SYNOPSIS

Title of the study: An open-label, multicenter study evaluating the long-term safety of satavaptan (SR121463B) and maintenance of normonatremia in patients with dilutional hyponatremia who have previously been treated in studies LTS5066, EFC4489, or SFY5904 (LTS10208/TESSY).
Investigator(s): [redacted]
Study center(s): 12 centers in 8 countries (Australia,Belgium, Brazil, Canada, Germany, Hungary, Switzerland, and USA)
Publications (reference): Not applicable.
Study period: Date first patient enrolled: 05 June 2007 (date of first signed informed consent) Date last patient completed: 06 October 2008 (date of last patient last visit)
Phase of development: III
Objectives: **Primary:** To assess the long-term safety and tolerability of satavaptan in patients with dilutional hyponatremia. **Secondary**: To monitor the long-term maintenance of normonatremia in patients with dilutional hyponatremia treated with satavaptan.
Methodology: Open-label, non-comparative, multicenter study, assessing the long-term safety of flexible doses of satavaptan (5, 10, or 25 mg). This was an extension study to any of the 3 completed studies conducted in patients with syndrome of inappropriate antidiuretic hormone secretion (SIADH): LTS5066 (itself an extension to DFI4488), EFC4489, or SFY5904.
Number of patients: Planned: All patients who completed a minimum 1-year treatment with satavaptan in any of the ongoing studies were to be enrolled in LTS10208 (68 patients maximum) Included: 51 patients were included in LTS10208 (5 from LTS5066, 22 from EFC4489, and 24 from SFY5904) Treated: 51 Efficacy/Safety: For efficacy and safety analyses, all patients who received at least 1 dose of satavaptan in LTS10208 or any of the original studies DFI4488/LTS5066, EFC4489, or SFY5904 were taken into account (total of 168 patients). Pharmacokinetics: Not applicable
Diagnosis and criteria for inclusion: Patients eligible to participate in Study LTS10208 were those who had completed a minimum of 1 year in Studies LTS5066, EFC4489, or SFY5904, and for whom no treatment discontinuation longer than 4 days occurred between the original study and the start of the LTS10208 study.
Investigational product: Satavaptan 5 mg and 25 mg tablets Dose: Flexible doses of 5, 10, or 25 mg once daily Administration: Oral Batch numbers: [redacted]

Duration of treatment: Up to 1 year in LTS10208

Duration of observation: One year plus 2 weeks of follow-up in LTS10208

Reference therapy: None.

Criteria for evaluation: The current report is a synopsis style clinical study report, and as such, only the safety results are being presented in full and the efficacy results are limited to the maintenance of correction of serum sodium for more than 5 years. The following safety criteria were evaluated, and analyzed using descriptive statistics: adverse events (AEs) reported by the patients or noted by the Investigator, standard laboratory tests (biochemistry, hematology), vital signs, and electrocardiogram (ECG) parameters.

Statistical methods: Safety analyses were performed on safety population, ie, all patients who received at least 1 dose of satavaptan in LTS10208 or any of the original studies DFI4488, LTS5066, EFC4489, or SFY5904. 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:

Safety results:

Of the 168 patients who participated in one of the SIADH studies, 143 (85.1%) patients experienced at least one treatment-emergent adverse event (TEAE). Most of the TEAEs could be related to the patients' underlying disease, including multiple infections and cancer-related complications.

A total of 89 (53.0%) patients had treatment-emergent serious adverse events (SAEs), including TEAEs associated with a fatal outcome in 47/168 (28.0%) patients. The most frequent causes of death were cancer (15/168) and infections (13/168). Sudden death occurred in 4 patients: 3 elderly hyponatremic patients in EFC4489 and 1 additional patient in LTS5066 who died in her sleep probably due to right ventricular failure secondary to pulmonary embolism.

Sixty-two (36.9%) patients discontinued treatment due to TEAEs, mainly due to infections (12/168) and cancer (13/168).

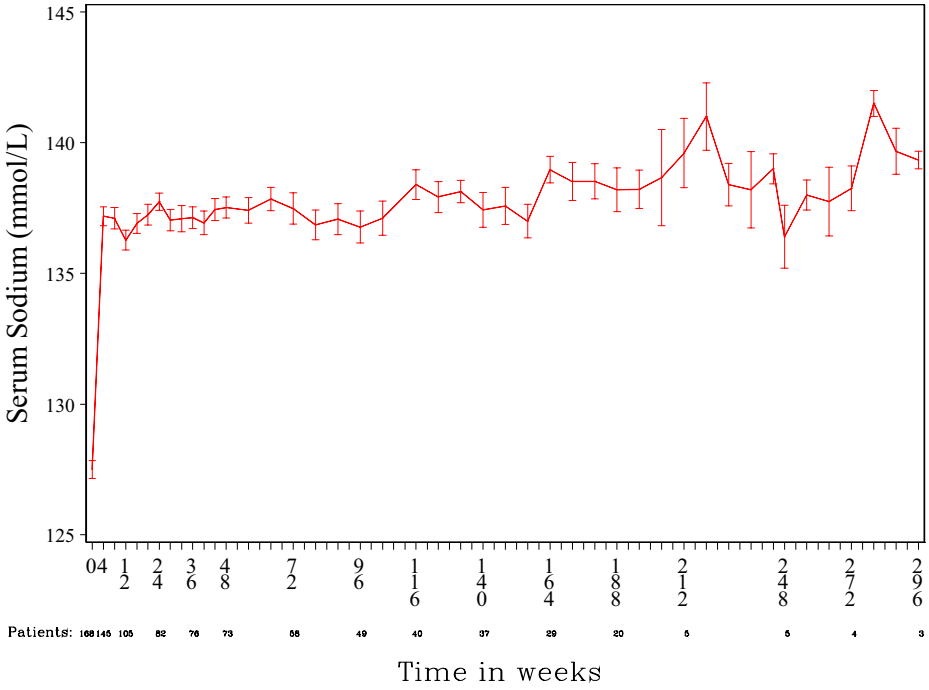
The most frequently reported PCSA for laboratory parameters was decreased creatinine clearance: 56/150 (37.3%) patients experienced a mild renal impairment (decrease in creatinine clearance between 50 and 80 mL/min); half of them had an already abnormal renal function at baseline.

The most frequently reported PCSA for vital signs was orthostatic hypotension, observed in more than 65% of patients. For ECG parameters, prolonged QTcF was observed in 23/150 (15.3%) patients, including 8/150 patients with QTcF ≥ 500 ms, and QTcF increase from baseline >60 ms was observed in 16/148 (10.8%) patients. Of the 23 patients with prolonged QTcF values, 7 patients had abnormal QTcF values at baseline and 6 patients took concomitant drugs known to increase QT.

Specifically in the LTS10208 study, 37/51 patients experienced at least 1 TEAE including 12 patients with treatment-emergent SAEs. Five patients experienced a TEAE associated with a fatal outcome. Death was related to cancer in 3 subjects, infection in 1 subject, and cardiorespiratory arrest in a context of ischemic heart disease with respiratory insufficiency and chronic obstructive pulmonary disease in the remaining subject. In addition, 8 patients discontinued treatment due to AE. The safety profile of satavaptan was comparable to that observed in the previous SIADH studies and no new safety findings were identified in this extension study.

Efficacy results:

Long-term maintenance of serum sodium within the normal range (135 to 145 mmol/L) was observed for up to 296 weeks in patients receiving flexible doses of satavaptan (25 mg for most patients). At least 80% of patients had serum sodium concentration ≥135 mmol/L and/or increased ≥5 mmol/L from baseline for up to 5.5 years.



Conclusion:

[redacted]

Date of report: 06-Feb-2009