SYNOPSIS

Title of the study: Satavaptan in the Prevention of Ascites Recurrence: a double-blind, randomised, parallel-group comparison of satavaptan at 5 to 10 mg daily versus placebo with concomitant diuretics in patients with recurrent ascites due to cirrhosis of the liver (EFC4493)

Investigator: [redacted]

Study centers: The study was conducted in 132 centers in 24 countries

Publications (reference): Not applicable

Study period:

Date first patient enrolled: 05/Jul/2006

Date last patient completed: 16/Oct/2008

Phase of development: Phase 3

Objectives:

Primary: To evaluate the efficacy of satavaptan on top of diuretic drugs in reducing the recurrence of ascites

Secondary: To evaluate the tolerability and safety of satavaptan on top of diuretic drugs over a 52-week treatment period in patients with cirrhosis of the liver and recurrent ascites

The study was prematurely discontinued due to the Sponsor's decision.

Methodology: Multicenter, multinational, double-blind, randomized, placebo-controlled, parallel-group study.

Number of patients: Planned: 450 Randomized: 501 Treated: 496

Efficacy: 496 (intent-to-treat [ITT]) Safety: 496 Pharmacokinetics: 488

Consequently to the Sponsor's decision following the recommendation of the data safety monitoring board regarding the over-mortality observed in the satavaptan group, 33 (19.5%) of the patients in the placebo group and 64 (19.3%) of the patients in the satavaptan group were prematurely withdrawn from the study. At the time of stopping the study, all patients had completed at least 6 months of treatment (unless discontinued previously).

Diagnosis and criteria for inclusion: Patients ≥18 years of age with cirrhosis of the liver, a history of recurrent ascites, and who had undergone 1 paracentesis for the removal of ascites in the previous 24 hours and at least 1 other therapeutic paracentesis in the previous 3 months.

Investigational product: Satavaptan (5 mg tablet)

Dose: 5 or 10 mg, once daily

Administration: Oral, in the morning

Batch numbers: [redacted]

Duration of treatment: 52 weeks

Duration of observation: 54 weeks

Patients received the blinded treatment during a 52-week period. A posttreatment assessment was performed 2 weeks after the end of the treatment. For patients having withdrawn from the study before Week 52, contact was to be made to establish the status of the patient as dead or alive 52 weeks after randomization, and collect the date of death and associated serious adverse event (SAE) when appropriate.

Reference therapy: Placebo (matching tablet)

Dose: Not applicable

Administration: Oral, in the morning

Batch numbers: [redacted]

Criteria for evaluation: The current report is a synopsis-style report, and as such, only the safety results are being presented in full, and the efficacy results are limited to the number of therapeutic paracenteses performed during the first 12 weeks (primary efficacy endpoint), and the time to the first recurrence of ascites and increase in ascites (2 secondary endpoints). The following safety criteria were evaluated, and analyzed using descriptive statistics: adverse events (AEs) reported by the patient or noted by the Investigator, standard laboratory tests (biochemistry, hematology), vital signs, and electrocardiogram (ECG) parameters.

The plasma concentrations of satavaptan and its metabolites (SSR108434 and SR122621) were assayed using a validated liquid chromatography with tandem mass spectrometry method with a lower limit of quantification (LLOQ) of 0.05, 0.05, and 0.5 ng/ml respectively.

Statistical methods:

Efficacy: The efficacy analysis was performed on the ITT population, defined as all randomized and exposed patients. The mean cumulative number of paracenteses as a function of time was estimated using the Nelson-Aalen nonparametric estimator (the extension of the Kaplan-Meier estimator for recurrent events) and plotted for the first 12 weeks of the study by treatment group. A descriptive analysis of the data during the 52 weeks of treatment was also performed. The number of therapeutic paracenteses performed during the first 12 weeks of the study in the 2 treatment groups was compared using an Andersen-Gill model (the extension of the Cox model for recurrent events). The proportion of patients with a recurrence of ascites was estimated in each treatment group using the Kaplan-Meier estimator and plotted by treatment group up to 12 weeks.

Safety: Safety analyses were performed on the safety population, defined as all randomized and exposed patients regardless of the amount of treatment received. Adverse events were coded according to the medical dictionary for regulatory activities (version 11.1). Abnormalities in laboratory data, vital signs, and ECG parameters were assessed using potentially clinically significant abnormality (PCSA) criteria.

Summary:

Of the 501 patients randomized (ratio 2:1 [satavaptan:placebo]), 38 (22.5%) patients in the placebo group and 70 (21.1%) in the satavaptan group completed the 52-week treatment period.

Demographic and baseline characteristics

In the overall ITT population, patients were between 26 and 85 years of age (mean age ± SD =58.3±10.0 years), 27.4% being ≥65-year-old. Of these patients, 70.6% were males and 29.4% were females. Demographic characteristics were comparable in the 2 treatment groups, except age showing a higher proportion of the youngest patients in the placebo group and a higher proportion of the oldest patients in the satavaptan group. The most frequently reported causes of cirrhosis were alcoholism (75.2%) and hepatitis C (17.5%). Disease characteristics at baseline were comparable in the 2 treatment groups.

Table 1 – Summary of cirrhosis grading and origin – ITT population

	Placebo (N=168)	Satavaptan (N=328)	All (N=496)
Child-Pugh class			
Number	168	327	495
A: 5-6	1 (0.6%)	10 (3.1%)	11 (2.2%)
B: 7-9	119 (70.8%)	217 (66.4%)	336 (67.9%)
C: 10-15	48 (28.6%)	100 (30.6%)	148 (29.9%)
MELD score			
Number	166	325	491
Mean (SD)	13.3 (3.9)	13.3 (3.8)	13.3 (3.8)
Median	12.8	12.9	12.9
Min : Max	7 : 28	7 : 25	7 : 28
MELD-NA score			
Number	166	325	491
Mean (SD)	15.4 (6.2)	15.5 (6.3)	15.5 (6.2)
Median	14.1	14.1	14.1
Min : Max	7 : 38	7 : 45	7 : 45
Etiology of cirrhosis (possible multiple etiology)			
Number	168	328	496
Alcoholism	122 (72.6%)	251 (76.5%)	373 (75.2%)
Hepatitis B	17 (10.1%)	27 (8.2%)	44 (8.9%)
Hepatitis C	34 (20.2%)	53 (16.2%)	87 (17.5%)
Hepatitis D	1 (0.6%)	2 (0.6%)	3 (0.6%)
Non-alcoholic steatohepatitis	4 (2.4%)	6 (1.8%)	10 (2.0%)
Primary biliary cirrhosis	1 (0.6%)	4 (1.2%)	5 (1.0%)
Autoimmune hepatitis	3 (1.8%)	2 (0.6%)	5 (1.0%)
Hemochromatosis	1 (0.6%)	1 (0.3%)	2 (0.4%)
Primary sclerosing cholangitis	1 (0.6%)	0	1 (0.2%)
Cryptogenic/unknown	9 (5.4%)	17 (5.2%)	26 (5.2%)
Other	3 (1.8%)	6 (1.8%)	9 (1.8%)
Time since diagnosis of cirrhosis (years)			
Number	168	328	496
Mean (SD)	5.4 (6.8)	4.9 (6.1)	5.1 (6.3)
Median	3.0	2.7	3.0
Min : Max	0 : 53	0 : 37	0 : 53

In the overall ITT population, at baseline, the mean time ± SD since the first episode of ascites was 2.1±2.8 years. The most frequent ascites classification was refractory due to lack of response to high dose of diuretics (47.2% overall; 44.0% in the placebo group compared with 48.8% in the satavaptan group). The mean number ± SD of paracenteses in the last 12 months was 7.5±8.5, with 24.9±20.8 days (mean time ± SD) since the last paracentesis. Regarding the medical history relevant to the complications of an end-stage liver disease, 20.4% of the patients had a history of oesophageal varices bleeding, 15.6% had a history of spontaneous bacterial peritonitis, and 26.1% had a history of hepatic encephalopathy.

Efficacy

Primary endpoint

Satavaptan did not reduce the number of therapeutic paracenteses during the first 12 weeks of treatment (relative risk [95%CI] =0.89 [0.76 to 1.05] and p-value =0.1702) (Table 2 and Figure 1) and over the 52 weeks of treatment (Figure 2).

Table 2 – Summary of number of therapeutic paracenteses during the first 12 weeks of the study - ITT population

Number of therapeutic paracentesis during the first 12 weeks	Placebo (N=168)	Satavaptan (N=328)
Number of events per patient		
Number assessed	168	328
0	37 (22.0%)	93 (28.4%)
1-3	65 (38.7%)	121 (36.9%)
4-6	39 (23.2%)	70 (21.3%)
7-9	18 (10.7%)	25 (7.6%)
≥ 10	9 (5.4%)	19 (5.8%)
Number of events per patient		
Number	168	328
Mean (SD)	3.36 (3.22)	3.00 (3.07)
Median	3.00	2.00
Min : Max	0 : 13	0 : 13
Reason for censoring		
Completed 12-week follow-up	131 (78.0%)	258 (78.7%)
End of study	31 (18.5%)	63 (19.2%)
Liver transplant	3 (1.8%)	6 (1.8%)
TIPS or other shunt	3 (1.8%)	1 (0.3%)
Cumulative mean number of events at specific time-points (95% CI)		
4-week estimate	1.16 (0.96 to 1.36)	1.00 (0.86 to 1.13)
8-week estimate	2.51 (2.14 to 2.87)	2.21 (1.96 to 2.45)
12-week estimate	3.70 (3.16 to 4.23)	3.37 (3.00 to 3.75)
Comparison versus Placebo		
Relative risk (95% CI)	-	0.89 (0.76 to 1.05)
P-value	-	0.1702

Cumulative mean number of events determined using Nelson-Aalen estimate, 95% CI determined using robust variance estimation.
Relative risk, 95% CI and p-value determined from Andersen-Gill model, with adjustment for baseline interval between paracenteses, starting diuretic regimen, baseline serum sodium and geographic area.

Figure 1 – Number of therapeutic paracenteses during the first 12 weeks of the study - ITT population

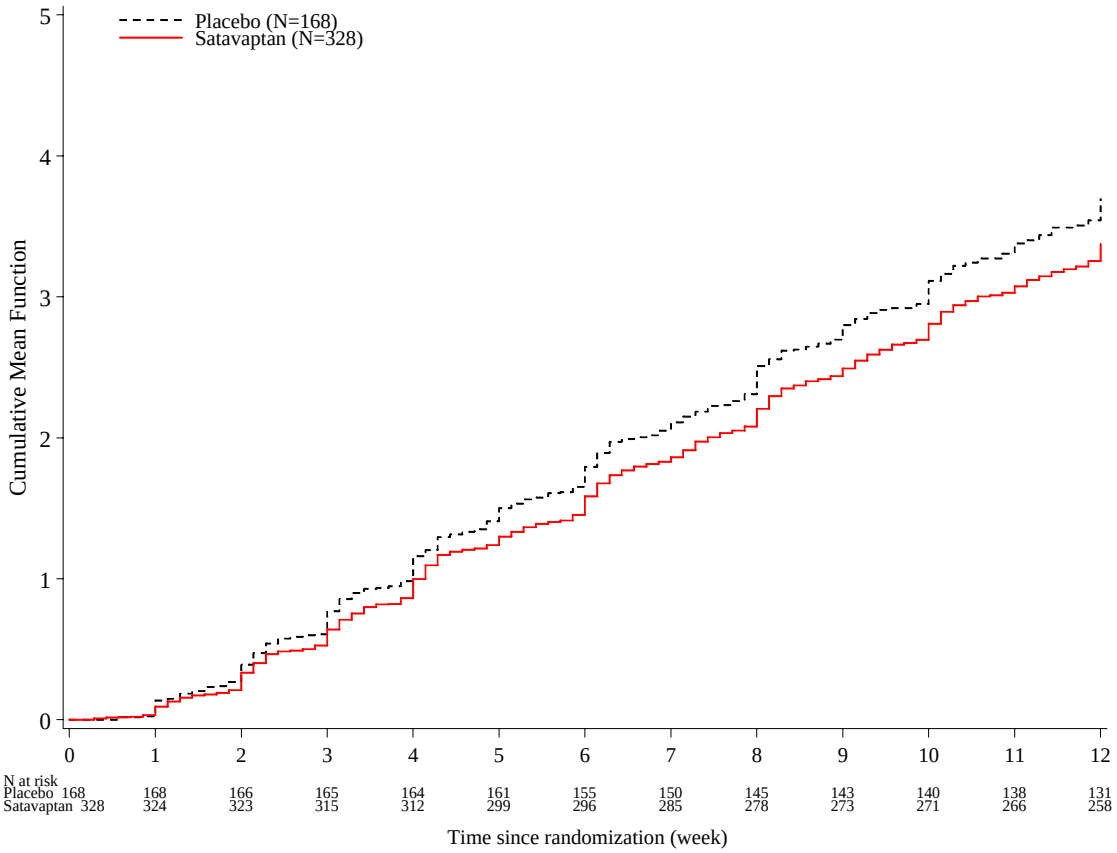
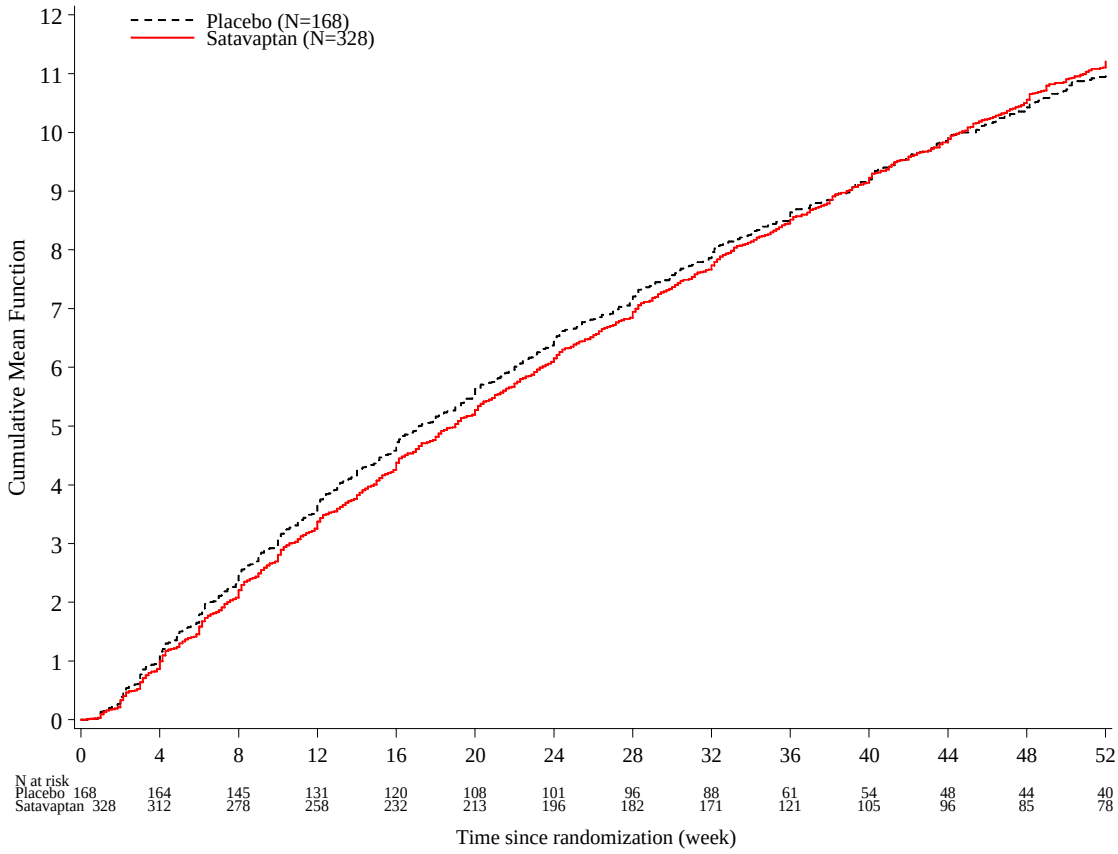


Figure 2 – Number of therapeutic paracenteses during the 52 weeks of treatment – ITT population



Secondary endpoints

During the first 12 weeks of treatment, the treatment with satavaptan delayed the time to the first recurrence of ascites by 0.4 weeks (3 days). The median time (95% CI) to the first recurrence was 2.0 weeks (1.9 to 2.3) in the satavaptan group compared with1.6 weeks (1.3 to 1.9) in the placebo group (relative risk [95%CI] =0.74 [0.60 to 0.90]; p-value =0.0032). The mean increase in ascites per week was 2.00 kg/week in the satavaptan group compared with 2.42 kg/week in the placebo group (difference in LS mean slope [95%CI] =-0.42 [-0.78 to –0.06], p-value =0.0207).

Safety

An overview of the AEs reported during the study is presented in Table 3. The main difference between the 2 treatment groups concerned AEs associated with a fatal outcome, and especially treatment-emergent adverse events (TEAEs) associated with a fatal outcome, which were reported for 15.2% of the patients in the satavaptan group compared with 8.4% in the placebo group.

Table 3 – Overview of patients with adverse events – Safety population

	Placebo (N=166)	Satavaptan (N=330)
Patients with any TEAE	144 (86.7%)	290 (87.9%)
Patients with any serious TEAE	91 (54.8%)	199 (60.3%)
Patients with any TEAE leading to permanent study drug discontinuation	47 (28.3%)	111 (33.6%)
Patients with any TEAE with fatal outcome	14 (8.4%)	50 (15.2%)
Patients with any AE (treatment-emergent or not) with fatal outcome	37 (22.3%)	101 (30.6%)

n (%) = number and pourcentage of patients with at least one adverse event
TEAE: Treatment Emergent Adverse Event

When considering the time to death for the safety population, the Kaplan-Meier estimate of mortality over the 52-week treatment period was 31.5% in the satavaptan group compared with 21.2% in the placebo group (Figure 3). The corresponding relative risk of mortality for patients receiving satavaptan was 1.47 (with a 95% CI from 1.01 to 2.15). Increased percentages of deaths in the satavaptan group compared with the placebo group were observed as early as 4 weeks after randomization. The difference between the 2 groups progressively increased over the 52-week treatment period. When restricting the analysis to the TEAEs associated with a fatal outcome, the Kaplan-Meier estimate of mortality over the 52-week treatment period was 21.2% in the satavaptan group compared with 10.9% in the placebo group (Figure 4). The corresponding relative risk of mortality for patients receiving satavaptan was 1.82 (with 95% CI from 1.00 to 3.29).

Figure 3 – Kaplan-Meier graph of time to death – Safety population

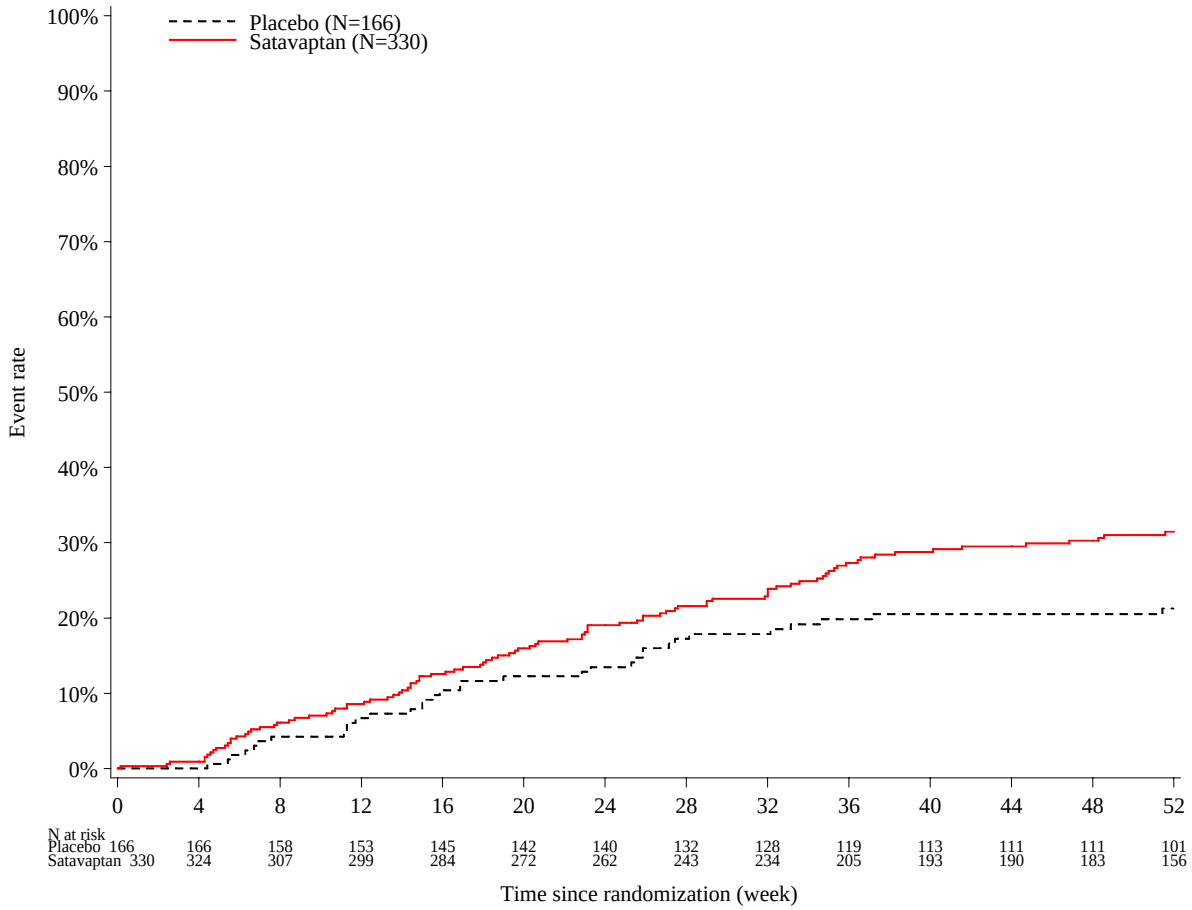
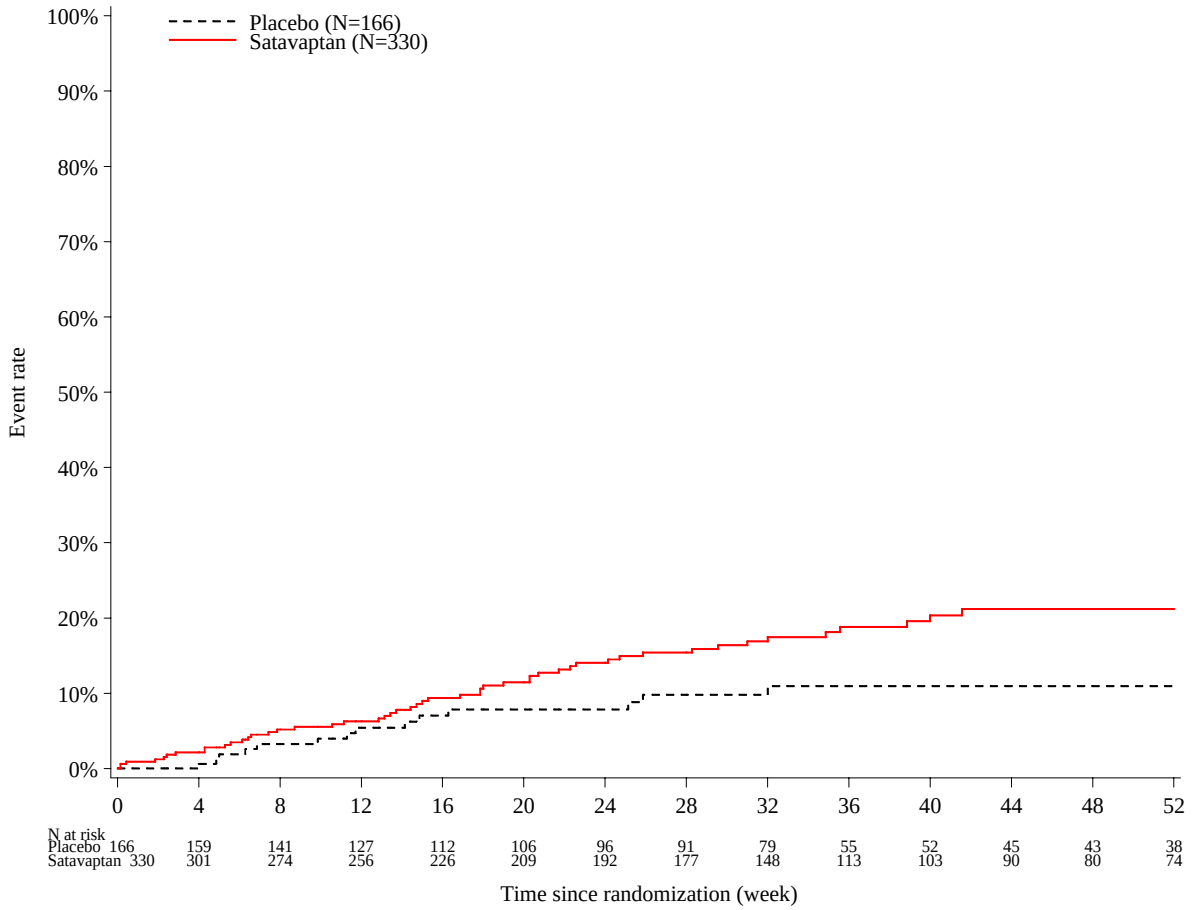


Figure 4 - Kaplan-Meier graph of time to TEAE with fatal outcome - Safety population



The most frequent AEs (treatment-emergent or not) associated with a fatal outcome were events related to complications of an end-stage liver disease. In the satavaptan group, 4.5% of the deaths were associated with gastrointestinal disorders, mainly esophageal varices hemorrhage, compared with 1.8% in the placebo group, 4.2% of the deaths had unknown causes compared with 1.2% in the placebo group, 1.2% of the deaths were associated with cardiac disorders compared with none in the placebo group, and 3.3% of the deaths were associated with vascular disorders compared with 1.8% in the placebo group. Renal and urinary disorders were associated with 0.6% of the deaths in the satavaptan group compared with 1.2% in the placebo group. Narratives for all cases of death are provided in the CSR Appendix.

Exploratory analyses of the TEAEs associated with a fatal outcome revealed increased mortality in:

- Patients with more severe liver disease, ie, patients with high model for end-stage liver disease (MELD) or MELD-sodium score, with baseline serum sodium ≤130 mmol/L, with baseline international normalized ratio (INR) ≥1.7, or with history of hepatic encephalopathy
- Patients taking high or very high dose of diuretics, primarily loop diuretics and thiazides (mainly furosemide)
- Patients having received proton pump inhibitors, cytochrome P450 (CYP3A) inhibitors, drugs known to prolong QT, or drugs known to increase serum potassium
- Patients from Asia

Serious TEAEs were reported for 60.3% of the patients in the satavaptan group compared with 54.8% in the placebo group. The serious TEAEs the most frequently reported in the satavaptan group belonged to the class of gastrointestinal disorders (28.2% of the patients compared with 21.7% in the placebo group) (especially oesophageal varices hemorrhage), nervous system disorders (17.3% of the patients compared with 21.7% in the placebo group) (especially hepatic encephalopathy), and infections and infestations (16.4% of the patients compared with 19.3% in the placebo group) (especially bacterial peritonitis).

Treatment-emergent AEs leading to study treatment discontinuation were reported for 33.6% of the patients in the satavaptan group compared with 28.3% in the placebo group. The TEAEs leading to study treatment discontinuation the most frequently reported in the satavaptan group belonged to the class of gastrointestinal disorders (6.4% of the patients compared with 1.8% in the placebo group) (especially oesophageal varices hemorrhage), hepatobiliary disorders (5.5% of the patients compared with 4.8% in the placebo group), and nervous system disorders (4.8% of the patients compared with 6.6% in the placebo group).

The TEAEs of specific interest reported in the satavaptan group were renal impairment-related events (30.9% of the patients compared with 24.7% in the placebo group), hepatic encephalopathy-related events (23.9% of the patients compared with 27.1% in the placebo group), hyperkalemia-related events (17.9% of the patients compared with 16.9% in the placebo group), ascites-related events (13.0% of the patients compared with 12.0% in the placebo group), spontaneous bacterial peritonitis-related events (10.6% of the patients compared with 11.4% in the placebo group), and variceal bleeding-related events (8.2% of patients compared with 4.8% in the placebo group).

The PCSAs in laboratory parameters the most frequently reported in the satavaptan group were increases in the change from baseline in creatinine value (increase >30% in 62.5% of the patients compared with 57.8% in the placebo group) and decreases in the glomerular filtration rate (modification of diet in renal disease) changes from baseline (decrease >30% in 51.5% of the patients compared with 50.6% in the placebo group). Increase in creatinine values from baseline >50% to a value >133 µmol/L was reported in 26.8% of the patients in the satavaptan group and 27.7% in the placebo group, and hyperkalemia (potassium ≥5.5 mmol/L) in 27.4% of the patients in the satavaptan group and 30.1% in the placebo group. The percentage of patients with at least 1 PCSA in INR was similar in the 2 treatment groups. Increases in alanine aminotransferase values compared with baseline were reported in 28.0% (>2-fold increase), 11.6% (>3-fold increase) and 3.7% (>5-fold increase) of the patients in the satavaptan group compared with 21.7%, 6.0%, and 1.8%, respectively, in the placebo group. Increases in aspartate aminotransferase values compared with baseline were reported in 24.1% (>2-fold increase), 9.5% (>3-fold increase) and 2.7% (>5-fold increase) of the patients in the satavaptan group compared with 16.3%, 3.0%, and 0.6%, respectively, in the placebo group.

In regard to ECG parameters, prolonged QTcF (QT interval corrected according to Fridericia formula) ≥500 ms were observed in 7 (2.2%) patients in the satavaptan group and 7 (4.2%) in the placebo group. Six (1.8%) patients in the satavaptan group were withdrawn from the study treatment due to an AE of ECG QT prolonged compared with 4 (2.4%) in the placebo group. Increases in QTcF >60 ms were observed in 15 (4.7%) patients in the satavaptan group compared with 11 (6.7%) in the placebo group.

Pharmacokinetics

The minimum and the maximum values observed for the plasma samples taken postdose for the patients treated with 5 and/or 10 mg were <LLOQ and 28.9 ng/mL, respectively.

Conclusion

[redacted]

Date of report: 25-May-2009