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 in the absence of diuretics in patients with recurrent ascites due to cirrhosis of the liver (EFC6682)
Investigator: [redacted]
Study centers: The study was conducted in 94 centers in 19 countries
Publications (reference): Not applicable
Study period: Date first patient enrolled: 02/Aug/2006 Date last patient completed: 09/Dec/2008 The study was prematurely discontinued due to the Sponsor's decision following the recommendation of the drug safety monitoring board (DSMB) regarding an unfavorable benefit/risk ratio in the satavaptan group.
Phase of development: Phase 3
Objectives: **Primary**: To evaluate the efficacy of satavaptan in the absence of concomitant diuretic drugs in reducing the recurrence of ascites **Secondary**: To evaluate the tolerability and safety of satavaptan in the absence of concomitant diuretic drugs over a 52-week treatment period in patients with cirrhosis of the liver and recurrent ascites
Methodology: Multicenter, multinational, double-blind, randomized, placebo-controlled, parallel-group study
Number of patients: Planned: 225 Randomized: 241 Treated: 240 Efficacy: 240 (intent-to-treat [ITT]) Safety: 240 Pharmacokinetics: 240 Consequently to the Sponsor's decision, 10 (12.5%) patients in the placebo group and 21 (13.0%) in the satavaptan group were prematurely withdrawn from the study.
Diagnosis and criteria for inclusion: Patients ≥18 years of age with cirrhosis of the liver, resistant to, intolerant of, or unsuitable for treatment with diuretics, with 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 For patients having withdrawn from the study before Week 52, contact was to be made to establish the status of the patient as dead or alive 52 weeks after randomization, and collect the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 (MedDRA, version 11.1). Abnormalities in laboratory data, vital signs, and ECG parameters were assessed using potentially clinically significant abnormality (PCSA) criteria.

Summary:

Of the 241 patients randomized (ratio 2:1 [satavaptan:placebo]), 12 (15.0%) patients in the placebo group and 35 (21.7%) in the satavaptan group completed the 52-week treatment period.

In the safety population, the median duration of exposure to satavaptan was 149 days compared with 79 days for placebo. In the satavaptan group, 19.9% of the patients had an exposure of at least 52-week compared with 13.9% in the placebo group. Higher proportions of patients in the placebo group permanently discontinued treatment due to own request (15% compared with 8.1% in the satavaptan group) or due to lack of efficacy (10% compared with 6.8% in the satavaptan group).

Demographic and baseline characteristics

In the overall ITT population, patients were between 32 and 85 years of age (mean age ± SD =56.3±9.7 years), 17.9% being ≥65-year-old. Of these patients, 65.8% were males and 34.2% were females. Demographic characteristics were comparable in the 2 treatment groups.

Regarding disease characteristics at baseline, the proportion of patients with Child-Pugh class B was higher in the satavaptan group (67.5% compared with 52.5% in the placebo group) (Table 1). The proportion of patients with Child-Pugh class C, however, was lower in the satavaptan group (31.3% compared with 46.3% in the placebo group). The patients with the highest scores in the model for end-stage liver disease corrected for serum sodium (MELD-NA) were also in the placebo group. The most frequently reported causes of cirrhosis were alcoholism (61.5% overall, with a higher proportion in the satavaptan group) and hepatitis C (23.4% overall, with a lower proportion in the satavaptan group).

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

	Placebo (N=80)	Satavaptan (N=160)	All (N=240)
Child-Pugh class			
Number	80	160	240
A: 5-6	1 (1.3%)	2 (1.3%)	3 (1.3%)
B: 7-9	42 (52.5%)	108 (67.5%)	150 (62.5%)
C: 10-15	37 (46.3%)	50 (31.3%)	87 (36.3%)
MELD score (Model End Stage Liver Disease)			
Number	80	159	239
Mean (SD)	14.4 (4.6)	13.7 (4.3)	13.9 (4.4)
Median	13.6	13.1	13.3
Min : Max	7 : 28	7 : 28	7 : 28
MELD-NA score			
Number	80	159	239
Mean (SD)	19.1 (9.4)	16.8 (7.4)	17.6 (8.2)
Median	16.7	15.6	15.9
Min : Max	7 : 46	7 : 41	7 : 46
Etiology of cirrhosis (possible multiple etiology)			
Number	80	159	239
Alcoholism	45 (56.3%)	102 (64.2%)	147 (61.5%)
Hepatitis B	5 (6.3%)	13 (8.2%)	18 (7.5%)
Hepatitis C	24 (30.0%)	32 (20.1%)	56 (23.4%)
Hepatitis D	1 (1.3%)	2 (1.3%)	3 (1.3%)
Non-alcoholic steatohepatitis	2 (2.5%)	6 (3.8%)	8 (3.3%)
Primary biliary cirrhosis	0	3 (1.9%)	3 (1.3%)
Autoimmune hepatitis	0	1 (0.6%)	1 (0.4%)
Hemochromatosis	0	1 (0.6%)	1 (0.4%)
Primary sclerosing cholangitis	0	0	0
Cryptogenic/unknown	7 (8.8%)	11 (6.9%)	18 (7.5%)
Other	3 (3.8%)	5 (3.1%)	8 (3.3%)

In the overall ITT population, at baseline, the most frequent ascites classifications were refractory due to intolerance to diuretics (47.5% overall; 48.1% in the satavaptan group compared with 46.3% in the placebo group) and refractory due to lack of response to high dose of diuretics (42.5% in each group). The mean number ± SD of paracenteses in the last 12 months was 8.1±9.7, with 26.7±26.5 days (mean time ± SD) since the last paracentesis. Regarding the medical history relevant to the complications of an end-stage liver disease, 19.2% of the patients had a history of oesophageal varices bleeding (17.0% in the satavaptan compared with 23.8% in the placebo group), 17.2% had a history of spontaneous bacterial peritonitis (18.9% in the satavaptan compared with 13.8% in the placebo group), and 32.5% had a history of hepatic encephalopathy (32.5% in each group).

Efficacy

Primary endpoint

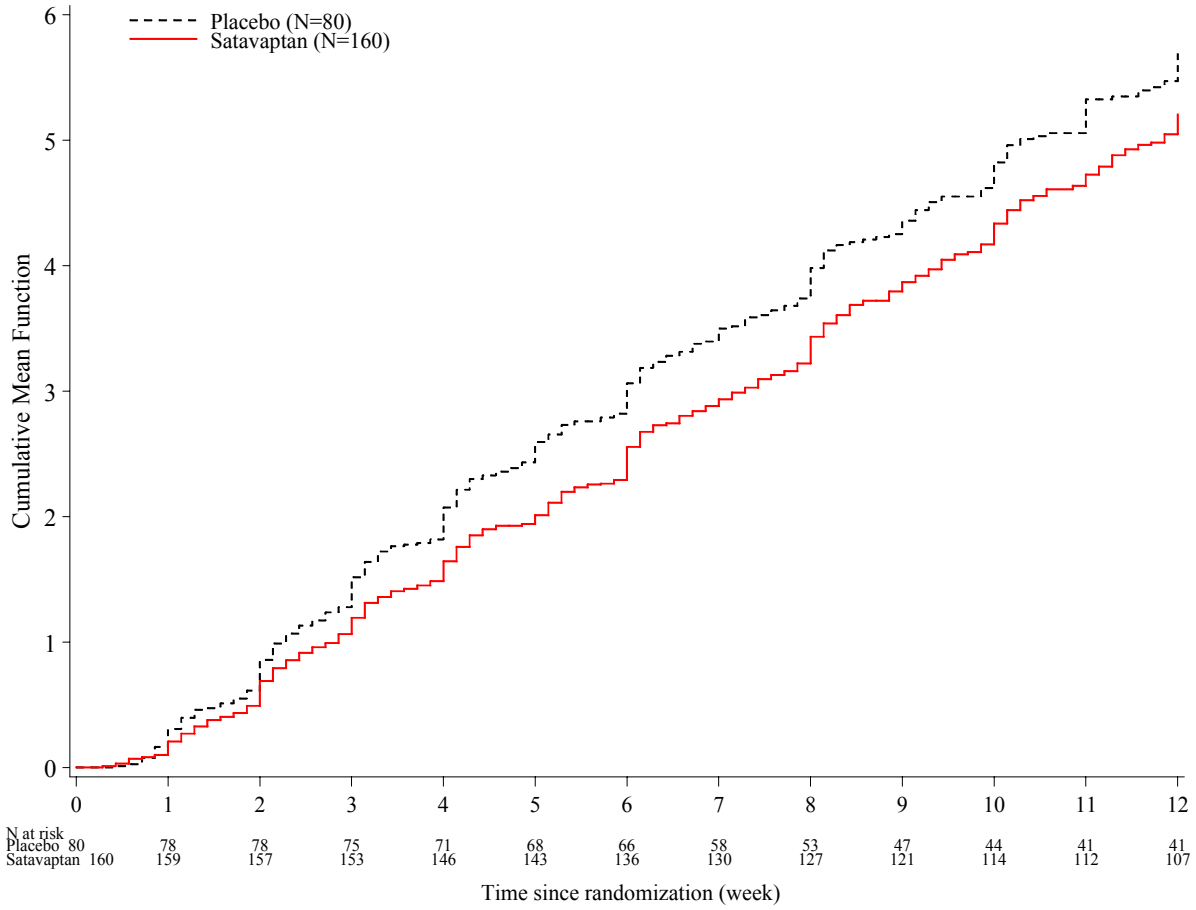
Satavaptan did not reduce significantly the number of therapeutic paracenteses during the first 12 weeks of treatment (relative risk [95%CI] =0.90 [0.74 to 1.09] and p-value =0.2737) (Table 2 and Figure 1)and over the 52 weeks of treatment (relative risk [95%CI] =0.99 [0.79 to 1.25]).

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=80)	Satavaptan (N=160)
Number of events per patient		
Number assessed	80	160
0	11 (13.8%)	29 (18.1%)
1-3	25 (31.3%)	54 (33.8%)
4-6	25 (31.3%)	35 (21.9%)
7-9	10 (12.5%)	24 (15.0%)
≥ 10	9 (11.3%)	18 (11.3%)
Number of events per patient		
Number	80	160
Mean (SD)	4.41 (3.81)	4.37 (4.03)
Median	4.00	3.00
Min : Max	0 : 21	0 : 23
Reason for censoring		
Completed 12-week follow-up	41 (51.3%)	107 (66.9%)
End of study	34 (42.5%)	47 (29.4%)
Liver transplant	5 (6.3%)	5 (3.1%)
TIPS or other shunt	0 (0.0%)	1 (0.6%)
Cumulative mean number of events at specific time-points (95% CI)		
4-week estimate	2.07 (1.72 to 2.43)	1.64 (1.42 to 1.86)
8-week estimate	3.98 (3.28 to 4.68)	3.43 (2.97 to 3.90)
12-week estimate	5.72 (4.66 to 6.77)	5.21 (4.48 to 5.93)
Comparison versus Placebo		
Relative risk (95% CI)	-	0.90 (0.74 to 1.09)
P-value	-	0.2737

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, baseline serum sodium and geographic area.

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



Secondary endpoints

During the first 12 weeks of the study, the treatment with satavaptan delayed the time to the first recurrence of ascites by 0.3 weeks (2 days). The median time (95% CI) to the first recurrence was 1.3 weeks (1.1 to 1.7) in the satavaptan group compared with 1.0 week (0.9 to 1.1) in the placebo group (relative risk [95%CI] =0.67 [0.50 to 0.89]; p-value =0.0063). The mean increase in ascites per week was 3.47 kg/week in the satavaptan group compared with 3.59 kg/week in the placebo group (difference in LS mean slope [95%CI] = -0.12 [-0.80 to 0.56], p-value =0.7334).

Safety

An overview of the AEs reported during the study is presented in Table 3.

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

	Placebo (N=79)	Satavaptan (N=161)
Patients with any TEAE	69 (87.3%)	140 (87.0%)
Patients with any serious TEAE	46 (58.2%)	98 (60.9%)
Patients with any TEAE leading to permanent study drug discontinuation	28 (35.4%)	65 (40.4%)
Patients with any TEAE with fatal outcome	7 (8.9%)	30 (18.6%)
Patients with any AE (treatment-emergent or not) with fatal outcome	27 (34.2%)	55 (34.2%)

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

When considering the time to treatment-emergent adverse events (TEAEs) associated with a fatal outcome, the Kaplan-Meier estimate of mortality over the 52-week treatment period was 28.0% in the satavaptan group compared with 13.8% in the placebo group (Figure 2). The corresponding relative risk of mortality for patients receiving satavaptan was 1.68 (with 95% CI from 0.74 to 3.83). 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 considering all AEs (treatment-emergent or not) associated with a fatal outcome, the Kaplan-Meier estimate of mortality over the 52-week treatment period was 32.3% in the satavaptan group compared with 34.7% in the placebo group (Figure 3). The corresponding relative risk of mortality for patients receiving satavaptan was 0.95 (with 95% CI from 0.60 to 1.51).

Figure 2 - Kaplan-Meier graph of time to TEAE with fatal outcome - Safety population

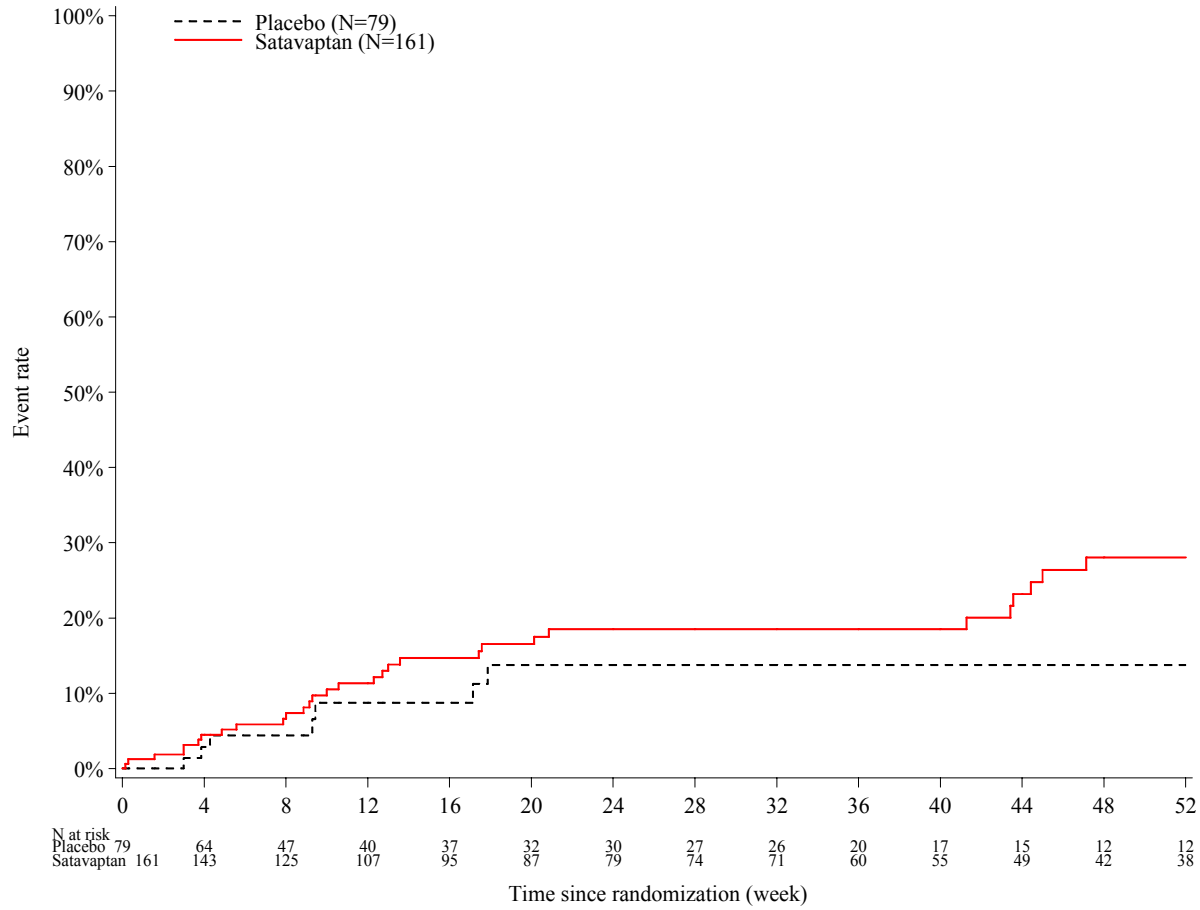
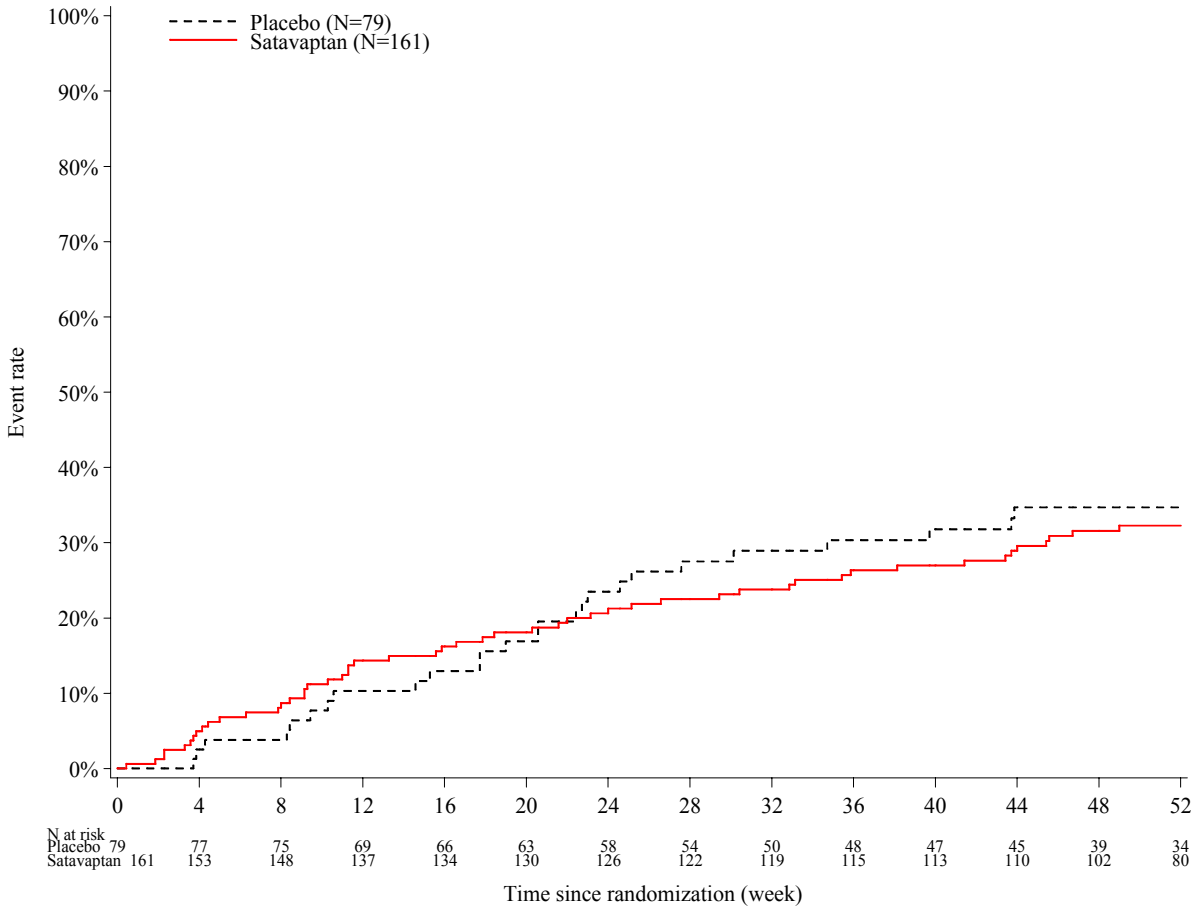


Figure 3 - Kaplan-Meier graph of time to death - Safety population



The most frequent TEAEs associated with a fatal outcome were events related to complications of an end-stage liver disease (Table 4). The main differences between the 2 treatment groups concerned the system organ classes of infections and infestations (6.2% of the patients in the satavaptan group compared with 1.3% in the placebo group), hepatobiliary disorders (especially hepatorenal syndrome reported in 3.1 % of the patients in the satavaptan group compared with 0% in the placebo group), and nervous system disorders (especially hepatic encephalopathy reported in 3.1% of the patients in the satavaptan group compared with 0% in the placebo group). Narratives for all cases of death are provided in the CSR Appendix.

Table 4 - Number (%) of patients experiencing TEAEs with a fatal outcome - Safety population

Primary System Organ Class Preferred Term	Placebo (N=79)	Satavaptan (N=161)
Any class	7 (8.9%)	30 (18.6%)
Gastrointestinal disorders	2 (2.5%)	6 (3.7%)
Oesophageal varices haemorrhage	1 (1.3%)	2 (1.2%)
Gastric ulcer haemorrhage	0	1 (0.6%)
Gastrointestinal haemorrhage	1 (1.3%)	0
Pancreatitis acute	0	1 (0.6%)
Upper gastrointestinal haemorrhage	0	1 (0.6%)
Peritoneal haemorrhage	0	1 (0.6%)
Infections and infestations	1 (1.3%)	10 (6.2%)
Peritonitis bacterial	1 (1.3%)	4 (2.5%)
Sepsis	0	3 (1.9%)
Septic shock	0	3 (1.9%)
Cholecystitis infective	0	1 (0.6%)
Pleural infection	0	1 (0.6%)
General disorders and administration site conditions	0	1 (0.6%)
Multi-organ failure	0	1 (0.6%)
Nervous system disorders	0	6 (3.7%)
Hepatic encephalopathy	0	5 (3.1%)
Coma	0	1 (0.6%)
Hepatobiliary disorders	3 (3.8%)	9 (5.6%)
Hepatorenal syndrome	0	5 (3.1%)
Hepatic cirrhosis	1 (1.3%)	1 (0.6%)
Hepatic failure	1 (1.3%)	2 (1.2%)
Acute hepatic failure	0	1 (0.6%)
Haemobilia	1 (1.3%)	0
Respiratory, thoracic and mediastinal disorders	0	2 (1.2%)
Pulmonary oedema	0	1 (0.6%)
Respiratory failure	0	1 (0.6%)
Vascular disorders	1 (1.3%)	2 (1.2%)
Deep vein thrombosis	0	1 (0.6%)
Shock haemorrhagic	1 (1.3%)	0
Hypovolaemic shock	0	1 (0.6%)
Psychiatric disorders	0	1 (0.6%)
Alcohol abuse	0	1 (0.6%)
Cardiac disorders	1 (1.3%)	0
Myocardial infarction	1 (1.3%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	2 (1.2%)
Hepatic neoplasm malignant	0	1 (0.6%)
Metastatic neoplasm	0	1 (0.6%)

n (%) = number and pourcentage of patients with at least one adverse event
MedDRA version 11.1

Serious TEAEs were reported for 60.9% of the patients in the satavaptan group compared with 58.2% in the placebo group. The serious TEAEs the most frequently reported in the satavaptan group belonged to the system organ classes of infections and infestations (23.6% of the patients compared with 16.5% in the placebo group) (especially bacterial peritonitis), nervous system disorders (21.1% of the patients compared with 20.3% in the placebo group) (especially hepatic encephalopathy), gastrointestinal disorders (19.9% of the patients compared with 19.0% in the placebo group) (especially oesophageal varices hemorrhage), and hepatobiliary disorders (14.3% of the patients compared with 10.1% in the placebo group) (especially hepatorenal syndrome).

Treatment-emergent AEs leading to study treatment discontinuation were reported for 40.4% of the patients in the satavaptan group compared with 35.4% in the placebo group. The TEAEs leading to study treatment discontinuation the most frequently reported in the satavaptan group belonged to the system organ classes of metabolism and nutrition disorders (8.1% of the patients compared with 11.4% in the placebo group) (especially hyperkalemia) and hepatobiliary disorders (8.1% of the patients compared with 6.3% in the placebo group) (especially hepatorenal syndrome), and infections and infestations (6.8% of the patients compared with 0% in the placebo group) (especially bacterial peritonitis).

The TEAEs of specific interest reported with a frequency >10% in the satavaptan group were renal impairment-related events (30.4% of the patients compared with 21.5% in the placebo group), hepatic encephalopathy-related events (22.4% of the patients compared with 22.8% in the placebo group), hyperkalemia-related events (21.7% of the patients compared with 22.8% in the placebo group), spontaneous bacterial peritonitis-related events (17.4% of the patients compared with 15.2% in the placebo group), and ascites-related events (11.8% of patients compared with 17.7% 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 56.5% of the patients compared with 35.4% in the placebo group) and decreases in the glomerular filtration rate (modification of diet in renal disease) changes from baseline (decrease >30% in 48.4% of the patients compared with 36.7% in the placebo group). Increase in creatinine values from baseline >50% to a value >133 µmol/L was reported in 28.0% of the patients in the satavaptan group and 20.3% in the placebo group, and hyperkalemia (potassium ≥5.5 mmol/L) in 36.6% of the patients in the satavaptan group and 32.9% in the placebo group. Increases in alanine aminotransferase values compared with baseline were reported in 20.5% (>2-fold increase), 9.9% (>3-fold increase) and 3.7% (>5-fold increase) of the patients in the satavaptan group compared with 17.7%, 5.1%, and 0%, respectively, in the placebo group. Increases in aspartate aminotransferase values compared with baseline were reported in 23.0% (>2-fold increase), 9.9% (>3-fold increase) and 3.1% (>5-fold increase) of the patients in the satavaptan group compared with 13.9%, 5.1%, and 0%, respectively, in the placebo group.

In regard to ECG parameters, prolonged QTcF (QT interval corrected according to Fridericia formula) ≥500 ms were observed in 10 (6.3%) patients in the satavaptan group compared with none in the placebo group. Four (2.5%) patients in the satavaptan group permanently discontinued the study treatment due to an AE of ECG QT prolonged compared with none in the placebo group. Increases in QTcF >60 ms were observed in 16 (10.4%) patients in the satavaptan group compared with 5 (6.5%) 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 73.6 ng/mL, respectively.

Conclusions

[redacted]

Date of report: 29-Jun-2009