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Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: sanofi-aventis **Drug substance(s):** ataciguat (HMR1766)	**Study Identifier:** NCT00799656 **Study code:** DFI10569
Title of the study: Efficacy and safety of oral ataciguat (HMR1766) 200 mg administered once daily for 28 days on pain reduction in patients with Neuropathic Pain. A randomized, double-blind, placebo-controlled, cross-over study.	
Study center(s): 12 centers in Europe	
Study period: Date first patient enrolled: 26/Nov/2008 Date last patient completed: 10/Sep/2009	
Phase of development: Phase 2 (exploratory)	
Objectives: Primary: To assess the efficacy of ataciguat administered as 200 mg once daily for 28 days in comparison to placebo in reducing pain intensity in patients with chronic neuropathic pain. Secondary objectives: Safety:To investigate the safety and tolerability of 200 mg ataciguat once daily (OD) in comparison to placebo. Pharmacokinetic (PK): To assess the exposure to ataciguat.	
Methodology: Multinational, randomized, double-blind, placebo-controlled 2-way cross-over study with a post treatment follow-up period in patients with chronic neuropathic pain due to diabetic polyneuropathy or a peripheral nerve lesion following a surgical intervention.	
Number of patients:	Planned: approximately 60 Randomized: 62 Treated: 62 Efficacy: 62 (25 in the post-surgery stratum and 37 in the diabetic stratum) Safety : 62 (25 in the post-surgery stratum and 37 in the diabetic stratum) Pharmacokinetics : 59
Diagnosis and criteria for inclusion: Patients of either gender, 18 to 75 years of age, with chronic neuropathic pain due to diabetic polyneuropathy or a peripheral nerve lesion following a surgical intervention. The neuropathic pain had a distinct neuroanatomically plausible distribution demonstrated by at least one confirmatory test (e.g., clinical sensory examination, electrophysiology) and was present for more than 3 months.	

Investigational product: ataciguat 50 mg liquid-filled soft gelatin capsules

Dose: 200 mg (4 capsules) once daily (OD)

Administration: oral (PO), with or without food, swallowed with water, between 7 and 9 AM after awakening

Duration of treatment: 8 weeks (2 periods of 4 weeks)

Duration of observation: up to 14 weeks, including up to 2 week screening and washout, 4-week treatment, 2-week washout, 4-week treatment, 2-week post-treatment follow-up

Reference therapy: Placebo matching ataciguat capsules

Dose: 0 mg

Administration: Per os (PO), with or without food, swallowed with water, between 7 and 9 AM after awakening

Criteria for evaluation:

Efficacy: The primary efficacy endpoint was the absolute change from baseline to endpoint in the average daily pain intensity (calculated from the pain intensity over the last 12 hours measured twice daily – in the morning and evening – on the self-rated 11-point Numerical Rating Scale (NRS) in the electronic patient diary), defined as the mean of the last 7 post-baseline days of each treatment period.

Safety: The following safety criteria were evaluated, and analyzed using descriptive statistics: adverse events (AEs) reported by the patient or noted by the Investigator, standard hematology and blood chemistry, physical examination, vital signs, and electrocardiogram (ECG).

Statistical methods:

Efficacy analysis: The primary analysis of the primary endpoint (change from baseline in the average daily pain intensity on the self-rated 11-point Numerical Rating Scale [NRS]) was implemented on modified intent-to-treat (m-ITT) population and used a 3-way linear mixed model with 3 fixed effects (sequence, treatment, period), 1 random effect (patient within sequence), and covariates (baseline pain intensity score and origin of neuropathic pain).

Safety analysis: The analysis was implemented on all treated population and assessed AEs, laboratory data, vital signs, and ECG. Descriptive statistics was used.

Pharmacokinetic analysis: Descriptive statistics on C_{trough} was provided at each sampling time.

Summary: This Clinical Study Report (CSR) has been prepared as abbreviated.

The primary efficacy analysis of the change from baseline of the average daily pain intensity as measured on the 11-point NRS did not show a significant difference between the placebo and ataciguat treatment groups, in both treatments the average daily pain intensity decreased. Similarly, no significant difference between the placebo and ataciguat group was found for the changes of the mean Neuropathic Pain Symptom Inventory (NPSI) total score and its sub-scores, the decrease of pain intensity as documented on the 100 mm Visual Analog Scale (VAS) for current pain intensity (VAS-PI), pain relief (VAS-PR) and mechanical allodynia. The use of rescue medication was virtually the same during the placebo and ataciguat treatment.

Analyses of the subgroups of patients with pain due to underlying diabetic neuropathy or neuropathy due to surgical nerve lesion showed overall comparable efficacy of the placebo and ataciguat treatments. Notably, a larger response, similarly for placebo and ataciguat, was found in the patients with underlying diabetic neuropathy as compared with the patients with underlying neuropathy due to surgical nerve lesion for the average daily pain intensity (11-point NRS), the NPSI total score and some of its sub-scores, the current VAS-PI and VAS-PR. These findings could not be attributed to an improved glycemic control in the diabetes patients, as the mean glycohemoglobin (HbA1c) did not change during the study period.

Exploratory analyses showed higher pain intensity reported at baseline and similarly larger decreases during treatment as well as a higher use of rescue medication in both the placebo and ataciguat treated patients enrolled in Romania as compared with the patients enrolled in Austria or Czech Republic.

Overall, the study treatments were well tolerated. Study treatment was permanently discontinued due to a treatment-emergent adverse event (TEAE) in one ataciguat patient only (transient hyperbilirubinemia likely related to Gilbert's syndrome). There were no serious AEs (SAEs) or deaths reported in this study.

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