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Clinical Report Synopsis for Protocol PD0015

Name of Sponsor: UCB BioSciences GmbH

Name of Investigational Medicinal Product (IMP): Rotigotine transdermal patch
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(For National Authority Use Only)

Protocol Title: An open-label study to investigate the safety and the efficacy of rotigotine add-on therapy with low-doses of pramipexole or ropinirole in patients with advanced Parkinson's disease.

Investigator(s): 25 investigators ([redacted])

Study Sites: 25 study sites in 5 countries (Korea, Taiwan, Malaysia, Australia, and Singapore; [redacted])

Publications (Literature in which the results of this study have been reported): None

Study Period:
Date of first signed informed consent: 19 October 2012

Date of end-of-study examination in last subject: 18 April 2013

Clinical Phase/Study Type: Phase 3b/Therapeutic exploratory

Objectives: To investigate the safety and the efficacy of rotigotine add-on therapy with low-doses of pramipexole or ropinirole in patients with advanced-stage Parkinson's disease (PD) who have insufficient response to therapy with L-dopa and a low-dose dopamine receptor agonist.

Methodology: This was a Phase 3b, multicenter, open-label study to investigate the safety and the efficacy of rotigotine add-on therapy with low-doses of pramipexole or ropinirole in patients with advanced-stage PD. The study consisted of a screening period, a treatment period, and a Safety Follow-up period. The treatment period consisted of an 8-week Titration/Maintenance Period and a 1-week taper period. In the Titration Period, the dose was increased to the subject's optimal dose of rotigotine between 2 mg/24 hour and 8 mg/24 hour. The subject was to be on a stable dose of L-dopa and a low-dose dopamine receptor agonist for at least 28 days prior to the Baseline visit.

Number of Subjects (Planned and Analyzed):

Overall

A total of 50 subjects were planned for evaluation. A total of 112 subjects were enrolled in the study, and 90 subjects were treated.

Diagnosis and Main Criteria for Inclusion:

- Subject was male or female, aged ≥ 30 and < 80 years at date of informed consent.
- Subject had idiopathic PD, of more than 3 years duration, as defined by the cardinal sign, bradykinesia, and the presence of at least 1 of the following: resting tremor, rigidity, impairment of postural reflexes, and without any known or suspected cause of Parkinsonism.
- Subject had motor fluctuations such as wearing off, on-off phenomena, delayed on or no-on, dyskinesia.
- Subject had sleep disorder or early-morning motor impairment as determined by the investigator.
- Subject had experienced nocturias for at least 3 nights within 7 days prior to the Baseline (Visit 2).
- Subject was taking levodopa (L-DOPA, immediate, and/or controlled release) in combination with benserazide or carbidopa and was to be on a stable dose of L-DOPA for at least 28 days prior to the Baseline (Visit 2).
- Subject was taking a non-ergot dopamine receptor agonist (pramipexole ≤ 1.5 mg/day or ropinirole ≤ 6.0 mg/day) and was to be on a stable dose of non-ergot dopamine receptor agonist for at least 28 days prior to the Baseline (Visit 2).

IMP, Dose, Mode of Administration, Batch or Lot No(s):

Rotigotine transdermal patch

Strength and dosage form: The 2 mg/24 hour patch contains 4.5 mg rotigotine in 10 cm^2
The 4 mg/24 hour patch contains 9.0 mg rotigotine in 20 cm^2
The 6 mg/24 hour patch contains 13.5 mg rotigotine in 30 cm^2

Lot No.:

Product Description	Batch/Lot No.	Expiry Date
Rotigotine 2 mg/24 h Patch	7023352	30-Sep-13
Rotigotine 4 mg/24 h Patch	7022862	30-Sep-13
Rotigotine 6 mg/24 h Patch	7022882	30-Sep-13

Treatment Period:

This study consisted of an 8-week treatment period, a 1-week Taper Period and a 2-week Safety Follow-up Period.

Titration Period:
Dose was titrated over 1 to 4 weeks in weekly in 2 mg (10 cm^2) /24 hour steps up to the optimal dose or the maximum dose, and the maintenance dose was between 2 mg/24 hour and 8 mg /24 hour. If the subject reported an adverse event(s) (AE) that might be the result of excessive dopaminergic stimulation (eg, intolerable nausea/vomiting), investigator was allowed to back-titrate the subject's rotigotine dose once during the Titration Period. The subject was requested to visit the study site within approximately 1 week after dose reduction before proceeding to the Maintenance Period.

Maintenance Period:
Dose adjustment was not allowed during the Maintenance Period. If a dose adjustment was required, the subject was to be withdrawn from the study. Depending on the duration of the Titration Period, the duration of the Maintenance Period was between 4 weeks and 7 weeks.

Taper Period:
The taper period lasted up to 7 days, depending on the maintenance dose. Doses were reduced in 2 mg/24 hour steps every other day to 0 mg/24 hour.

Safety Follow-up:
A post-treatment observation was performed 2 weeks after completion of study treatment (end of the taper period or withdrawal visit) to confirm the subject's safety.

Criteria for Evaluation:
Safety:
The primary variable in this study was Clinical Global Impression (CGI) Item 4 (side effects) at the end of Titration/Maintenance Period. The other safety evaluations included the extent of exposure, analysis of AEs, physical and neurological examinations, changes in laboratory tests, vital signs (including orthostatic hypotension assessment), 12-lead electrocardiograms (ECGs), results of skin irritation score and Columbia-Suicide Severity Rating Scale (C-SSRS).

Efficacy:
Efficacy was evaluated with the following variables:

- Patient Global Impression of Change (PGIC)
- Unified Parkinson's Disease Rating Scale (UPDRS) Part III score ("on" state)
- UPDRS Part II score (average of "on" and "off" state)
- UPDRS Part II score ("on" state) and Part II score ("off" state)
- Absolute time spent "off" (subject diary), time spent "on" without troublesome dyskinesia and time spent "on" with troublesome dyskinesia
- Parkinson's Disease Sleep Scale Version 2 (PDSS-2)
- Global score of the Pittsburg Sleep Quality Index (PSQI)

- Eight-item Parkinson's Disease Questionnaire (PDQ 8)

Efficacy was also evaluated with the following measurements:

- The number of awakenings during sleep
- The number of nocturias

Statistical Methods:

Feasibility of add-on therapy:
If the withdrawal rate (number of subjects that withdrew/number of subject who were treated with the investigational drug) was less than 15%, the rotigotine add-on therapy was defined as a feasible therapy.

Main Safety Variable:
The primary variable was CGI Item 4 at the end of Titration/Maintenance Period. The primary variable was categorically summarized, where categories were each score and score of "3 or 4," and score of "0" was excluded from summary because score of "0" means "missing." Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 16.0. Medication was coded using the World Health Organization Drug Dictionary (WHO-DD) (Version Q2/2004). The analysis of the safety variables was based on the Safety Set (SS).

Main Efficacy Variables:
The change from Baseline to end of Titration/Maintenance Period in the following efficacy variables were summarized with univariate statistics, and 95% confidence interval (CI) were calculated:

1) UPDRS Part III total score ("on" state) with Last Observation Carried Forward (LOCF)
2) UPDRS Part II total score (average of "on" and "off" state) with LOCF
3) Absolute time spent "off" (hrs) with LOCF

The analysis set for 1) and 2) was Full analysis set (FAS).
The analysis set for 3) was subjects with "time spent off" at Baseline in the FAS.

Summary-Conclusions:

Safety Results:

- In this study, it was defined that rotigotine add-on therapy was feasible if the withdrawal rate was less than 15%. As the withdrawal rate was 12.2%, this study indicated that rotigotine add-on therapy was considered feasible.
- Most subjects (93.3%) had a CGI Item 4 score of < 3 at the end of Titration/Maintenance Period. Only 6 subjects (6.7%) had a score of 3 or 4 at the end of Titration/Maintenance Period.
- A total of 58 subjects (64.4%) experienced at least one Treatment-Emergent Adverse Event (TEAE). The majority of reported TEAEs were mild or moderate in severity.

A total of 6 subjects (6.7%) experienced at least one severe TEAE during all study periods.

- No deaths were reported in this study. Six serious adverse events (SAEs) were reported in 5 subjects. Six subjects were prematurely withdrawn due to TEAEs. Down-titration was performed in 15 subjects due to TEAEs.
- No safety concerns were observed in other safety measurements (physical and neurological examinations, change from Baseline to the end of the Titration/Maintenance Period in laboratory test, vital signs, 12-lead ECG, skin irritation scores, and C-SSRS).

Efficacy Results:

- The majority of subjects (71 of 88 subjects, 80.7%) showed improvement in PGIC score, with 33.0% reporting "Much improved" or "Very much improved."
- The mean change in UPDRS Parts III score ("on" state) (± Standard deviation, SD) from Baseline to the end of Titration/Maintenance Period was -5.3 ± 8.3 (95% CI: -7.1, -3.6). The upper limit of 95% CI was below 0, suggesting improvement in motor performance.
- The mean change in UPDRS Part II score (average of "on" and "off" state) (±SD) from Baseline to the end of Titration/Maintenance Period was -1.5 ± 3.8 (95% CI: -2.3, -0.7). The upper limit of 95% CI was below 0, suggesting improvement in ability to perform daily activities.
- Rotigotine add-on therapy with low-dose oral dopamine receptor agonists reduced mean absolute time spent "off" (±SD) by -2.1 ± 2.9 hours (95% CI: -2.7, -1.5) and prolonged time spent "on" without troublesome dyskinesia by 1.9 ± 3.1 hours (95% CI: 1.2, 2.5) at the end of Titration/Maintenance Period.
- The mean change of PSQI global score (±SD) from Baseline to the end of Titration/Maintenance Period was -0.7 ± 3.0 (95% CI: -1.4, -0.1). The upper limit of 95% CI was below 0, suggesting improvement in sleep disturbance.
- The mean change of PDSS-2 total score (±SD) from Baseline to the end of Titration/Maintenance Period was -3.2 ± 7.5 (95% CI: -4.8, -1.6). The upper limit of 95% CI was below 0, suggesting improvement in sleep and in nocturnal disability in PD.
- The mean changes (±SD) in the number of awakenings during nighttime and nocturias from Baseline at the end of Titration/Maintenance Period were -0.2 ± 0.6 (95% CI: -0.31, -0.04) and -0.2 ± 0.5 (95% CI: -0.3, -0.1), respectively. The upper limits of their 95% CI were below 0.
- The mean change of PDQ-8 SI score (±SD) from Baseline to the end of Titration/Maintenance Period was -6.6 ± 14.2 (95% CI: -9.7, -3.6). The upper limit of 95% CI was below 0, suggesting improvement in the occurrence of various issues associated with PD.

Conclusions:

- No safety concerns were identified in this study when rotigotine was added to a treatment regimen of L-dopa and low-dose oral DA.
- From the results of UPDRS Parts II and III scores, improvements in subjects' motor function and ability to perform daily activities were observed.
- Time spent "off" reduced, and time spent "on" without troublesome dyskinesia was prolonged.
- Sleep disturbances improved as supported by PSQI global score, PDSS-2 total score, the number of nocturnal awakenings during nighttime and the number of nocturias.
- Results of this study suggest that add-on therapy of rotigotine transdermal system to a low-dose oral dopamine receptor agonist was feasible and associated with clinical benefit.

Report Issued: 13 Dec 2013