# SYNOPSIS

**Title of the study:** A randomized, double-blind, placebo-controlled, parallel-group, multicenter study evaluating the efficacy and safety of satavaptan in patients with syndrome of inappropriate antidiuretic hormone secretion (EFC4489C)

**Investigator:** [redacted]

**Study centers:** The study was conducted in 17 active centers in 11 countries

**Publications (reference):** Not applicable

**Study period:**

Date first patient enrolled: 04 May 2004

Date last patient completed: 27 September 2007

**Phase of development:** 3

**Objectives:**

***Primary***

To assess the efficacy of satavaptan in correcting low serum sodium concentration in patients with Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)

***Secondary***

To assess the long-term efficacy of satavaptan in maintaining normal serum sodium concentration in patients with SIADH as well as the safety and tolerability of satavaptan in patients with SIADH

**Methodology:** Multicenter, randomized, double-blind (DB), placebo-controlled, parallel-group, fixed-dose, with an open-label (OL) flexible-dose period including a drug discontinuation period "drug holiday"

**Number of patients:** Planned: 75 Randomized: 77 Treated: 77

**Evaluated:**

Efficacy: 76 (ITT), 59 (PP)

Safety: 77

Pharmacokinetics: Randomized: 76, Exposed:76, ITT: 75

**Diagnosis and criteria for inclusion:** Male or female patients, aged 18 years or older, with SIADH of any origin, and with serum sodium concentration between 115 and 132 mmol/L

**Investigational product:** Satavaptan (size 0 capsules)

Dose: 25 and 50 mg daily during DB period, extended to 5 mg, 12.5 mg, 25 mg, and 50 mg during the OL period (the 50 mg dose was withdrawn from the OL period following Protocol Amendment No. 4).

Administration: Oral

Batch numbers:

- 5 mg capsules: [redacted]
- 12.5 mg capsules: [redacted]
- 25 mg capsules: [redacted]

**Duration of treatment:** Double-blind period: Up to 4 days. Open-label period: Up to 3 years

**Duration of observation:** Up to 3 years

**Reference therapy:** Placebo (size 0 matching capsules)

Dose: Not applicable

Administration: Oral

Batch number: [redacted]

**Criteria for evaluation:**

***Efficacy***

Primary criteria

Serum sodium: percentage of responder patients (ie, patients having a serum sodium concentration $\geq$135 mmol/L, and/or increased serum sodium concentration $\geq$5 mmol/L) for a duration of at least 24 hours during the DB period.

Secondary criteria

Serum osmolality, free water clearance (FWC), urine volume, urine osmolality, urine electrolytes, body weight, thirst index, water intake, plasma arginine vasopressin (AVP) concentration as well as quality of life (EQ-5D, satisfaction) and pharmacoeconomics. Changes from baseline at the end of the DB period were compared between satavaptan groups and placebo using analysis of covariance (ANCOVA) models. Descriptive summary statistics (N, mean, SD, median, range) was also presented.

***Safety***

Occurrence of treatment emergent adverse events (TEAEs), physical examination, laboratory evaluations, vital signs, and electrocardiograms (ECGs).

***Pharmacokinetics***

Satavaptan plasma concentrations were assessed.

**Pharmacokinetic sampling times and bioanalytical methods:**

***Sampling***

At predose and 2 hours following satavaptan administration on Days 3 to 5 (Visit 6) and 32 (Visit 9); at predose on Day 60 (Visit 10) and 2 hours following satavaptan administration on Days 88 (Visit 18) and 172 (Visit 21).

***Assay***

Satavaptan plasma concentrations were determined using a validated liquid chromatography-tandem mass spectrometry method with lower limit of quantification of 0.05 ng/mL.

**Statistical methods:**

***Efficacy***

Primary efficacy analysis

*Double-blind period*

The percentage of responders by the end of the DB period was analyzed using Fisher's exact test (on both intent-to-treat [ITT] - defined as randomized unique patients who received at least 1 dose of DB treatment, with at least 1 post-randomization assessment during the DB period, and, when appropriate, a relevant baseline assessment and per protocol [PP] populations), comparing each dose of satavaptan with placebo.

Multiple comparison/multiplicity

The Hochberg procedure was used to adjust the comparison of multiple satavaptan doses (25 and 50 mg) to placebo. The test was significant if either dose level reaches P≤0.025, or if both dose groups reach P≤0.05.

Additional analyses for the primary variables

Changes from baseline of serum sodium concentration and time to response considered as supportive to the primary responder analysis were to be performed only if the respective test of the satavaptan versus placebo was found significant regarding the response rate.

*Open-label period*

During the OL period the evaluation of efficacy was only descriptive (N, mean, standard deviation [SD], median, minimum, maximum) due to the possibility of dose-adjustment and the absence of a control group. The serum sodium concentration changes from baseline, the proportions of patients with normalized serum sodium concentration or having ≥5 mmol/L increase from baseline at the first 2 days of the OL period and then once each 4 or 8 weeks were presented. For the first 3 visits in the OL period (Days 1, 2, and Week 4) the efficacy parameters were reported by the randomized treatment allocated during the DB period. Finally, exploratory data on drug holiday was provided

Secondary efficacy analyses

*Double-blind period*

At the end of the DB period, the urine osmolality, serum osmolality, FWC, urine volume, urine electrolytes, body weight, thirst index, water intake, Plasma AVP were summarized. The change from baseline for each parameter is also analyzed between each dose and placebo using ANCOVA.

*Open-label period*

Weight, thirst index, quality of life assessment (EQ-5D), satisfaction score, plasma AVP level and pharmacoeconomic data were summarized by visit in the OL period using descriptive statistics.

***Pharmacokinetics***

Plasma concentrations of satavaptan were summarized using descriptive statistics (mean, geometric mean, SD, coefficient of variation, minimum, maximum, and median).

***Pharmacokinetic/pharmacodynamic relationships***

The relationship between pharmacodynamic responses (serum sodium, QTcB and QTcF) and plasma concentrations were explored using graphical and regression methods.

***Safety***

Safety analyses were performed on all randomized patients who had taken at least 1 dose of study treatment. All TEAEs recorded during the course of the study were coded to high-level term, high-level group term and preferred term according to the medical dictionary for regulatory activities (version 10.0), and assigned to a system-organ class.

Abnormalities in laboratory data, vital signs, and ECG parameters were assessed using mean changes from baseline, and potentially clinically significant abnormality criteria.

**Summary:**

Study population: A total of 77 patients, aged between 37 and 93 years (mean age ± SD: 67.7 ± 14.75 years) participated in the study. Overall, 47.4% of patients were females and 52.6% were males. The most frequently reported causes of SIADH were idiopathic (40.8%), malignant tumor (38.2%) or were drug induced (15.8%).

Duration of exposure: During the DB period, patients were exposed to either placebo or satavaptan for a mean duration of 3.8 ± 0.51 days and 3.5 ± 0.76 days, respectively. Mean duration of the OL period was 385.2 ± 428.49 days, ranging from 1 to 1131 days. In the OL period, almost all patients (72/75) received at least once a daily dose of 25 mg.

***Efficacy results***

Double-blind period

At the end of the DB period, the responder rate (patients with serum sodium concentration ≥135 mmol/L and/or serum sodium increase ≥5 mmol/L over 24 hours duration) reached 84% and 88% in the satavaptan 25 and 50 mg groups, respectively compared with 11.5% in the placebo group (p<0.0001, Hochberg adjusted p-value).

Responders n (%) at the end of DB period - ITT population

| | Placebo (N=26) | Satavaptan 25 mg (N=25) | Satavaptan 50 mg (N=25) |
|---|---|---|---|
| Responder patients [n (%)] | 3 (11.5) | 21 (84.0) | 22 (88.0) |
| p-value vs Placebo | | <.0001 | <.0001 |
| Adjusted p-value (Hochberg method) | | <.0001 | <.0001 |
| Patients with serum sodium ≥135 mmol/L over 24h duration [n (%)] | 0 (0) | 13 (52.0) | 15 (60.0) |
| p-value vs Placebo | | <.0001 | <.0001 |
| Patients with serum sodium increase ≥5 mmol/L over 24h duration [n (%)] | 3 (11.5) | 15 (60.0) | 18 (72.0) |
| p-value vs Placebo | | 0.0004 | <.0001 |

Note: P-value determined from Fisher's exact test.

The median response time was 1.98 and 1.87 days in satavaptan 25 and 50 mg groups respectively, both significantly shorter (p<0.0001) than >4.02 days in the placebo group.

At the end of the DB period, the mean change of serum sodium concentration from baseline was significantly higher in the satavaptan 25 mg group (+ 7.82 mmol/L; p<0.0001) and satavaptan 50 mg group (+ 7.5 mmol/L; p<0.0001) as compared with placebo (+ 1.16 mmol/L).

At the end of the DB period, FWC in both satavaptan groups was significantly increased compared with placebo. This was associated with significant increase of serum osmolalility and a decrease in urine osmoalility in 25 and 50 mg satavaptan groups.

The mean plasma AVP increased in a dose dependent manner in satavaptan treated patients.

The above-described effects in satavaptan treated patients were accompanied with an improvement in the quality of life as measured by EQ-5D.

Open-label period

On Day 32 (OL Week 4) the percentage of patients with serum sodium concentration ≥135 mmol/L and/or an increase in serum sodium concentration ≥5 mmol/L was about 90% and was maintained up to Day 1012 (OL Week 114) at similar high levels.

Drug holiday:

Overall, 36 of the 43 patients with serum sodium ≥135 mmol/L entered the drug holiday period. Most of the patients (20/36) who entered drug holiday (on Day 60 and 61) were previously receiving satavaptan 25 mg/day.

Nine patients remained normonatremic (serum sodium ≥135 mmol/L) during at least 28 days without taking satavaptan and were considered as cured. A total of 25 patients resumed treatment after 8.3 ± 11.07 days of drug discontinuation. In these patients the mean serum sodium decreased from the start of the drug holiday by -5.7 ± 3.01 mmol/L. After the restart of satavaptan treatment, serum sodium concentration increased within 28 days to normonatremic levels with mean serum sodium of 137.9 mmol/L. Two patients discontinued the drug holiday period before the 28-day time point, due to adverse event in 1 patient and patient request for the second patient.

***Safety results***

Double-blind period

During the DB period, 17/77 patients (10 in satavaptan groups and 7 in the placebo group) experienced at least 1 TEAE with no dose effect in the satavaptan groups. One patient in satavaptan 25 mg group and 2 patients in placebo group (including 1 serious adverse event [SAE] of bronchopulmonary aspergillosis with fatal outcome) experienced SAEs. Two patients discontinued the study due to TEAEs (1 patient in the placebo group who experienced bronchopulmonary aspergillosis, and 1 patient in satavaptan 25 mg group who experienced thirst).

A rapid correction in serum sodium concentration ≥12 mmol/L (n = 6/50) was mainly observed after the administration of the first satavaptan dose without neurological symptoms. During the course of the study, 3 patients (2 in satavaptan 25 mg group and 1 in satavaptan 50 mg group) had a serum sodium concentration >145 mmol/L.

One patient receiving satavaptan 50 mg had serum potassium values ≥5.5 mmol/L.

Orthostatic changes in systolic and diastolic blood pressure (SBP/DBP) were the most frequently reported vital signs abnormalities in the satavaptan groups, however comparable incidences were observed in the placebo group.

During the DB period, 2 patients in satavaptan groups had prolonged QTcF, including 1 patient with prolonged QTcF at baseline. However no QTcF value ≥500 ms, nor increase from baseline >60 ms were reported. When considering the last value on treatment, there was an increase in mean change from baseline without dose dependency (0.9 ms for placebo, 9.9 ms for satavaptan 25 mg, and 3.3 ms for satavaptan 50 mg).

Open-label period

During the OL period, 65/75 patients (86.7%) experienced TEAEs. A total of 44/75 (58.7%) had at least 1 SAE, leading to death in 27 patients. Sudden death occurred in 3 elderly hyponatremic patients (≥75 years). Overall 32 patients withdrew due to TEAEs. Most of the TEAEs could be related to patients underlying diseases, including multiple infections and cancer related complications.

During the OL period 12/74 (16.2%) patients had a serum sodium concentration >145 mmol/L.

Nine patients had potassium ≥5.5 mmol/L; however 3 of these 9 patients were receiving concomitant drugs known to increase potassium.

No relevant changes from baseline were found in other laboratory parameters.

Orthostatic changes in heart rate and in DBP and SBP were the most frequently reported vital signs abnormalities.

During the OL period, 6 patients had prolonged QTcF values, reaching QTcF value ≥500 ms in 2 patients; 2 of these patients had already prolonged QTcF values during the DB period. For 4 of these 6 patients, prolonged QTc was reported as a TEAE. Moreover 2 patients had an increase in QTcF from baseline >60 ms. When considering the last value on treatment, mean change from baseline was 2.0 ms in QTcF.

***Pharmacokinetic results***

At the end of the double-blind period [Days 3-5; Visit 6], the mean (SD) Ctrough were 1.56 (2.71) ng/ml [25 mg] and 9.58 (20.6) ng/mL [50 mg]; the mean C2h were 8.15 (11.8) ng/ml [25 mg] and 25.3 (17.2) ng/mL [50 mg].

At Visit 9 [Day 32, open label period], the mean (SD) Ctrough were 0.470 (0.574) ng/mL [12.5 mg], 3.26 (4.43) ng/ml [25 mg] and 10.5 (10.6) ng/mL [50 mg]; the mean C2h were 3.26 (3.27) ng/mL [12.5 mg], 8.13 (9.15) ng/ml [25 mg] and 30.2 (24.2) ng/mL [50 mg].

There was a statistically significant increase in serum sodium concentrations with increase in satavaptan plasma trough concentrations (p=0.0096). There was no significant relationship between change from baseline in QTcB and QTcF and satavaptan plasma concentrations at the end of the DB period, as well as during the OL period (all visits combined).

***Conclusions***

[redacted]

**Date of report:** 25-Jul-2008