SYNOPSIS

Title of the study: A single-blind, placebo-controlled, multicentre study evaluating continued long-term treatment with satavaptan (SR121463B) in patients with acsites due to liver cirrhosis who have previously been treated in studies LTS5634 or LTS5635 (LTS10209)

Investigator(s): [redacted]

Study center(s): There were 24 centers (in 11 countries)

Publications (reference): None

Study period:

Date first patient enrolled: 11 June 2007 (date of first informed consent signed)

Date last patient completed: 03 December 2008 (date of last patient last visit)

Phase of development: Phase 2b

Objectives:

The objective of this study was to monitor the long-term safety and tolerability of satavaptan in patients with ascites due to liver cirrhosis

Methodology:

This study represented the extension of treatment duration for patients from two randomized, single-blind, placebo-controlled phase IIB studies, LTS5634 and LTS5635. It was a multicentre, multinational study with a single-blind, parallel-group design and two treatment groups, satavaptan and placebo. Each patient participated in this study for a treatment period of up to 52 weeks and a post-treatment period of 2 weeks after the last intake of study medication. Treatments (satavaptan [5 mg/day or 10 mg/day] and placebo) were given on top of any standard diuretic agents which were required for the control of ascites, and all patients were instructed to follow a low sodium diet limiting daily sodium intake to 88 mmol/day for the duration of the study. Patients continued on treatment to which they were randomised under the previous protocol (LTS5634 or LTS5635), except for those previously receiving 12.5 mg capsules satavaptan, who received 10 mg (two 5 mg tablets/day) in this study.

After the first 7 days, in the satavaptan group, the satavaptan dose could be adjusted between 5 mg and 10 mg/day, if necessary, according to efficacy and tolerability. Assessment visits were performed at 4-weekly intervals for 12 months throughout the study. Additional assessments were performed after any dose change. At 12 months after entering the study, treatment was terminated. There was a post-treatment period of 2 weeks after the last intake of the study medication.

Number of patients: Planned: maximum 80 Randomized: 53 Treated: 53 Safety : 53

Diagnosis and criteria for inclusion:

Patients who completed a minimum of 1 year of study treatment in studies LTS5634 or LTS5635 and for whom no treatment discontinuation longer than 7 days occured between the original study and the start of the study LTS10209.

Investigational product: Satavaptan (SR121463B) 5 mg tablets

Dose: 5 mg or 10 mg (2 times 5 mg)

Administration: Oral administration in the morning

Batch number(s): [redacted]

Duration of treatment: 1 year

Duration of observation: 2 weeks

Reference therapy: Placebo tablets

Dose: NA

Administration: Oral administration in the morning

Batch number(s): [redacted]

Criteria for evaluation:

Although this study was completed as planned, the development of satavaptan was terminated due to unfavourable benefit/risk assessment in other SR121463B studies. Consequently, in this synopsis-style report, only TEAEs with fatal outcome, serious TEAEs and TEAEs are described.

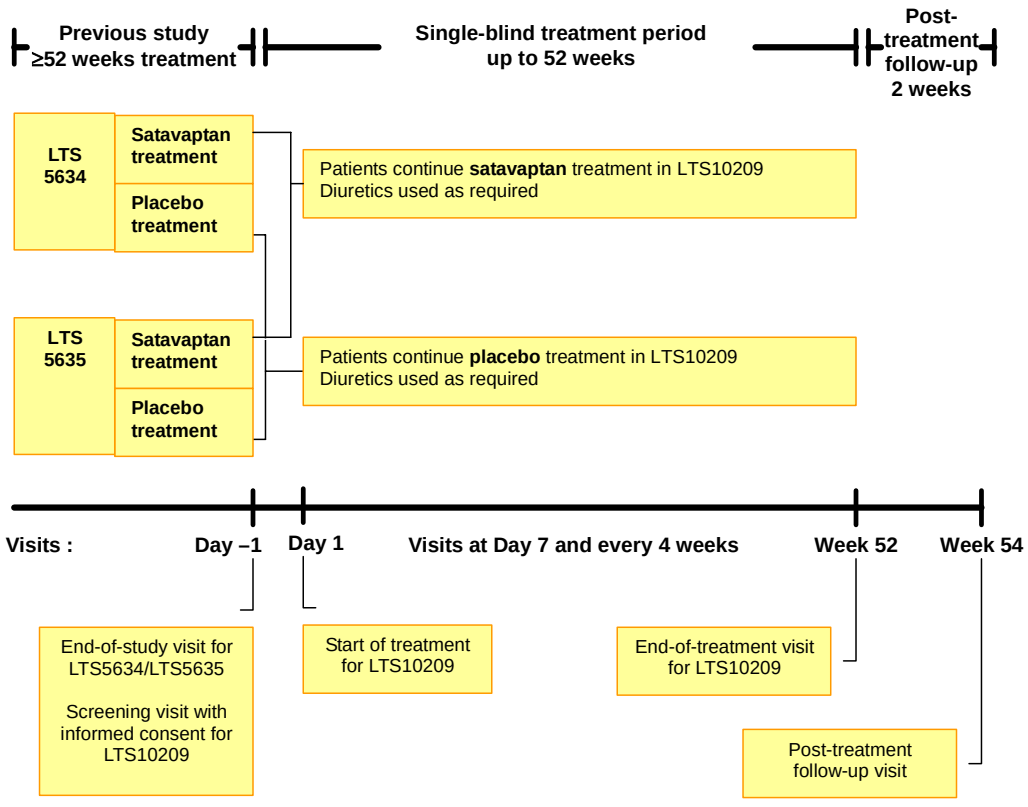
Statistical methods:

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).

Summary:

A summary of the study design is provided below.

Figure 1 – Graphical study design



Demographic and baseline characteristics

Of the 53 patients randomized and exposed, 6/7 (85.7%) patients in the placebo group and 36/46 (78.3%) patients in the satavaptan group completed the 1-year treatment period. In the overall population, patients were between 42 and 81 years of age (mean age ± SD = 57.2 ± 9.0 years). In the overall population, 69.8% were males and 30.2% were females. Demographics characteristics were comparable in the 2 treatment groups, except age showing a higher proportion of patients between 18 and 44 years in the placebo group in comparison with the satavaptan group (28.6% versus 6.5%) and a higher proportion of patients over the age of 65 years in the satavaptan group in comparison with the placebo group (23.9% versus 0%).

The most frequently reported cause of cirrhosis was alcoholism (84.9%). Alcoholism was more frequently reported as the cause of cirrhosis in the placebo group than in the satavaptan group (100% versus 82.6%). Hepatitis C was the second most important cause of cirrhosis in the satavaptan group (10.9%). At baseline, disease characteristics between the 2 groups were comparable.

Exposure

The median duration of exposure during the entire study, reported for both groups, was similar.

Safety

In the placebo group, 4/7 (57.1%) patients experienced TEAEs, whereas 30/46 (65.2%) patients experienced TEAEs in the satavaptan group.

The most frequently reported TEAEs in the satavaptan group were in the SOC gastrointestinal disorders, with an overall incidence of 30.4% (14/46 patients), including 4 reports of various gastrointestinal bleeding and 3 patients with haemorrhoids, compared to 0 patients in the placebo group :

Other SOCs or preferred terms of interest, were:

- In the SOC infections and infestations: events reported in 7 (15.2%) patients on satavaptan compared to 0 patients on placebo;
- Muscle spasms reported in 4/46 (8.7%) patients on satavaptan compared to 0 on placebo;
- Hepatic encephalopathy reported in 3/46 (6.5%) patients on satavaptan compared to 0 patients on placebo;
- Renal failure reported in 2/46 (4.3%) satavaptan-treated patients, compared to 1/7 (14.3%) in the placebo group;

In the satavaptan group, two patients (2/46 [4.3%]) experienced a TEAE with a fatal outcome and none was reported amongst the placebo patients.

- One of the two patients, experienced neutropenia, while receiving satavaptan 5mg/day in LTS5635. Eight weeks after starting satavaptan (10 mg/day) in study LTS10209, the patient's pre-existing neutropenia worsened leading to hospitalization 1 month later. Satavaptan was permanently discontinued. The patient was diagnosed with myelosdysplastic syndrome confirmed by bone marrow biopsy. He received 4 units of PRBC as corrective treatment. The patient died from myelodysplastic syndrome, more than 4 months after stopping satavaptan.
- The second patient was hospitalized for portal hypertensive gastropathy bleeding, approximately 4 months after starting satavaptan (5mg/day) in study LTS10209. Seven days later, he developed dyspnea and wheezing due to atelectasis. Haemodynamic instability was finally diagnosed. The patient received albumin, vitamin K and magnesium as corrective treatments. He died from haemodynamic instability, 8 days after the last satavaptan intake.

Serious TEAEs were reported by 12/46 (26.1%) patients in the satavaptan group and 2/7 (28.6%) patients in the placebo group. The most frequently reported serious TEAE in the satavaptan group was hepatic encephalopathy reported in 3/46 (6.5%) patients.

Five patients (5/46 [10.9%]) in the satavaptan group discontinued the treatment due to a TEAE whereas none discontinued the treatment in the placebo group for this reason. Two of the 5 patients, reported fatal TEAEs. The reasons for the treatment discontinuation were: gastric haemorrhage, alcoholic hepatitis, electrocardiogram qt prolonged, myelodysplastic syndrome, and haemodynamic instability.

Conclusion : [redacted]

Date of report: 30-Apr-2009