SYNOPSIS

Title of the study: An open-label, multicenter study evaluating the long-term safety and efficacy of SR121463B in patients with syndrome of inappropriate antidiuretic hormone secretion (SFY5904B)

Investigator: [redacted]

Study centers: The study was conducted in 16 centers in 11 countries.

Publications (reference): None

Study period:

Date first patient enrolled: 26 July 2005

Date last patient completed: 28 August 2007

Phase of development: Phase 3

Objectives:

Primary

To assess the long-term safety and tolerability of SR121463B (satavaptan) in patients with Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH).

Secondary

To assess the long-term efficacy of satavaptan in maintaining normonatremia in patients with SIADH.

Methodology: Multicenter, multinational, open-label study including a drug discontinuation period.

Number of patients: Planned: 52 Included: 57 Treated: 57

Evaluated: Efficacy: 57 Safety: 57 Pharmacokinetics: 57

Diagnosis and criteria for inclusion: Patients with SIADH having serum sodium between 115 and 132 mmol/L.

Investigational product: satavaptan (size 0 capsules of 5, 12.5, and 25 mg).

Dose: Day 1: 25 mg; from Day 2 to the end of study: 5, 12.5, 25, or 50 mg/day of satavaptan, depending on response to treatment (dose was limited to a maximum of 25 mg/day by Protocol Amendment No. 3).

Administration: Oral

Batch numbers: 5 mg capsules: [redacted]; 12.5 mg capsules: [redacted]; 25 mg capsules: [redacted].

Duration of treatment: Up to 104 weeks.

Duration of observation: Up to 104 weeks.

Reference therapy: Not applicable.

Criteria for evaluation:

Safety: Monitoring of adverse events (AEs), laboratory evaluations, vital signs, and electrocardiograms (ECGs).

Efficacy: The primary efficacy variable was the serum sodium level measured at each scheduled visit.

Exploratory efficacy variables assessed were serum osmolality, body weight, and quality of life.

Pharmacokinetics: Satavaptan plasma concentrations were assessed

Pharmacokinetic/pharmacodynamic relationships: The relationships between change from baseline in QTcB and in QTcF and plasma concentrations were explored during the study (all visits combined) using graphical and regression methods.

Pharmacokinetic sampling times and bioanalytical methods:

Sampling

Plasma samples to determine satavaptan concentration were collected at baseline on Day –1, at predose on Day 56; at predose and 2 hours following satavaptan administration on Day 4 and Day 28, and 2 hours following satavaptan administration on Day 84 and Day 168.

Assay

Satavaptan and its metabolites SR122621 and SSR108434 plasma concentrations were determined using a validated liquid chromatography-tandem mass spectrometry method with a lower limit of quantification of 0.05 ng/mL for satavaptan and SSR108434 and 0.5 ng/mL for SR122621.

Statistical methods:

Safety: Safety analyses were summarized by descriptive statistics. Potentially clinically significant abnormalities in clinical laboratory results, vital signs, and ECGs were flagged and analyzed.

Efficacy:

Primary analysis

The proportion of the intent-to-treat (ITT) population with serum sodium concentration $\geq$135 mmol/L, or having a $\geq$5 mmol/L increase from baseline at each visit, were reported as the primary analysis. Serum sodium concentrations were summarized by descriptive statistics and were also classified according to a pre specified range.

Additional analyses for the primary variables

A short-term analysis was performed. The responders were defined as any patients achieving a postbaseline serum sodium concentration ≥135 mmol/L, and/or having a ≥5 mmol/L increase from baseline, for a duration of at least 24 hours during the time period from the first intake of study drug to Day 4. The proportion of the responders was summarized using descriptive statistics.

Exploratory analysis

The exploratory efficacy variables were summarized for the ITT population using descriptive statistics by scheduled visit.

All descriptive statistics were provided on observed cases (no last observation carried forward imputation was performed). Graphical illustration was provided, when appropriate.

Pharmacokinetics: Plasma concentrations of satavaptan and its metabolites were summarized using descriptive statistics (mean, geometric mean, standard deviation [SD], coefficient of variation, minimum, maximum, and median).

Summary:

Safety results: During the study, 47/57 patients (82.5%) experienced TEAEs. Most of the TEAEs could be related to the patients' health status and underlying disease, including multiple infections and cancer related complications.

Twenty-six patients had treatment emergent SAEs, leading to death for 9 patients. Of those patients who suffered fatal serious adverse events (SAEs), 6 had SIADH of cancer origin (3 died from progression of their pre existing cancer, 2 died from neutropenic sepsis following chemotherapy, and 1 died from physical health deterioration in the context of chemotherapy complications) and 3 had idiopathic SIADH (1 patient with Biswanger's disease died in the context of general physical health deterioration, 1 patient with multiple neoplasms died from cardiorespiratory arrest after a recent neoplasm surgery, and 1 patient died from esophageal cancer).

Thirteen patients discontinued the study due to treatment emergent adverse events (TEAEs) including 8 patients who experienced SAEs with fatal outcomes, 1 patient experienced a TEAE of prolonged QTcF, 1 patient had myocardial ischemia, 1 patient had tachycardia, myocardial ischemia, and alanine aminotransferase increased, 1 patient had hematemesis and thrombocytopenia, and 1 patient experienced an AE of thirst of moderate intensity.

A rapid correction in serum sodium concentration ≥12 mmol/L/24h was observed in 3 patients, only after the administration of the first dose of satavaptan; no concomitant neurological symptoms were reported in these patients. During the study, 2/57 (3.5%) patients had a serum sodium concentration >145 mmol/L, 6/55 patients (10.9%) had hyperkalemia (serum potassium concentration ≥5.5 mmol/L), reported as a TEAE for 4 patients. Four of the 6 patients with hyperkalemia were receiving concomitant medication known to increase potassium. A slight decrease in creatinine clearance was noted during the study, however 32 patients out of 56 (57.1%) had abnormal creatinine clearance at baseline. No relevant changes from baseline were found in other laboratory parameters.

The most frequently reported abnormalities in vital signs were orthostatic changes in SBP and DBP. During the study, 2 patients had prolonged QTcF≥500 ms with increase in QTcF from baseline >60 ms. A further 6 patients had increase from baseline >60 ms (with concomitant prolonged QTcF [>450 ms in male, >470 ms in female, and <500 ms] in 4 patients). Among these 8 patients, 2 were receiving concomitant medications known to prolong the QT interval.

Efficacy results: During the first 4 days of the study, the majority of patients (36/57; 63.2%) were considered as responders in terms of improved hyponatremia (serum sodium concentration ≥135 mmol/L and/or an increase from baseline ≥5 mmol/L for a duration of at least 24 hours).

Long-term maintenance of serum sodium within normal range (135 to 145 mmol/L) was observed for up to 92 weeks in patients receiving flexible doses of satavaptan (the majority of patients receiving 25 mg). From Day 4 up to Day 644 (Week 92), most patients (≥75% of patients) had serum sodium concentration ≥135 mmol/L and/or an increase from baseline ≥5 mmol/L.

Thirty patients with serum sodium concentration ≥135 mmol/L on Day 56 (Week 8) discontinued treatment during a planned drug holiday. Among the 23 patients who resumed treatment, a decrease in mean serum sodium (-4.9 ± 2.60 mmol/L) to abnormally low values was observed when satavaptan was discontinued; when treatment was restarted, mean serum sodium returned within normal range.

Pharmacokinetic results: For satavaptan, at Visit 7 (Day 28), the mean (SD) C_{trough} were 0.812 (1.54) ng/mL (12.5 mg), 2.44 (3.78) ng/ml (25 mg) and 6.03 (7.05) ng/mL (50 mg); the mean C_{2h} were 4.60 (5.78) ng/mL (12.5 mg), 9.40 (8.91) ng/ml (25 mg) and 32.2 (30.3) ng/mL (50 mg).

Pharmacokinetic/Pharmacodynamic: No significant relationship was observed between change from baseline in QTcB and QTcF and satavaptan plasma concentrations during the study (all visits combined).

Conclusions: [redacted]

Date of report: 23-Jun-2008