1                | 0               |  |
| Electrocardiogram ST segment abnormal                 |                  |                 |  |
| subjects affected / exposed                           | 1 / 20 (5.00%)   | 0 / 10 (0.00%)  |  |
| occurrences (all)                                     | 1                | 0               |  |
| Injury, poisoning and procedural complications        |                  |                 |  |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| Back injury<br>subjects affected / exposed<br>occurrences (all)  | 1 / 20 (5.00%)<br>1  | 0 / 10 (0.00%)<br>0  |  |
| Dialysis device complication<br>subjects affected / exposed<br>occurrences (all)   | 1 / 20 (5.00%)<br>1  | 0 / 10 (0.00%)<br>0  |  |
| Vascular disorders<br>Hypertension<br>subjects affected / exposed<br>occurrences (all)   | 2 / 20 (10.00%)<br>2 | 0 / 10 (0.00%)<br>0  |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)   | 2 / 20 (10.00%)<br>3 | 0 / 10 (0.00%)<br>0  |  |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)   | 1 / 20 (5.00%)<br>1  | 0 / 10 (0.00%)<br>0  |  |
| Somnolence<br>subjects affected / exposed<br>occurrences (all)   | 1 / 20 (5.00%)<br>1  | 0 / 10 (0.00%)<br>0  |  |
| General disorders and administration<br>site conditions<br>Application site pruritus<br>subjects affected / exposed<br>occurrences (all) | 1 / 20 (5.00%)<br>1  | 0 / 10 (0.00%)<br>0  |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)  | 0 / 20 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1 |  |
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)  | 0 / 20 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1 |  |
| Eye disorders<br>Eye haemorrhage<br>subjects affected / exposed<br>occurrences (all)   | 1 / 20 (5.00%)<br>1  | 0 / 10 (0.00%)<br>0  |  |
| Gastrointestinal disorders   |                      |                      |  |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| Constipation<br>subjects affected / exposed<br>occurrences (all)   | 1 / 20 (5.00%)<br>1  | 0 / 10 (0.00%)<br>0  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)  | 1 / 20 (5.00%)<br>1  | 2 / 10 (20.00%)<br>2 |  |
| Gastrooesophageal reflux disease<br>subjects affected / exposed<br>occurrences (all)                                 | 1 / 20 (5.00%)<br>1  | 0 / 10 (0.00%)<br>0  |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)   | 4 / 20 (20.00%)<br>5 | 0 / 10 (0.00%)<br>0  |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)   | 3 / 20 (15.00%)<br>3 | 0 / 10 (0.00%)<br>0  |  |
| Respiratory, thoracic and mediastinal disorders<br>Dyspnoea<br>subjects affected / exposed<br>occurrences (all)      | 2 / 20 (10.00%)<br>2 | 0 / 10 (0.00%)<br>0  |  |
| Sleep apnoea syndrome<br>subjects affected / exposed<br>occurrences (all)  | 1 / 20 (5.00%)<br>1  | 0 / 10 (0.00%)<br>0  |  |
| Psychiatric disorders<br>Confusional state<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 20 (5.00%)<br>1  | 0 / 10 (0.00%)<br>0  |  |
| Depression<br>subjects affected / exposed<br>occurrences (all)   | 1 / 20 (5.00%)<br>1  | 0 / 10 (0.00%)<br>0  |  |
| Dysphoria<br>subjects affected / exposed<br>occurrences (all)  | 1 / 20 (5.00%)<br>1  | 0 / 10 (0.00%)<br>0  |  |
| Musculoskeletal and connective tissue disorders<br>Muscle spasms<br>subjects affected / exposed<br>occurrences (all) | 1 / 20 (5.00%)<br>1  | 0 / 10 (0.00%)<br>0  |  |

|   |                     |                     |  |
|---|---------------------|---------------------|--|
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)     | 1 / 20 (5.00%)<br>1 | 0 / 10 (0.00%)<br>0 |  |
| Metabolism and nutrition disorders  |                     |                     |  |
| Anorexia<br>subjects affected / exposed<br>occurrences (all)              | 1 / 20 (5.00%)<br>1 | 0 / 10 (0.00%)<br>0 |  |
| Diabetic ketoacidosis<br>subjects affected / exposed<br>occurrences (all) | 1 / 20 (5.00%)<br>2 | 0 / 10 (0.00%)<br>0 |  |
| Fluid overload<br>subjects affected / exposed<br>occurrences (all)        | 1 / 20 (5.00%)<br>3 | 0 / 10 (0.00%)<br>0 |  |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)        | 1 / 20 (5.00%)<br>2 | 0 / 10 (0.00%)<br>0 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 20 October 2011  | The protocol was amended in order to add the CGI Item 1 to Day 14 of the Maintenance Period (Visit 6) and to specify options for post-study treatment of RLS.   |
| 18 November 2011 | The protocol was amended in order to clarify that subjects who switched to commercially available rotigotine (Neupro) or who entered the NPP would not be scheduled for a Safety Follow-Up Visit.   |
| 14 January 2013  | The primary purpose of this protocol amendment was to revise the inclusion and exclusion criteria, based on the recommendations of the investigators, to make them less restrictive and to adapt them to the specific needs of the target patient population for the study. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

N/A

Notes: