SYNOPSIS

Title of the study: Long term safety and tolerability of satavaptan in patients with cirrhosis of the liver that have been previously randomized and completed treatment in any of the phase III studies: EFC4492; EFC4493 or EFC6682: a double blind parallel group study comparing satavaptan at 5 to 10 mg daily versus placebo (LTS10036)

Investigator: [redacted]

Study centers: The study was conducted in 84 centers in 25 countries

Publications (reference): Not applicable

Study period:

Date first patient enrolled: 19/Jul/2007

Date last patient completed: 10/Jan/2009

The study was prematurely discontinued due to the Sponsor's decision following the recommendations of the drug safety monitoring board (DSMB) regarding an overmortality in the EFC4493 study and an unfavorable benefit/risk assessment in the EFC6682 study.

Phase of development: Phase 3

Objectives:

Primary: To evaluate the long term safety and tolerability up to 2 years of treatment with satavaptan in patients with cirrhosis of the liver previously treated for 52 weeks with satavaptan in any of the phase III studies

Secondary:

- Number and time (from randomization in the previous phase III EFC studies) of therapeutic paracentesis, defined as the removal of $\geq$2 liters of ascitic fluid by paracentesis
- Increase in ascites measured by body weight and volume of ascites removed by paracentesis (to be expressed as increase per unit of time to avoid any bias due to withdrawl)
- Diuretics regimen at each scheduled visit according to a predefined classification

Methodology: Multicenter, multinational, double-blind, randomized, placebo-controlled, parallel-group study. The study was an extension of treatment duration for patients from 3 double-blind, randomized, placebo-controlled, parallel-group phase 3 studies (EFC4492, EFC4493, and EFC6682). Patients were administered the same treatment to which they were randomized in the initial study.

Number of patients: Planned: 550 Randomized: 278 Treated: 278

Efficacy: Not applicable Safety: 278 Pharmacokinetics: 22

Consequently to the Sponsor's decision, 89 patients in the placebo group and 133 in the satavaptan group were prematurely withdrawn from the study.

Diagnosis and criteria for inclusion: Patients eligible to participate in the LTS10036 study were patients who had completed the 52-week treatment and the 2-week follow-up periods in one of the EFC4492, EFC4493, or EFC6682 studies and for whom no treatment discontinuation longer than 18 days occurred between the last treatment intake in the original study and the start of the LTS10036 study.

Investigational product: Satavaptan (5 mg tablet)

Dose: 5 or 10 mg, once daily

Administration: Oral, in the morning

Batch numbers: [redacted]

Duration of treatment: Up to 1 year in LTS10036

Duration of observation: Up to 1 year treatment plus 2 weeks follow-up in LTS10036

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, due to the early termination of the study, only safety data are being presented. These are limited to treatment-emergent adverse events (TEAEs), TEAEs associated with a fatal outcome, serious TEAEs, and TEAEs leading to treatment discontinuation.

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

Statistical methods:

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).

Summary:

Of the 278 patients randomized and treated (167 in the satavaptan group and 111 in the placebo group), 6 patients in each group completed the 1-year treatment period.

Demographic and baseline characteristics

Overall, patients were between 31 and 81 years of age (mean age ± SD =57.0±9.7 years), 21.9% being ≥65-year-old. Of these patients, 72.7% were males and 27.3% 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.

Regarding disease characteristics at baseline, the proportion of patients with Child-Pugh class B was higher in the satavaptan group (73.7% compared with 64.0% in the placebo group). Conversely, the proportion of patients with Child-Pugh class C was lower in the satavaptan group (12.0% compared with 18.0% than in the placebo group). The most frequently reported causes of cirrhosis were alcoholism (74.8%) and hepatitis C (15.8%).

Safety

The median duration of exposure during the study was 150.0 days in the satavaptan group and 140.0 days in the placebo group.

During the study, TEAEs were reported by 51.5% of the patients in the satavaptan group compared with 55.9% in the placebo group. The TEAEs the most frequently reported in the satavaptan group belonged to the following system organ classes: gastrointestinal disorders (21.0% of the patients compared with 18.0% in the placebo group, including 8 patients with nausea in the satavaptan group compared with 0 in the placebo group), infections and infestations (19.8% of the patients compared with 17.1% in the placebo group), metabolism and nutrition disorders (13.2% of the patients compared with 15.3% in the placebo group, including patients with hyperkalemia), nervous system disorders (12.6% of the patients compared with 11.7% in the placebo group, including patients with hepatic encephalopathy), and musculoskeletal and connective tissue disorders (12.6% of the patients compared with 7.2% in the placebo group).

Adverse events (treatment-emergent or not) associated with a fatal outcome were reported for 9.6% of the patients in the satavaptan group compared with 5.4% in the placebo group. Treatment-emergent adverse events associated with a fatal outcome were reported in 9 patients (5.4%) in the satavaptan group (1 septic shock, 1 postprocedural sepsis, 1 peritoneal tuberculosis, 1 recurrent gastric cancer, 1 hepatic encephalopathy, 1 myocardial ischemia, 1 pneumonia aspiration, 1 intestinal obstruction, 2 hepatic failures, and 1 hepatorenal syndrome) and in 4 patients (3.6%) in the placebo group (1 septic shock, 1 intervertebral discitis, 1 non-small-cell metastatic lung cancer, 1 hepatic encephalopathy, and 1 constipation).

Serious TEAEs were reported for 19.8% of the patients in the satavaptan group compared with 18.9% in the placebo group. The serious TEAEs the most frequently reported in the satavaptan group were gastrointestinal disorders, especially ascites (2.4% compared with 0.9% in the placebo group) and esophageal varices hemorrhage (1.8% compared with 0.9% in the placebo group), and nervous system disorders, especially hepatic encephalopathy (5.4% compared with 6.3% in the placebo group).

Treatment-emergent adverse events leading to permanent study treatment discontinuation were reported in 10.2% of the patients in the satavaptan group compared with 6.3% in the placebo group.

Conclusion

[redacted]

Date of report: 25-Jun-2009