SP0506

CLINICAL STUDY REPORT SYNOPSIS

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Sponsor:

UCB Pharma GmbH

(formerly: Schwarz Pharma AG)

Alfred-Nobel-Strasse 10

40789 Monheim

Germany

Official study title:

A multicenter, randomized, double-blind, placebocontrolled, parallel-group, dose-ranging study to assess the efficacy, safety, and tolerability of escalating transdermal doses of rotigotine (SPM 962) in subjects with early-stage Parkinson's disease

CLINICAL TRIAL REPORT SYNOPSIS: SP506

<table>
<tr><td>Name of company:
UCB Pharma</td><td>Individual study table referring to part of the dossier:
Not applicable</td><td>(For National Authority Use Only)</td></tr>
<tr><td>Name of finished product:
Neupro</td><td>Volume: Not applicable</td><td></td></tr>
<tr><td>Name of active ingredient:
Rotigotine</td><td>Page: Not applicable</td><td></td></tr>
<tr><td colspan="3">Title of trial: A multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study to assess the efficacy, safety, and tolerability of escalating transdermal doses of rotigotine (SPM 962) in subjects with early-stage Parkinson’s disease</td></tr>
<tr><td colspan="3">Investigator(s): Multicenter trial</td></tr>
<tr><td colspan="3">Study site(s): 51 sites total; 4 sites in India</td></tr>
<tr><td colspan="3">Publication (reference): Parkinson Study Group. A controlled trial of rotigotine monotherapy in early Parkinson’s disease. Arch Neurol 2003;60:1721-8.</td></tr>
<tr><td colspan="2">Studied period:
First subject enrolled (India): 23 Jun 2000
Last subject completed (India): 06 Oct 2000</td><td>Phase of development: 2b</td></tr>
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Objective(s): To compare with placebo the efficacy, safety, and tolerability of 4 dosages of rotigotine transdermal delivery system over 12 weeks in early Parkinson's disease patients.

Methodology: This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging trial to compare the efficacy, safety, and tolerability of rotigotine transdermal delivery system ("patch") versus placebo in early-stage Parkinson's disease patients during a 12-week period. Subjects were randomized to receive 1 of 4 target doses of rotigotine (4.5, 9.0, 13.5, or 18.0mg) or placebo.

The trial consisted of a 28-day (maximum) screening period that included a 4- to 7-day open-label, placebo-run-in period; a 28-day double-blind, dose-titration period (dose titration occurred on a weekly basis); a 49-day dose-maintenance period; and a 7-day dose de-escalation period. There was also a 14-day safety follow-up period during which the subject was off trial medication.

An Independent Data Monitoring Committee (IDMC) was established to be responsible for safety assessment on a regular basis. The IDMC was provided with partially unblinded results for their meetings. No formal interim analysis for efficacy was performed.

Number of subjects (planned and analyzed):

Planned (overall): 300 enrolled (screened), 225 randomized, 215 evaluable

Analyzed (overall): 400 enrolled (screened), 329 randomized, 316 evaluable

Analyzed (Indian subjects): 32 enrolled(screened), 30 randomized, 29 evaluable

Diagnosis and main criteria for inclusion: Men and women ≥30 years of age with idiopathic Parkinson's disease, with at least 2 of the listed cardinal signs (bradykinesia, resting tremor, rigidity, postural instability), without any other known or suspected cause of Parkinsonism; Hoehn and Yahr Stage ≤3.0; Mini Mental State Examination score of ≥24; and on stable dose of selegiline, anticholinergic agents or amantadine (if applicable). Subjects having prior or concurrent therapy with a dopamine agonist or carbidopa/L-dopa within 28 days of the baseline visit were excluded from the trial.

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Test product, dose(s) and mode of administration, batch number(s): rotigotine; transdermal delivery system "patch" containing 4.5mg rotigotine (10cm^2); dosed as 1 (4.5mg), 2 (9.0mg), 3 (13.5mg), or 4 (18.0mg) patches daily. [redacted] The active drug, rotigotine, was formulated in an adhesive matrix that contained rotigotine.

In the titration period, subjects applied 4 patches (containing a combination of placebo and 4.5mg active patches) with a total area of 40cm^2 to the upper abdomen (above the umbilicus).

Subjects were titrated in 10cm2 steps (4.5mg rotigotine or placebo) on a weekly basis to a randomized target dose of 4.5, 9.0, 13.5, or 18.0mg rotigotine or placebo, starting with 4.5mg (or placebo). The titration regimen was designed so that each subject started treatment on his/her target dose during the fourth week of titration so that subjects in all treatment groups received 8 weeks of exposure at their target dose (1 week titration and 7 weeks maintenance).

In the maintenance period, subjects applied 4 patches (to maintain the blind) with a total area of 40cm^2 to the upper abdomen, containing 4.5, 9.0, 13.5, or 18.0mg rotigotine or placebo.

Rotigotine 4.5mg (10cm²) batches: WE10927, WE10938, WE11114, WE11346, WE11182

Duration of treatment: The treatment period included a 28-day double-blind, dose-titration period (dose titration occurred on a weekly basis) and a 49-day dose-maintenance period. Subjects down-titrated to 0mg during a 7-day dose-de-escalation period.

Reference therapy, dose(s) and mode of administration, batch number(s): placebo; transdermal patch; nearly identical to test product except patches did not contain rotigotine

Placebo batches: WE10934, WE11115, WE11170, WE11253, WE11318, WE11334

Criteria for evaluation:

Efficacy: The primary efficacy variable was the change in Unified Parkinson's Disease Rating Scale (UPDRS) [Parts II + III] score from baseline visit (Visit 2, Day 0) to Week 11 (Visit 6, Day 77).

Secondary efficacy variables included the change in UPDRS Part I (mentation, behavior and mood), Part II (activities of daily living [ADL]), and Part III (motor examination) from baseline visit to Week 11 and the change in Hoehn and Yahr stage from baseline visit to Week 11.

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Pharmacokinetics/pharmacodynamics: Plasma levels of rotigotine were measured.

Safety: The safety profile of rotigotine was determined by the analysis of the frequency and severity of adverse events (AE) and changes in vital signs, electrocardiograms (ECG), and clinical laboratory values recorded over the course of the trial.

The tolerability of rotigotine was determined by the number of subjects who completed the trial on the original treatment assignment, the number of subjects who completed the trial, and the number of subjects who completed the trial with at most 1 dosage reduction.

Statistical methods: Subjects were analyzed both as randomized and as treated since back titration was allowed prior to entering the maintenance period. The primary outcome variable was imputed by the last observed value prior to any missing score. The null hypothesis was that the mean change would be the same across the 5 treatment groups.

The secondary outcome variables for efficacy and other outcome variables for efficacy were analyzed using the same methods stated above for the primary outcome variable for efficacy.

Summary and conclusions:

Subject disposition: Of the 30 treated Indian subjects, 25 (83%) completed the trial and 5 (17%) discontinued trial participation prematurely. Of the 29 subjects in the FAS (Randomized), 25 (86%) completed the trial and 4 (14%) prematurely discontinued the trial. In both the SS and FAS, the most common reason for premature discontinuation from the trial was AEs (1 subject randomized to placebo, 1 subject randomized to 13.5mg rotigotine, and 1 subject randomized to 18.0mg rotigotine).

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Efficacy results:

Rotigotine was efficacious in treating the manifestations of Parkinson's disease as measured by UPDRS Part II + III scores. All 4 rotigotine treatment groups (4.5mg, 9.0mg, 13.5mg, and 18.0mg) had greater numerical improvements from baseline in the UPDRS II + III total scores at the end of treatment compared with placebo.

Although the sample size of this analysis of Indian subjects was not large enough to reliably detect clinically meaningful differences between the rotigotine and placebo treatment groups in changes from baseline (5.0-point difference in improvement of UPDRS II + III scores), the 4.5 and 9.0mg rotigotine treatment groups demonstrated differences from placebo of this magnitude.

Consistent numerical improvements following treatment with each of the 4 doses of rotigotine compared with placebo were seen on multiple secondary endpoints, including the change from baseline to endpoint in the UPDRS Part II scores, the UPDRS Part III scores, the UPDRS I + II + III total scores, as well as the percentage of subjects who achieved either a ≥20% or ≥30% decrease from baseline to endpoint in the sum of the motor and ADL components of the UPDRS.

Pharmacokinetics/pharmacodynamics results: Not applicable.

Safety results: The most common AEs reported by rotigotine-treated subjects during treatment were nausea (7 subjects; 30%), vomiting (4 subjects; 17%), dizziness (4 subjects; 17%), and giddiness (3 subjects; 13%). Each of these AEs occurred at a higher incidence in the rotigotine treatment group compared with placebo. Only 1 SAE was reported among subjects enrolled at sites located in India. One (13%) placebo subject and 2 (9%) rotigotine subjects withdrew from the trial due to AEs.

None of the Indian subjects experienced an application site reaction during treatment. One subject experienced an application site reaction during the placebo run-in period. During the trial, none of the Indian subjects experienced an AE of orthostatic hypotension. However, 1 subject did experience an AE of dizziness postural (verbatim term: dizziness with change in posture). The incidence of cardiovascular and heart rate and rhythm adverse events were similar between the placebo and rotigotine groups.

No notable differences were observed between treatment groups in laboratory tests, vital signs, or ECGs.

With respect to tolerability, there were no important differences between placebo and any rotigotine group regarding the number of subjects completing the trial and the number completing the trial with up to 1 back titration.

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Conclusions:

- Similar to the results from the overall population, in those subjects enrolled at sites in India, rotigotine numerically improved UPDRS scores without associated safety issues or concerns in subjects with early-stage Parkinson's disease. Most AEs were mild or moderate and did not lead to discontinuation more frequently than in the placebo group. The benefit of rotigotine was justified by clinically relevant improvement without substantial safety concerns.
- All 4 rotigotine treatment groups (4.5mg, 9.0mg, 13.5mg, and 18.0mg) had greater numerical improvements from baseline in the UPDRS II + III total scores at the end of treatment compared with placebo. Although no clear dose-response was evident, this is likely due to the relatively small sample size.
- Although the sample size of this sub-analysis of Indian subjects was not large enough to reliably detect clinically meaningful differences between rotigotine and placebo in changes from baseline (5.0-point difference in improvement of UPDRS II + III scores), the 4.5 and 9.0mg rotigotine treatment groups demonstrated differences from placebo of this magnitude.
- Consistent numerical improvements following treatment with each of the 4 doses of rotigotine compared with placebo were seen on multiple secondary endpoints, including the change from baseline to endpoint in the UPDRS Part II scores, the UPDRS Part III scores, the UPDRS I + II + III total scores, as well as the percentage of subjects who achieved either a ≥20% or ≥30% decrease from baseline to endpoint in the sum of the motor and ADL components of the UPDRS.
- Only 1 SAE was reported, and the incidence of Indian subjects who discontinued the trial due to an AE was low and similar between the placebo (1 subject; 13%) and rotigotine treatment groups (2 subjects; 9%).
- No safety concerns with respect to laboratory findings, ECGs, or vital signs were identified.

Report date: 10 Aug 2010