SYNOPSIS

Title of the study:	Multinational, multicenter, randomized double-blind, placebo-controlled, parallel-group study of efficacy and safety of SAR292833 administration for 4 weeks in patients with chronic peripheral neuropathic pain (ACT11917).
Coordinating Investigator:	[redacted]
Study centers:	53 active centers in 7 countries (Czech Republic, Hungary, Poland, Russian Federation, Slovakia, Ukraine, and the United States of America)
Publications (reference):	Not applicable
Study period:	
Date first patient enrolled:	26 March 2012
Date last patient completed:	08 May 2013
Phase of development:	Phase 2a
Objectives:	

Primary objectives: To assess the efficacy of SAR292833 versus placebo in reducing pain intensity associated with chronic peripheral neuropathic pain using 11-point numerical rating scale (NRS).

Secondary objectives:

To compare the effects of SAR292833 with placebo on the change of neuropathic pain symptoms versus baseline Neuropathic Pain Symptoms Inventory (NPSI);

To evaluate the effects of SAR292833 in comparison to placebo on the change in pain intensity of mechanical allodynia;

To investigate the safety and tolerability of SAR292833 in comparison to placebo;

To investigate the pharmacokinetics (PK) and the relationships between main efficacy parameters or pharmacodynamic (PD) effect and pharmacokinetics (PK/PD) of SAR292833 in patients with chronic peripheral neuropathic pain.

Methodology: Multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group study with 3 treatment arms. The study consisted of a 2-week screening period (single-blind placebo administration), followed by a 4-week treatment period (double-blind) and a 3-week post-treatment follow-up period.

A randomization ratio of 1:1:1 was applied. Randomization was stratified by center and by patient diagnosis related to the chronic peripheral neuropathic pain (associated with diabetic polyneuropathy or post-herpetic neuralgia [PHN]).

Number of patients:

Planned: upper bound of 198 randomized patients Randomized: 191 Treated: 189

Evaluated:

Efficacy: 176 Safety : 189 Pharmacokinetics: 188

Diagnosis and criteria for inclusion: The study included adult patients of either gender, 18 to 85 years of age, who signed the informed consent form, and were presenting with chronic peripheral neuropathic pain associated with diabetic polyneuropathy or PHN.

The neuropathic pain must have had a distinct neuro-anatomically plausible distribution with sensory signs and symptoms confirmed by DN4 (Douleur Neuropathique en 4 questions) score of ≥4 and being present for more than 3 months. SAR292833 was to be taken in fed condition. Therefore, only patients who were judged to be reliable to fulfill this condition (used to have breakfast and dinner) could be included in the study.

Study treatments

Investigational medicinal product: SAR292833

Formulation: Granule-filled capsules containing 20 or 40 mg SAR292833

Route of administration: Oral

Dose regimen: SAR292833 120 mg: 3 capsules of 40 mg twice daily
SAR292833 20 mg: 1 capsule of 20 mg + 2 capsules of matching placebo twice daily

Batch numbers: [redacted]

Investigational medicinal product: Placebo

Formulation: Matching granule-filled capsules containing placebo

Route of administration: Oral

Dose regimen: During screening period: 1 capsule on Day -14. The number of capsules was increased to 6 from Day -14 to Day -9 (1 more capsule each day). All patients continued to take 6 capsules per day (3 in the morning and 3 on the evening) until Day -1.

During treatment period: 3 placebo capsules twice daily

Batch numbers: [redacted]

Noninvestigational medicinal products: Acetaminophen/paracetamol

Formulation: Tablets containing 500 mg acetaminophen/paracetamol

Route of administration: Oral

Dose regimen: Maximum single dose of 1g of acetaminophen/paracetamol (2 tablets of 500 mg) for a maximum daily dose of 4 g acetaminophen/paracetamol (8 tablets of 500 mg).

Batch numbers: Not applicable as acetaminophen/paracetamol was used under the commercial labeling.

Duration of treatment: 4 weeks

Duration of observation: 9 weeks including 2-week screening, 4-week treatment, and 3-week follow-up

Criteria for evaluation:

Efficacy:

Primary endpoint: Change from baseline to the fourth week of treatment in the average daily pain intensity as measured by the 11-point NRS; the average daily pain intensity is the mean of the last consecutive 7 days.

Secondary endpoints:

- Responder rate: Percentage of patients with reduction in pain intensity of at least 30% and 50% at endpoint compared to baseline derived from the primary efficacy endpoint.
- NPSI: Change in NPSI after 4 weeks treatment compared to baseline.
- Patient global impression of change (PGIC) after 4 weeks treatment.
- Rescue medication: Amount of and time to first rescue medication intake during the treatment period.
- Mechanical allodynia: Change in intensity of the mechanical allodynia after 4 weeks treatment compared to baseline using visual analog scale (VAS).
- Daily Sleep Interference Score (DSIS): Change in DSIS after 4 weeks treatment compared to baseline.
- Clinical global impression of change (CGIC) after 4 weeks treatment.

Criteria for evaluation (cont'd):

Safety: Adverse events (AEs) reported by the patient or noted by the investigator, clinical laboratory tests, vital signs and physical examinations reported by the Investigator, and 12-lead electrocardiogram (ECG).

Pharmacokinetics: Plasma level of SAR292833 at Visit 3 (Day 1) (2 to 4 hours postdose), Visit 4 (Day 8) (at predose and 2 to 4 hours postdose), Visit 5 (Day 15) (at predose and 2 to 4 hours postdose), Visit 6 (Day 22) (4 to 8 hours postdose), and Visit 7 (Day 29) (12 to 24 hours postdose).

Plasma concentrations of SAR292833 were determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method with lower limit of quantification (LLOQ) of 0.5 ng/mL. A descriptive analysis on concentrations according to time windows and visit was performed.

Pharmacodynamics: The "Pain right now" was documented using self-reported 11-point NRS at visit 2 (baseline), visits 4 and 5, and on the evening of Day 29 (24 hours after the last administration).

Statistical methods:

Efficacy analysis:

Fifty-nine (59) patients per arm were needed to ensure an 80% power to detect a difference of 1.2 points at the fourth week of treatment between the highest dose of SAR 292833 and placebo (main comparison) assuming a standard deviation (SD) of 2.3 points at the 0.05 level.

The efficacy population was defined as the randomized population with evaluable average daily pain intensity both at baseline and at least at one of the 4 planned on-treatment weeks. Considering that, at most, 10% of randomized patients would not be included in the efficacy population, 66 patients per arm were to be randomized.

A blinded sample size reassessment was performed after at least 138 patients have been randomized. Targeted power and difference from placebo were not modified, nor type I error rate; the assumed SD and anticipated non evaluable rate were the only assumptions reassessed. The planned target of 198 randomized patients was retained as an upper bound, considering the 2.3 value for the SD as a reasonably conservative assumption.

Primary analysis: A mixed-effect model with repeated measures (MMRM) was applied to change from baseline in the average daily pain intensity (11-point NRS), adjusted on baseline, treatment, diagnosis stratum, time, and the following interactions: treatment*time, diagnosis*time, baseline*time, treatment*diagnosis, and treatment*diagnosis*time.

Analysis of secondary endpoints: The continuous secondary endpoints were analyzed using a similar MMRM approach.

The proportion of responders was analyzed using a generalized Cochran-Mantel-Haenzel test, accounting for stratification on the diagnosis.

Safety analysis:

Safety data were evaluated in the safety population. The treatment-emergent adverse event (TEAE) period for safety data was defined as the period from the first intake of the study investigational medicinal product (IMP) up to 3 weeks after last intake.

Summary:

Population characteristics: A total of 191 patients were randomized into the study. The study population consisted mainly of diabetic patients with diabetic polyneuropathy (90% versus 10% of patients with PHN). Demographic characteristics at baseline were similar across all treatment groups. The mean age of population was 59.6 years; 63.9% were male, 95.3% were Caucasian, and the BMI was ≥30 kg/m² in 53.9% of the patients. Disease characteristics including NRS, DN4, and NPSI at baseline were similar across all treatment groups. Mean NRS and DN4 at baseline were 6.45 (0.98) and 6.5 (1.4), respectively.

Summary (cont'd):

Efficacy and pharmacodynamic results: The primary efficacy analysis of the change from baseline in the average daily pain intensity as measured on the 11-point NRS did not show a significant difference between the placebo and the SAR292833 treatment groups. Likewise, no difference between SAR292823 treatment groups and placebo was found when assessing the responders rate.

A significant difference was found between the placebo and SAR292833 120 mg group for the changes in the mean NPSI total score (p=0.0024) as well as for 3 different dimensions of NPSI such as deep spontaneous pressing pain, paroxysmal pain, and evoked pain.

For CPIG, there was a slight trend in favor of SAR292833, but results were not statistically significant. There were no differences for PGIC in all treatment groups.

The percentage of days spent on rescue medication was lower in the SAR292833 groups compared to the placebo group.

Assessments of pain "right now" over time were similar in all treatment groups.

Safety results: Overall, the study treatment was well tolerated. Study treatment was permanently discontinued due to a TEAE in one patient on SAR292833 20 mg (creatine phosphokinase [CPK] increase related to physical exercise started prior to randomization and worsened during treatment). Hyperglycemia was the most frequently reported adverse event in all groups, consistent with the main underlying disease in the study population. There were no deaths reported in this study. The number of patients with treatment-emergent serious adverse event (SAE) was 2 (3.2%) in placebo group and 2 (3.0%) in SAR292833 20 mg group, with no treatment-emergent SAE in SAR292833 120 mg group. All SAEs were distributed over five different System Organ Classes (SOCs) without a notable increase in any specific SOC.

Pharmacokinetic results: SAR292833 concentrations increased on average by 4 to 4.5-fold for a 6-fold increase in dose between 20 and 120 mg.

In both 20 mg and 120 mg groups, on Day 1 and Day 15 , SAR292833 plasma concentrations were in agreement with those obtained or predicted in Phase 1 studies at the same doses/dosing regimen and day of administration.

Conclusions: [redacted]

Date of report: 14-Oct-2013