Parkinsonism and Related Disorders xxx (2016) 1–7

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Rotigotine transdermal patch in Chinese patients with early Parkinson's disease: A randomized, double-blind, placebo-controlled pivotal study

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ARTICLE INFO

Article history:
Received 20 January 2016
Received in revised form
15 April 2016
Accepted 21 April 2016

Keywords:
Chinese
Parkinson's disease
Rotigotine
Treatment

ABSTRACT

Introduction: Two phase3 studies (SP512; SP513) involving mostly Caucasian patients showed that rotigotine (≤8 mg/24 h) was efficacious and welltolerated in early-stage Parkinson's disease (PD). We report results from a phase 3 study (SP0914/NCT01646268) investigating rotigotine in Chinese patients with early-stage PD.

Methods: Patients were randomized 1:1 to rotigotine or placebo, titrated over 1–4 weeks, maintained at optimal/maximum dose (≤8 mg/24 h) for 24 weeks. Primary efficacy variable: change in Unified Parkinson's Disease Rating Scale (UPDRS) II + III total score from Baseline to End-of-Maintenance. Secondary variables: UPDRS II + III responders (≥20% decrease in UPDRS II + III) and changes in UPDRS II (activities of daily living [ADL]) and III (motor examination) subscores.

Results: Of 247 patients randomized, 113/124 (91.1%) rotigotine- and 107/123 (87.0%) placebo-treated patients completed the study. Patients: mean (SD) age: 59.4 (10.2) years; time since PD diagnosis: 1.01 (1.22) years, 60.7% male. Rotigotine significantly improved UPDRS II + III total score (change from Baseline LSmean [95%CI] treatment difference, −4.82 [−7.18 to −2.45]; $P < 0.0001$). UPDRS II + III responder rates were higher with rotigotine (42.3% vs 22.3%; $P = 0.0006$). UPDRS II and III subscores improved with rotigotine (both subscores: $P < 0.0005$ vs. placebo). Most frequent adverse events (AEs): nausea (8.9% rotigotine, 3.3% placebo), dizziness (8.1%, 5.7%), pruritus (8.1%, 4.1%), somnolence (8.1%, 3.3%), erythema (6.5%, 1.6%), and vomiting (5.6%, 1.6%). Thirteen (5.3%) patients discontinued due to AEs (6 rotigotine, 7 placebo).

Conclusions: Rotigotine was efficacious in Chinese patients with early-stage PD, providing benefits to control of ADL and motor function. Rotigotine was generally welltolerated, with similar AEs to those observed in Caucasian patients.

1. Introduction

Parkinson's disease (PD) is a chronic and progressive neurological disease involving both motor and non-motor complications, and has a detrimental effect on the quality of life of patients [1,2], as well as on caregivers, families, and society [2]. The global burden of PD is expected to rise in the future as a result of aging populations and increasing life expectancies [3]. As the world's most populated country, and with 13.26% of its total population over the age of 60 years [4], China faces the largest number

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http://dx.doi.org/10.1016/j.parkreldis.2016.04.022
1353-8020/

of patients with PD in the world [4]. Indeed, it has been estimated that the number of patients with PD in China will rise from 1.99 million in 2005 to 4.94 million in 2030 [3]. Thus, there is an urgent need for treatments to effectively manage and care for the increasing numbers of patients with PD in China.

Dopamine receptor agonist (DA) monotherapy is the cornerstone of symptomatic treatment for the early stages of PD [5]. Rotigotine is a non-ergoline DA developed as a once-daily transdermal patch for continuous drug delivery, providing stable plasma drug levels for 24 h following application [6]. The efficacy and tolerability of rotigotine has been demonstrated in two pivotal 6-month double-blind randomized studies (SP512: North America [7]; SP513: Europe, Australia, New Zealand, Israel, and South Africa [8]) in patients with early-stage PD. The studies found statistically significant and clinically relevant improvements in the Unified Parkinson's Disease Rating Scale (UPDRS) II + III total score and a significantly greater number of UPDRS II + III responders (≥20% improvement) with rotigotine versus placebo. In these studies, more than 95% of patients were Caucasian. The efficacy and safety of treatment with the rotigotine transdermal patch in Chinese patients with early-stage PD has yet to be evaluated. Here, we report results of the SP0914 study, a pivotal study of rotigotine in Chinese patients with early-stage PD.

2. Methods

2.1. Study design

SP0914 (ClinicalTrials.gov: NCT01646268) was a multicenter, double-blind, randomized, placebo-controlled phase 3 study that evaluated the efficacy, safety, and tolerability of rotigotine transdermal patches in Chinese patients with early-stage idiopathic PD (Supplementary Fig. 1).

The study was conducted at 24 sites in the People's Republic of China in accordance with current versions of the applicable regulatory and International Conference on Harmonization Good Clinical Practice requirements, and the laws of China. All patients provided written, informed consent before study participation. The study protocol and patient informed consent were reviewed by independent ethics committees at each study site.

2.2. Patients

2.2.1. Key inclusion criteria

Patients were male or female ≥30 years of age at Screening with idiopathic PD of ≤5 years' duration (defined by the cardinal sign, bradykinesia, plus ≥1 of the following: resting tremor, rigidity, or impairment of postural reflexes, and without any other known or suspected cause of Parkinsonism); Hoehn & Yahr stage ≤3; Mini Mental State Examination score ≥25; and a Baseline UPDRS Part III (motor) score of ≥10.

Permitted medications for the treatment of PD included anticholinergics, monoamine oxidase-B inhibitors, and *N*-methyl-D-aspartate antagonists (e.g., amantadine) that were at stable doses for ≥28 days prior to Baseline (Visit 2), and were to be maintained on that dose for the duration of the study. Central nervous system active therapy (e.g., sedatives, hypnotics, antidepressants, anxiolytics) also was permitted if it was at stable doses for ≥28 days prior to Baseline and if it was likely to remain stable for the duration of the study.

2.2.2. Key exclusion criteria

Patients were excluded from the study if they had a current diagnosis of dementia, active psychosis or hallucinations, severe depression, or evidence of impulse control disorder at Screening; had a current diagnosis of epilepsy, history of seizures as an adult, history of stroke, or a transient ischemic attack within 1 year prior to Screening; had clinically relevant hepatic, renal, or cardiac dysfunction; had received therapy with a DA within 28 days prior to Baseline; had received therapy with levodopa/carbidopa and/or levodopa/benserazide within 28 days of Baseline or received such therapy for over 6 months since diagnosis; or had received therapy with alpha-methyldopa, metoclopramide, reserpine, neuroleptics (except specific atypical neuroleptics: olanzapine, ziprasidone, aripiprazole, clozapine, quetiapine), monoamine oxidase-A inhibitors, methylphenidate, or amphetamine within 28 days prior to Baseline.

2.3. Protocol

Following assessment of eligibility criteria at the Screening (Visit 1), patients were randomized 1:1 to rotigotine or placebo at Baseline (Visit 2) via an interactive voice/web response system. Study treatment was administered via a transdermal patch (UCB Pharma SA, Braine-l'Alleud, Belgium); active and placebo patches were matched in size and appearance, with rotigotine patch sizes of 10, 20, 30, and 40 cm^2 corresponding to doses of 2, 4, 6, and 8 mg/24 h, respectively. Patches were applied daily for 24 h.

Patients received rotigotine or placebo patches in escalating weekly doses (starting with daily doses of rotigotine 2 mg/24 h or matching placebo and increasing by 2 mg/24 h each week) until an optimal or maximal dose of rotigotine 8 mg/24 h or matching placebo was achieved. When the Titration period (lasting up to 4 weeks) was complete or both the patient and the investigator decided that the dose was optimal (defined by the absence of, or maximal reduction in, PD symptoms without intolerable side effects), the patient remained at that dose and commenced the 24-week Maintenance period (Visit 6). If a patient experienced an adverse event (AE) during the Titration period that was thought to be the result of excessive dopaminergic stimulation (e.g., intolerable nausea/vomiting), a single back-titration of rotigotine/placebo was permitted. If the patient was back-titrated to the previous dose, he/she commenced the Maintenance period immediately and remained at the back-titrated dose throughout the Maintenance period.

During the Maintenance period, visits occurred every 28 (±7) days. The End of Maintenance (EoM) visit (Visit 12) was followed by a De-escalation period during which the dose was de-escalated by 2 mg/24 h every 2 days. A Safety Follow-up visit occurred within 28 days thereafter (Visit 13). Patients who withdrew prematurely were asked to return for a Withdrawal visit.

2.4. Outcome measures

2.4.1. Efficacy

The primary efficacy variable was change from Baseline to EoM in UPDRS [9] II + III total score. Secondary efficacy variables were UPDRS II + III responders (patients with ≥20% decrease in total score) and change from Baseline to EoM in UPDRS II (activities of daily living) and UPDRS III (motor examination) subscores. A sensitivity analysis of responder status (with responders defined as patients with a ≥25% and ≥30% decrease in UPDRS II + III from Baseline to EoM) was also conducted. Other efficacy measures included change in Clinical Global Impressions (CGI) [10] Item 1 (severity of disease) score from Baseline to EoM, CGI Item 2 (global improvement) score, and CGI Item 3 (efficacy index) score, and change in Parkinson's Disease Questionnaire (8-item short form) [11] total score from Baseline to EoM.

Please cite this article in press as: Z.-X. Zhang, et al., Rotigotine transdermal patch in Chinese patients with early Parkinson's disease: A randomized, double-blind, placebo-controlled pivotal study, Parkinsonism and Related Disorders (2016), http://dx.doi.org/10.1016/j.parkreldis.2016.04.022