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Sponsor / Company: sanofi-aventis **Drug substance(s):** Nerispirdine (HP184)	**Study Identifier:** NCT00811902, EudraCT 2008-001999-67 **Study code:** DRI10566
Title of the study: A 14-week, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy, safety, and tolerability of Nerispirdine 50 mg, 100 mg, and 200 mg in patients with multiple sclerosis	
Study center(s): 68 centers in 7 countries, namely Canada, Finland, France, Germany, Norway, Spain, and United States of America	
Study period: Date first patient enrolled: 29 December 2008 Date last patient completed: 02 March 2010	
Phase of development: Phase 2, dose ranging	
Objectives: The objectives of the study were as follows**:** Primary: to assess the activity of Nerispirdine in improving ability to walk, defined as a consistent improvement in walking speed as measured by the timed 25-foot walk [T25-FW] in patients with multiple sclerosis [MS]. Secondary: • To assess other measures of walking ability, fatigue, lower limb muscular strength, spasticity, global clinical assessment by subject and global clinical assessment of change by Investigator, • To assess the duration of activity of Nerispirdine by a T25-FW evaluation at 24 hours post-dose at one visit (on Day 99), • To assess the safety and tolerability of Nerispirdine, • To evaluate the pharmacokinetic parameters of Nerispirdine and its active metabolite HP183.	
Methodology: This was a randomized (stratified by region and MS type), double-blind, 4-parallel-group, placebo-controlled study with 2-week, single-blind placebo run-in and run-out (follow-up) periods.	
Number of patients: Planned: 368 Randomized: 405 Treated: 401 **Evaluated:** Efficacy: 401 Safety: 401	
Diagnosis and criteria for inclusion: Patients >18 years of age, with clinically definite MS (McDonald criteria), which included patients with remitting-relapsing, secondary progressive, progressive-relapsing, or primary progressive MS and walking disability due to MS (untreated or treated with a stable regimen of a marketed compound for treatment of MS, limited to beta interferons or glatiramer acetate), without MS exacerbation or clinical relapse within 6 months prior to the screening visit and having given informed consent. Patients had to be able to complete 2 trials of the T25-FW in an average time of 8 to 45 seconds at screening.	
Investigational product: Nerispirdine (HP184) Formulation: 50 mg tablet Dose: 50 mg, 100 mg, or 200 mg once daily Administration: Oral route, to be taken in the morning 2 hours after breakfast	

Duration of treatment: 14 weeks

Duration of observation: Approximately 19 weeks in total, comprising a 3-week screening period inclusive of a 2-week placebo run-in period, a 14-week treatment period, and a 2-week placebo run-out (follow-up) period

Reference therapy: Placebo

Dose: 0 mg

Administration: Oral route

Criteria for evaluation:

Efficacy: The primary evaluation criterion for efficacy was the T25-FW test, a quantitative walking and leg function performance test based on a timed 25 feet walk (average speed for 2 completed trials).

Patients were requested to perform the T25-FW:

- at screening (Day -21),

- on Days -14, -7 and -1 during the placebo run-in period,

- on Days 14, 42, 70 and 98 during the treatment period,

- on Days 99 and 112 during the placebo run-out (follow-up) period.

A patient had to have at least 3 on-treatment and at least 3 off-treatment measurements of T25-FW including Days -14, -1 and 112 to be considered a responder. All other randomized patients were automatically defined as non-responders.

The primary efficacy endpoint was the response rate based on consistency of improved response in walking speed on the T25-FW. A responder was defined as a patient whose last T25-FW measurement on treatment and at least 2 other T25-FW measurements on treatment were faster than the fastest speed recorded during any of the 3 off drug visits (Days -14, -7, and -1) before double-blind treatment and the visit at the end of the 2-week placebo run-out period.

Other efficacy endpoints based on T25-FW were the change in walking speed from baseline to 2 weeks after the end of treatment, the change in walking speed from baseline to 24 hours after last dose of investigational product (Day 99) to evaluate the duration of effect of Nerispirdine, and the rate of modified responders, the latter defined as a patient with a faster walking speed for at least 3 of the 4 visits during the double-blind treatment period, as compared to the maximum walking speed achieved at any of the 4 pre-treatment visits and the 2-week post-treatment visit.

Secondary evaluation criteria were the 12-item MS walking scale [MSWS-12], the Modified Fatigue Impact Scale, the Lower Extremity Manual Muscle Test for grading strength, the Modified Ashworth Scale for grading spasticity and Subject and Clinician Global Impression scores. The key secondary endpoint was the average change from baseline in the MSWS-12.

Safety: Safety was monitored via adverse events [AE] spontaneously reported by the patients or observed by the Investigator, clinical laboratory tests, vital signs, and 12-lead electrocardiograms**.**

Pharmacokinetics: Plasma Nerispirdine and HP183 concentrations at pre-dose (Day -1) and other time points.

Statistical methods:

Efficacy: The response rate was compared between each dose of Nerispirdine and placebo for all patients in the intent-to-treat [ITT] population, defined as all randomized patients exposed to double-blind treatment. Patients were analyzed in the treatment group to which they were randomized. The ITT population was used for the analyses of all efficacy variables. The difference in the response rate between each dose of Nerispirdine and placebo was tested using the Cochran Mantel Haenszel method after adjusting for the effects of type of MS and region (North-America/Europe). Multiplicity due to the multiple doses was controlled using the Hommel method.

Safety: Adverse events were coded according to the Medical Dictionary of Regulatory Affairs (MedDRA) Version 12.1 and summarized by treatment group using descriptive statistics. Treatment-emergent AE [TEAE] were defined as AE that developed or worsened or became serious during the on-treatment period, defined as the time from first dose of study medication up to 2 weeks (>5 half lives) after the last dose of study medication. Potentially clinically significant abnormalities in clinical laboratory test results, vital signs, and ECG parameters were flagged and summarized for each treatment.

The safety population consisted of all randomized patients who were exposed to any dose of study medication during the double-blind period. Patients were analyzed in the group corresponding to the treatment which they actually received irrespective of the group to which they were randomized.

Pharmacokinetics: As no safety concerns were raised during the study, a complete pharmacokinetic analysis was not performed and pharmacokinetic results are not presented.

Summary:

Patient disposition: Out of 405 randomized patients, 57 (14.1%) prematurely discontinued study treatment. The frequency of premature discontinuation was higher in the Nerispirdine dose groups, with 17 (16.7%), 20 (20.0%) and 13 (12.7%) discontinuations in the 50 mg, 100 mg and 200 mg groups, respectively, than in the placebo group, in which there were 7 (6.9%). There were no differences between the Nerispirdine dose groups in terms of overall frequency and reason for discontinuation. In all treatment groups, most treatment discontinuations were due to AE.

Demographics: The mean age (Standard Deviation [SD]) was 53.7 (8.8) years and most patients were female (64.4%). The MS type was secondary-progressive in 55.1% of patients, relapsing-remitting in 21.5%, primary-progressive in 18.3% and progressive-relapsing in 5.2%. The mean time since first symptoms (SD) was 19.45 (9.59) years, and the mean baseline Expanded Disability Status Scale (SD) was 5.58 (1.06).

Efficacy results: There was no evidence of a statistically significant difference in frequency of responders between individual Nerispirdine doses and placebo. The highest number of responders was observed in the placebo group.

Summary of T25-FW response rate - ITT population

		Nerispirdine		
	Placebo	50mg	100mg	200mg
T25-FW	(N=101)	(N=101)	(N=99)	(N=100)
Responders [n(%)]	17 (16.8%)	11 (10.9%)	14 (14.1%)	9 (9.0%)
Non-responders [n(%)]	84 (83.2%)	90 (89.1%)	85 (85.9%)	91 (91.0%)
P-value vs placebo	-	0.2272	0.6186	0.1052
Hommel-adjusted p-value	-	1.0000	1.0000	1.0000

T25-FW = timed 25-foot walk, ITT = intent to treat
Note: % calculated using number of ITT patients as denominator

No trend in favor of any dose of Nerispirdine was observed in the analysis of modified responders.

Some average improvement from baseline in T25-FW walking speed was observed in all treatment groups, starting at first on-treatment visit, but no difference in favor of any Nerispirdine dose group was observed versus placebo in the analysis of the average percent change from baseline in T25-FW walking speed.

Walking speed did not decrease from peak to 24 hours after last intake of double-blind study medication in any treatment group, as illustrated by the lack of decrease of mean percent change from Day 98 to Day 99 in T25-FW walking speed.

None of the analyses of the secondary efficacy endpoints showed any trend in favor of Nerispirdine.

Safety results: There were no deaths during the study, and a limited number of serious TEAE were observed in all treatment groups. There were no differences between treatment groups in the overall frequency of TEAE. The percentage of patients with TEAE leading to premature treatment discontinuation in the Nerispirdine dose groups ranged from 8.0% to 14.1% compared with 3.0% in the placebo group.

Overview of TEAE - Safety population

		Nerispirdine		
Criteria [n (%)]	**Placebo (N=101)**	**50mg (N=101)**	**100mg (N=99)**	**200mg (N=100)**
Patients with any TEAE	69 (68.3%)	74 (73.3%)	73 (73.7%)	68 (68.0%)
Patients with any serious TEAE	4 (4.0%)	7 (6.9%)	6 (6.1%)	2 (2.0%)
Patients with any TEAE leading to death	0	0	0	0
Patients with any TEAE leading to permanent treatment discontinuation	3 (3.0%)	11 (10.9%)	14 (14.1%)	8 (8.0%)

TEAE = Treatment Emergent Adverse Event
Note: n (%) = number and percentage of patients with at least one TEAE

Serious TEAE that occurred with higher incidence in at least one Nerispirdine dose group versus placebo were mainly infections and infestations (4.0% in the Nerispirdine 50 mg group versus 1.0% in placebo group) although no pattern was observed in the nature of the infections.

The most frequent TEAE leading to premature treatment discontinuation were diarrhea (5.1% of patients in the Nerispirdine 100 mg group versus 0% in the placebo group) and MS relapse (3.0% of patients in the Nerispirdine 200 mg group versus 0% in the placebo group).

The most frequent TEAE and with a higher frequency in at least one Nerispirdine group than placebo were the following (presented by decreasing overall frequency on Nerispirdine): diarrhea, fall, headache, fatigue, dizziness, upper respiratory tract infection, influenza, MS relapse, paresthesia, upper abdominal pain, and anxiety.

Concerning laboratory tests, there was little difference between all treatment groups on most measures, with the exception of prothrombin time [PT] and gamma-glutamyl transferase [GGT]. For both laboratory tests, a higher number of patients had values above the upper limit of normal range [ULN] in the Nerispirdine dose groups than in the placebo group. For PT, the percentage of patients with values above ULN was 17.8% on 50 mg, 16.5% on 100 mg and 18.2% on 200 mg versus 7.9% on placebo. Furthermore, the TEAE “activated partial thromboplastin time prolonged” was more frequent on Nerispirdine 200 mg (3.0%) than on placebo (1.0%). For GGT, the percentage of patients with values above ULN was 16.8% on 50 mg, 14.3% on 100 mg and 20.2% on 200 mg versus 9.9% on placebo.

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