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Sponsor/Company: sanofi-aventis **Drug substance**: SR46349 (eplivanserin)	**Study Identifier**: NCT00313885 **Study code**: ACT5400

Title of the study:

Efficacy and safety of SR46349B (1 and 5mg/day) administered during 8 weeks in patients with sleep disorders in Fibromyalgia: multicenter, randomized, double-blind, placebo-controlled study.

Study center(s): International, multicenter study with 20 centers in 2 countries

Study period:

Date first subject/patient enrolled:	20-Apr-2004
Date last subject/patient completed:	02-Jun-2005

Phase of development: 2A

Objectives:

The primary objective of this study was to evaluate the effects of eplivanserin 1 mg/day and 5 mg/day in comparison to placebo on the refreshing quality of sleep in patients with sleep disorders in fibromyalgia, using patient sleep questionnaires.

Secondary objectives were to assess the effects of eplivanserin 1 mg/day and 5 mg/day, in comparison to placebo, on associated symptoms of sleep disorders in fibromyalgia including fatigue, pain and mood, and to assess the safety and tolerability of eplivanserin 1 mg/day and 5 mg/day in comparison to placebo.

Methodology:

Multicenter, randomized, double-blind, placebo-controlled study in 3 parallel groups of patients.

Number of subjects/patients:

Planned:	180
Randomized:	205
Treated:	204
Intent-to-treat (ITT) population:	202
Efficacy population:	143
Safety population:	204

Diagnosis and criteria for inclusion:

Male or female patients between 18 to 64 years of age with sleep disorders (poor or not refreshing sleep), and fulfilling the American College of Rheumatology (ACR) criteria for fibromyalgia

Investigational product:SR46349 (eplivanserin) tablets

Dose: 1mg and 5mg

Administration: oral, taken with the evening meal

Reference therapy: Placebo tablets

Administration: oral, taken with the evening meal

Duration of treatment: 8 weeks

Duration of observation: Approximately 10 weeks including run-in (screening), treatment, and run-out periods

Criteria for evaluation:

Efficacy:

Primary endpoint:

The primary endpoint was the change from baseline to end of treatment in refreshing quality of sleep measured using patient sleep questionnaire.

Secondary endpoints:

The secondary endpoints were the change from baseline to end of treatment in the sleep parameters (maintenance, duration, induction and quality), the global impression both by the patient (PGI) and the clinician (CGI), and patient-reported symptoms related to fatigue visual analog scale (VAS), pain (widespread pain assessment, and VAS), and mood, Hospital Anxiety and Depression (HAD) scale.

Safety:

Safety was assessed through spontaneously reported adverse events (AEs) and other safety information, clinical examinations, vital signs, electrocardiogram (ECG), standard clinical laboratory tests.

Other related sleep parameters included next day residual effect (subjectively measured from the morning questionnaire to assess sleepiness and ability to concentrate) and rebound effect, patient-reported total sleep time (pr-TST), and patient-reported wake after sleep onset (pr-WASO) after the abrupt discontinuation of study treatment.

Statistical methods:

Efficacy:

The comparisons of the sleep refreshing quality (change from baseline) at the end of double-blind treatment between the 2 doses of eplivanserin versus placebo were performed, on the Intent-to-Treat (ITT) population with an analysis of covariance (ANCOVA) using as covariate the baseline value of the parameter analyzed in the model. A 2-sided significance level of 5% was used without any adjustment for multiple comparisons (2 doses).

Safety:

Safety data were summarized by treatment group using descriptive statistics. The Sponsor defined the thresholds for potentially clinically significant abnormalities (PCSAs) in clinical laboratory tests, vital signs, and ECG. Analyses of the residual and rebound effects were also performed.

Summary:

Efficacy results:

Eplivanserin 1 mg/day and 5 mg/day was tested on a population suffering from sleep disorders in fibromyalgia and was selected on poor refreshing sleep quality which corresponds to one of the main complaints of fibromyalgic patients.

The results of this study indicate that eplivanserin 1 mg/day and 5 mg/day did not demonstrate a statistically significant effect on the primary efficacy parameter – change from baseline to end of treatment in refreshing quality of sleep using patient sleep questionnaires.

The patient-reported number of awakenings at end of treatment was statistically significantly lower in the eplivanserin 1 mg/day group than in the placebo group. In addition, in the PGI assessment at end of treatment, the eplivanserin 5 mg/day group had more favorable responses for “help for sleeping” and “time to fall asleep” compared with the placebo group. No treatment effect of eplivanserin versus placebo at end of treatment was observed on the other measures of the patient sleep questionnaire, difficulty of doing activities due to sleeping problems, pain or fatigue assessments, or CGI. This population known for a prevalence of psychiatric distress showed a slight improvement in terms of intensity of depressive and anxiety symptoms as reported through the HAD scale at end of treatment.

Safety results:

Safety results are shown in the table below.

	Placebo (N=70) n (%)		Eplivanserin 1 mg (N=68) n (%)		Eplivanserin 5 mg (N=66) n (%)	
Subjects with any TEAE	53	(75.7)	42	(61.8)	45	(68.2)
Subjects with any SAE	0	(0)	0	(0)	1	(1.5)
Deaths	0	(0)	0	(0)	0	(0)
Subjects permanently discontinued due to AE	4	(5.7)	3	(4.4)	8	(12.1)

The number of patients with at least 1 TEAE was lower in the eplivanserin groups than in the placebo group.

The most common TEAEs (preferred term incidence ≥5% in any group) were: headache, dizziness, nasopharyngitis, nausea, dry mouth, diarrhea, upper respiratory tract infections, edema peripheral, dyspepsia, muscle spasms, and upper abdominal pain. Of these, nausea and dry mouth occurred with a higher incidence in both eplivanserin groups than in the placebo group.

One patient (eplivanserin 5 mg group) experienced an SAE: hospitalization due to impaired gastric emptying (not related to the study drug). There were no fatal outcomes.

The incidence of TEAEs leading to discontinuation was comparable between the placebo and eplivanserin 1 mg group, but was slightly greater in the eplivanserin 5 mg group.

There were no clinically significant mean changes from baseline in any laboratory parameter. The incidence of PCSAs was similar between the groups for all laboratory parameters, except for blood glucose (≥7 mmol/L in fasting condition), reported in 1/54 patients in the placebo group, 1/53 patients in the eplivanserin 1 mg group and 5/52 patients in the eplivanserin 5 mg group. Among the 5 patients in the eplivanserin 5 mg group, 2 had elevated values at baseline and 2 were diabetic.

Few clinically non-relevant changes in vital signs and ECG parameters were reported. Regarding ECG parameters, no prolonged QTcB-interval or change from baseline >60 ms was reported in eplivanserin groups.

There was no evidence of symptoms related to residual effects (at the end of the double-blind treatment period) or rebound effects (sleep parameters after the end of the double-blind treatment period) from eplivanserin.

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