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Sponsor / Company: sanofi-aventis **Drug substance(s):** Nerispirdine (HP184)	**Study Identifier:** NCT00772525 **Study code:** ACT10573

Title of the study: A double-blind, placebo-controlled, randomized crossover, activity study of single oral doses of 50 mg and 400 mg Nerispirdine on visual function in patients with multiple sclerosis

Study center(s): 3 centers in the USA.

Study period:

Date first patient enrolled: 29 September 2008

Date last patient completed: 04 June 2009

Phase of development: Phase 2a

Objectives:

Primary objective: To evaluate the effect of 50 mg or 400 mg Nerispirdine on Visual Evoked Potential (VEP) P100 latency.

Secondary objectives: To evaluate the effect of Nerispirdine on VEP P100 amplitude and other visual parameters.
To evaluate the safety and tolerability of Nerispirdine in patients with Multiple Sclerosis (MS).

Methodology: Multicenter, double-blind, placebo-controlled, randomized, crossover with 3 treatment periods 1 week apart and 6 treatment sequences.

Number of patients: Planned: 30

Randomized: 31

Treated: 30

Evaluated: Efficacy: 30

Safety: 30

Diagnosis and criteria for inclusion: Men and women aged ≥ 18 years with clinically definite MS (McDonald criteria), which included patients with remitting/relapsing, secondary progressive, progressive-relapsing, and primary progressive MS who have had a past history of optic neuritis.

Investigational product: Nerispirdine (HP184) 50 mg tablet

Dose: 50 mg or 400 mg

Administration: Oral

Duration of treatment: 1 day per treatment period

Duration of observation: Approximately 5 weeks (2-week screening period, 3 evaluation visits separated by 1 week and a follow-up visit 1 week after last drug intake).

Reference therapy: Placebo

Dose: 0 mg

Administration: Oral

Criteria for evaluation:

Efficacy:

Primary endpoint: The primary efficacy variable was the VEP P100 latency on the most appropriate eye for the study. The eye selection for primary analysis was based on the visual measurements at screening visit.

Secondary endpoints:

- Pelli-Robson Contrast Sensitivity (CS) score, Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity score and VEP P100 amplitude on the eye selected for the study;
- VEP P100 latency, Pelli-Robson CS score, ETDRS visual acuity score and VEP P100 amplitude on the other eye.

Safety: Adverse events (AE) reported by the subject or noted by the Investigator and standard laboratory, vital sign and electrocardiogram (ECG) parameters.

Statistical methods:

Efficacy: Efficacy data was analyzed with a linear mixed effect model with fixed terms for baseline (defined as the predose measurement for each treatment period), treatment (50 mg Nerispirdine, 400 mg Nerispirdine or placebo), sequence and period, and subject as random effect (SAS® PROC MIXED procedure). Comparisons between Nerispirdine and placebo, and two Nerispirdine doses were obtained using linear contrasts within the mixed model framework. Results from these comparisons were presented as least square (LS) means differences with their 2-sided 95% confidence intervals (CI). Only p-values comparing Nerispirdine and placebo were reported. No multiplicity adjustment was made.

Safety: The safety evaluation was based on review of individual values and descriptive statistics. The number and percentage of patients with at least 1 treatment-emergent adverse event (TEAE) was summarized and listed by system-organ class and preferred term (Medical Dictionary for Regulatory Activities [MedDRA] version 12.0). Abnormalities in laboratory, vital signs, and ECG parameters were assessed using potentially clinically significant abnormality (PCSA) criteria, and patients with PCSA on-treatment were summarized and listed.

Summary:

Efficacy results*:* The LS means of change from predose to postdose in VEP P100 latency were 0.6, 0.7 and 0.3 ms in placebo, 50 mg Nerispirdine and 400mg Nerispirdine groups, respectively (Note: a negative change implies a decrease, i.e., an improvement in VEP P100 latency).

The LS mean difference between 50 mg Nerispirdine and placebo was 0.1 with a 95% CI of (-3.40, 3.54) and p value = 0.9681; LS mean difference between 400 mg Nerispirdine and placebo was -0.3 with a 95% CI of (-3.71, 3.18) and p-value = 0.8782.

A numerical increase (reflecting an improvement) in VEP P100 amplitude was observed with 50 mg and 400 mg doses: the 95% unadjusted CI of mean differences versus placebo were respectively (0.05, 1.22) µV and (-0.13, 1.03) µV for 50 mg and 400 mg Nerispirdine.

There were no consistent changes for the visual function parameters, ie, the Pelli-Robson CS score and the ETDRS visual acuity score. No consistent changes were observed on all endpoints on the other eye (including for the VEP P100 amplitude).

Safety results*:* No serious adverse events were reported. One patient withdrew from study after intake of 400 mg of Nerispirdine, due to myalgia, gait disturbance, and fatigue. The frequency of TEAE was slightly higher in the 50 mg Nerispirdine (27.6%) and 400 mg Nerispirdine (36.7%) groups than that in the placebo group (23.3%). Treatment-emergent adverse events were generally of mild or moderate intensity. No TEAE were reported in more than 5% of patients on 50 mg Nerispirdine. A few TEAE were reported with a higher frequency with 400 mg Nerispirdine than with placebo: dizziness (13.3% compared to 3.3%), fatigue (10.0% compared to 0%), nausea (6.7% compared to 0%), myalgia (6.7% compared to 0%) and headache (6.7% compared to 3.3%). Only few and unremarkable PCSA in vital signs, clinical laboratory or ECG parameters were observed at the end of the last period and at follow-up.

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