SYNOPSIS

Title of the study: Satavaptan Cirrhotic Ascites Treatment Study: a double-blind, randomized, parallel-group comparison of treatment with satavaptan at 5 to 10 mg daily versus placebo on top of conventional treatment in patients with ascites due to cirrhosis of the liver (EFC4492).
Investigator(s): [redacted]
Study center(s): The study was conducted in 98 centers in 21 countries.
Publications (reference): None.
Study period: Date first patient enrolled: 06/Jul/2006 Date last patient completed: 30/Dec/2008
Phase of development: 3
Objectives: Primary: To evaluate the efficacy of satavaptan on top of conventional treatment in the treatment of clinically evident ascites in patients with cirrhosis of the liver. Secondary: To evaluate the tolerability and safety of satavaptan over a 52-week treatment period in patients with cirrhosis of the liver and ascites.
Methodology: This was a multinational, multicenter, double-blind, randomized, parallel-group comparison of 2 groups, satavaptan versus placebo.
Number of patients: Planned: Approximately 440 (220 per treatment arm).
Randomized: 463 patients overall (232 in the satavaptan group and 231 in the placebo group)
Treated: 462 patients overall (232 in the satavaptan group and 230 in the placebo group)
Evaluated: Efficacy: 462 patients overall (232 in the satavaptan group and 230 in the placebo group)
Safety: 462 patients overall (232 in the satavaptan group and 230 in the placebo group)
Pharmacokinetics: 462 patients overall (232 in the satavaptan group and 230 in the placebo group)
Diagnosis and criteria for inclusion: Patients aged >18 years with cirrhosis of the liver; clinically evident ascites primarily managed by diet and/or diuretics; stable treatment of ascites for at least the previous 2 weeks without paracentesis.
Investigational product: satavaptan (tablets of 5 mg).
Dose: Starting dose of 5 mg/day to max dose of 10 mg/day (2x5 mg/day) during the study.
Administration: Oral.
Batch number(s): [redacted]

Duration of treatment: 52 weeks double-blind treatment. **Duration of observation:** 54 weeks (52 weeks double-blind treatment plus 2 weeks post-treatment follow-up).
Reference therapy: Placebo tablets.
Dose: Not applicable.
Administration: Oral.
Batch number(s): [redacted]
Criteria for evaluation: The development of satavaptan was terminated as a consequence of a Drug Safety Monitoring Board recommendation to stop another satavaptan study (EFC4493) prematurely due to excess mortality. Consequently, was decided to provide a synopsis style report with the most relevant data, as presented in sections below.
Efficacy: Efficacy results were limited to the proportion of ascites worsening during the first 12 weeks (primary endpoint), the proportion of ascites worsening at 24 weeks and the time to reduction of ascites (main secondary endpoints).
Safety: The following safety criteria were evaluated, and analyzed using descriptive statistics: adverse events (AEs), standard laboratory tests (biochemistry, hematology), vital signs, and electrocardiogram (ECG) parameters.
Pharmacokinetics: Concentrations of SR121463 and of its metabolites, SSR108434 and SR122621.
Pharmacokinetic sampling times and bioanalytical methods: Plasma samples were collected 1 to 4 hours after drug intake on Days 7, 14, 28, and 84. On Days 14 and 28, pre-dose samples were also collected. Concentrations were assayed using liquid chromatography with tandem mass spectrometry bioanalytical methods.
Statistical methods: Efficacy: The efficacy analysis was performed on the intent-to-treat (ITT) population, defined as all randomized and exposed patients. The proportion of patients with ascites worsening was estimated in each treatment group using the Kaplan-Meier estimator and plotted by treatment group. The time to successful reduction of ascites was analyzed using methods for time-to-event data. The proportion of patients having experienced a successful reduction of ascites was estimated using the Kaplan-Meier estimator and plotted by treatment group up to 12 weeks. The relative risk (hazard ratio) and its 95% confidence interval were determined using a Cox model with adjustment on the starting dose of diuretics, the serum sodium at baseline and the geographical area. Safety: The analysis was 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:

Disposition of patients

About 40% of patients in each treatment group did not complete the study treatment (101 in the placebo group vs 93 in the satavaptan group). The major reason for study treatment discontinuation was adverse events in both treatment groups (22.1% in the placebo group vs 24.1% in the satavaptan group, Table 1).

Table 1 - Summary of patients disposition - Number (%) - Randomized population

	Placebo (N=231)	Satavaptan (N=232)
Patient disposition at the end of study treatment period		
Completed study treatment period	129 (55.8%)	139 (59.9%)
Did not complete the study treatment	101 (43.7%)	93 (40.1%)
Reason for study treatment discontinuation	101 (43.7%)	93 (40.1%)
Lack of efficacy/disease progression	13 (5.6%)	5 (2.2%)
Adverse event	51 (22.1%)	56 (24.1%)
Poor compliance to protocol	2 (0.9%)	8 (3.4%)
Recovery	0	0
Subject's request	19 (8.2%)	8 (3.4%)
Subject lost to follow-up	1 (0.4%)	1 (0.4%)
Liver transplantation	13 (5.6%)	9 (3.9%)
Tips placement	1 (0.4%)	1 (0.4%)
Sponsor decision	0	1 (0.4%)
Other	1 (0.4%)	4 (1.7%)

Demography and baseline characteristics

There were minor differences in the distribution of demographic characteristics between the two treatment groups. There were more of the oldest patients as well as more females in the satavaptan group, although mean age at baseline did not differ. Patients from North America were more frequently randomized in the placebo group and patients from southern Europe were more frequently randomized in the satavaptan group.

Overall, patients were similar in the two treatment groups for model for end-stage liver disease (MELD) score and for aetiology of cirrhosis, but there were fewer patients in Child-Pugh class C in the satavaptan group. Ascites severity at baseline appeared to be similar in the two treatment groups. (Table 2 and Table 3).

Table 2 - Summary of cirrhosis grading and origin - ITT population

	Placebo (N=230)	Satavaptan (N=232)	All (N=462)
Child-Pugh class			
Number	230	232	462
A: 5-6	43 (18.7%)	41 (17.7%)	84 (18.2%)
B: 7-9	142 (61.7%)	158 (68.1%)	300 (64.9%)
C: 10-15	45 (19.6%)	33 (14.2%)	78 (16.9%)
MELD score			
Number	229	231	460
Mean (SD)	13.1 (3.8)	12.8 (4.4)	13.0 (4.1)
Median	12.5	12.2	12.3
Min : Max	6 : 24	6 : 36	6 : 36
Etiology of cirrhosis (main etiology)			
Number	230	232	462
Alcoholism	151 (65.7%)	148 (63.8%)	299 (64.7%)
Hepatitis B	20 (8.7%)	18 (7.8%)	38 (8.2%)
Hepatitis C	49 (21.3%)	61 (26.3%)	110 (23.8%)

Table 3 - Summary of ascites and paracentesis history - ITT population

	Placebo (N=230)	Satavaptan (N=232)	All (N=462)
Ascites classification			
Number	230	232	462
Refractory	33 (14.3%)	35 (15.1%)	68 (14.7%)
Due to lack of response to high dose of diuretics	27 (11.7%)	25 (10.8%)	52 (11.3%)
Due to intolerance to diuretics	4 (1.7%)	7 (3.0%)	11 (2.4%)
Recidivant	29 (12.6%)	35 (15.1%)	64 (13.9%)
Neither	168 (73.0%)	162 (69.8%)	330 (71.4%)
Number of paracenteses in the last 12 months			
Number	230	232	462
Mean (SD)	0.5 (1.4)	0.6 (1.0)	0.5 (1.2)
Median	0.0	0.0	0.0
Min : Max	0 : 15	0 : 7	0 : 15

Medical history

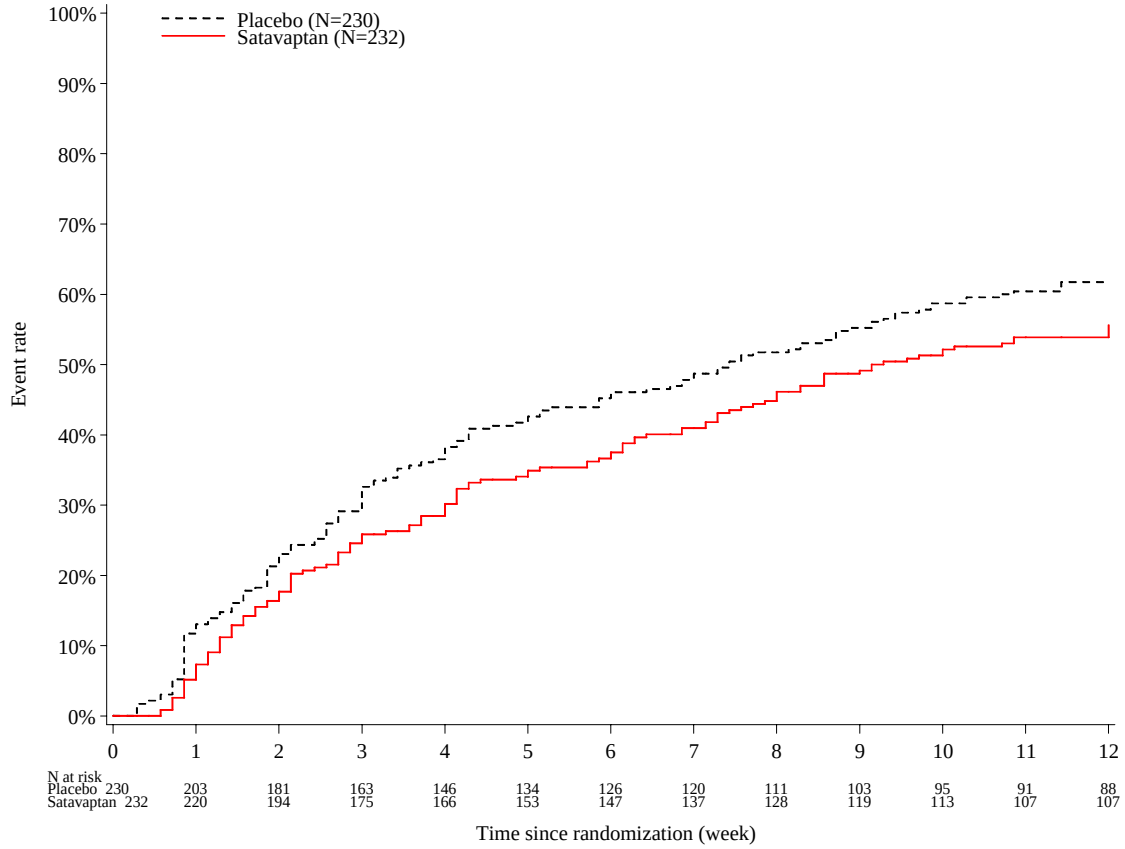
There were no major differences between the groups in the frequency of a recent history of other major complications of cirrhosis.

Efficacy

Primary endpoint

The median time to worsening of ascites was 9.2 weeks for satavaptan versus 7.4 weeks for placebo, but overall there was no statistically significant effect on the satavaptan group compared with placebo in reducing the incidence of ascites worsening in the first 12 weeks of treatment (relative risk 0.85, p-value 0.2034). A relative risk in the same range and still not statistically significant is observed over 24 and 52 weeks of treatment and in all supportive analyses during the first 12 weeks (Figure 1).

Figure 1 - Time to first ascites worsening during the first 12 weeks - ITT population



Main secondary efficacy endpoints

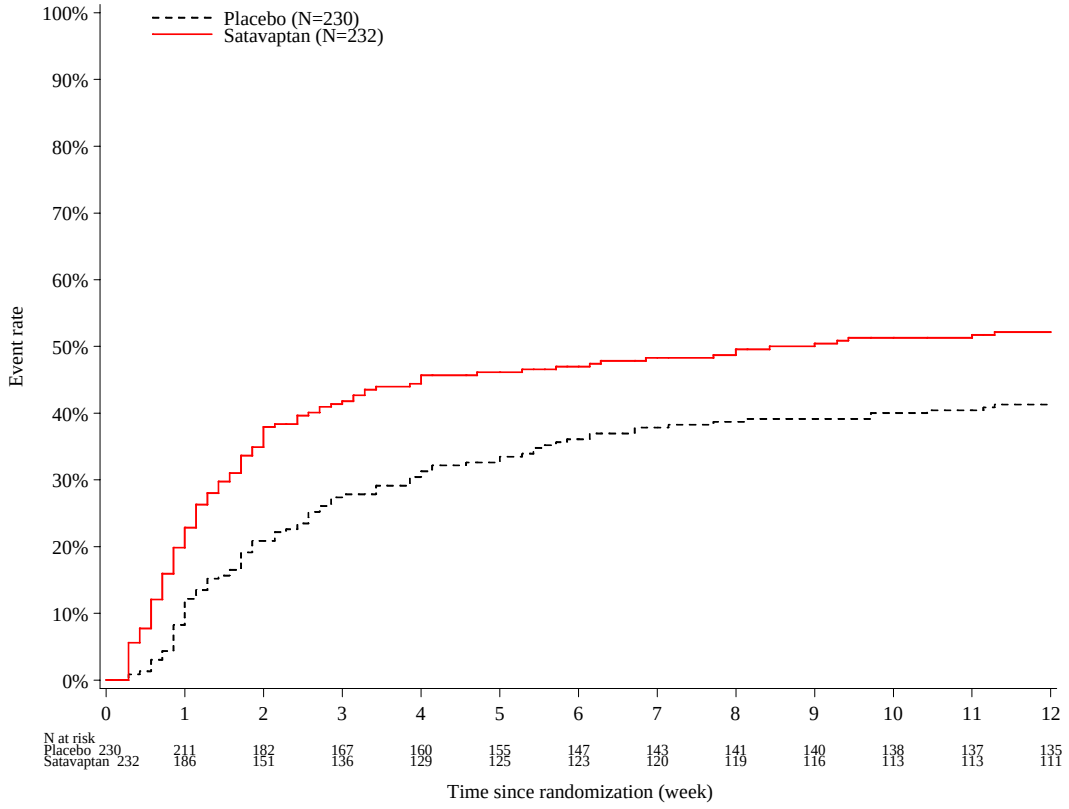
Proportion of ascites worsening at 24 weeks

A relative risk in the same range as that seen in the primary endpoint and still not statistically significant is observed over 24 and 52 weeks of treatment using a threshold of 4 kg weight increase to define ascites worsening.

Time to first reduction of ascites

The time to first reduction of ascites is significantly reduced on satavaptan compared to placebo (relative risk 1.48, p-value 0.0050, Figure 2).

Figure 2 - Time to first reduction of ascites during the first 12 weeks - ITT population



Safety results:

The main difference between the treatment groups emerged from the treatment-emergent adverse events with a fatal outcome (12.5% in the satavaptan group versus 6.1% in the placebo group). Considering smaller difference between the groups when taking into account emergent and post-treatment deaths (20.3% in the satavaptan group versus 17.4% in the placebo group), the higher mortality observed in the satavaptan group seems mainly driven by TEAE with a fatal outcome (Table 4).

Table 4 - Overview of patients with adverse events - Safety population

	Placebo (N=230)	Satavaptan (N=232)
Patients with any TEAE	198 (86.1%)	197 (84.9%)
Patients with any serious TEAE	114 (49.6%)	110 (47.4%)
Patients with any TEAE leading to permanent study drug discontinuation	51 (22.2%)	56 (24.1%)
Patients with any TEAE with fatal outcome	14 (6.1%)	29 (12.5%)
Patients with any AE (treatment-emergent or not) with fatal outcome	40 (17.4%)	47 (20.3%)

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

Deaths

The estimated 1-year mortality rates associated with TEAEs were 6.4% in the placebo group and 14.1% in the satavaptan group. The Kaplan-Meier curve showed that a higher mortality was observed as soon as 4 weeks after randomization and was maintained over the 52-week study period. This resulted in a relative risk of mortality of 2.01 (with 95% CI from 1.06 to 3.80) for patients on satavaptan (Table 5 and Figure 4). When including all deaths (treatment-emergent and post-treatment AE with a fatal outcome), the relative risk was 1.18 (with 95% CI from 0.78 to 1.81, Table 6). Narratives for all cases of death are provided in the CSR Appendix.

Table 5 - Summary of time to TEAE with fatal outcome - Safety population

TEAE with fatal outcome	Placebo (N=230)	Satavaptan (N=232)
Overall		
Number assessed	230	232
Number of events, n (%)	14 (6.1%)	29 (12.5%)
Number censored, n (%)	216 (93.9%)	203 (87.5%)
Reason for censoring		
Completed study treatment period	128 (55.7%)	138 (59.5%)
Discontinuation of study treatment	88 (38.3%)	65 (28.0%)
Kaplan-Meier event rate at specific time-point (95% CI)		
4-week estimate	0.4% (0.0% to 1.3%)	1.7% (0.0% to 3.4%)
8-week estimate	1.4% (0.0% to 2.9%)	2.6% (0.6% to 4.7%)
12-week estimate	1.8% (0.1% to 3.6%)	4.1% (1.5% to 6.7%)
24-week estimate	3.9% (1.2% to 6.6%)	8.0% (4.3% to 11.6%)
52-week estimate	6.4% (2.8% to 9.9%)	14.1% (9.2% to 18.9%)
Comparison versus Placebo		
Relative risk (95% CI)	-	2.01 (1.06 to 3.80)

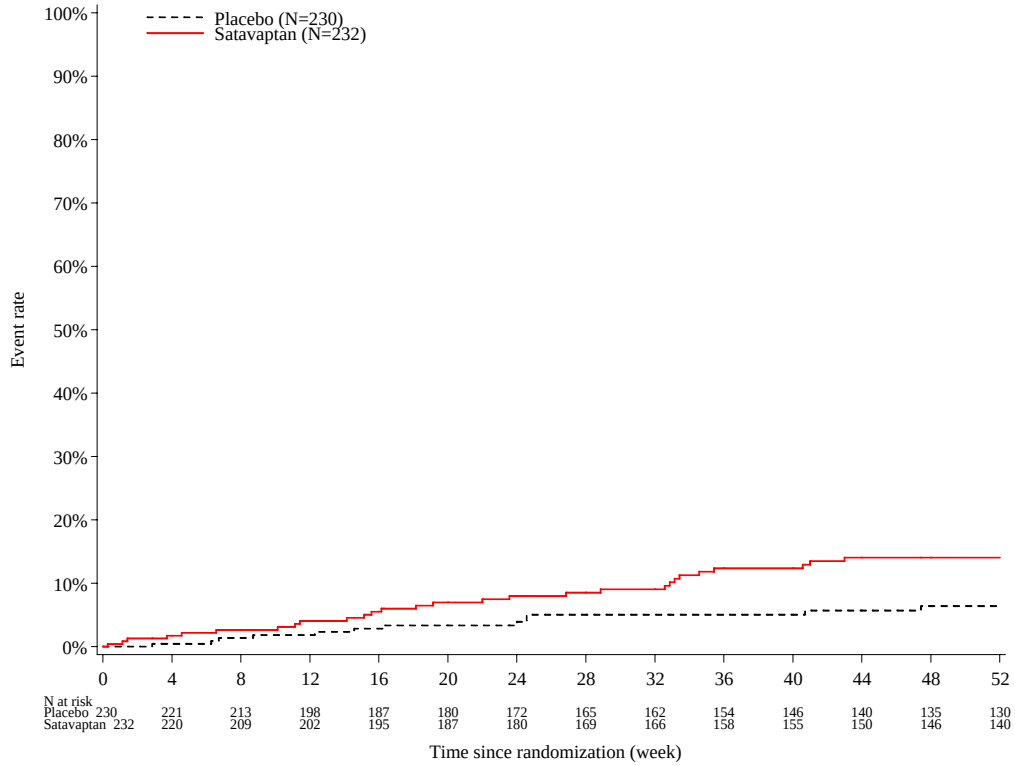
Relative risk and 95% CI determined from Cox model with no adjustment for covariate.

Table 6 - Summary of time to death (treatment-emergent and post-treatment AE with fatal outcome) - Safety population

Death	Placebo (N=230)	Satavaptan (N=232)
Overall		
Number assessed	230	232
Number of events, n (%)	40 (17.4%)	47 (20.3%)
Number censored, n (%)	190 (82.6%)	185 (79.7%)
Reason for censoring		
End of follow-up	190 (82.6%)	185 (79.7%)
Kaplan-Meier event rate at specific time-point (95% CI)		
4-week estimate	0.4% (0.0% to 1.3%)	1.3% (0.0% to 2.7%)
8-week estimate	2.2% (0.3% to 4.1%)	3.0% (0.8% to 5.2%)
12-week estimate	3.5% (1.1% to 5.9%)	5.2% (2.3% to 8.0%)
24-week estimate	8.4% (4.8% to 12.0%)	8.7% (5.0% to 12.3%)
52-week estimate	15.4% (10.6% to 20.1%)	18.1% (13.1% to 23.2%)
Comparison versus Placebo		
Relative risk (95% CI)	-	1.18 (0.78 to 1.81)

Relative risk and 95% CI determined from Cox model with no adjustment for covariate.

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



In order to identify the subgroup of patients with high risk of mortality exploratory analyses were performed on TEAEs with fatal outcome. As summarized in the table below, patients with more severe liver cirrhosis at baseline, high or very high doses of diuretics as well as doses of loop diuretics/thiazides > 50 mg at baseline and /or during the study and the absence of non-selective beta-blockers were identified as being associated with the mortality observed on satavaptan (Table 7).

Table 7 - TEAE with a fatal outcome by subgroups - Safety population

	Patients with TEAE with fatal outcome n / N (%)		Relative risk
Subgroups	**Placebo**	**Satavaptan**	**(95% CI)**
All patients	14/230 (6.1%)	29/232 (12.5%)	2.01 (1.06 to 3.80)
Baseline severity of liver cirrhosis			
Child-Pugh class C	4/45 (8.9%)	11/33 (33.3%)	4.28 (1.36 to 13.44)
MELD score ≥ 15	5/61 (8.2%)	19/66 (28.8%)	3.50 (1.30 to 9.39)
MELD-Na score ≥ 20	4/35 (11.4%)	14/33 (42.4%)	3.45 (1.13 to 10.48)
Total bilirubin >51 µmol/L	3/42 (7.1%)	16/44 (36.4%)	5.61 (1.63 to 19.26)
Dose of diuretics at baseline			
High or very high overall dose	2/71 (2.8%)	16/76 (21.1%)	7.76 (1.78 to 33.78)
Dose of loop diuretics/thiazides > 50mg	3/56 (5.4%)	11/53 (20.8%)	4.15 (1.16 to 14.88)
Median dose of diuretics during the treatment period			
High or very high overall dose	1/84 (1.2%)	13/76 (17.1%)	15.96 (2.09 to 122.1)
Average dose of loop diuretics/thiazides > 50mg	3/67 (4.5%)	8/64 (12.5%)	2.92 (0.77 to 11.02)
Medications received at baseline			
No non-selective beta-blockers	7/111 (6.3%)	22/127 (17.3%)	2.77 (1.18 to 6.48)
Medications received during the treatment period			
No non-selective beta-blockers	6/98 (6.1%)	19/103 (18.4%)	3.05 (1.22 to 7.65)

Regarding the adverse events of specific interest, few differences were observed in the incidence of specific classes of adverse events. There were trends to a reduction under satavaptan treatment in the number of patients experiencing a bacterial peritonitis and an increase in the number experiencing an event potentially related to ventricular arrhythmia.

Other safety parameters

With respect to laboratory parameters, there was little evidence that changes in liver function or renal function were more frequent in the satavaptan group compared with the placebo group, beyond small increases in the numbers of patients with the largest increase in the creatinine or decrease in estimated glomerular filtration rate (GFR) (Table 8).

Table 8 - Patients with at least one PCSA in laboratory data during the treatment period - Safety population

Laboratory criteria PCSA n/N(%)	Placebo (N=230)	Satavaptan (N=232)
ALT (SGPT-ALAT)		
Increase > 2 times baseline value	44/230 (19.1%)	52/231 (22.5%)
Increase > 3 times baseline value	22/230 (9.6%)	18/231 (7.8%)
Increase > 5 times baseline value	7/230 (3.0%)	5/231 (2.2%)
Increase > 10 times baseline value	1/230 (0.4%)	3/231 (1.3%)
AST (SGOT-ASAT)		
Increase > 2 times baseline value	44/230 (19.1%)	50/231 (21.6%)
Increase > 3 times baseline value	19/230 (8.3%)	17/231 (7.4%)
Increase > 5 times baseline value	7/230 (3.0%)	8/231 (3.5%)
Increase > 10 times baseline value	1/230 (0.4%)	2/231 (0.9%)
Total bilirubin		
Increase > 2 times baseline value	56/230 (24.3%)	69/231 (29.9%)
Increase > 2.5 times baseline value	44/230 (19.1%)	44/231 (19.0%)
Increase > 3 times baseline value	34/230 (14.8%)	34/231 (14.7%)
Creatinine (µmol/L)		
Increase from baseline > 50% to a value > 133 µmol/L	47/230 (20.4%)	46/231 (19.9%)
Creatinine (µmol/L)		
≥ 150 µmol/L	47/230 (20.4%)	47/231 (20.3%)
≥ 175 µmol/L	23/230 (10.0%)	35/231 (15.2%)
Creatinine - Change from baseline		
Increase > 30%	109/230 (47.4%)	117/231 (50.6%)
Increase > 50%	69/230 (30.0%)	67/231 (29.0%)
Increase > 100%	30/230 (13.0%)	36/231 (15.6%)
GFR (MDRD) (mL/min/1.73m²)		
≥ 50 - ≤ 80 mL/min/1.73m² (mild renal impairment)	85/230 (37.0%)	75/231 (32.5%)
≥ 30 - < 50 mL/min/1.73m² (moderate renal impairment)	59/230 (25.7%)	58/231 (25.1%)
< 30 mL/min/1.73m² (severe renal impairment)	26/230 (11.3%)	32/231 (13.9%)
GFR (MDRD) - Change from baseline		
Decrease > 30%	95/230 (41.3%)	86/231 (37.2%)
Decrease > 50%	42/230 (18.3%)	47/231 (20.3%)
Potassium (mmol/L)		
< 3 mmol/L	9/230 (3.9%)	4/231 (1.7%)
≥ 5.5 mmol/L	53/230 (23.0%)	51/231 (22.1%)
International Normalized Ratio		
1st limit: ≥ 1.7 and ≤ 2.3	54/229 (23.6%)	51/229 (22.3%)
2nd limit: > 2.3	34/229 (14.8%)	36/229 (15.7%)

Note: PCSA: Potentially Clinically Significant Abnormalities
% are calculated using the number of patients with at least one event (n) over the number of patients assessed (N)
Both central and local laboratory values are taken into account in this analysis.

There was no excess of high values for QTcF in the satavaptan group, for QTcF ≥ 500 ms the incidence was 2.6 % for the placebo versus 2.2% for satavaptan (Table 9).

Table 9 - patients with at least one PCSA in ECG during the treatment period - Safety population

ECG Parameter PCSA n/N(%)	Placebo (N=230)	Satavaptan (N=232)
QTc Fridericia (ms)		
Borderline: 431-450 ms (male), 451-470 ms (female)	65/229 (28.4%)	54/230 (23.5%)
Prolonged: > 450 ms (male), > 470 ms (female)	70/229 (30.6%)	64/230 (27.8%)
≥ 500 ms	6/229 (2.6%)	5/230 (2.2%)
QTc Fridericia (ms)		
Increase ≥ 30 and ≤ 60 ms	69/227 (30.4%)	81/227 (35.7%)
Increase > 60 ms	9/227 (4.0%)	12/227 (5.3%)

Note : PCSA: Potentially Clinically Significant Abnormalities
% are calculated using the number of patients with at least one event (n) over the number of patients assessed (N)

Pharmacokinetics

The minimum and the maximum satavaptan concentrations observed in the plasma samples taken post-dose for the patients treated with 5 and/or 10 mg were <LLOQ and 30.1 ng/mL, respectively, with mean post-dose plasma concentrations of 3.28 ng/mL at 7 days and 4.80 ng/mL at 84 days.

Conclusions:

[redacted]

Date of report: 09-June-2009