SYNOPSIS

Title of the study: A multicenter, randomized, placebo-controlled, double-blind trial evaluating the effect of 2 doses of a vasopressin V2 receptor antagonist (SR121463B) on serum sodium in patients with dilutional hyponatremia (EFC5816/DILIPO).
Investigator(s): [redacted]
Study center(s): 48 active centers in 15 countries
Publications (reference): None
Study period: Date first patient enrolled: 23/Jun/2005 (date of first signed informed consent) Date last patient completed: 18/Jul/2007
Phase of development: 3
Objectives: The primary objective was to assess the efficacy of satavaptan in correcting hyponatremia in patients with dilutional hyponatremia (DH) excluding known syndrome of inappropriate antidiuretic hormone secretion (SIADH) or cirrhosis. Secondary objectives were to assess the long-term efficacy of satavaptan in maintaining normonatremia in these patients, and to assess the safety and tolerability of satavaptan.
Methodology: Multicenter, randomized, placebo-controlled, double-blind (DB), 3-parallel group study assessing 2 fixed doses of satavaptan (25 and 50 mg) versus placebo, followed by an open-label (OL), non-comparative study period with flexible doses and including a temporary drug discontinuation period.
Number of patients: Planned: 108 (per Protocol Amendment 5) Randomized: 118 Treated: 122 including 4 patients not randomized through the interactive voice-response system (IVRS) **Evaluated:** Efficacy: Double-blind period: Intent-to-treat (ITT): 117 / Per protocol (PP): 90 - Open-label period: 101 (ITT) Safety: Double-blind period: 122 - Open-label period: 103 Pharmacokinetics: 122
Diagnosis and criteria for inclusion: Male or female patients aged 18 years and older, Patients with DH excluding known SIADH or cirrhosis, Serum sodium between 115 and 132 mmol/L
Investigational product: Satavaptan 12.5 and 25 mg capsules Dose: 25 or 50 mg during the DB period, and 12.5, 25, or 50 mg (the highest dose was limited to 25 mg after Protocol Amendment 4) during the OL period Administration: Oral Batch numbers: [redacted]

Duration of treatment: up to 4 days (5 days in 5 patients) in the DB period, and up to 1 year (343 days) in the OL period

Duration of observation: 1 year

Reference therapy: Placebo matching capsules

Dose: 0 mg

Administration: oral

Batch number(s): [redacted]

Criteria for evaluation:

Efficacy: The primary efficacy variable was serum sodium; the primary endpoint was the responder rate, which is defined as the percentage of patients with serum sodium ≥135 mmol/L and/or having an increase of serum sodium ≥5 mmol/L from baseline for a duration of at least 24 hours during the DB period.

Safety: Adverse events (AEs) reported by the patients or noted by the Investigator, physical examination, vital signs, electrocardiogram (ECG), and standard hematology and blood chemistry.

Pharmacokinetics: Satavaptan plasma concentrations.

Pharmacokinetic sampling times and bioanalytical methods:

Sampling: at baseline on Day -1 (Visit 1); at predose on Day 60 (Visit 16); at pre-dose and anytime after dose (but after ECG) on Days 4 (Visit 5) and 32 (Visit 15), at anytime after dose (but after ECG) on Days 88 (Visit 17) and 172 (Visit 20), and in case of serious adverse event (SAE).

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:

***Analysis populations*:** The ITT population consisted of all randomized patients who received at least 1 dose of DB treatment and who had a baseline assessment and at least 1 post-baseline assessment during the DB period. The PP population consisted of all randomized patients without any major protocol deviations and who had sufficient data to determine response status. The exposed population consisted of all patients who received at least 1 dose of DB treatment.

Efficacy analyses: The responder rate was analyzed in the ITT population. The response in the satavaptan treatment groups was compared to that of the placebo group using Fisher's exact test. No adjustment for covariates was made. The closed testing procedure was used for adjusting multiplicity due to the 2 doses of satavaptan. This analysis was also performed on the PP population. The time to serum sodium response analysis was conducted on the ITT population using Cox model with treatment as factor and baseline serum sodium as covariate, followed by a 2 pairwise comparison testing each dose of satavaptan versus placebo. Changes from baseline in serum sodium concentrations and weight, at the end of the DB period were analyzed by an analysis of covariance (ANCOVA) including treatment as main effect and baseline as covariate.

Pharmacokinetic analyses: Plasma concentrations of satavaptan and its metabolites were summarized using descriptive statistics.

Pharmacokinetic/pharmacodynamic analyses: Relationships between pharmacodynamic responses (serum sodium, QTcB and QTcF data) and plasma concentrations were explored using graphical and regression methods.

Safety analyses: Safety analyses were performed on the exposed population. All AEs recorded during the course of the study were coded to a preferred term according to the medical dictionary for regulatory activities (version 10.0). Abnormalities in laboratory data, vital signs, and ECG parameters were assessed using mean changes from baseline, and potentially clinically significant abnormality criteria.

Summary:

Population characteristics: Out of the 122 patients who participated in the study and were exposed to study treatment, 118 patients were randomly allocated to one of the 3 treatment groups: satavaptan 25 mg (35), satavaptan 50 mg (41), or placebo (42) in the DB period, while 4 patients were not randomized through the IVRS. A total of 105 patients completed the DB period and 17 patients prematurely withdrew from the study during or at the end of this period. The rate of permanent study discontinuation due to AEs was higher in the satavaptan 50 mg group (14.6%) compared to the 2 other groups (5.7% and 2.4% for satavaptan 25 mg and placebo, respectively). Thus, 101 randomized patients participated in the OL period, 19 of whom completed this period and 82 patients prematurely withdrew from this study period, the 3 main reasons being recovery (27.7%), AE (29.7%), and Subject/Investigator's request (12.9%).

All demographic and baseline characteristics were similar between the 3 treatment groups. In most of the randomized patients (90, 76.3%), the cause of DH was congestive heart failure (CHF), which was of severe degree in the majority of patients (55.9% patients had CHF New York Heart Association Class III or IV).

Efficacy results:

Double-blind period: At the end of the DB period, the rate of responders (ITT population) was higher in the satavaptan 25 mg (48.6%) and satavaptan 50 mg groups (61.0%) compared with the placebo group (26.8%); the difference versus placebo was statistically significant for the 50 mg dose (p = 0.0035) and approached statistical significance for the 25 mg dose (p = 0.0599).

Responders at the end of DB period – ITT population

	Placebo	Satavaptan	
	(N=41)	25 mg (N=35)	50 mg (N=41)
Responder patients [n (%)]	11 (26.8)	17 (48.6)	25 (61.0)
p-value for intersection test (vs Placebo)		0.0070	
p-value vs Placebo		0.0599	0.0035
[Na^+] ≥ 135 mmol/L over 24h duration [n (%)]	7 (17.1)	10 (28.6)	18 (43.9)
p-value vs Placebo		0.2764	0.0155
Increase [Na^+] ≥ 5 mmol/L over 24h duration [n (%)]	8 (19.5)	14 (40.0)	22 (53.7)
p-value vs Placebo		0.0751	0.0026

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

The responder rate analysis performed in the PP population confirmed the efficacy of satavaptan at the 50 mg dose.

In the overall exposed population and in the large subgroup of patients with CHF, the responder rate was statistically significantly higher in both satavaptan 25 mg and 50 mg groups compared with placebo.

The median time to response was 3.30 and 2.79 days in the satavaptan 25 mg and 50 mg groups respectively, both significantly shorter than the placebo group (>4 days, p = 0.0278 and 0.0004, respectively).

At the end of the DB period, the mean serum sodium concentration was higher in the satavaptan 25 mg and 50 mg groups (134.0 mmol/L and 135.7 mmol/L, respectively) compared with the placebo group (130.9 mmol/L). Baseline-adjusted mean changes of serum sodium from baseline were increased in the satavaptan 25 mg group (6.25 mmol/L) and the 50 mg group (7.75 mmol/L) versus placebo (2.67 mmol/L); the differences versus placebo were statistically significant (p = 0.0001 for 25 mg and p<0.0001 for 50 mg, ANCOVA).

Open-label period: During the long-term, OL, non-comparative maintenance period during which all patients had been switched to satavaptan, and when the daily dose of satavaptan was adjusted depending on serum sodium and the clinical conditions of the patients, the increased serum sodium was maintained. More than 70% of patients had serum sodium concentration ≥135 mmol/L and/or their serum sodium had increased ≥5 mmol/L from baseline on the sixth day of the OL period, and a similar high level was maintained throughout the duration of the OL period.

Efficacy results (continued):

A total of 37 patients entered the drug holiday period, which was scheduled to start between Day 15 and Day 20. Of these, 16 patients discontinued the study due to recovery (serum sodium ≥135 mmol/L on 2 consecutive visits 28 days apart after drug discontinuation), and 6 patients discontinued the study due to other reasons (AE, poor compliance to the protocol, Investigator/subject's request or lack of efficacy). The 15 remaining patients resumed study treatment after a median duration of 7 days. After the restart of treatment with satavaptan, serum sodium concentration increased within 28 days to normal levels with mean serum sodium of 136.5 mmol/L.

Safety results:

Double-blind period: The percentage of patients with treatment-emergent adverse events (TEAEs) was higher in the satavaptan 25 mg and 50 mg groups (40.0% and 40.5%, respectively) compared with the placebo group (33.3%). The percentage of patients with treatment-emergent SAEs was comparable between the satavaptan 25 mg and placebo groups (5.7% and 6.7%, respectively), but higher in the satavaptan 50 mg group (9.5%). Two patients in the placebo group experienced TEAEs that led to a fatal outcome in the OL period. The number of patients with TEAEs leading to permanent treatment discontinuation was higher in the satavaptan 50 mg group (19.0%) compared to the satavaptan 25 mg and placebo groups (8.6 and 4.4%, respectively).

Overview of TEAEs in DB period – Exposed population

	Placebo	Satavaptan		
	(N=45) n (%)	25 mg (N=35) n (%)	50 mg (N=42) n (%)	Total (N=77) n (%)
Patients with any TEAE(s) (including SAEs)	15 (33.3)	14 (40.0)	17 (40.5)	31 (40.3)
Patients with any treatment-emergent SAE(s) (including SAEs leading to death)	3 (6.7)	2 (5.7)	4 (9.5)	6 (7.8)
Patients with any TEAE(s) leading to death	2 (4.4)	0 (0)	0 (0)	0 (0)
Patients with any TEAE(s) leading to permanent treatment discontinuation*	2 (4.4)	3 (8.6)	8 (19.0)	11 (14.3)

Note: % calculated using the number (N) of exposed patients as the denominator.
*4 patients had TEAEs in DB period that led study discontinuation in OL period

In patients receiving satavaptan, the most frequently reported TEAEs (incidence ≥2% in the total satavaptan group) were atrial fibrillation (7.1% for satavaptan 50 mg, none for satavaptan 25 mg and placebo), hypertension (4.8% and 2.9% for satavaptan 50 mg and 25 mg, respectively, versus 2.2% for placebo), hypotension (2.4% and 5.7% for satavaptan 50 mg and 25 mg, respectively, versus none for placebo), ECG QTc interval prolonged (4.8% and 2.9% for satavaptan 50 mg and 25 mg, respectively, versus none for placebo), bronchitis (2.4% and 2.9% for 50 mg and 25 mg, respectively, versus 2.2% for placebo), blood sodium increased (2.4% and 2.9% for 50 mg and 25 mg, respectively, versus none for placebo), and pyrexia (2.4% and 2.9% for 50 mg and 25 mg, respectively, versus none for placebo).

Two out of 77 (2.6%) patients receiving satavaptan (25 mg or 50 mg) experienced TEAEs of hypernatremia/blood sodium increased, which led to permanent treatment discontinuation in both cases. In addition, serum sodium values >145 mmol/L were recorded in 2 (2.6%) patients receiving satavaptan 50 mg versus 1 patient on placebo, without associated TEAE in any case. A rapid correction of serum sodium ≥12 mmol/L within 24 hours after the administration of the study drug at anytime during study treatment was observed in 11.4% and 14.3% patients receiving satavaptan 25 mg and 50 mg, respectively, versus 4.4% patients on placebo; there were no neurological consequences in any case.

Only one patient, who was receiving satavaptan 50 mg, experienced thirst during the DB period; the event led to permanent treatment discontinuation.

Serum potassium values ≥5.5 mmol/L were recorded in 5/25 (20%) and 2/35 (5.7%) patients receiving satavaptan 25 mg and 50 mg, respectively, versus 3/41 (7.3%) patients in the placebo group. This was reported as a TEAE in one placebo patient.

Safety results (continued):

The number of patients with a weight decrease ≥5% was higher in satavaptan 25 mg and 50 mg groups (14.7% and 12.2%, respectively) compared with placebo (6.8%). No other relevant differences in vital signs were observed between satavaptan and placebo groups.

Two patients receiving satavaptan 50 mg had prolonged QTcF values ≥500 ms; both had abnormal QTcF values at baseline. In one of them, prolonged QT interval was reported as a TEAE, which led to premature study treatment discontinuation. Two additional patients receiving satavaptan (25 mg or 50 mg) had a QTcF increase from baseline >60 ms, reported as a TEAE in one of them. Two out of these 4 patients were receiving concomitant medications known to increase QT interval.
Three patients receiving satavaptan experienced prolonged QTc interval reported as TEAEs and that led to permanent treatment discontinuation; all 3 patients had borderline or prolonged QTcF values at baseline. In the satavaptan 25 mg group, a decrease in mean QTcF values (-13.7 ms) was observed from baseline to last value on treatment (versus –8.7 ms in the placebo group and -2.1 ms in the 50 mg group). There were no clinically significant changes from baseline for any other ECG parameters.

Open-label period: Out of 103 patients entering the OL period, 71 (68.9%) experienced at least 1 TEAE, which was considered as serious in 40 (38.8%) patients. Twelve patients had TEAEs with fatal outcome, which reflected the poor medical status of the population. The most frequently reported TEAEs were related to the patients' underlying disease: cardiac failure and cardiac failure congestive (9.7% and 4.9% patients, respectively). Other TEAEs reported with an incidence ≥2% included nausea (4.9%), bronchitis, anemia, hypokalemia, thirst, and ECG QT/QTc interval prolonged (each reported by 3.9% patients), urinary tract infection, hyperkalemia, anxiety, depression, atrial fibrillation, hypotension, and epistaxis (each reported by 2.9% patients). Twenty-four (23.3%) patients withdrew from the study due to TEAEs.

Ventricular-arrhythmia events were reported by 7 patients: 2 non-serious TEAEs of ventricular tachycardia leading to permanent treatment discontinuation in one of them and 5 TEAEs of prolonged QT/QTc leading to permanent treatment discontinuation in all cases.

Thirst was reported by 4 patients during OL period; thirst was of mild or moderate intensity and did not require permanent treatment discontinuation in any patient.

Eight patients had a serum sodium concentration >145 mmol/L, reported as a TEAE in 2 patients. One of these 2 patients, who was receiving concomitant treatment with intravenous (IV) fluconazole and IV voriconazole, had a serum sodium concentration >160 mmol/L (162 mmol/L), considered as a serious TEAE.

Nine patients had serum potassium values ≥5.5 mmol/L, reported as a TEAE in 2 patients. In one of the 2 patients, who had been receiving potassium for months, hyperkalemia was considered as serious and led to permanent treatment discontinuation. There were no concomitant cardiac AEs reported in either case. Seven of the 9 patients were receiving concomitant medications known to increase potassium.

An increase in serum creatinine was observed during the OL period and 36/67 patients had creatinine clearance values below 50 mL/min recorded in this period; all but 2 patients had abnormal baseline values.

The most frequently reported vital signs abnormalities were decreased orthostatic diastolic blood pressure (44.3%) and systolic blood pressure (22.7%), as well as weight decrease (30.6%).

Seven patients had a QTcF increase from baseline >60 ms, including one patient with a QTcF value ≥500 ms, and one additional patient had a prolonged QTcF value ≥500 ms, reported as a TEAE and leading to treatment discontinuation. Three of these 8 patients were receiving concomitant medications known to increase QT interval.

Pharmacokinetic results: At the end of the DB period [Days 3 to 5; Visit 6], the mean (standard deviation [SD]) satavaptan Ctrough (plasma concentration observed before treatment administration during repeated dosing) were 6.64 (ND) ng/mL [12.5 mg], 3.78 (3.61) ng/ml [25 mg] and 10.9 (10.7) ng/mL [50 mg]; the mean C_{2h} (plasma concentration taken at approximately 2 hours post dosing) were 8.26 (4.72) ng/mL [25 mg] and 35.9 (27.6) ng/mL [50 mg].

At Visit 15 [Day 32, open label period], the mean (SD) satavaptan C_{trough} were 1.04 (ND) ng/mL [12.5 mg], 2.53 (ND) ng/ml [25 mg] and 9.88 (ND) ng/mL [50 mg]; the mean C_{2h} were 3.04 (2.15) ng/mL [12.5 mg], 8.41 (7.31) ng/mL [25 mg] and 57.3 (ND) ng/mL [50 mg].

Pharmacokinetic/pharmacodynamic results: There was positive correlation of the pre-dose serum sodium value at the end of the DB period with C_{trough}, but this was not statistically significant, may be due to the variability observed in the data and the small sample size. There was a significant relationship observed between change from baseline in QTcB and QTcF and satavaptan plasma concentrations at the end of the DB period. This relationship was probably driven by 3 individuals. However, no significant relationship was observed between satavaptan plasma concentrations and change from baseline in QTcB and QTcF in the OL period (all visits combined).

Conclusions:

[redacted]

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