European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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WITHDRAWAL ASSESSMENT REPORT
FOR
AQUILDA

International Nonproprietary Name:
satavaptan

Procedure No. EMEA/H/C/873

Day 120 Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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I. RECOMMENDATION

Based on the CHMP review of the data on quality, safety and efficacy, the CHMP considers that the application for AQUILDA in the treatment of euvolemic and hypervolemic dilutional hyponatremia, is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time.

The major objections precluding a recommendation of marketing authorisation pertain to the following principal deficiencies:

- Pre-Clinical
- Clinical Efficacy
- Clinical Safety

Questions to be posed to additional experts

None

Inspection issues

No inspections issues are identified during the assessment of the application.

II. EXECUTIVE SUMMARY

II.1 Problem statement

This is an application for satavaptan 5 and 25 mg film-coated tablets. The claimed indication is treatment of euvolemic and hypervolemic dilutional hyponatraemia.

Serum sodium accounts for nearly all of the osmotic activity of the plasma and is the primary extracellular electrolyte to which osmoreceptors respond. The antidiuretic hormone (ADH) arginine-vasopressin (AVP) maintains the balance of water that keeps the serum sodium concentration in the normal range between 135 and 145 mmol/L. The primary physiologic role of AVP is to act as a water-retaining hormone. In the absence of AVP, large volumes of maximally diluted urine are excreted (water diuresis). If AVP is present in excess, solute-free water is reabsorbed in the collecting ducts of the kidney, resulting in the excretion of small volumes of concentrated urine.
Clinical symptoms of hyponatremia are primarily of neurological nature and are related to the osmotic water shift leading to increased intracellular volume, which is of special concern in the brain (cerebral oedema). Symptoms ranging from headache and nausea to disorientation, confusion, and focal neurological deficits appear with decreasing sodium. The severity of the symptoms depends on the rapidity and magnitude of the decrease in serum sodium concentration. In cases with severe hyponatremia or a very rapid change in serum sodium concentration, stupor, seizures and coma may occur. Acute, severe hypoosmolality, although less common, is associated with substantial morbidity, and mortality rates of up to 50%.

In general, hyponatremia is defined as follows:

Mild	Serum sodium concentration 130 - <135 mmol/L
Moderate	Serum sodium concentration 125 - <130 mmol/L
Severe	Serum sodium concentration <125 mmol/L

Furthermore, hyponatremia can be classified according to the volume status of the patient as euvolemic, hypervolemic or hypovolemic:

- Euvolemic dilutional hyponatremia is most commonly found in the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and develops due to persistent detectable or elevated plasma AVP despite hypo-osmolality. The diagnosis is based on hypotonic hyponatremia, natriuresis, inappropriately concentrated urine, normal renal and adrenal function, and absence of oedema and volume depletion. Common causes of SIADH are neoplasia, central nervous system (CNS) disorders, lung diseases and a variety of drugs, e.g. carbamazepine, tricyclic antidepressants, or thiazide diuretics.

- In hypervolemic dilutional hyponatremia persistent non-osmotic AVP release is responsible for water retention, as it may be found in patients with liver cirrhosis or CHF. Water retention in excess of total body sodium occurs in patients with cardiac failure or liver cirrhosis. Although hyponatremia and hypo-osmolality would suppress AVP in normal subjects, inappropriately elevated AVP concentrations have been found in these patients. Arterial underfilling either due to decreased cardiac output or peripheral vasodilatation (e.g., in liver cirrhosis) increases baroreceptor mediated, nonosmotic AVP release and the renin-angiotensin-aldosterone system and sympathetic nervous system are activated. In fact, elevated AVP has been found in patients with CHF or cirrhosis.

- Hypovolemic dilutional hyponatremia was excluded from the clinical development program and will be a contraindication for satavaptan.

The current treatment of dilutional hyponatremia primarily involves fluid/water restriction, and judicious use of diuretics, in addition to the treatment of the underlying disease. Water restriction is an effective treatment of hyponatremia but is in practice associated with poor compliance. Most hyponatremic patients with neurological symptoms receive continuous infusion of hypertonic saline, since patients with SIADH do not respond to isotonic saline. Although this therapy is effective and life-saving, the use of hypertonic saline requires careful dosing because of the risk of osmotic demyelination syndrome.
Drugs such as lithium and demeclocycline have been administered (mostly on an off-label basis) based on their side effects on the renal collecting duct, making it unresponsive to AVP. However, both agents show inconsistent efficacy and may cause serious side effects; therefore, the use of these drugs is limited and not recommended for long-term treatment. Urea is an osmodiuretic that increases the osmolality of the plasma and thereby expands extracellular fluid volume. Urea is contraindicated in impaired renal function and liver failure. Moreover, due to its poor palatability repeated use is problematic.
The administration of an agent that selectively blocks ADH action in the kidney, thereby addressing a central mechanistic step in the generation and maintenance of dilutional hyponatremia, is a rational approach to therapy of the SIADH condition.
The ADH-mediated water retention contributes to the oedematous state in patients with liver cirrhosis or CHF. Fluid restriction is a basic therapeutic measure for this condition, but it is associated with low compliance. Aggressive diuretic regimens may even enhance dilutional hyponatremia by preferentially promoting the excretion of sodium. Blocking the ADH activity at the V2 receptor in this condition results in the elimination of the water (resulting in correction of the hyponatremia) and will allow a more effective treatment of ascites and oedema and a more effective utilization of diuretic therapeutic agents.

Hyponatremia is defined as the diminution of serum sodium concentration below 135 mmol/l associated with diminution of osmolality; and is classified as hypervolemic, hypovolemic, or euvolemic, based on the patient's volume status.

II.2 About the product

Satavaptan (SR121463B) is a selective vasopressin 2 (V2) receptor antagonist. V2 receptor antagonists act by blocking vasopressin receptors on the basolateral surface of the principal cells in the renal collecting ducts, causing a reduced expression of aquaporin-2 water channels. As a result, distal re-absorption of water in the collecting ducts decreases and free water excretion increases. Satavaptan exhibits high affinity for renal V2 receptors of several species including man and is highly selective for V2 receptors with an affinity ratio of 112 [V2 versus vasopressin 1a (V1a) receptors]. In vitro and in vivo, satavaptan behaves as a full V2 receptor antagonist without intrinsic agonist effects. Pharmacological studies in rats, dogs and

monkeys demonstrated that intravenous (IV) and oral (PO) administration of satavaptan increases urine volume, decreases urine osmolality and induces free water elimination. The effect of satavaptan is mainly aquaretic, and unlike with classical diuretics, no major changes in urine sodium excretion over 24 hours are observed.

Claimed indication:
The proposed indication of Aquilda is: "treatment of euvolemic and hypervolemic dilutional hyponatremia".

There is no paediatric development programme for this product.

Proposed posology:
Satavaptan is available as 5 and 25 mg film-coated tablets (scored for 25 mg) for oral administration. The proposed dosing regimen is as follows:

"The recommended starting dose is one 25 mg tablet to be taken once daily, with or without food. In patients with cirrhotic ascites, the recommended starting dose is one 5 mg tablet, once daily.

After achievement of stable serum sodium concentrations within normal limits, monitoring of serum sodium should be done periodically. Dose adjustments should be made based on patient sodium level.

The maintenance dose is 5 mg, 12.5 mg or 25 mg Aquilda once daily. In patients with cirrhotic ascites, the maintenance dose for Aquilda is 5 mg or 12.5 mg once daily.

Aquilda should be maintained as long as the underlying condition causing dilutional hyponatremia persists."

II.3 The development programme/Compliance with CHMP Guidance/Scientific Advice

The clinical development program of satavaptan in dilutional hyponatremia comprises the following studies:

Biopharmaceutics (5 studies)
Bioequivalence tablet-capsule (5 mg); bioequivalence tablet-capsule (25 mg); food effect (capsule); food effect (tablet).

Clinical pharmacology (23 studies)
- Pharmacokinetics and tolerability in healthy subjects: single ascending dose; multiple ascending dose; excretion balance, pharmacokinetics, metabolism; variability; effect on electrocardiogram (ECG) parameters;
- effect of age, gender, hepatic and renal impairment on satavaptan: age and gender; severe renal impairment; hepatic impairment in patients with liver cirrhosis;
- effect of other drugs on satavaptan: atorvastatin; erythromycin; ketoconazole; carbamazepine;
- effect of satavaptan on other drugs: omeprazole; simvastatin; metoprolol; warfarin; oral contraceptive; digoxin.

Overall, 615 subjects, including 11 patients with renal impairment, and 36 patients with hepatic impairment were enrolled in the clinical pharmacology studies.

Clinical efficacy studies (12 studies)
- 4 studies with primary objective of treatment of hyponatremia in patients with euvolemic dilutional hyponatremia (SIADH): DFI4488/LTS5066, EFC4489, and SFY5904;
- 2 studies with primary objective of treatment of hyponatremia in patients with hypervolemic dilutional hyponatremia associated with cirrhotic ascites: DFI4521 and LTS5634;
- 1 study mainly conducted in patients with hypervolemic dilutional hyponatremia not related to known SIADH or cirrhotic ascites , mainly associated with CHF: EFC5816;

- 4 studies in patients with hypervolemic dilutional hyponatremia associated with cirrhotic ascites or CHF, conducted with the primary objective of investigating the efficacy of satavaptan on the management of these diseases; effects on natremia in hyponatremic subpopulations were also evaluated: DFI4522, DFI5563, and LTS5635 (cirrhotic ascites) and DFI4510 (CHF).

In addition, 1 study (DFI4789) was conducted to examine the potential antihypertensive effects of satavaptan; no hyponatremic patients were included in this study.
In total, 1422 individual patients were included (12 clinical studies + 1 clinpharm study in patients with hepatic impairment). Due to the re-randomization schemes in some studies a total of 1091 patients were exposed to satavaptan and 458 patients to placebo in the clinical efficacy and safety studies.

No guidelines related to the sought indications exist.

Scientific advice:
No Scientific Advice was requested for the dilutional hyponatremia indication.

The development of the product in the paediatric population has not at all been commented upon by the Applicant. However, the conditions applied for may as well occur in children.

II.4 General comments on compliance with GMP, GLP, GCP

GMP
No issues during assessment of the dossier give any reasons for asking for a GMP inspection prior to authorisation.

GLP
The majority of the safety pharmacology studies were conducted prior to publication of the guidelines (ICH S7A and S7B). Therefore, the safety pharmacology studies were not conducted in compliance with GLP. However, study PAT0141 was conducted after the ICH S7B came into effect but has not been conducted in compliance with GLP. Exposure to satavaptan was not assessed at the time when the *in vivo* safety pharmacology studies were conducted.
Studies of general toxicity (pivotal single and repeat doses), carcinogenicity, genotoxicity, fertility, embryo-foetal development and pre- and postnatal development were performed in accordance with Good Laboratory Practices (GLP) regulations and in compliance with relevant regulatory guidelines. The only exception being the toxicokinetic (TK) studies as the TK measurements in the control group animals were not performed as described in the guideline (CPMP/SWP/1094/04). However, these studies were conducted before the guideline came into effect.

GCP
According to the Applicant, all studies were conducted in compliance with good clinical practice (GCP), as required by the International Conference on Harmonisation ICH E6 Guideline for Good Clinical Practice (01 May 1996), and in agreement with the Declaration of Helsinki. The studies were also carried out in accordance with standard operating procedures for clinical investigations and documentation of the Sponsor, and according to local legal requirements.

II.5 Type of application and other comments on the submitted dossier

This application concerns the centralised procedure (Regulation (EC) No 726/2004, Article 3(2)(a)). It is submitted in accordance with Article 8(3) in Directive 2001/83/EC for a new active substance.
Conditional approval, an approval under exceptional circumstances or an accelerated review are not requested.

Sanofi-aventis is seeking market authorization for 2 film-coated tablet formulations, 5 mg and a scored 25 mg tablet.

The quality documentation is in general acceptable and adheres to current ICH guidelines.

Non-Clinical:
The majority of the submitted study reports comprise a summary in tabulated format which facilitated the assessment. However, a few study reports had inconsistencies in data, missing pages or lacked raw data, which have led to several other concerns in the LoQ. In general, the electronic application was of high quality especially due to extensive use of hyperlinks. Furthermore, the use of scanned documents was sparse which facilitated the preparation of the assessment rapport.

A risk management plan has been submitted.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

There are no major objections on the chemical and pharmaceutical part of the dossier. Other concerns are raised and need to be addressed before final approval.
The questions are given in the List of Questions. A summary of the drug substance and the drug product sections is provided below.

Drug substance
Satavaptan phosphate monohydrate (SR121463B).
Its CAS name is Benzamide, N-(1,1-dimethylethyl)-4-[[*cis*-5'-ethoxy-4-[2-(4-morpholinyl)ethoxy]-2'-oxospiro[cyclohexane-1,3'-[*3H*]indol]-1'(*2'H*)-yl]sulfonyl]-3-methoxy-, phosphate, hydrate (1:1:1).

Satavaptan phosphate monohydrate is a white or almost white powder, very slightly soluble in water. The octanol:water logP is 1.82. Satavaptan phosphate monohydrate is not hygroscopic.

Information on the active substance is presented in the form of an ASMF. A detailed description of the manufacturing process is provided in the restricted part. Some concerns are raised to the documentation provided in the restricted part of the ASMF. They concern the manufacture and control of the starting materials used in the synthesis of satavaptan phosphate monohydrate. Critical steps are identified.

Information on the active substance is presented in the form of an ASMF. A detailed description of the manufacturing process is provided in the restricted part. The manufacturing process is a convergent route of synthesis which yields satavaptan. Then, a salt formation and isolation step gives satavaptan phosphate monohydrate. In relation to the starting materials, some information about the routes of synthesis, manufacturer, chemical characterisation, and specifications, including an impurity profile which is based on results of in-dept impurity studies are presented. Some concerns are raised to the documentation provided in the restricted part of the ASMF. They concern the manufacture and control of the starting materials used in the synthesis of satavaptan phosphate monohydrate. Critical steps are identified.
The manufacturing batch size is given as a typical batch size but a fixed batch size or interval, in accordance with the presented batch analysis data, has been laid down.

Satavaptan phosphate monohydrate has been satisfactorily characterised. It was confirmed that monohydrate A is the only polymorph present in the drug substance and drug product.

A summary of the impurities which may be present in satavaptan phosphate monohydrate is provided. The impurities are classified as potential organic impurities arising from the synthesis, including potential organic impurities with a structural alert presented by the molecule and organic impurities arising from degradation (based on stress stability studies), residual solvents and inorganic impurities.

The drug substance specification is considered adequate and includes all the relevant parameters, with the exception of assay, which should be tightened in view of the batch analysis data and stability results. All analytical methods have been satisfactorily described and validated in agreement with ICH guidelines.

Batch analysis data are provided for the drug substance batches used in toxicological studies, in clinical trials, in bioequivalence studies and in primary stability studies.

A long term stability study at 25°C/60% RH with three primary drug substance stability batches is ongoing. Data are reported for 18 months long term storage and 6 months accelerated storage. The drug substance is very stable at both storage conditions. However, an impurity was identified originating from the simulated packaging material used in the stability studies. The proposed re-test period of 30 months (12 months are extrapolated), when stored in double food-grade low density polyethylene (LDPE) bags closed by a tamper-evident plastic tie and placed in a cardboard drum, is considered acceptable. The re-test period should be continued to cover the entire re-test period. The data do not support the need for a specific storage condition, although a storage statement for the labelling "substance is sensitive of light and should be stored in the proposed container" should be included for the drug substance based on the results of the stress test.

Drug Product

The drug product is satavaptan phosphate monohydrate immediate release tablets, in two strengths, 25 mg and 5 mg (the strength of the tablet is expressed as base equivalent). For strength 25 mg the finished tablets are scored. The film-coated tablets will be packed in aluminium-aluminium blister packs.
The unit composition, visual appearance and pharmaceutical development of the satavaptan drug product have been comprehensively described and supported by experimental data. A discriminating dissolution method has also been developed as supportive tool for the pharmaceutical and manufacturing process development. A film-coating is applied on the tablets due to core tablet sensitivity to intense light.

The manufacture of the drug product takes place at Sanofi Winthrop Industrie, Tours, France. The tablets are manufactured using standard processes that include wet granulation, drying, lubrication, compression and film-coating. The manufacturing process and process controls have been satisfactorily described. Results obtained from in-process controls and finished product release testing demonstrates that the process is adequately controlled, reproducible and robust. The process parameters studied during the validation process are based on conclusions of development and scale-up studies. Satisfactory manufacturing process validation schemes are presented.

All excipients used in the manufacture of Aquilda tablets comply with the corresponding Ph.Eur, monographs. An in-house specification is provided for the coating powder Opadry® II white. All the single components of the film-coating however are pharmacopoeial. There are no excipients of human or animal origin except lactose monohydrate.

The finished product specification is in general in accordance with ICH guidelines and the Ph.Eur. monograph for film-coated tablets. The test for uniformity of dosage units/ content uniformity on film-coated tablets is not performed at release on routine manufacturing batches but instead replaced by content uniformity test on core tablets performed according to the method described in FDA draft guidance entitled "Powder Blends and Finished Dosage Units – Stratified In-process Dosage Unit Sampling and Assessment (October 2003 with revised attachments)". This is accepted. However, it is requested that content uniformity according to the method in described in Ph.Eur. 2.9.40 "uniformity of dosage units" is included in the specifications and must be complied with, if tested. The limits for specified degradation products and total degradation products have been requested to be tightened with respect to the actual levels seen. The analytical methods have been adequately described and validated in agreement with ICH guidelines with the exception of the validation of the dissolution method which should be supplemented with results from validation of repeatability and intermediate precision. Satisfactory certificates of analysis are provided for one pilot batch and two industrial batches of both tablet strengths demonstrating compliance with the proposed finished product specifications.

Satisfactory specifications are presented for the packaging components. Declarations of suitability for food application and compliance with Ph.Eur. are enclosed as well.

Three batches, one pilot scale and two industrial scale batches, of both strengths, have been placed on stability, in the aluminum-aluminum blister pack proposed for marketing. Data from 12 months long term storage at 30°C/65% RH and 6 months accelerated storage at 40°C/75% RH are reported. The results remain within specifications at all times and at both storage conditions. A slight formation of a degradation product can be observed, the degradation in the 5 mg tablet being more enhanced than in the 25 mg tablet. The Applicant proposes a shelf-life of 24 months (12 months extrapolated) with no special storage condition, which is considered acceptable. The on-going stability studies should be continued to cover the entire the shelf-life. Photostability testing has been carried out as well and the film-coated tablets are not photolabile.

III.2 Non clinical aspects

Pharmacology

Primary pharmacodynamics

Satavaptan is a selective vasopressin V_2 receptor antagonist. Marked species differences for AVP/OT analogues in terms of affinity and function (agonistic versus antagonistic effects) at AVP/OT receptors have been reported in the literature. However, no significant species-related heterogeneity in affinity or in aquaretic function of satavaptan was observed in the *in vitro* and *in vivo* studies conducted.

The Applicant has shown that satavaptan is a potent aquaretic agent in several *in vivo* studies in normal hydrated rats and one pathophysiological animal model of cirrhotic rats with impaired water excretions. It dose-dependently decreases urine osmolality and increases urine volume. Minor changes in sodium and potassium were noted mainly during the first 6 hours after administration, but no significant change was noted in urines collected over 24 hours. This aquaretic effect was dose-dependent, and occurred from oral doses of 25 µg/kg and 850 µg/kg in rats and dogs, respectively, and from IV dose of 30 µg/kg in monkeys. Using the same animal model (rat), variations in response to the same dose of satavaptan were observed. It can be explained by a large inter-individual variability, which has been reported for rats (and humans) in relations to AVP secretion, thirst, and the level of urinary concentrating activity.

G-protein-coupled receptors are known to desensitize and internalize upon prolonged and repeated exposure to receptor ligands. Tachyphylaxis has been reported for AVP V_2 receptor antagonists, e.g., OPC-31260. The Applicant has erroneously stated in the non-clinical overview that no tachyphylaxis (or desensitization) occurred during the repeated administration of satavaptan. Satavaptan showed clear signs of tachyphylaxis (decreased by around 40% on the 6^{th} day of treatment and remained stable thereafter) in the aquaretic effect during a 4-weeks repeat-dose study in normal rats and a 10-days repeat-dose study in a pathophysiological animal model of cirrhotic rats with impaired water excretions.

Secondary pharmacodynamics

The secondary pharmacodynamic data are explicitly supporting the high selectivity of satavaptan as the K_i value of satavaptan was at least 100-fold greater for the AVP V_2 receptor than for the other receptor systems tested. Satavaptan does not, or only weakly, interact at several non-related AVP/OT receptors, ion channels or enzymes when investigated *in vitro* (IC_{50} or K_i values $\geq$ 0.1 to 30 µM). Thus, it is unlikely that satavaptan will interact with a wide variety of receptor systems at concentrations similar to or slightly above the clinical plasma levels. However, satavaptan is expected to interact with extrarenal AVP V_2 receptors as it counteracted the effect of exogenous AVP V_2 receptor agonist on clotting factor release.

Safety pharmacology

Safety pharmacology studies indicated that satavaptan may cause adverse effects on the CNS, gastrointestinal and cardiovascular system. The effects on the renal system could be ascribed to the pharmacological effects of satavaptan. The CNS effects consisted of a decrease in motor activity, apathy, dyspnoea, decreased alertness among others, whereas the effect on the GI system was inhibition of gastric emptying.

Several observations were done in the cardiovascular safety studies. Inhibition of cardiac cation channels (hERG, K_V 4.3 and calcium channels) were observed *in vitro* at concentrations from 0.1 µM satavaptan (SR121463B) and upwards. The IC_{50}-value was 2.4 µM and around 6 µM for the calcium and hERG channel, respectively. Also *in vitro*, changes in action potential parameters were observed in NZ rabbit Purkinje fibers at 30 µM satavaptan (SR121463B) but not in Guinea pig ventricular myocytes (tested up to 10 µM). The safety margin for the therapeutic dose of 25 mg satavaptan is more than 57-fold with respect to the IC_{50}-values of the human cation channels expressed *in vitro*. However, as inhibition was observed at much lower concentrations (≥0.1 µM), satavaptan can influence human cardiac cation channel properties with a safety margin as low as 2.4-fold at the therapeutic dose of 25 mg. The Applicant has not addressed these findings in relation to the clinical observations. The Applicant is asked to elaborate.
In anesthetised dogs, administration of 3 mg/kg IV, 30 mg/kg ID or 100 mg/kg ID satavaptan did not induce major modifications of cardiovascular parameters. However, a transient decrease in mean blood pressure, increase in cardiac output and decrease in total peripheral resistance have been observed in anesthetised dogs following IV administration of 10 mg/kg. The Applicant has not reported any satavaptan-related effects on the electrocardiogram during the repeat-dose studies in dogs (study #TSA1048, TXC1031, TXC1076 and TSA1053). All the observed changes in the electrocardiogram did not suggest any satavaptan-related effects at the dosages tested (3, 10, 30 mg/kg IV and 2.5, 10, 40, 50, 250 mg/kg PO). Therefore, the cardiac effects observed in the toxicity studies were not considered to be toxicologically significant.

Pharmacokinetics

Absorption

A high interspecies variation was observed in the oral bioavailability (F) of satavaptan: rat (73%), dog (1.5%) and human (9%). According to the Applicant, the low oral bioavailability of satavaptan is due to significant first pass metabolism mediated mainly by CYP3A. Following oral administration, the C_{max} was reached after 0.5-2 hours in rats, 1-3 hours in dogs and 1.73-3 hours in humans. The terminal half-life ($T_{½}$) was significantly higher in human (14-17 h) than rat (2.04 h) and dog (2.46 h). The apparent volume of distribution of satavaptan after IV administration was 7.09 L/kg in male Wistar rats, 5.97 L/kg in male Beagle dogs, and 6.9-9.7 L/kg in humans (calculated using a 70-kg person). These values are up to approximately 10-fold the volume of the total body water in the respective species indicating some extravascular distribution.
Kinetics seems to be linear in rats, with no difference between male and female. Such a conclusion cannot be drawn in dogs from available toxicokinetic data (high variability and male/female differences probably related to weak bioavailability of satavaptan in this species).

Distribution

Plasma is a suitable matrix for monitoring of satavaptan, since [^{14}C]-SR121463B mainly distributed into the plasma fraction of blood in rat, dog and humans. The plasma protein binding of satavaptan was high (92-98%) and comparable to human (95-96%) for the species used in the toxicology studies (mouse, rat, rabbit and dog). Tissue distribution was studied in rats. The tissues with the highest concentration were well-perfused (lung, pancreas, and spleen) as well as those associated with metabolism and excretion (liver, kidney and gastrointestinal tract). Satavaptan displayed affinity for melanin-containing tissues. No change in distribution pattern of satavaptan was noted after repeated administration in comparison to single administration. Fourteen days after the last dosing, radioactive concentrations were still quantifiable in the adrenal glands, blood, colon, gut wall, liver, plasma, spleen and thyroid gland indicating a long tissue half-life of satavaptan in these tissues. Detection of radioactivity in the colon, the gut wall and the liver after 14 day post dosing could reflect reabsorption of radioactive biliary compounds. In both rats and rabbits, satavaptan-related radioactivity was observed in foetus and in foetal tissues with a foetus to placenta concentration ratios up to 0.81 in rats and up to 5.89 in rabbits. The highest foetal content was observed in the liver of the rat foetus and the gut of the rabbit foetus.

Metabolism

Large quantitative and qualitative interspecies variations were observed in the *in vitro* and *in vivo* metabolism of satavaptan. The major plasma metabolites detected in humans were SR122621 (8.5% of total

dose), SR121823 (16.9%) and SSR108434 (10.1%). In separate studies, SR121823 and SSR108434 were not detected in the plasma of mice, rats or dogs (study #MET0372, MET0295, MET0383 and MET0296). Although the relative plasma exposure was not determined, SSR108434 was, however, detected in the plasma of rats in study MIS0005. SR122621 constituted 5% of the total dose in plasma from mice (study #MET0372) and was detected without further quantification of the exposure level in the plasma from rats and dogs (study #MIS0005). The Applicant has characterised the pharmacological properties of SR122621 and SSR108434: 1) the two metabolites show similar selective and antagonist properties for the AVP V_2 receptor as the parent compound, 2) they are not expected to interact with a range of secondary receptors and enzyme at clinically relevant concentrations and 3) they are weaker inhibitors of the hERG current than satavaptan. The plasma exposure levels of SR122621, SR121823 and SSR108434 were not investigated in the pivotal non-clinical studies. The Applicant has determined the plasma exposure (AUC) of satavaptan, SR122621 and SSR108434 in 4-week repeat-dose toxicity studies conducted in CD1 mice, SD rats and Beagle dogs. However, the majority of the pivotal toxicity studies and the carcinogenicity study were conducted using the Wistar rat. Strain differences leading to a 10-fold difference in exposure has been reported between Wistar vs. SD rats. Only very low plasma exposure levels of the major human metabolites SR122621 and SSR108434 were obtained in the species applied for non-clinical testing. Furthermore, the safety of human metabolite SR121823 has not been evaluated. Thus, the Applicant is asked to elaborate on the safety of the three major human metabolites and a major objection has been raised.
According to data discussed in the clinical pharmacology assessment report, CYP3A was the primary isoform involved in the oxidative metabolism of satavaptan, SR122621 and SSR108434. Additionally, to a smaller extent, CYP2D6 was involved in the metabolism of satavaptan and SR122621, as well as CYP2C9 and CYP2C19 in the metabolism of SR122621.

Excretion
In CD1 mouse, Wistar rat and Beagle dog, the majority of the administrated dose of satavaptan was recovered in faeces regardless of the route of administration (PO or IV). Thus, the major route of excretion is presumably via the bile. The urine excretion was less than 8% in all studies. The majority of the dose (>80%) is excreted within the first 48 h. No major differences in excretion were observed due to sex or route of administration except for the amount of unchanged satavaptan excreted via faeces in the dog, which was highly affected by the route of administration. It is probably due to the low bioavailability of satavaptan in the dog (<2%), which then leads to a higher excretion of drug unchanged in faeces. Milk excretion of radioactivity was demonstrated in rats.

Pharmacokinetic drug interactions
An increase in liver weight and total CYP450 liver content was observed following repeated administration of satavaptan to dogs and rats, respectively. However, none of these findings were associated with an induction of CYP1A, CYP2B, CYP2C, CYP2E and CYP3A. A large number of studies have addressed the risk for clinical pharmacokinetic drug interactions and this issue is further discussed in the clinical pharmacology assessment.

Toxicology
Single-dose toxicity
Single-dose PO and IV administration of satavaptan gave rise to mortalities at doses of 500 mg/kg PO and 150 mg/kg IV in mice and of 1500 mg/kg PO and 50 mg/kg IV in rats. Gender differences in sensitivity were observed as females in general displayed toxicological signs (including death) at lower dosages than male animals. The maximum non-lethal doses for male and female mice were below 1000 mg/kg PO (the lowest dose tested) and 250 mg/kg PO, respectively, and 150 mg/kg IV and 50 mg/kg IV, respectively. The maximum non-lethal doses for male and female rats were 1500 mg/kg PO and 1000 mg/kg PO, respectively, and 50 mg/kg IV and 10 mg/kg IV, respectively.
Severe acute toxicological signs of central nervous system effects (decreased motor activity, ataxia, changes in respiration, tremors and convulsions) that in some cases lead to death of the animal were observed. All deaths were interpreted as compound-related and were observed 2-7 days after PO administration and usually immediately following IV administration.

In general, loss of body weight gain was observed the first 1-2 days following dosing, after which the animals gained weight in a normal manner. The loss of body weight can probably be ascribed to the pharmacological effect of satavaptan as an extremely high urine output combined with an inadequate compensatory thirst response can lead to dehydration of the animals.

Repeat-dose toxicity

The repeat-dose toxicity studies were conducted in mice, rats and dogs. Several of the toxicological observations could be ascribed to exaggerated pharmacologic effects of satavaptan, i.e., impairment of urinalysis and chemical chemistry results, lung lesions secondary to the effects on the gastro-intestinal system. Following PO administration, the target organs of toxicity were the liver for the mouse, rat and dog, the GI system for the rat and dog, bone marrow for the rat, and lymph nodes, spleen and thymus for the rat and dog.

Hepatotoxicity consisted of intrahepatic cholestasis, foamy macrophages and hepatocellular necrosis/atrophy. The safety margin to human use was 28- and 112-fold in the mouse and rat. In the dog, hepatocellular cytoplasmic inclusions were observed at a safety margin to human use of 8-fold. However, liver lesions were observed at a safety margin to human use of 515-fold. The Applicant is asked to discuss the clinical significance of the toxicological findings regarding the hepatocellular cytoplasmic inclusions. Full recovery from the satavaptan-related hepatotoxicity was not observed at the end of the 6-week recovery period in the 6-month pivotal repeat-dose study in the rat (study #TXC1030). The Applicant has investigated the recovery from the hepatic lesions in two additional repeat-dose toxicity studies (study #DIV0863 & DIV0815). In study DIV0863, satavaptan (175 or 275 mg/kg/day PO) were administrated to male Wistar rats for 71-79 days and observed during a recovery phase of 317-325 days. It was not possible to assess this study report as the Applicant has only filed a summarized report. However, several observations in this study are objects for clarification. Clinical signs of bad physiological conditions (dehydrated appearance, piloerection, hunched appearance etc.), in addition to continued pharmacological effects on urine excretion, were observed at the end of the recovery period. Furthermore, the summarized report states that the active metabolite SR122621 was detected in the liver up to nine months after recovery of oral dosing with satavaptan (275 mg/kg). These data suggests that the metabolite SR122621 accumulates in the liver during repeated oral dosing of satavaptan. Therefore, SR122621 may be responsible for the toxicological findings observed at the end of the recovery period. The Applicant is asked to supply the full study report of study DIV0863. Furthermore, the Applicant should elaborate on the accumulation of SR122621 and whether SR122621 or other metabolites may be responsible for the continued exacerbated pharmacological effects and the toxicological effects observed after 10 months post-dosing. The Applicant should also address the clinical significance of the accumulation of SR122621 or other metabolites upon repeated use of satavaptan in humans.

Acute/chronic inflammation of mucosa/submucosa of the stomach in addition to cystic and vascular degeneration of the stomach were observed in the rat and dog with a safety margin of 79- and 1920-fold, respectively, to the human use. Lymphoid atrophy/apoptosis of the submandibular and mesenteric lymph nodes, spleen and thymus were observed in the rat and dog at a safety margin of 56- and 79-fold in the rat and dog, respectively. These lesions are considered to be a stress-response related to toxicity and/or action of vasopressin at pituitary V_{1b} receptors, both pathways inducing the release of ACTH and adrenal cortical hormones. Haematopoietic atrophy/necrosis and pigmented macrophages were observed in rat bone marrow with a safety margin of 444-fold to human use. Due to the large safety margins, these findings are most likely not relevant to humans treated with satavaptan at a dose of 25 mg/day.

Increases in the incidence of renal pelvic dilation occurred for males and females rats that received 100 mg/kg/day for 6 months.

Genotoxicity and carcinogenicity

The genotoxicity of satavaptan has been studied with respect to gene mutations in bacteria and mammalian cells and chromosomal aberrations *in vitro* and *in vivo*. Additionally, test of DNA repair in mammalian cells *in vitro* have been conducted. Satavaptan showed no signs of genotoxicity in these studies. The exposure safety margins in this study was large (>1000) as compared to human therapeutic dose.

Satavaptan-related neoplastic microscopic findings (adenomas) were noted in the liver of male mice receiving 80 mg/kg/day PO satavaptan for 2 years. The higher incidence of these benign tumours can be

explained by the hepatotoxicity of the compound. The Applicant has claimed that benign tumours are often observed in mice treated for two years with compounds that cause hepatocellular hypertrophy. However, the Applicant has not provided evidence for this statement. Nevertheless, satavaptan is non-genotoxic with at least a 35-fold safety margin. Therefore, the mouse liver tumours are most likely not relevant to humans treated with satavaptan at a dose of 25 mg/day.
In the rat, no satavaptan-related neoplastic findings were observed. The NOAEL was 4 mg/kg/day PO, since a deceased in survival rates were observed at all doses above 4 mg/kg/day PO. The exposure level at 4 mg/kg/day was approximately 15-fold the expected human exposure at the maximal therapeutic dose of 25 mg/day.

Reproductive and developmental toxicity
Male and female fertility was not adversely affected in rats following treatment with doses of up to 175 mg/kg satavaptan. Therefore, the animal:human safety margin of satavaptan following PO administration is significantly large (>2500) with regards to male and female fertility. However, following IV administration, a reduction in the female fertility index was observed at doses of 2 mg/kg IV and above. Reduced weights of the male reproductive organs (seminal vesicle, prostate gland and epididymal weights) and alterations of the female oestrus cycle (oestrous cycle irregularities, reduced number of times in oestrus and elongated metestrus/diestrus phase) were observed at doses of 40 mg/kg PO and above. The safety margin of satavaptan following PO administration with regards to these effects is also substantial (>68). Thus, satavaptan is not likely to pose a risk to male and female fertility.
Embryo-foetal toxicity studies performed in rats showed a teratogenic potential for satavaptan. Malformations of digits (ectrodactyly, syndactyly and brachydactyly) and of the eyes (microphthalmia and anophthalmia) were observed. Decreased foetal weight and viability were also noted, as well as ossification delays, and visceral and skeletal variations. At the developmental NOAEL (10 mg/kg/day), safety margins amounted to at least 38. No foetotoxic or teratogenic effect was observed in rabbits at exposure levels 160-fold higher those achieved in humans. In a pre-and postnatal study, eye defects occurred for F1 animals thereby confirming previous results obtained in rats. Kidney malformations were also noted. Moreover, the onset of puberty, the development of male reproductive organs, and the overall fertility of F1 males and females were affected at 30 mg/kg/day and to a lesser extent, at 10 mg/kg/day. The NOEL for the F1 generation amounted to 3 mg/kg/day

In rabbits, satavaptan monophosphate monohydrate is a moderate ocular irritant, whereas no sign of dermal irritation was noted after application on intact and abraded skin. Evidence of potential to induce phototoxicity or photoallergy was not found in guinea pigs after oral administration. Oral treatment of rats with satavaptan for 28 days at doses up to 100 mg/kg/day did not affect specific parameters monitored in an immunotoxicity study.

Environmental risk assessment
The Applicant has based the Fpen calculation on an estimated maximum forecasted annual production of satavaptan in the first five years of marketing. The Applicant claims that this value has been based on epidemiological data on incidence for dilutional hyponatremia and marketing projections for the estimated percentage of those diagnosed with the indication expected to be treated with satavaptan. However, the Applicant has not accounted for this estimate and should therefore elaborate on the calculation of the Fpen. Otherwise, it is more appropriate to use the default penetration factor (Fpen= 0.01) for the calculation of $PEC_{Surfacewater}$.

III.3 Clinical aspects

Clinical pharmacology
The initial safety, tolerability, pharmacodynamics, and pharmacokinetics of satavaptan were investigated in studies using single (up to 200 mg) and repeated doses (up to 100 mg/day for up to 12 days) of satavaptan in healthy subjects, in a single-dose study in patients with severe renal impairment, and in a repeated dose study in cirrhotic patients with hepatic impairment. The maintenance dose applied for is 5 mg, 12.5 mg or 25 mg Aquilda once daily.

Pharmacokinetics
The current therapeutic options for treatment of dilutional hyponatremia are not satisfactory. Therapies that correct hyponatremia in a controlled, predictable manner will therefore represent an important therapeutic step forward in the treatment of hyponatremic patients. The use of satavaptan, a new, targeted agent that selectively inhibits the excess activity of vasopressin, is a rational approach to the treatment of this condition.

It was not possible from the application to determine, which of the studies concerning pharmacokinetics and pharmacodynamics that should be considered pivotal. All studies in healthy subjects contained a very limited number of participants with average 5-6 persons in each evaluated group.
Of the various intrinsic factors investigated (gender, age, race, weight, renal and hepatic impairment, SIADH), only increase in age and moderate to severe hepatic impairment resulted in a higher exposure.

Satavaptan pharmacokinetic characteristics in healthy volunteers

Process	**Parameters**	
Absorption	Steady-state C_{max} [Mean (SD), 25 mg]	7.16 (4.20) ng/mL
	Steady-state t_{max} [Median] [b]	1.75 – 3 h
	Steady-state AUC_{0-24} [Mean (SD), 25 mg]	59.1 (44.5) ng.h/mL
	Bioavailability [Mean (95% CI)]	9 (6 - 11)%
Distribution	Binding to plasma proteins (in vitro)	88.7 - 90.4%
	Volume of distribution (IV)	484 - 682 L
Metabolism	Enzyme	CYP3A
	Circulating metabolites [a]	SR122621, SSR108434
Elimination	Terminal half-life	14 - 17 h
	Plasma clearance (IV)	52 - 67 L/h
	Fecal recovery	89% of the administered dose
	Urinary recovery	<3% of the administered dose
Others	Time to steady-state [Median] [b]	≤ 4 days
	Accumulation	<2-fold
	C_{max} ratio for a dose ratio of 2.5 [b]	3.4- to 5.8-fold
	AUC ratio for a dose ratio of 2.5 [b]	4.5-fold

[a] relevant metabolites based on a combination of high affinity for renal V_2 receptors in vitro and relative plasma exposure in vivo;
[b] 10 to 25 mg.

These findings reveal the following problems:
Satavaptan was found to be highly protein bound to human plasma. This is of upper most importance and should be included when discussing volume of distribution, accumulation of drug, pharmacokinetic models (1-compartment vs. multiple compartments), and final t½.

The desired indication for Aquilda is *Treatment of euvolemic and hypervolemic dilutional hyponatremia*. Satavaptan was fully not characterised in this group of patients. It is believed that some of the cirrhotic patients with ascites fulfil this criterion; however the study was not conducted in order to explore clinical pharmacology in the target population.
Furthermore, the pharmacodynamic effects were only assessed after repeated oral doses for up to 12 days, which must be characterized as rather short time considering the application in diseases as cirrhotic ascites and severe renal impairment.

The pharmacokinetic (PK) profile of satavaptan was characterized by: a rapid absorption with P-glycoprotein (P-gp) mediated transport, a large distribution with high and non-saturable plasma protein binding (mainly to albumin), high first pass metabolism mediated by CYP3A and elimination, mainly by the liver.
Details are presented hereafter; the key points pertained to the following PK assessment:

Absorption

The Applicant claims that satavaptan is a BCS class 2 compound with low solubility and high permeability. In vitro permeability has been convincingly demonstrated in the Caco-2 cells study, at saturating conditions for transport proteins and with mannitol and testosterone as low and high permeability controls, respectively. However, the absolute bioavailability of satavaptan is low (9%, study TDU3434) which appears in contradiction with the definition of a high permeable compound characterized by an in vivo absorption greater than 85 or 90%.

The implication of P-glycoprotein as transport protein is correctly established and this would require to document specific drug-drug interactions with other BCS class 2 compounds like cyclosporine, a well known critical dose drug.

Bioavailability

With intra-individual variability > 30% for Cmax and AUC, satavaptan can be considered as a highly variable drug. Bioequivalence between the capsule and the solution is not shown regarding Cmax but with only 16 subjects included, the statistical power of this study was not sufficient for a highly variable drug. However, this point is not an issue for formulations not intended to reach the market.

TDU3434 was a single intravenous ascending dose tolerability study of SR121463B in healthy male subjects conducted as a single-center, double-blind, placebo-controlled, randomized, ascending dose, parallel group study designed to assess the tolerability of satavaptan following single IV (bolus) doses of 1, 5, 10, 25, 50 and 100 mg, and to assess the preliminary pharmacokinetic and pharmacodynamic profile of the drug in healthy male subjects and the bioavailability. For the 10 mg group, a second period was carried out with a 50 mg single oral dose to assess the absolute bioavailability of the product. In each dose group, 8 healthy male subjects received the study drug (6 active, 2 placebo) in a fasted condition. Blood samples were collected at specified time points over 48 h after the IV bolus infusion/oral administration. (Plasma concentration observed at the end of an IV infusion (C_{end}), AUC_{0-24}, area under the plasma concentration versus time curve extrapolated to infinity (AUC), $t_{1/2z}$, volume of distribution at the steady state (V_{ss}) and plasma clearance (CL) of satavaptan were determined by non-compartmental pharmacokinetic analysis Results are summarized in the table below:

Mean (SD) SR121463 Pharmacokinetic Parameters

Dose (mg)	C_{end} (ng/mL)	AUC_{0-24} (ng.h/mL)	AUC (ng.h/mL)	$t_{1/2z}$ (h)	V_{ss} (L)	CL (L/h)
1	22.3 (35.0)	17.2 (3.24)	19.9 (3.83) [a]	10.4 (1.01) [a]	487 (123) [a]	51.9 (11.0) [a]
5	152 (257)	85.0 (16.7)	96.8 (19.7)	13.7 (3.55)	506 (107)	53.2 (9.33)
10	519 (142)	170 (7.16)	194 (10.5)	13.4 (2.23)	484 (47.1)	51.7 (2.79)
25	514 (357)	340 (35.9)	379 (47.7)	11.4 (2.38)	564 (26.8)	66.8 (8.16)
50	1250 (1410)	708 (151)	794 (172)	11.6 (1.47)	599 (187)	65.8 (16.0)
100	1890 (2430)	1320 (115)	1530 (177)	12.3 (2.85)	682 (127)	66.0 (7.63)

Mead (SD) SR121463 Pharmacokinetic Parameters after Oral Administration (50 mg Dose) and i.v. Administration (10 mg Dose)

Dose (mg)	Route	C_{end} (ng/mL)	C_{max} (ng/mL)	t_{max} [f] (h)	AUC_{0-24} (ng.h/mL)	AUC (ng.h/mL)	$t_{½z}$ (h)
50	Oral	NA	14.0 (5.04)	1.5 (1.3)	75.7 (22.3)	89.7 (25.5)	14.6 (3.2)
10	i.v.	519 (142)	NA	NA	170 (7.16)	194 (10.5)	13,4 (2.23)

The absolute bioavailability, determined after a single oral 50 mg dose administration of satavaptan compared to IV administration of 10 mg, was 9% (95% CI: 6-11) (TDU3434). In addition, after a 50 mg/70 µCi single oral dose of [$^{13}C/^{14}C$]-satavaptan, the fraction of the dose absorbed could range from

55 to 99%. The low oral bioavailability of satavaptan is due to significant first pass metabolism mediated mainly by CYP3A.

Since many of the pharmacokinetic parameters are dose dependent (ex volume of distribution, AUC, $t_{½}$), the bioavailability cannot be assessed by extapolation of data. Futhermore, data from two groups of 6 healthy subjects cannot be considered sufficient to determine bioavailability.

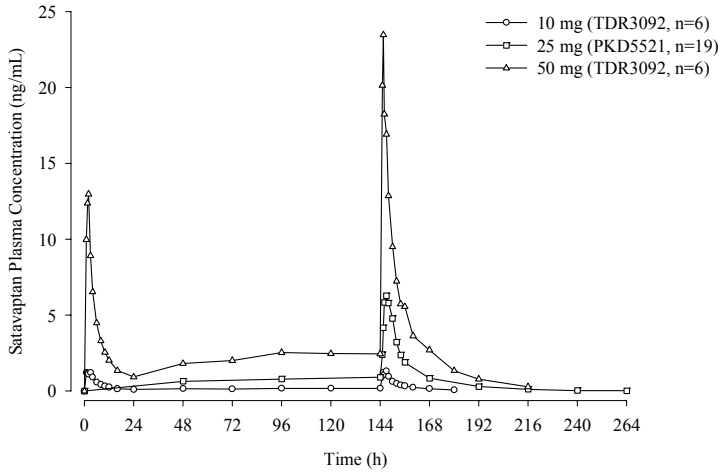
Bioequivalence

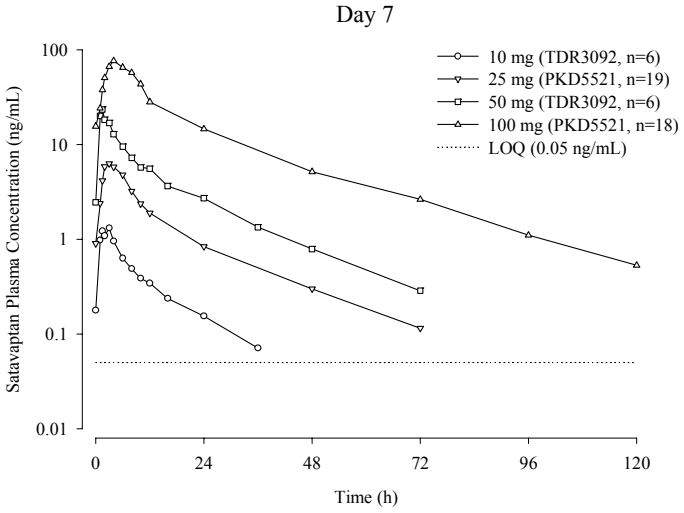
Two pivotal bioequivalence studies have been conducted to demonstrate the bioequivalence between the tablet (5 mg and a scored 25 mg) and capsule formulation in the fasted state. Bioequivalence between the final tablet formulation and the capsule used during the great majority of the clinical program has been adequately demonstrated. In both studies, large inter-individual variability was confirmed with values over 80% for C_{max} and 120% for AUC in study BEQ 5781, decreasing to 70% for both parameters in study BEQ 5782. Unfortunately, no intra-subject variability estimated from ANOVA-CVerror was given. The use of stable isotope in bioequivalence studies is known since the 1980s. Convincing arguments that the pharmacokinetic analysis of satavaptan is not modified by any isotopic effect are needed, considering the drop in inter-subject variability between the two studies.

Multiple dosing

Following once-daily dosing with satavaptan, statistical analysis on C_{trough} showed that satavaptan individual steady state is reached at a median time of 4 days or fewer within the proposed therapeutic dose range (3 to 4 days for 10 to 25 mg) and slightly longer at higher doses (6 to 7 days for 50 to 100 mg) after the first administration (based on data from TDR3092, INT4919, and PKD5521). There was a modest accumulation of less than 2-fold for C_{max}, and for AUC_{0-24} within therapeutic range, following repeated dosing. The accumulation ratio was slightly higher at higher doses (2.19 for 50 mg; 3.61 for 100 mg) for AUC_{0-24}, but not for C_{max} (TDR3092). As the half-lives of the relevant metabolites (SR122621 and SSR108434) or the total radioactivity do not exceed that of satavaptan, a preferential accumulation of other drug-related material is unlikely

Day 1 (0-24 h) to Day 7 (144-168 h) full PK profiles; C_{trough} between Day 1 and Day 7





Mean (SD) plasma concentrations of satavaptan in healthy subjects following repeated once daily dosing

The accumulation of drug is not considered sufficiently described taking into account the small number of participants in each group. It cannot be ruled out that increasing the number in each group will result in statistical differences in the valuated parameters. More data characterizing drug accumulation in healthy subjects as well as in the target population will have to be provided.

Influence of food

In the efficacy/safety studies, the patients were instructed to take the drug either between 8 AM and 9 AM under fasting conditions, in the morning before breakfast, or in the morning. Based on the minimal effect of food on satavaptan total exposure and the drug administration conditions in efficacy/safety studies, the Applicant recommended that the tablet be taken in the morning without regard to meals.

The influence of food on the rate of absorption is different between the capsule (+21% in C_{max}) and the tablet (-15% in C_{max}), while a similar 17-18% increase is observed on the extent of absorption. The tablet being the to-be-marketed formulation, we could be tempted to agree that satavaptan can be taken with or without food, as long as there is no correlation between peak value and the clinical response. The Applicant should discuss this point while adding for study ALI 5949 a non parametric statistical bioequivalence analysis on the constant t_{max}.

Distribution

Satavaptan is a highly protein-bound drug through a permissive binding since its volume of distribution is fairly large, around 8 l/kg on average. Then, the risk of drug-drug interactions due to protein displacement is very unlikely. The Applicant has also validated a technique to measure plasma protein binding of satavaptan and metabolites SSR108434 and SR122621 after ultrafiltration from ex vivo samples collected with EDTA as anticoagulant. However, the role of these two metabolites in the global mechanism of action of satavaptan remains unclear. One study (please find details in the table above) described the assessment of Volume of distribution following a single IV dose administration. The volume of distribution at steady state was determined to be between 484 L to 682 L.

It seems, from the sparse data obtained from one single study designed to provide preliminary pharmacokinetic assessment, that the volume of distribution is increased in a dose- dependent way. The data was obtained from healthy volunteers. Thus the current data on volume of distribution are not considered sufficient.

It is not described whether satavaptan distributes according to a one-compartment model or a model containing several compartments. According to the increasing t½ with multiple dosing and the large volume

of distribution the latter seems likely. The dossier lacks data on relationship between metabolism and serum concentration. It is thus not possible to determine whether the hepatic conversion follows a 0.-order or 1.-order kinetics. This determination is considered crucial.

Excretion

The elimination of satavaptan can be considered sufficiently well characterized, even if in the mass balance study, almost 10% of the administered radioactivity has not been recovered. Considering the very small daily amount of radioactivity excreted by day 6 post dose, one can postulate the existence of a deep compartment in slow equilibrium with plasma, in accordance with the large volume of distribution of satavaptan. The fecal route is almost the sole elimination way for satavaptan, either as unchanged drug or under various metabolites formed in the liver. The renal route is only anecdotal.

Metabolism

The metabolite characterization is far from being clearly described. Despite the great analytical difficulty to obtain reliable qualitative and quantitative measurements, metabolites SSR108434 and SR122621 declared elsewhere as active compounds are not even quoted in study BEX 3826. The Applicant should carefully review the data supporting the efficacy of these two metabolites since at this stage; it seems premature to deliver such information in section 5.2 of the SPC.

It is agreed that satavaptan should be classified as a high hepatic clearance drug. However, the dossier lacks data on relationship between metabolism and serum concentration. It is thus not possible to determine whether the hepatic conversion follows a 0.-order or 1.-order kinetics. According to the increasing t½ with multiple dosing and the large volume of distribution the latter seems likely. This determination is considered crucial since a clear dose-concentration relationship has not been determined.

From in vitro experiments, CYP3A and CYP2D6 are mainly involved in the oxidative metabolism of satavaptan. If satavaptan has no inducing potency, it can inhibit various CYP in the micromolar range, mainly CYP2B6, CYP2C9 and CYP2C19. Following therapeutic regimen with satavaptan 25 mg, peak plasma values are in the nanomolar range. Assuming an important hepatic first pass effect, micromolar concentrations in hepatocytes may occur which justifies the various interaction studies conducted by the Applicant.
Since satavaptan is metabolized by polymorphically distributed CYP2D6, the relation between dose and plasma concentrations may theoretically be altered in either poor or ultra extensive metaboliser phenotypes. However, CYP3A being much more involved than CYP2D6 in satavaptan disposition, pharmacogenetic assessments are probably not an issue.

Dose proportionality

For a 2.5-fold increase in dose from 10 mg to 25 mg (within the recommended dose filed for), C_{max} and AUC_{0-24} values increased in a more than dose proportional manner In this dose range, C_{max} values were 3.4 times higher (90% CI: 2.65, 4.35) after single dose and 5.84 times higher after repeated doses. AUC values were 4.5 times higher after single dose administration. **The Applicant states that this supra-dose proportionality after oral administration is probably related to a saturation of the presystemic first pass metabolism with increase in dose.** This supra-dose proportionality was confirmed in the population pharmacokinetic analysis where dose was found to be a covariate affecting satavaptan availability. It must therefore be considered upper most important to evaluate the dose proportionality in the patient population since it cannot be ruled out that the speculated saturation is reached earlier in this group.

Gender and age

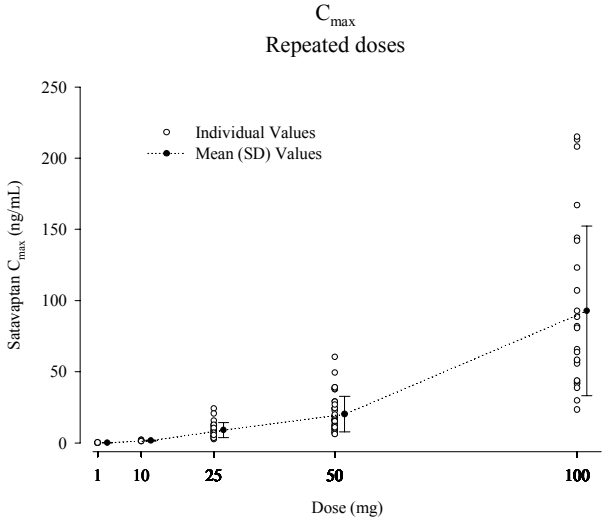
PKM3814 (Effect of age and gender on pharmacodynamic and pharmacokinetic properties of a single oral dose of SR121463B) was a single-center, open-label study in 4 parallel groups of 12 subjects (young males, elderly males, young females and elderly females), designed to assess the effect of age (≥65 years) and gender on the pharmacodynamic and pharmacokinetic profiles of satavaptan after a single 25 mg oral dose administered in fasted conditions. Water intake was controlled (1800 mL at specific times on Day –1 and Day 1). Blood samples were collected at specified time points over 48 hours postadministration.

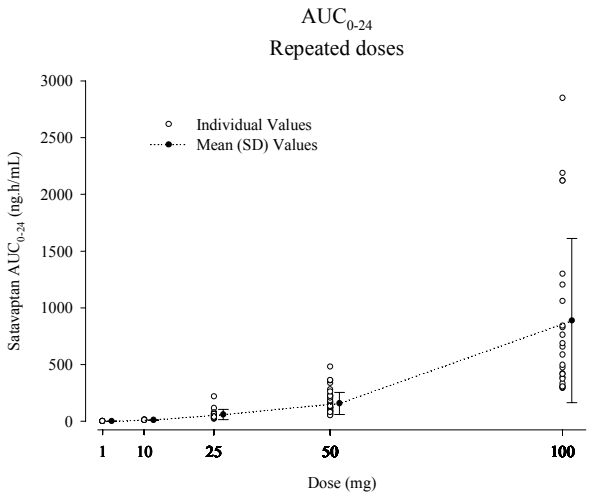
C_{max}, t_{max}, AUC_{0-24}, AUC and $t_{1/2z}$ of satavaptan were determined by noncompartmental pharmacokinetic analysis. The effect of age and gender was assessed on the pharmacodynamic parameters: urinary volume, urinary flow rate, free water clearance, thirst effect (VAS score), plasma and urine osmolality, plasma and urinary electrolytes, and hormonal assessment (AVP, plasma renin activity, and aldosterone). Plasma concentrations of satavaptan appeared rapidly in the systemic circulation following oral administration: median satavaptan t_{max} was between 1 and 2 hours. Age had a small effect on t_{max} values, with satavaptan t_{max} values slightly longer in young subjects (median t_{max} for young subjects was 2 hours, compared with 1 hour for elderly subjects). Additionally, gender and age appeared to have a small effect on $t_{1/2z}$ values, with satavaptan $t_{1/2z}$ values longest in elderly female subjects (mean value was 16.4 hours) and shortest in young male subjects (mean value was 10.9 hours).

Age and gender seem to influence on pharmacokinetics

Time dependency

In addition to dose dependency, the pharmacokinetics of satavaptan display an important time dependency. Once again, the largest differences are observed at higher doses (over 50 mg) that are not supposed to be given to target populations. However, differences are observed within the dosing range applied for as illustrated in the figures below. Furthermore, since it has not been fully determined whether the elimination follows a 0-order, 1-order, or more likely a combination, small differences in drug exposure as could be the result of a decline in serum-albumin could result in non-expected increases in serum-concentration of drug, which again would be even more increased due to the time dependency. This is considered of uppermost importance and should be elucidated. Results from study TDU 3091 and study TDR 3092 on day 1 being very consistent, and the steady-state being reached by day 4-6, it does not seem an issue to further document this point. However, the importance of dose and time dependency of the pharmacokinetics of satavaptan in conjunction with the putative role for active metabolites SSR108434 and SR122621 should be discussed.





The described differences were observed after 7 days dosing. It is not determined whether a further increase in serum-concentration will be seen after longer time exposure. Taking into account that the drug will be given as treatment in chronic diseases this is another very important issue.

Inter intra variability

This point has been already discussed in bioavailability section. Satavaptan displays a fairly large variability in healthy subjects, with inter-subject CV around 50% and intra-subject CV around 30%. A variability of the same magnitude in target population is observed (see next section).

PK in target population

- Following a single 50 mg oral dose in cirrhotic patients with ascites, the kinetic profile is similar to that observed in healthy subject receiving a single 100 mg oral dose. Knowing that satavaptan undergoes a high first-pass metabolism followed by an almost exclusive elimination by the biliary route, such a result is not unexpected. The difference could be even larger at steady-state. Again, the recommended posology with maintenance dose of 12.5 mg daily is expected to minimize the kinetic modifications due to dose and time dependency as well as mild to moderate liver insufficiency; however, this has not been shown. Special note: for spironolactone, the plasma determinations of canrenone and thiomethyl spironolactone were made by MDS Pharma – Canada during the period 2000-2004, the FDA has significant concerns about the validity of several reported studies.

- The pharmacokinetics of satavaptan in patients with hepatic impairment has been documented in 3 clinical efficacy/safety studies, where 310 patients with cirrhotic ascites, most with a Child Pugh score in class B or C, received 5, 12.5 or 25 mg of satavaptan. In addition, 28 patients with cirrhotic ascites received 30 to 75 mg of satavaptan in a preliminary efficacy study. The data from these studies were used in a population pharmacokinetic analysis, please see below. Moderate and severe hepatic impairment resulted in a 2.5-fold higher C_{max} and a 4.0-fold higher AUC, compared to patients with mild or no hepatic impairment (POH0092).

- The Applicant has submitted a high-quality population PK analysis. The report contains the required information regarding the goals of the study, the origin of data to be analyzed, the software and method, the procedures for building the pharmacostatistical model and the covariate model. In particular, the model evaluation is based on a comprehensive use of GOF plots, data splitting (building dataset and validation dataset), outlier selection and bootstrapping techniques. Overall, based on these results, the Applicant concluded as follows:
  - Satavaptan PK in patients was not dependent on gender, race, weight, body mass index, BSA, patient type (with or without SIADH), level of renal impairment, and concomitant administration of weak CYP3A inhibitor, diuretic or anti-acid;

- The following were identified as significant covariates affecting the pharmacokinetics of satavaptan: CYP3A inducer, dose, hepatic impairment, and age.

However, despite the quality of the methodology, this population PK analysis is penalized by a large variability so that estimates are still subject to great uncertainties. The included covariates only explained a rather small part of the inter-individual variability in the pharmacokinetics of satavaptan, reducing the CV on CL/F from 78.5 to 61.2% and that of V2/F to106% to 88.9%. From study TDU 3434, the absolute bioavailability of satavaptan was 9% (CL = 51.9 – 66 l/h and Vss = 484 – 682 l). By comparison, the calculation of F from the estimates CL/F (535 l/h) and V2/F (2460 l) in a young patient with normal liver function gives a similar estimate of F in the range [9.7 – 12%] from CL but in the 2-fold range [19.7 – 27.7%] from V2. Among the subjects patients included in the dataset, a great majority was receiving a 50 mg dose of satavaptan. Knowing the dose and time dependency of the pharmacokinetics, this may have lead to a large amount of variability in the model. Since the recommended maintenance dose is 25 mg, causing probably less variability in the pharmacokinetics, the use of this population PK model for simulations could be problematic. This point should be further discussed, including the putative role of active metabolites (not taken into account in this model) and it should be clearly indicated whether the submitted population PK model can support dosing recommendations.

Special populations

Although satavaptan has a high hepatic clearance and plasma protein binding that could result in renal impairment having an effect on its pharmacokinetics, POP5948 showed that the systemic exposure (C_{max}, AUC_{last}, AUC) of satavaptan in patients with severe renal impairment was not appreciably different (mean values ≤1.16-fold) from healthy subjects following a single 50 mg dose. Mean unbound fraction of satavaptan appeared to be unaffected by renal status. Unbound C_{max} and AUC were similar in healthy subjects and in patients with renal impairment. Overall, severe renal impairment had no appreciable effect on the single dose pharmacokinetics of the drug. Nevertheless, satavaptan is highly metabolized by the liver and therefore impairment of hepatic function modifies the pharmacokinetics of the drug.
Age had a small effect on t_{max} values, while age and gender appeared to have a moderate effect on $t_{1/2z}$ values. Satavaptan clearance was dependent on age with lower clearance as age increases. No dose adjustment based on gender and age is required, following the assumption of the Applicant. This discrepancy should be discussed.
The pharmacokinetics of satavaptan has not been evaluated in paediatric subjects.

Impaired hepatic function increases C_{max} and AUC. No data on $t_{½}$ or plasma concentration are given. Since patients with impaired liver function often have a substantially lower protein level it cannot be ruled out that the serum concentration of satavaptan in this patient group will reach a level resulting in increased risk for adverse events.

Interactions

The Applicant provided *in vitro* and *in vivo* studies that assessed the interaction profile of satavaptan.

In vitro

In vitro studies indicated that satavaptan and its two metabolites, SR122621 and SSR108434 were primarily metabolised by CYP3A. Satavaptan was also found to be a P-gp substrate.
In vitro, satavaptan did not show potential to induce CYP450 isoenzymes at relevant clinical concentrations in human hepatocytes.

In vivo

All drug-drug pharmacokinetic interaction studies were conducted in healthy subjects using open-label and crossover design. These interaction studies were performed at one of the 2 doses of satavaptan considered to be the anticipated therapeutic dose of satavaptan at the time of study (25 and 50 mg), in fasted

conditions (except for the metoprolol study, where administration was in fed state), up to steady-state conditions, and using the usual therapeutic dose/regimen for the other drugs.

The effect of the other drugs on satavaptan was evaluated at repeated, currently used doses of the other drugs and a single dose of satavaptan in therapeutic range.
Tested drugs were: atorvastatin, erythromycin, ketoconazole, carbamazepine and omeprazole.

The effect on satavaptan on other drugs was assessed at repeated 25 or 50 mg doses once daily for 7 to 12 days and single or repeated doses of the other drugs.
Tested drugs were: digoxin, warfarin, simvastatin, metoprolol, omeprazole, carbamazepine and oral contraceptives steroids.

CYP3A inhibitors and inducers were expected to affect satavaptan in vivo. Consistent with *in vitro* data, a 12-fold and a 32-fold increase in satavaptan exposure, was observed when erythromycin and ketoconazole were respectively co-administered.

The lack of CYP3A induction by satavaptan was confirmed *in vivo* based on no change in urinary 6-β hydroxycortisol/cortisol ratios after repeated satavaptan doses in the study with an estroprogestative.

Summary of the results of drug-drug interaction studies

Mechanism	Interacting Drug (Dose)	Substrat (Dose)	Substrat Ratio (90%CI) [a]	
			C_{max}	AUC
CYP3A inhibition	Atorvastatin (80 mg OD)	Satavaptan (25 mg OD)	0.93 [0.80, 1.08]	1.05 [0.92, 1.20]
	Erythromycin (500 mg TID)	Satavaptan (10 mg)	**7.8 [5.7, 10.7]**	**11.8 [8.7, 16.2]**
	Ketoconazole (400 mg OD)	Satavaptan (50 mg)	**13.4 [9.6, 18.8]**	**31.7 [22.2, 45.3]**
CYP3A induction	Carbamazepine (200 mg BID)	Satavaptan (50 mg OD)	**0.10 [0.09, 0.12]**	**0.07** [b] **[0.06, 0.09]**
pH effect	Omeprazole (20 mg OD)	Satavaptan (50 mg OD)	**0.65 [0.53, 0.80]**	**0.80** [b] **[0.66, 0.96]**
Effect of satavaptan on other drugs				
CYP3A inhibition	Satavaptan (25 mg OD)	Simvastatin (40 mg)	**1.88 [1.51, 2.35]**	**1.73** [c] **[1.45, 2.05]**
	Satavaptan (50 mg OD)	Carbamazepine (200 mg BID)	0.89 [0.84, 0.93]	0.89 [d] [0.86, 0.93]
		Ethinylestradiol (0.03 mg)	1.14 [1.04, 1.26]	1.00 [b] [0.87, 1.15]
		Levonorgestrel (0.15 mg)	0.96 [0.90, 1.03]	1.05 [b] [0.98, 1.12]
CYP2C9 inhibition	Satavaptan (25 mg)	S-warfarin (30 mg)	0.96 [0.90, 1.02]	1.15 [1.09, 1.22]
		R-warfarin (30 mg)	0.93 [0.87, 1.00]	1.06 [1.02, 1.10]
CYP2C19 inhibition	Satavaptan (50 mg OD)	Omeprazole (20 mg OD)	**1.21 [0.93, 1.57]**	**1.23** [c] **[1.03, 1.46]**
CYP2D6 inhibition	Satavaptan (50 mg OD)	Metoprolol (100 mg)	0.95 [0.84, 1.07]	1.01 [0.91, 1.11]
Pgp inhibition	Satavaptan (50 mg OD)	Digoxin (0.25 mg OD)	**1.33 [1.26, 1.40]**	1.19 [b] [1.15, 1.23]
Coadministered drug	Satavaptan (50 mg)	Spironolactone (150 mg OD) [Canrenone]	1.01 [0.96, 1.07]	1.04 [b] [1.00, 1.08]
		Spironolactone (150 mg OD) [7-α-thiomethyl) spironolactone]	1.05 [0.97, 1.15]	1.11 [b] [1.01, 1.21]

BID: twice a day; OD: once a day; TID: three times a day

[a] (coadministered treatment)/(reference treatment alone) ratio;

[b] AUC_{0-24};

[c] AUC_{last};

[d] AUC_{0-12}.

The in vitro and in vivo interactions studies performed by the Applicant have been satisfactorily addressed provide a good assessment of the satavaptan interaction profile.

The metabolism of satavaptan can be summarised as follows:

1) It appears to be a substrate of CYP3A4 with a close, although higher affinity, than that of statins.
Hence, atorvastatin does not modify its exposure whereas it increases that of simvastatin almost two-fold.
On the other hand, its metabolism is strongly affected by CYP3A4 inhibitors: erythromycin increases satavaptan exposure in an important manner (AUC x 12) and, as expected, ketoconazole, one of the most potent CYP3A4 inhibitor, increases its AUC by 32-fold.
Consequently it does not seem to be a CYP3A4 inhibitor, as shown by the lack of variations of carbamazepin plasma levels.
Also not surprising is the huge decrease of satavaptan concentrations when given together with carbamazepin, a strong CYP3A4-inducer.
This is in line with Ki values and other in vitro results showing that CYP3A4 is almost entirely involved in satavaptan metabolism.

2) Satavaptan does not appear to be a CYP3A4 inducer as shown by the lack of variation of the 6ß-OH-cortisol/cortisol ratio and the fact that ethinylestradiol, although partially metabolised through CYP3A4, does not vary either.

3) Satavaptan does not inhibit CYP2D6 in vivo. The possible but marginal involvement of CYP2D6 in its metabolism does not warrant a specific study with a CYP2D6 inhibitor.

4) In vitro studies have shown that satavaptan could be a P-gp inhibitor (IC50 = 1,7 µM). In vivo, this effect is only significant on digoxin C_{max}, which rather indicates an effect on digoxin absorption rather than on its renal elimination. The clinical consequences, if any, may remain mild.
The Applicant should however perform a study with a probe P-gp inhibitor in order to assess a possible effect on satavaptan overall exposure.

5) The study with omeprazole indicates a slight although significant decrease (20%) in AUC exposure of satavaptan. We agree with the Applicant that this may be due to the omeprazole-induced pH variation since it notably impacts on satavaptan C_{max}, with a mean 35% decrease; however, omeprazole is known to be a CYP2C19 inducer.
The Applicant should discuss the possibility of an inducing effect of omeprazole on satavaptan metabolism. If possible, half-life values, even truncated over the 24h-assay period, should be provided in order to allow a comparison of satavaptan clearance to be made when given alone or in combination with omeprazole.

6) Given the Ki values of satavaptan on CYP2C19, the Applicant should discuss the possibility of another mechanism of action than the proposed CYP2C19 inhibitory process that could explain the slight increase of omeprazole concentrations.

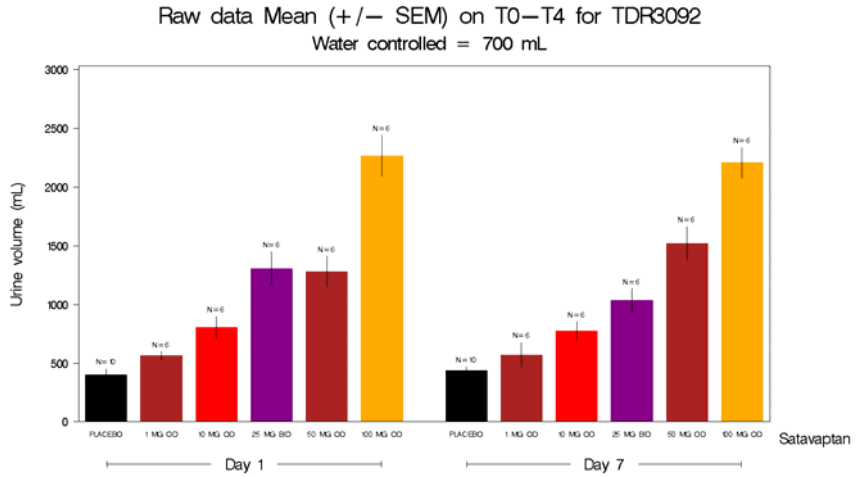
7) Of note, contrary to what is mentioned in the above-table, the R-enantiomer of warfarin is not metabolised through CYP2C9 but CYP1A2.

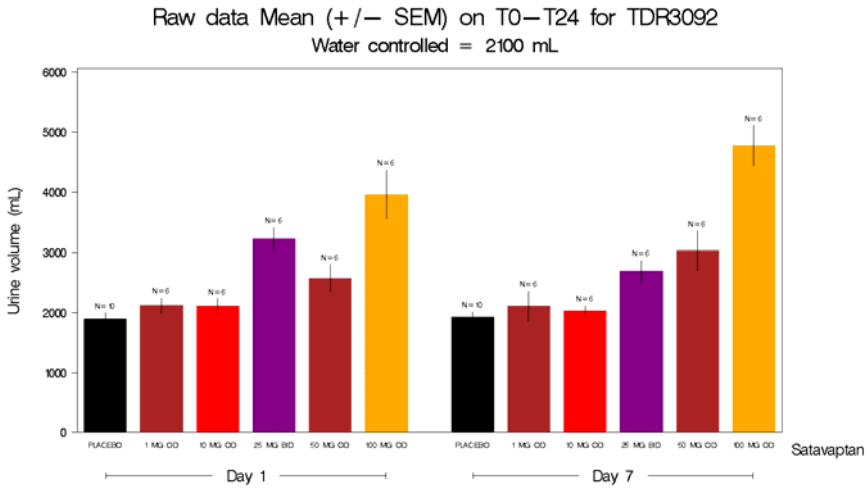
Pharmacodynamics
Mechanism of action
Vasopressin receptor antagonists act by blocking vasopressin-2 receptors in the collecting tubules of the kidney and subsequently the insertion of specific aquaporin water channels (AQP-2), preventing distal reabsorption of water and inducing free water excretion.
Considering the mechanism of action, the selective action of satavaptan on V2 receptors could be of interest.
Pharmacological studies by the oral and IV route in rats, dogs, and monkeys have demonstrated that satavaptan increase urine volume, decrease urine osmolality and induce free water excretion. This aquaretic effect was observed with no major change in sodium and potassium excretion.

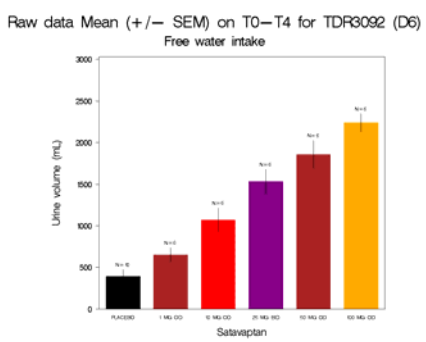
Primary pharmacology

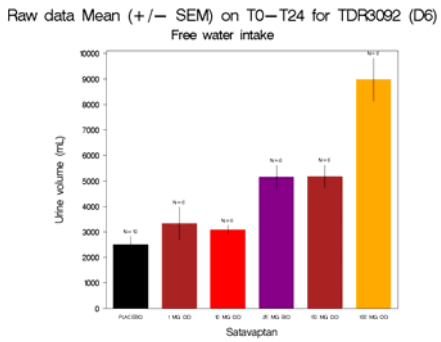
In all pharmacology studies, satavaptan was confirmed to be a potent aquaretic product, showing clear dose-dependent pharmacodynamic (PD) effects with a significant difference versus placebo at satavaptan doses from 10 to 30 mg upwards in the first 4 hours after administration; the main effects observed in this time interval were a large increase in urinary output and a corresponding decrease in urine osmolality. As a consequence, plasma osmolality increased (for doses above 25 or 30 mg/day), as did plasma vasopressin concentrations and thirst (from 3 to 8 hours postdose). At the same time, serum sodium concentrations increased. However these differences in pharmacodynamics were not shown to be statistically different after 7 days of administration. Furthermore, there only seems to be effect on urine volume the first 24 h after administration of the highest dose applied for.

Satavaptan administered at doses between 30 mg and 75 mg had a statistically significant effect on the pharmacodynamic parameters studied in cirrhotic patients with ascites. These effects included an increase in urinary flow rate, and free water clearance accompanied by an increase in plasma sodium concentration and osmolality. However, the doses used in the study ACT3817 do not match with the proposed posology in the SPC for this population and it is thus not determined whether the proposed dosing has any effect in these patients. Furthermore, it should be kept in mind that treatments of these categories of patients often extend more than 7 days.



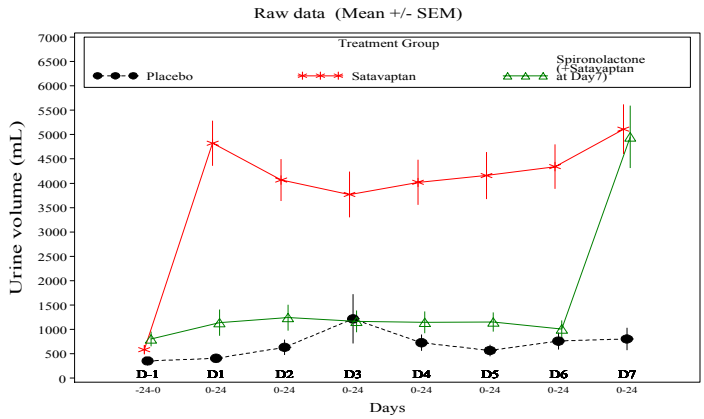






The effect was clearly demonstrated within the limits of the recommended daily dose in the 4 hours following administration, and was less clear when considering the 24-hour interval post-administration in these limits.

In the target population administration of satavaptan 7 days on top of spironolactone treatment resulted in a similar increase of the urinary parameters, indicating that coadministration of the 2 compounds does not affect the diuretic properties of satavaptan. Thus, Pharmacodynamics was not sufficient assessed in the target population.



Secondary pharmacology

According to the Applicant, this study confirmed the lack of evidence for any potential for prolongation of ventricular repolarization with a 25 mg dose of SR121463B. SR121463B 100 mg produced a small increase in QTcF and QTcNi intervals; the mean increases versus placebo were 6.25 ms and 6.84 ms, respectively, in the 1 to 5 hours after administration (T1 to T5). However, such a potential is not completely excluded. A formal QT prolongation study has been performed neither in healthy volunteers (using a positive control) nor in patients. Given the fact that the drug is given to patients that are especially at risk of arrhythmias, and with drugs known to increase the risk of rhythm disturbances, this possible QT increasing potential needs further discussion and/or assessment.

Pharmacokinetic/pharmacodynamic relationship

The overall quality of the pharmacokinetics and pharmacodynamics do not allow conclusions on the pharmacokinetic/pharmacodynamic relationship.

Clinical efficacy

The Applicant seeks marketing authorisation for the indications euvolemic and hypervolemic dilutional hyponatremia.

Dose-finding studies and pivotal studies are not differentiated. At best, it is differentiated between studies and supportive efficacy data.

EUVOLEMIC DILUTIONAL HYPOVOLAEMIA

In this indication the Applicant has submitted 4 clinical studies. Studies SFY5904, an on-going non-comparative long-term safety study, and LTS5066 (open label uncontrolled extension of DFI4488) are not relevant for efficacy and will as such not be commented upon. The remaining studies are the phase II study DFI 4488, and the phase III study EFC 4489B. The design of both studies was similar: Conducted in patients with SIADH, a placebo-controlled blinded period of 4/5 days (satavaptan 25 or 50 mg/day or placebo), followed by an open-label period with flexible doses (range of 5 to 50 mg/day) depending on patients' response. The Phase 1 data indicated that administration in healthy subjects was safe up to 100 mg repeated dosing and that the terminal elimination half-life was within 14 to 17 hours, thus compatible with a once daily administration. However, appropriate dose-findings studies have not been performed and the justification of the applied doses is insufficient.

Study DFI 4488 applied 2 dose groups of satavaptan, 25mg od and 50 mg od. The study was an exploratory study only, a sample size calculation was not performed and statistical hypothesis were not stated. The study consisted of a 5 days DB period and an uncontrolled open label period (with administration of satavaptan 25 or 50mg od, depending on serum sodium concentrations) of up to 23 days. A total of 35 patients with SIADH of any origin and serum sodium between 115 and 132 mmol/L were enrolled but due to insufficient exclusion criteria it cannot be reassured that all patients actually suffered from SIADH. There were major changes during the conduct of the study, including the primary endpoint. The primary endpoint, assessed at the end of the DB period, was serum sodium concentration and percentage of responders (defined as achievement of serum sodium concentration of 135 mmol/L or a 5 mmol/L increase from baseline at the end of the DB period). The results may, at best, be an early indication that satavaptan might be useful in the treatment of hyponatremia in SIADH. The results of this study are, however, of very limited use as they are based on a very heterogenous study population, as no statistical hypotheses had been generated and no clinically relevant effect parameters had been defined. The preliminary findings should be confirmed in dose finding studies (lower doses may be sufficient) and in appropriately designed confirmatory phase III studies involving relevant study populations and clinically more relevant endpoints.

In Study EFC4489B total of 77 patients were enrolled, 25 patients each in the 25mg and 50mg dose groups and 27 in the placebo group. As mentioned above, these doses were not justified, either. Given the results of study DFI 4488 on serum sodium lower doses might have been sufficient. Patients with SIADH of any origin (including drug-induced SIADH limited to carbamazepin and derivates and antidepressants if these drugs could not be discontinued or easily replaced) and with serum sodium between 115 and 132 mmol/L, urine osmolality >200 mosm/kgH_2O, and urine sodium >30mmol/L were enrolled. SIADH was idiopathic in 40.8% of patients, due to a malignant tumor in 38.2% and drug induced in 15.8% (other reasons in 5.3%). However, apart from some imbalances for demographic characteristics, there were also differences in origin between the treatment groups, drug induced SIADH for instance was diagnosed in 12% in the 25mg group, 20% in the 50mg group and 15.4% in the placebo group. It is surprising that carbamazepin induced SIADH was allowed in the study as carbamazepin is an inducer of CYP3A4 (use of other CYP3A4 inducers was an exclusion criterion) and satavaptan exposure may have been reduced in these patients.

It should be noted that patients were neither required to be symptomatic with respect to hyponatremia, nor is it stated whether they suffered from acute or chronic hyponatremia which would have impact on the correction rate, nor were the chosen serum sodium limits justified. Patients were treated for up to 4 days in a DB manner and continued thereafter in a non-comparative open label period (on-going) for up to1012 days with the possibility to adjust the satavaptan dose from 5-50 mg od.

The primary endpoint was percentage of serum sodium responders at the end of the DB period (responders were defined as achieving a serum sodium concentration ≥135 mmol/L and/or with increased serum sodium concentration (from baseline) ≥5 mmol/L, for at least 24 hours.) Secondary endpoints included mostly other laboratory parameters (such as serum osmolality, urine osmolality), urine volume, body weight, fluid intake etc.

Outcome of the primary endpoint is shown in the following table:

Responder patients n (%) at the end of DB period - ITT population

	Placebo		Satavaptan	
			25 mg	50 mg
	(N=26)		(N=25)	(N=25)
Responder patients [n (%)]	3 (11.5)		21 (84.0)	22 (88.0)
p-value vs Placebo			<.0001	<.0001
Adjusted p-value (Hochberg method)			<.0001	<.0001
Patients with serum sodium ≥ 135 mmol/L over 24h duration [n (%)]	0	(0)	13 (52.0)	15 (60.0)
p-value vs Placebo			<.0001	<.0001
Patients with serum sodium increase ≥ 5 mmol/L over 24h duration [n (%)]	3 (11.5)		15 (60.0)	18 (72.0)
p-value vs Placebo			0.0004	<.0001

The time to response was 1.98 and 1.87 days in the 25mg and 50mg dose groups, respectively, compared to >4.02 days in the placebo group.

The results of the open label extension periods of both trials will not be commented upon as no conclusion for efficacy can be drawn from this uncontrolled period. It can be noted, however, that 24/35 patients had completed the 23 days OL period in study DFI 4488 and 25/75 were on-going in study EFC4489B at the cut-off date. Most discontinuations in EFC4489B were due to AEs, however, due to the uncontrolled nature of the trial this is not assessable.

In summary, 2 placebo controlled clinical trials, one phase II and one phase III trial have been submitted in the indication euvolemic dilutional hyponatremia. The methodological quality of the phase II trial is very poor, corresponding to a very early exploratory trial.
Despite statistically significant results of the primary and several of the secondary endpoints in the phase III trial; it is not possible to draw any efficacy conclusions for the proposed indications. Problems relate to the following:

- Very low patient numbers (25 patients in the only potentially relevant dose group of 25 mg – as mentioned previously, lower doses might have been suitable).
- Too short placebo blinded periods.
- Different aetiologies of SIADH included in the trial, which indeed hampers the interpretation of the results.
- Patients were not required to be symptomatic with respect to hyponatremia.
- It is not stated whether patients suffered from acute or chronic hyponatremia. Considering the median time from diagnosis to randomization for the studies in SIADH and CHF patients and the time between two checks of hyponatremia in cirrhotic patients, it can be hypothesized that the hyponatremia status of the patients was chronic. Chronic hyponatremia should be cautiously corrected, since patients have a risk of osmotic demyelination if the serum sodium level is corrected by more than 12mmol/l/24h.
- The chosen serum sodium limits are not justified.
- No data have been provided on the water regimen status of the patients before inclusion. As the limitation of fluid intake is recognised as the standard treatment of SIADH patients throughout the literature, this type of information would have been of great importance in order to discuss the results in light of these baseline data. Limitation of fluid intake was recommended all along the studies (<1.5L), but was controlled only during the DB period.
- The clinical relevance of the chosen laboratory endpoints including the demonstrated effect of satavaptan on sodium concentration remains to be shown. Other clinical parameters, e.g. hospitalisations, morbidity and mortality, would have been relevant.
- The submitted uncontrolled long-term data is insufficient in light of the intended chronic administration of the drug.

HYPERVOLEMIC DILUTIONAL HYPONATREMIA

Hyponatremia in the setting of an extracellular volume expansion is a very common manifestation of conditions with oedematous states such as liver cirrhosis, congestive heart failure or nephrotic syndrome. In these disorders hyponatremia is the final result of a decrease in the circulating arterial volume resulting in thirst, increasing AVP levels and a stimulation of the renin-angiotensin-aldosteron system. It should be remembered, however, that these conditions actually are associated with increased total body sodium.

In overall terms, it can be questioned whether the Applicant's approach to treat hyponatremia, not being a disease but a manifestation of several disorders, is appropriate.

- For hypervolemic dilutional hyponatremia associated with cirrhotic ascites two phase II studies, DFI4521 and LTS5634, were submitted.
  So-called supportive data come from study DFI4522 in patients with cirrhotic ascites, its long term extension LTS5635 and study DFI 5563 in cirrhotic ascites. None of these studies is, however, related to the proposed indication dilutional hyponatremia.
  The pharmacology study ACT3817 in patients with liver cirrhosis and ascites showed that the impaired hepatic function led to modification of the pharmacokinetic profile of satavaptan with higher exposure compared with healthy subjects (increased by approximately 2 to 3 times). Consequently studies in this population used a lower dose range of satavaptan, namely 5, 12.5 and 25mg.

  Study DFI4521 was a DB, placebo controlled dose ranging study with satavaptan doses 5mg, 12.5mg or 25mg od. This treatment was given on top of suboptimal diuretic therapy with spironolactone 100mg daily. Patients ≥18 years with cirrhosis of the liver confirmed by ultrasound, endoscopic examination, or biochemical evidence were included, furthermore they were required to have moderate or tense ascites defined as Grade 2 or 3 according to the Consensus Meeting of the International Ascites Club on the Management of Ascites, in Dallas, 1999, and hyponatremia, defined as a serum sodium concentration of ≤ 130 mmol/L on both Day –5 and Day –1. Due to the diagnostic inclusion criterion a very heterogenous population may have been included. The appropriateness of the inclusion criterion of serum sodium ≤ 130 mmol/L can be questioned. Patients with liver cirrhosis tend to develop hyponatremia gradually and the correction of hyponatremia is therefore not as urgent as for hyponatremia with rapid origin. Any treatment for this hyponatremia, apart from water restriction, would currently not be initiated unless serum sodium falls below 110-115 mmol/L. Fluid and sodium intake were restricted in these patients with anticipated liver cirrhosis, however, there was no control that these recommendations were followed.
  The treatment period was 14 days. The primary endpoints were change in body weight, measured from the baseline to the end of the study treatment period and change in serum sodium, measured from the baseline to the Day 5 assessment (or to the day of discharge, if the patient was discharged from hospital within 5 days). It should be noted that an assessment of ascites or oedema were not part of the body weight assessment. It should also be noted that laboratory evaluations were done locally, not centrally, which may hamper the comparability. Sample size calculations were performed based on the first co-primary endpoint only: Change in body weight from baseline to the end of study treatment period. A difference in body weight loss of 3 kg from study start after a 14-day treatment period was considered to be clinically relevant. The trial was a superiority trial aiming at demonstrating the superiority of at least one dose of SR121463B over placebo. No statistical comparisons between SR121463B doses were planned. The primary analysis was to be performed for both endpoints using the ITT population.
  Only the generation of randomisation codes, packaging and shipping and measures for unblinding were described. The study was stated to be double-blind, however, it is not described how blinding was assured.
  Overall, 110 patients were included, 28 in the placebo group, and 28 in the 5mg satavaptan group, 26 in the 12.5 mg satavaptan group and 28 in the 25 mg satavaptan group. The treatment groups were rather unbalanced with regard to demographics, in particular age distribution, gender, race, and weight. Imbalances also applied to previous use of diuretics. Also with respect to complications of liver cirrhosis the groups were imbalanced. Peculiarly, despite an inclusion criterion of serum sodium

≤ 130 mmol/l on day -5 and -1, 7/26 patients in the 12.5 mg group had a serum sodium of >130mmol/l on Day 1 (=randomisation).

Results of the coprimary endpoints:

Body weight at end of treatment (D14), ITT population

		Placebo (N=28)	**SR121463B**		
			5 mg (N=28)	**12.5 mg (N=25)**	**25 mg (N=28)**
Baseline weight (Kg)	N	28	28	25	28
	Mean (SD)	78.24 (20.93)	73.72 (15.42)	78.65 (21.80)	77.09 (18.20)
	Median	77.35	72.50	78.00	75.25
	Min; Max	45.4; 150.3	40.7; 103.7	50.4; 150.4	46.0; 116.6
End of treatment weight (Kg)	Mean (SD)	78.73 (20.85)	73.87 (17.13)	77.06 (20.04)	75.41 (17.34)
	Median	79.00	69.45	78.20	74.25
	Min; Max	44.5; 149.9	44.2; 108.5	44.3; 139.4	46.0; 110.2
Change from baseline (Kg)	Mean (SD)	0.49 (4.99)	0.15 (4.23)	-1.59 (4.60)	-1.68 (4.98)
	LS Mean	0.55	0.01	-1.51	-1.67
	Median	1.15	-0.85	-1.90	-2.00
	Min; Max	-12.5; 7.4	-6.5; 10.0	-11.0; 8.5	-19.4; 5.5
LS Mean Difference vs placebo	Estimate (SE)	-	-0.54 (1.25)	-2.06 (1.28)	-2.22 (1.24)
	95% CI	-	(-3.02, 1.93)	(-4.60, 0.48)	(-4.69, 0.24)
	Non adj. P-value	-	0.664	0.110	0.077
	Adj. p-value	-	0.664	0.221	0.221

Note: End of treatment weight is the weight recorded at D14. If the patient did not complete D14, last observation carried forward imputation is applied.
Note: p-values come from analysis of covariance adjusting for baseline, adjustment for multiplicity is done with Bonferroni-Hochberg method
CI=Confidence Interval SD=Standard Deviation SE=Standard Error

Serum sodium: mean change from baseline at Day 5 (or at hospital discharge if sooner) - ITT population

		Placebo (N=27)	**SR121463B**		
			5 mg (N=28)	**12.5 mg (N=26)**	**25 mg (N=28)**
Baseline sodium (mmol/L)	N	27	28	26	28
	Mean (SD)	126.1 (4.4)	127.1 (4.7)	128.0 (4.3)	126.3 (5.6)
	Median	128.0	128.5	129.0	129.0
	Min; Max	115; 131	116; 138	119; 139	113; 135
Serum sodium at Day 5 (or at discharge if sooner) (mmol/L)	Mean (SD)	127.4 (5.6)	131.6 (5.6)	132.5 (4.8)	132.9 (6.1)
	Median	127.0	133.0	131.5	133.0
	Min; Max	116; 141	120; 141	125; 142	122; 146
Change from baseline (mmol/L)	Mean (SD)	1.3 (4.2)	4.5 (3.5)	4.5 (4.8)	6.6 (4.3)
	LS Mean	1.1	4.5	4.7	6.5
	Median	1.0	5.0	4.5	7.0
	Min; Max	-6; 11	-8; 11	-5; 13	0; 17
LS Mean Difference vs placebo	Estimate (SE)	-	3.4 (1.1)	3.6 (1.1)	5.4 (1.1)
	95% CI	-	(1.2, 5.6)	(1.4, 5.9)	(3.2, 7.6)
	Non adj. P-value	-	0.003	0.002	<0.001
	Adj. p-value	-	0.003	0.003	<0.001

No clear dose response for satavaptan was evident.

The change in the co primary endpoint body weight was neither clinically nor statistically significant from placebo for any of the doses. As regards the change in serum sodium it was higher for all 3 satavaptan doses compared to placebo (statistically significant). For the secondary endpoint responders (increase of >=5 mmol/l serum sodium at Day 5 compared to baseline or serum sodium at Day 5 ≥135 mmol/l) on day 5/discharge a dose response was not noted, either. It should be noted that serum sodium was not part of the statistical considerations, i.e. no meaningful difference from placebo has been established in advance. The results on serum sodium from this study are therefore futile. Secondary endpoints included among others ascites worsening, 24-h-urinary volume, urine osmolality, urinary electrolytes excretion, quality of life (SF36 health survey questionnaire). Clinically or statistically significant differences were not observed. Thirst increased in all active treatment groups and appeared to be dose related. A dose dependent increase in the change from baseline plasma vasopressin concentrations was observed in the satavaptan groups.

Study LTS5634 was a single blind, randomised, parallel group comparison of a flexible dose regimen of satavaptan versus placebo concomitantly with standard diuretic agents (spironolactone was recommended but any diuretic regimen was permitted). This 2-year study started in April 2004 and is ongoing, an interim report including data up to 1 September 2006 was provided. The study was designed as an optional long-term extension to study DFI4521, however, after an amendment, patients with cirrhotic ascites and serum sodium<130 mmol/L could also enter directly into this study without having participated in DFI4521. The intention was to increase the sample size, which was aimed at 198 patients (this number is not justified). The randomization ratio satavaptan: placebo was 2:1. Satavaptan was initiated at 5 mg once daily, but could be increased to 12.5, 25, or 50 mg OD depending on response to treatment. However, due to the lack of additional benefit observed at the higher doses, the maximum dose was after amendment 5 limited to 12.5 mg. During any episode of hyponatremia, daily fluid intake was to be limited to 1.5 L/d. The primary objective of the study was the demonstration of safety. Secondary efficacy criteria included serum sodium, episodes of hyponatremia, number of paracenteses, ascites symptoms and others. A total of 140 patients were randomised, 73 ex-DFI patients and 67 direct entry patients. 139 patients were exposed, 47 to placebo and 92 to satavaptan. Only 10/47 placebo patients and 28/92 satavaptan patients completed 1 year of treatment, the main reasons for discontinuation were adverse events (46.8% in the placebo group, 34.8% in the satavaptan group), and more than twice as many patients in the satavaptan group discontinued due to lack of efficacy or disease progression.
Efficacy analyses were made for direct entry patients only. The provided results are thus based on 19 patients in the placebo group and 44 in the satavaptan group on day 2, decreasing gradually to 4 and 12 patients, respectively at week 52. As the study is very heterogenous with respect to entry criteria (imbalances for direct entry patients vs. DFI patients and for satavaptan vs. placebo groups for various baseline parameters/demographic characteristics), and to concomitant diuretic treatment, and considering the small number of patients completing 1 year of treatment (38/139) valid conclusions are not possible.

- For hypervolemic dilutional hyponatremia associated with congestive heart failure, one phase III study, EFC5816, was provided.
  Study 4510 in patients with CHF is provided as supportive for efficacy but is without relationship to the proposed indication.
  Study EFC5816 was a randomised, DB, placebo controlled trial evaluating two doses of satavaptan on serum sodium in patients with dilutional hyponatremia due to other than known SIADH or cirrhosis. The subgroup analysis in patients with CHF was not planned but added after the database had been opened. Due to insufficiently defined inclusion criteria ("Male or female patients aged 18 years and higher with dilutional hyponatremia with serum sodium between 115 and 132 mmol/L"), the target population of this study is not well-defined which makes clinical implications of the study questionable. The trial consisted of a 4-day DB period with a 1-year open label uncontrolled extension period. No justification for the satavaptan dose groups, 25mg and 50mg, was given. For the open label period,

all patients started to receive satavaptan 25mg with the possibility to adjust the dose between 12.5mg and 50 mg. After an amendment, however, satavaptan was to be administered at a dose of 12.5mg in the open label period with the possibility to increase the dose to 25mg, maintain at 12.5 mg or discontinue treatment. This decision was motivated by "studies in SIADH and ascites". Apart from the change in dosing, many changes were made during the study including major changes such as primary endpoint, sample size, and statistical procedures.

The primary endpoint was responder rate for serum sodium concentration (defined as percentage of patients reaching serum sodium >135 mol/L and/or having an increase of serum sodium >5 mmol/L relative to baseline for 2 consecutive measurements at least 24 hours apart) at the end of the DB period. A total of 118 patients were included in the study, 42 patients in the placebo group, 35 patients in the satavaptan 25 mg group, and 41 patients in the 50 mg group. 105 patients completed the DB period (there were 17 discontinuations in the satavaptan groups and 6 discontinuations in the placebo group), most of the discontinuations were due to AEs in the satavaptan groups. A total of 101 patients entered the open-label period of the trial, 2 patients completed, 34 are on-going and 65 discontinued (mostly due to AEs and recovery).

At baseline, most patients had dilutional hyponatremia associated with CHF (76.3%). Serum sodium values at baseline were comparable across treatment groups. Mean serum sodium was 128 mmol/L (SD 3.58). In 22 patients (18.6%) serum sodium was < 125 mmol/l. Regarding serum sodium baseline value one patient with serum sodium of 122 mmol/l on day -1 and serum sodium of >135 at baseline is mentioned. This underlines the uselessness of treating a laboratory value without consideration of clinical symptoms. The majority of patients were treated with drugs acting on the renin-angiotensin system and with diuretics which contribute to/cause hyponatremia. Especially thiazide diuretics are related to hyponatremia as well as hypokalemia. In case of hypokalemia water is moved from intracellular to extracellular and additionally serum sodium enters the cells. Hypokalemia at baseline should thus have been excluded.

Results, primary endpoint:

Responders at the end of DB period - ITT population*

	Placebo		**Satavaptan**			
			25 mg		**50 mg**	
	(N=41)		**(N=35)**		**(N=41)**	
Responder patients [n (%)]	11	(26.8)	17	(48.6)	25	(61.0)
p-value for intersection test (vs Placebo)			0.0070			
p-value vs Placebo			0.0599		0.0035	
[Na+] ≥ 135 mmol/L over 24h duration [n (%)]	7	(17.1)	10 (28.6)		18 (43.9)	
p-value vs Placebo			0.2764		0.0155	
Increase [Na+] ≥ 5 mmol/L over 24h duration [n (%)]	8	(19.5)	14 (40.0)		22 (53.7)	
p-value vs Placebo			0.0751		0.0026	

* 1 randomised patient was excluded from the ITT population as no post baseline serum sodium measurement was available.

The result of the primary endpoint was not statistically significant for the satavaptan 25mg dose, which is the only relevant dose according to the SPC proposal. For the (post-hoc) subgroup of CHF patients both doses were statistically significant in comparison to placebo (responder rates of 23.5%, 53.6% and 57.1% for placebo, 25mg and 50mg).

Efficacy results for the open label are not assessable due to the lack of a comparator and the fact that the majority of patients had discontinued during the study.

In summary, the proposed indication hypervolemic dilutional hyponatremia was differentiated by the Applicant by its relationship to liver cirrhosis, and non-liver cirrhosis /CHF post-hoc, respectively.

Problems relate to the following:

- For hyponatremia associated with liver cirrhosis no phase III study was performed.
- Only a phase II dose-ranging study in hyponatremic cirrhotic patients was performed. Doses of 5 mg, 12.5 mg and 25 mg were applied. A clear dose response on serum sodium was not seen. Even

the lowest applied satavaptan dose (5mg – lower doses were not investigated) could rapidly increase the serum sodium concentration. A lower dose of satavaptan might be sufficient.

- Fluid intake was restricted in both liver cirrhosis and CHF studies, however, it is not stated if these recommendations were followed. No data have been provided on the water regimens status of the patients before inclusion.
- It is not stated whether patients suffered from acute or chronic hyponatremia. Considering the median time from diagnosis to randomization for the studies in SIADH and CHF patients and the time between two checks of hyponatremia in cirrhotic patients, it can be hypothesized that the hyponatremia status of the patients was chronic. Chronic hyponatremia should be cautiously corrected, since patients have a risk of osmotic demyelination if the serum sodium level is corrected by more than 12mmol/l/24h.
- Clinically relevant endpoints were not used. It is not surprising that satavaptan increases serum sodium considering that the pharmacodynamic effect of satavaptan is aquaretic; it decreases distal re-absorption of water in the collecting ducts of the kidneys and increases the excretion of free water. Consequently serum sodium can be expected to increase. It is, however, essential to treat the patient for a disease which would be ascites/hypervolemia in liver cirrhosis and CHF respectively, and not to correct a laboratory value only.
- In CHF, for an insufficiently defined, inhomogenous patient population (hypervolemia not associated with SIADH or cirrhosis) no clinically relevant or statistically significant results have been demonstrated for the proposed dose of satavaptan 25mg in the proposed indication.
- The long-term data (either un-controlled or of poor methodological quality in study LTS5634) are insufficient.

Overall, the clinical efficacy endpoints chosen by the Applicant have demonstrated a pharmacological effect of satavaptan on natremia, without any established clinical benefit improvement. In other terms, these studies established activity rather than efficacy.

Clinical safety

The safety database generated from the whole satavaptan clinical development program included 615 healthy subjects and a total of 1422 patients, 1091 of whom were exposed to satavaptan. These 1091 patients had been exposed to satavaptan for a mean duration of 141.5 days (193.80): 539 satavaptan patients were exposed at least 12 weeks, 247 were exposed for at least 26 weeks, and 121 were exposed at least 52 weeks. The average exposure to satavaptan was 141.5 days (193.80), which was much longer than the average exposure to placebo [87.6 days (125.48)].

Of those 1091 patients exposed to satavaptan, only 594 patients were hyponatremic patients in the settings of the 2 indications applied for (euvolemic dilutional hyponatremia (SIADH) and hypervolemic dilutional hyponatremia (cirrhotic ascites and CHF)). These patients were exposed for at least 1 dose of satavaptan.

Most of the safety evaluation of satavaptan was based on very short treatment duration; 4 to 5 days double-blind (DB), placebo-controlled treatment period for the SIADH population (DFI4488 and EFC4489 studies), up to 12 weeks treatment for the cirrhotic ascites population (DFI4521, DFI4522, DFI5563, and ACT3817 studies), up to 4 days and 17 weeks for the CHF subpopulation in study EFC5816 and CHF population in study DFI4510 respectively, and throughout the duration of 6 weeks for the hypertension population (study DFI4789).

An unacceptably number of patients have been exposed for the relevant doses of satavaptan in the treatment of the 2 sought indications (5-25 mg for euvolemic dilutional hyponatremia and hypervolemic dilutional hyponatremia caused by CHF. 5-12.5 mg for hypervolemic dilutional hyponatremia caused by cirrotic ascites): *1)* In the pooled DB studies - Euvolemic dilutional hyponatremia (DFI4488 DB, EFC4489 DB) only 39 patients (25 mg) out of 76 were treated for a mean duration of 3.8 days. *2)* In the pooled DB studies - Hypervolemic dilutional hyponatremia for cirrhostic patients (DFI4521, DFI4522, DFI5563, subpopulation of patients with serum sodium < 135 mmol/l at baseline) only 53 (5 mg) and 50 (12.5 mg) patients out of 159 were treated for a mean duration of 22.1 and 27.6 days. *3)* In study EFC5816 - DB pe-

riod – Dilutional hyponatremia in patients not associated with cirrhosis/SIADH, only 35 patients (25 mg) out of 77 were treated for a mean duration of 3.7 days.

Long term safety data are also insufficiently represented. Only two studies, study LTS5634 and LTS5635 (ongoing extension studies to DFI4521 and DFI4522 in cirrhotic patients) included control groups. These two studies provide safety data for 1 year treatment. However, the number of patients exposed in these studies are very low; 139 in study LTS5634 (of which 92 received satavaptan treatment) and 234 in study LTS5635 (of which 186 received satavaptan treatment), only 30.4 % and 40.9 % respectively, completed 1 years treatment. Discontinuations were primarily due to adverse events. The deficiency in long term data is not acceptable especially in the light of the intended long term therapy for the sought indication.

Adverse events

The AEs have been presented by indication and have further more been divided into subpopulations. The generally low number of patients in each treatment group makes a potential causative and/or dose related connection between satavaptan treatment and AEs very difficult to assess. A complete overview (covering all studies) regarding AEs would have been helpful in order to make the safety data more transparent. However, due to the different study designs with regard to concomitant treatment, different doses of satavaptan used in the studies etc., a metaanalysis on safety data would be inappropriate to perform and therefore of no use.

Furthermore, a description of AEs by severity and causal relationship is missing. However, in the Rapporteur's opinion this information would not substantially contribute to the overall safety evaluation.

The most frequent AEs occurring in satavaptan population were: renal impairment, thirst, increased kalemia, abdominal pain, pyrexia, asthenia/fatigue, fall, muscle spasms, umbilical hernia, ventricular-arrhythmia-related events, constipation, pruritus, dyspnoea, hypotensive-related events, sepsis, anorexia, insomnia, oesophageal varices, dizziness, pain in extremity, and paresthesia.

A short overview of the important AEs is given here, more detailed data follow below for the different patient populations:

Rapid increases in serum sodium ≥12 mmol/L/24 hours were recorded in 10.7% of the patients with SIADH treated with satavaptan, but were less frequently reported in hyponatremic patients with CHF (6.9%) or cirrhotic ascites (1.6% versus 0%).

Serum potassium of at least 5.5 mmol/L was observed in the 3 main populations (patients with SIADH, cirrhotic ascites, or CHF) with higher incidences in patients with cirrhotic ascites or CHF. Serum potassium was consistently increased in the satavaptan groups as compared with placebo.

Renal impairment was observed especially in the cirrhotic ascites population, mainly in hyponatremic male patients with high Child Pugh scores. The frequency appeared to be higher in the satavaptan 25 mg group, as compared with satavaptan 5 and 12.5 mg groups.

Thirst was an almost commonly reported events accompanied with dry lip or dry mouth, with a trend to a dose effect.

Euvolemic hyponatremia associated with SIADH:

Table 39: Overview of TEAEs in pooled DB studies - Euvolemic dilutional hyponatremia
(DFI4488 DB, EFC4489 DB)

	Placebo		Satavaptan					
			25 mg		50 mg		Total	
	(N=36)		(N=39)		(N=37)		(N=76)	
	n (%)		n (%)		n (%)		n (%)	
Patients with any TEAE	9	(25.0)	8	(20.5)	6	(16.2)	14	(18.4)
Patients with any treatment-emergent SAE	3	(8.3)	1	(2.6)	0	(0)	1	(1.3)
Patients with any TEAE(s) leading to death	2*	(5.6)	0	(0)	0	(0)	0	(0)
Patients permanently discontinued due to TEAE	2	(5.6)	1	(2.6)	0	(0)	1	(1.3)

* 1 of these 2 patients died during the OL period while receiving satavaptan and is therefore counted in the pooled satavaptan population in section Deaths

The most frequently (≥2% with at least a 1% difference in the satavaptan group versus placebo group), reported TEAEs were urinary tract infection (25 mg, 2.6%; 50 mg, 5.4%; versus placebo, 0%), thirst (25 mg, 2.6%; 50 mg, 2.7%; versus placebo, 0%), dry mouth (25 mg, 2.6%; 50 mg, 2.7%; versus placebo, 0%), headache (25 mg, 2.6%; 50 mg, 2.7%; versus placebo, 0%).

Long term safety in the population with euvolemic dilutional hyponatremia: (DFI4488/LTS5066, EFC4489, and SFY5904):
81% of patients presented with TEAEs, 44.6% presented with SAE, 23.2% died, 29.2% discontinued satavaptan treatment (29.2%). However, due to the lack of control groups in these studies it is impossible to conclude a potential causative connection between satavaptan treatment and incidences of AE´s. Therefore no detailed information regarding long term safety is presented.

Hypervolemic hyponatremia associated with cirrhotic ascites:

Table 40: Overview of TEAEs in pooled DB studies - Hypervolemic dilutional hyponatremia
(DFI4521, DFI4522 (1), DFI5563 (1) (1) Subpopulation of patients with serum sodium < 135 mmol/l at baseline)

	Placebo (N=51) n (%)		**5 mg (N=53) n (%)**		**12.5 mg (N=50) n (%)**		**25 mg (N=56) n (%)**		**Total (N=159) n (%)**	
Patients with any TEAE	32	(62.7)	35	(66.0)	29	(58.0)	38	(67.9)	102	(64.2)
Patients with any treatment-emergent SAE	10	(19.6)	14	(26.4)	10	(20.0)	16	(28.6)	40	(25.2)
Patients with any TEAE leading to deaths	1	(2.0)	6	(11.3)	4	(8.0)	4	(7.1)	14	(8.8)
Patients permanently discontinued due to TEAE	6	(11.8)	7	(13.2)	4	(8.0)	9	(16.1)	20	(12.6)

For the cirrhotic patients AEs appeared to be slightly higher in the satavaptan groups compared to placebo. SAEs and AEs leading to deaths were distinctly higher in the satavaptan groups. A clear dose response was not evident.
AEs with a higher frequency in the satavaptan groups compared to placebo were as follows:
- Thirst: placebo 2.0%, satavaptan 5mg 5.7%, satavaptan 12.5 mg 18.0%, satavaptan 25mg 21.4%.
- Hyperkalaemia: placebo 7.8%, satavaptan 5mg 9.4%, satavaptan 12.5 mg 12.0%, satavaptan 25mg 14.3%.
- Hepatic encephalopathy: placebo 3.9%, satavaptan 5mg 9.4%, satavaptan 12.5 mg 8.0%, satavaptan 25mg 12.5%.
- renal failure: placebo 0%, satavaptan 5mg 5.7%, satavaptan 12.5 mg 4.0%, satavaptan 25mg 7.1%.
- pyrexia: placebo 2.0%, satavaptan 5mg 1.9%, satavaptan 12.5 mg 4.0%, satavaptan 25mg 5.4%.
- diarrhoea: placebo 3.9%, satavaptan 5mg 5.7%, satavaptan 12.5 mg 14.0%, satavaptan 25mg 7.1%.
- nausea: placebo 3.9%, satavaptan 5mg 5.7%, satavaptan 12.5 mg 2.0%, satavaptan 25mg 5.4%.
- vomiting: placebo 2.0%, satavaptan 5mg 3.8%, satavaptan 12.5 mg 4.0%, satavaptan 25mg 5.4%.

The higher incidences of hyperkalaemia and renal failure in the satavaptan groups are of special interest in the light of the already existing risk of developing hepatorenal syndrome in this fragile patient population. The higher incidence of hepatic encephalopathy is also grieving. Regarding the latter, it could be speculated whether too fast a correction of hyponatremia may have contributed. No information is available in the dossier regarding symptomatic versus non-symptomatic or acute versus chronic hyponatremia.

AEs with a higher frequency in the placebo groups compared to satavaptan:
- Ascites: placebo 7.8%, satavaptan 5mg 3.8%, satavaptan 12.5 mg 2.0%, satavaptan 25mg 3.6%.

Hypervolemic hyponatremia not associated with cirrhotic ascites or SIADH:

Table 41: Overview of TEAEs - EFC5816 - DB period – Dilutional hyponatremia

	Placebo (N=45) n (%)		**Satavaptan**					
			25 mg (N=35) n (%)		50 mg (N=42) n (%)		**Total (N=77) n (%)**	
Patients with any TEAE (including SAEs)	15	(33.3)	12	(34.3)	17	(40.5)	29	(37.7)

Patients with any treatment-emergent SAE (including SAEs leading to death)	3	(6.7)	2	(5.7)	4	(9.5)	6	(7.8)
Patients with any TEAE(s) leading to death	2	(4.4)	0	(0)	0	(0)	0	(0)
Patients with any TEAE(s) leading to permanent treatment discontinuation	2	(4.4)	3	(8.6)	7	(16.7)	10	(13.0)

The incidence of AEs (and also the SAEs) was slightly higher in the satavaptan groups compared to placebo. The incidence of AEs leading to treatment discontinuation was clearly higher. The mentioned distribution of incidences was also applied to the subgroup of CHF patients (92 out of 122).
AEs being higher in the satavaptan groups were the following:
- ventricular arrhythmias related events (25 mg, 5.7%; 50 mg, 4.8%; versus placebo, 0%);
-atrial fibrillation (25 mg, 0%; 50 mg, 7.1%; versus placebo, 0%);
-hypotension (25 mg, 5.7%; 50 mg, 2.4%; versus placebo, 0%);
-hypertension (25 mg, 2.9%; 50 mg, 4.8%; versus placebo, 2.2%);
-bleeding events (25 mg, 0%; 50 mg, 4.8%; versus placebo, 0%);
-pyrexia (25 mg, 2.9%; 50 mg, 2.4%; versus placebo, 0%);
-increased natremia (25 mg, 2.9%; 50 mg, 2.4%; versus placebo, 0%).
A major concern is the observed higher incidence of ventricular arrhythmia. Due to the apparent QTc prolonging potential of satavaptan which has been insufficiently investigated by the Applicant, this topic demands extremely further meticulous evaluation. Long term safety data including a control group is inevitable in this patient group.

QTc prolongation:
Study PKD5521 (a placebo controlled pharmacology study in healthy male and female subjects) was designed to evaluate the QT/QTc interval during 7 days OD 25 mg and 100 mg satavaptan treatment with moxifloxacin 400 mg single dose as positive control. No effect on the QT interval was observed for the 25 mg dose. The 100 mg dose induced a statistically significant increase in the QTcF intervals; mean difference versus placebo was +6.25 msec. The 400 mg moxifloxacin dose resulted in a +8.63 msec increase. After adjustment (Bootstrap method), satavaptan 100 mg induced a largest time-matched increase, with estimated differences versus placebo of 9.12 msec (QTcF), and the one-sided 95% upper limit 13.04 msec. According to the guideline on Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (CHMP/ICH/2/04) a "thorough QT/QTc study" is considered positive if the threshold level for prolongation in mean QT/QTc interval is more than 5 msec (as evidenced by an upper bound of the 95 % confidence interval around the mean effect on QTc of more than 10 msec). Study PKD5521 should thus, be considered positive. It is unacceptable that no expanded ECG safety studies have been performed, in particularly in the light of 1) the target patient population (CHF patients (with increased risk of ventricular arrhythmia) and patients with impaired liver function (with increased exposure to satavaptan; Cmax and AUC increased 2.5 fold and 4 fold compared to normal/mild impaired hepatic function, see pharmacology) and 2) the increased exposure of satavaptan when taken concomitantly with CYP3A4 inhibitors.

It is stated that no relevant findings on QT-interval were observed among the 22 clinical pharmacology studies in which automatic ECG reading were performed.

For the SIADH studies, only mean changes in QTcF intervals in the DB periods have been reported, not the actual values of the QT interval prolongations. For the cirrhosis studies and study EFC5816 (hypervolemic hyponatremia not associated with cirrhosis/SIADH) incidences of QTcF prolongations by dose group have not been recorded. This makes the safety data regarding QT interval prolongation very little transparent and limits the conclusiveness.

Euvolemic hyponatremia associated with SIADH:
Increased mean changes in QTcF intervals for the satavaptan groups were observed in the DB studies (DFI4488 and EFC4489): +11.6 msec and + 5.4 msec for the 25 mg and 50 mg versus + 1.0 msec for placebo. The one-sided 95% upper limit ranged from 12.10 to 14.14 msec.

In the pooled satavaptan studies (DFI4488/LTS5066, EFC4489 and SFY5904) 20 patients (out of 150 = 13.3 %) presented with prolonged QTcF (>470 msec in females, >450 msec in males), including 6 patients with QTcF≥500 msec. These prolongations were not associated with ventricular arrhythmia or with increased satavaptan plasma concentrations. However, no comparisons with placebo were given and study LTS5066 and SFY5904 were uncontrolled making conclusions not possible.

Hypervolemic hyponatremia associated with cirrhosis:
In the pooled combined DB and SB studies (DFI4521/LTS5634, DFI4522/LTS5635, and DFI5563), comparable incidences of QTcF increase from baseline ≥ 30 msec and ≤ 60 msec were observed for placebo versus satavaptan treatment (29/168=17.3 % and 78/467=16.7 % respectively). Increases > 60 msec were 5/168=3.0 % and 11/467=2.4% for placebo versus satavaptan.
Prolonged QTcF (male > 450 and < 500 msec, female >470 and < 500 msec) were reported in 78/483 (16.1 %) and 23/176 (13.1 %) for satavaptan and placebo treatment.
Prolonged QTcF ≥ 500 msec was observed in 6/483 (1.2 %, of which one experienced ventricular fibrillation and TdP) in the satavaptan groups and 4/176 (2.3 %) in the placebo group.
Regarding the sought indication, the above data have not been detailed for the hyponatremic patient population.
The Applicant states that no relationship has been observed between satavaptan plasma concentrations and QTcF.

Hypervolemic hyponatremia not associated with cirrhosis/SIADH:
In study EFC5816 19/99 patients (19.2 %) presented with prolonged QTcF (>450 msec in males and >470 msec in females), 18 of these belonged to the CHF subpopulation.
4 patients (all in the CHF subpopulation) had QTcF> 500 msec. None of these were associated with ventricular arrhythmia.
The high number of QT interval prolongations in CHF patients is of particular interest as CHF is a known risk factor for drug induced QTc prolongation in this patient population. More safety data in this patient category is inevitable.
The Applicant states that no relationship has been observed between satavaptan plasma concentrations and QTcF.

Serious adverse events:
As for the other subgroups of safety data the number of patients in each treatment group is extremely low, making assessment more or less impossible. Furthermore, due to lack of control groups combined with low number of patients, occurrence of SAEs in long term treatment have not been assessed.

Euvolemic hyponatremia associated with SIADH:
The number of serious adverse events was low (3 and 1 events in the treatment period for placebo and satavaptan respectively and 0 events for the post treatment period) however, seemingly comparable between satavaptan and placebo.

Hypervolemic hyponatremia associated with cirrhosis:
In the pooled DB studies (DFI4521, DFI4522 and DFI5563) 19.6 % in the placebo group and 25.2 % in the satavaptan group experienced SAEs. The following incidences were more frequently observed in the satavaptan group: infections (placebo 0%, satvaptan groups 7.5% (12/159) in the treatment period), hepatic encephalopathy related events (placebo 2.0% vs. satavaptan groups 6.3% (10/159) in the treatment period) and renal impairment (placebo 0% vs. satavaptan groups 6.3% (10/159) in the treatment period). Of particularly interest is the much higher incidence of hepatic encephalopathy related events in the satavaptan groups. One may speculate; 1) whether the hyponatremic state in conjunction with satavaptan treatment could trigger the development or 2) if the correction of the hypanatremic state has been too fast.

Hypervolemic hyponatremia not associated with cirrhosis/SIADH:

As for the Euvolemic hyponatremia associated with SIADH only few incidences of SAEs were reported in study EFC5816 (during the treatment period 3/45 in the placebo group and 6/77 in the satavaptan group). Therefore, meaningful comparisons are unfeasible.

Deaths:

To summarise, 164 (15%) deaths occurred in the 1091 patients who received satavaptan and 41 (8.9%) deaths in the 458 patients who received placebo. In the pool of DB hyponatremic cirrhotic patients, (mean duration of exposure in the total satavaptan group was 25.4 days and the median duration of exposure was 14 days), there was an excess of death in satavaptan groups. A detailed overview follows below:

No death occurred in the clinical pharmacology studies.

Euvolemic dilutional hyponatremia (SIADH):

In the pooled DB studies (DFI4488 and EFC4489) 1 patient out of 36 in the placebo group experienced a TEAE with a fatal outcome versus none in the satavaptan groups.

At the cut-off of 01 September 2006, in the pooled satavaptan population (DFI4488/LTS5066, EFC4489, and SFY5904) a total of 43/168 patients had died

– 39 patients died from TEAEs, where death occurred during treatment or within 30 days post last dose, 4 patients died from non-TEAEs.

In the light of study participants suffering from severe diseases a high mortality rate could be expected. The low number of study participants and the lack of control groups make assessment of a potentially causative relationship almost impossible. The assessment is further complicated by the lack of several patient data on 21 out of 27 patients, who died following TEAEs in Study EFC4489. No clear relationship between deaths and SR121463B treatment has been observed. However, of interest were 5 cases (out of 39 = 3.6 %) in which satavaptan induced ventricular arrhythmia related events could not be excluded. In one of these, the patient (who died on day 109) in addition had experienced at least two episodes of hyperkalemia (day 77: 5.5 mmol/l and day 108: 5.6 mmol/l). The deaths potentially caused by ventricular arrhythmia adds on to the need for further safety studies regarding satavaptan induced QT interval prolongation.

Hypervolemic hyponatremia associated with cirrhotic ascites:

Deaths in the DB studies (DFI4521, DFI4522 and DFI5563) were almost twice as high in the satavaptan group compared to the placebo group in the liver cirrhosis patients (23//310 = 7.4% vs. 4/99 = 4%). For the hyponatremic subpopulation of patients in the same studies the incidence of deaths in the satavaptan groups was even higher compared to placebo. (21/159 = 13.2% vs. 1/51 = 2%). Of the 21 cases, 14 =8.8% was a consequence of an AE occurring during the treatment period.

Most patients died from hepatic impairment (6/159 = 3.8 %) followed by infections/infestations (3/159 = 1.9 %) renal impairment (2/159 = 1.3 %) and bleeding events (2/159 = 1.3 %).

For the subpopulation with normal serum sodium concentrations in the above studies 3 patients (out of 48 = 6.3 %) died in the placebo group and 1 (out of 147 = 0.7%) after receiving satavaptan.

For all cirrhotic patients (at the cut-off date of 01 September 2006) in the pooled combined DB and SB studies (DFI4521/LTS5634, DFI4522/LTS5635, and DFI5563), a total of 122 deaths were reported:

– 3 patients died during the screening period and 119 died after randomization;

– 31 (16.7 %) patients died after receiving placebo, of whom 29 (15.7 %) as a consequence of an AE occurring during the treatment period;

– 88 (17.5 %) patients died after receiving satavaptan, of whom 69 (13.7 %) as a consequence of an AE occurring during the treatment period. Of interest in light of the sought indication, the majority of deaths in the satavaptan treatment group were in patients with hypervolemic dilutional hyponatremia (65 out of 88 deaths).

Overall, fatal TEAEs occurring at a higher frequency in the satavaptan group versus the placebo group included the following: renal impairment (2.2% versus 1.1%); infections (2.0% versus 1.6%): sepsis being the most frequent cause (0.8% versus 0.5%); clinical cardiovascular ventricular arrhythmia related events (0.8% versus 0%: 1 case of cardiac arrest, 1 case of sudden death, and 2 cases of death); multi-

organ failure: 1 case versus 0; asthenia: 1 case versus 0; pneumonia aspiration: 1 case versus 0; dyspnoea: 1 case versus 0; respiratory failure: 1 case versus 0; circulatory collapse: 1 case versus 0; adenocarcinoma: 1 case versus 0; bile duct cancer: 1 case versus 0; disseminated intravascular coagulation: 1 case versus 0; cardiac failure: 1 case versus 0; increased kalemia: 1 case versus 0; ischemic stroke: 1 case versus 0.
Fatal TEAEs occurring at a higher frequency in the placebo group versus the satavaptan group were, by decreasing order of frequency: hepatic encephalopathy related events (6.4% versus 3.2%); bleeding events (1.6% versus 1.2%: mainly oesophagal varices haemorrhage (1.6% versus 0.4%)); ascites related events: (1.1% versus 0.4%); malignant neoplasms (1.1% versus 0.4%); hemorrhagic shock (0.5% versus 0.2%), i.e., 1 case in each group; general physical health deterioration (0.5% versus 0.2%); anemia: 1 case versus 0; choking: 1 case versus 0; cardiac tamponade: 1 case versus 0; completed suicide: 1 case versus 0.

Hypervolemic hyponatremia not associated with cirrhosis/SIADH:
Study EFC5816: At the cut off of 01 September 2006, a total of 17/114 patients died during the study. Fifteen of these patients had dilutional hyponatremia associated with CHF. The 2 remaining patients were non-CHF patients.

For the DB period (4 days duration) no patients died in the satavaptan groups. In the same period 2 patients in the placebo group died.

During the OL period, 11 patients (out of 103 = 10.7 %) had fatal TEAEs. Most were due to a progression of the underlying disease in those patients with poor health status (high grade of CHF). In 3 cases of cardiac arrest/sudden cardiac death ventricular arrhythmia related events could not be excluded. Due to the lack of control group in the OL period in study EFC5816 assessment of a potential relationship between satavaptan treatment and deaths is impossible.

Laboratory findings

Rapid increase in serum sodium:
A total of 13/76 patients (17.1%) in the pooled double blind SIADH studies (DFI4488 and EFC4489) experienced a rapid increase in serum sodium of at least 12 mmol/L/24h compared to 0% in the placebo population. A dose-relationship was observed: 5/39=12.8% in the 25 mg group and 8/37= 21.6% in the 50 mg group.
This event was also observed after satavaptan administration in the hypervolemic dilutional hyponatremia studies but less frequently. In the pooled DB studies for cirrhotic patients (DFI4521, DFI4522 and DFI5563) 3/158 (1.9 %, for all dose groups) compared to 0% in the placebo group experienced a rapid increase of 12 mmol/l/24h. In study EFC5816 (hypervolemic hyponatremia not associated with cirrhosis/SIADH) a dose-dependent rapid increase was observed in a total of 10/77 (13%) in the satavaptan groups and 2/45 (4.4%) in the placebo group.
For all studies the rapid serum sodium increase was mainly observed after the first satavaptan dosing.
One patient (cirrhotic ascites) experienced associated neurological events: hepatic encephalopathy, concomitant to urinary tract infection in a 63-year-old cirrhotic hyponatremic male; the increase of serum sodium was ≥8mmol/L/24h. Otherwise no concomitant neurological symptoms were reported.

Hypernatremia (serum sodium>145 mmol/l):
- In the pooled satavaptan SIADH population (DFI4488/LTS5066, EFC4489, and SFY5904), 21/168 (12.5%) patients experienced high serum sodium value >145 mmol/L.
- In the pooled satavaptan cirrhotic population (DFI4521, DFI4522 and DFI5563) 5/159 patients (3.1%) had hypernatremia without apparent dose relationship compared to 0% in the placebo group.
- In the EFC5816 study (all patients, pooled satavaptan population), a total of 9/114 (7.9%) experienced serum sodium above 145 mmol/L and/or AEs related to increases in serum sodium.
Serum sodium >160 mmol/L was found in 5 patients treated with satavaptan (3 patients with SIADH, 1 patient with cirrhotic ascites and 1 patient with dilutional hyponatremia of unspecified origin). No cases

were reported for the placebo patients. All 5 patients were hyponatremic at baseline. The increases occurred shortly after introduction of satavaptan (Day 3 and 4) in 2 patients, and on Day 14 and Day 48 in the other 3 patients. In 3/5 patients, a drug that inhibits CYP3A (clarithromycin and fluconazole) was co-administered. In one case serum sodium was increasing also several days after discontinuation of satavaptan.
In a total of 3 deaths hypernatremia was involved in the course.

Hyperkalemia (serum potassium > 5.5 mmol/l):
- In the pooled DB SIADH studies (EFC4489 and DFI4488) one patient out of 76 (1.3%) experienced hyperkalemia compared to no events in the placebo group. In the pooled satavaptan SIADH population (DFI4488/LTS5066, EFC4489, and SFY5904, including open label periods) 16/168 (9.5%) presented with a serum potassium ≥5.5 mmol/L and/or AEs related to increase in serum potassium during satavaptan administration .None led to satavaptan discontinuation.
- In the pooled DB cirrhotic studies (DFI4521, DFI4522, and DFI5563, subgroup of hyponatremic patients (<135mmol/L)) 47/159 patients (29.6%) experienced hyperkalemia, without apparent dose relationship vs. 9/51 (17.6%) in the placebo group. The patients also received spironolactone. In the pooled combined cirrhotic DB and SB studies (DFI4521/LTS5634, DFI4522/LTS5635, and DFI5563, hyponatremic patients at baseline), an even higher incidence of hyperkalemia and/or AEs related to increase in serum potassium was reported in the satavaptan group (107/281 patients, 38.1%) compared to the placebo group (28/117 patients, 23.9%).
- In study EFC5816 (hypervolemic hyponatremia not associated with cirrhosis/SIADH) assessment of serum potassium was not planned as per protocol during the 4-day DB period. During the course of the study, an amendment was implemented to retrieve all available serum potassium values for patients enrolled in this study. Only one satavaptan treated patient (CHF subpopulation, DB period) out of 57 (1.8%) experienced hyperkalemia, compared to 2/35 (5.7%) in the placebo group.

Renal impairment/serum creatinine ≥ 150 µmol/l:
- In the pooled SIADH satavaptan population (DFI4488/LTS5066, EFC4489, SFY5904), 12/168 patients (7.1%) presented with serum creatinine ≥150 µmol/L and/or AE related to an increase in serum creatinine (reported by the Investigator as such, but with no specific definition) during pooled satavaptan administration. No data for placebo is given.
The Applicant states that that about 22.3% of the patients already presented with a moderate or severe renal impairment when entering the DB/OL periods of SIADH studies. Furthermore, it is stated that no relationship was observed between satavaptan plasma concentration and increased serum creatinine in SIADH patients.
-In the DB cirrhotic studies (DFI4521, DFI4522, and DFI5563), the incidences of patients with serum creatinine ≥175 µmol/L while receiving satavaptan was 17 % (27/159) compared to 7.8% (4/51) in placebo. Information on renal function in terms of GFR/MDRD as well as an association to intrinsic factors (demographic factors, Child-Pugh class, baseline GFR etc.) is not given for hyponatremic cirrhosis patients, only for the overall group of cirrhosis patients.
Increases in serum creatinine and/or renal impairment reported as an AE were reported in cirrhosis patients throughout the duration of satavaptan administration.
- In the EFC5816 study (hypervolemic hyponatremia not associated with cirrhosis/SIADH, CHF pooled satavaptan subpopulation), 16/87 patients (18.4%) presented with serum creatinine ≥150 µmol/L and/or an AE related to an increase in serum creatinine during pooled satavaptan administration. However, it should be noted that about 34.7% of the patients already presented with a moderate or severe renal impairment when entering the DB period. Two patients experienced SAEs of "renal failure" one of these patients died.
It should be noted that no data from the DB period is available, i.e. no placebo comparison. Data for the overall population from study EFC 5816 (i.e. not only the CHF sub-population) is not given.

Liver function
Liver enzymes were not checked during the DB periods of the trials, this is why no comparison with placebo is available for all indications.

-In the pooled SIADH satavaptan population (DFI4488/LTS5066, EFC4489, and SFY5904), perturbations in ALT (>2ULN), ALP (>1.5 ULN), GGT (>3 ULN), and total bilirubin (>34 µmol/L) were noted with the following frequencies 8.8%, 11.0%, 18%, and 3.5%, respectively, during satavaptan administration. The liver enzyme elevations are not assessable due to lack of control group.
- In the pooled combined DB and SB cirrhotic studies (DFI4521/LTS5634, DFI4522/LTS5635, and DFI5563) only data on overall liver cirrhosis patients are given. The incidences of increased AST, and total bilirubin were lower in satavaptan treated patients compared to placebo. Alkaline phosphatase was reported at higher incidence in the satavaptan group compared with the placebo group, and ALT (>5 ULN) were reported with comparable incidences across the groups. However, due to hepatic impairment induced by cirrhosis liver enzyme elevation in this patient population is unlikely.
- In the EFC5816 study (hypervolemic hyponatremia not associated with cirrhosis/SIADH, CHF pooled satavaptan subpopulation), perturbations in ALT (>2ULN), ALP (>1.5 ULN), GGT (>3 ULN), and total bilirubin (>34 µmol/L) were noted with the following frequencies 2.2%, 14.3%, 26.8% and 11.1%, respectively, during satavaptan administration. The liver enzyme elevations are not assessable due to lack of control group.

Haematology
Haematology parameters were not checked during the DB periods of the trials, this is why no comparison with placebo is available for all indications.
- In the pooled satavaptan SIADH population (DFI4488/LTS5066, EFC4489, and SFY5904), haematological disorders (8.7% with neutropenia, 8.1% with thrombocytopenia, and 12.8% with eosinophilia) were noted during satavaptan OL administration. One third of the patients had malignant extensive tumours requiring chemotherapy, which could explain the haematological changes.
- In the cirrhotic patients only data on overall liver cirrhosis patients are given. Incidences between satavaptan and placebo were comparable.
-In study EFC5816 (hypervolemic hyponatremia not associated with cirrhosis/SIADH) no data from the DB period is available, i.e. no placebo comparison.

Safety in special populations:

Pharmacology studies.
Subjects with mild to severe renal impairment
Study POP5948 compared the pharmacokinetic data after a single dose of satavaptan (50 mg) in healthy subjects vs. subjects with severe renal impairment. A single dose pharmacokinetic study in this patient population is not acceptable as steady state is not reached until several days of satavaptan treatment. Therefore, the data presented is of little use. However, C_{max}, AUC_{last} and AUC parameters were reported to increase less than a 1.16 fold in the renal impairment group.

Subjects with mild to severe hepatic impairment
With regard to the high incidence of renal impairment and hyperkalemia observed in cirrhotic satavaptan treated patients, it seems mysterious that no pharmacokinetic data for patients with hepatic impairment have been summarised in this section.

Clinical studies
Overall, no conclusions on TEAE´s related to age, gender and geographic area can be made: The number of patients in each subgroup is too low, no control groups exists for the SIADH studies. Further more the demographic issues mentioned above, have not been specified for the cause of SIADH or severity of cirrhosis/CHF.

Renal function at baseline
Euvolemic dilutional hyponatremia (SIADH)
Only 1 patient in the SIADH studies (DB and OL periods) had renal impairment (defined as baseline creatinine ≥ 150 mmol/l).
Clinical studies in patients with cirrhotic ascites (pooled DB and SB periods):

The interpretation of AEs in cirrhotic patients with renal impairment should be done cautiously. The used measure for renal impairment was GFR. As body weight is a factor involved in the calculation of GFR, the value obtained may be confounded by the hypervolemic condition resulting in disparate GFR results. Therefore, it would have been more appropriate to assess AEs in the context of renal impairment by using MDRD´s.
Overall, an increased reporting rate of TEAEs was noted with renal function impairment whatever the treatment group. However, in the light of the fragile patient population, (1) who are at risk of developing hepatorenal syndrome and 2) where the majority receives drugs known to increase serum potassium), it is of major concern that 33.8-50.0 % of the patients in the satavaptan group experienced increased kalaemia (compared to 18.2-30.4 % for the placebo group) and 19.4-37.0 % experienced worsening of the renal function (compared to 9.1-25.0 % in the placebo group).
Clinical studies in patients with CHF (pooled DB and SB periods):
The safety data have not been specified according to the degree of renal impairment or to the doses used in the study. Furthermore, the data refer to study DFI4510, a supportive study considered useless for the sought indication as the patients had normal serum sodium levels. Therefore the results are of no use for safety conclusions.
However, increased hypotensive related events were observed in patients with renal impairment at baseline (measured by serum creatinine > 150µmol/l) in the satavaptan group (6/49 = 12.2%) compared to placebo (2/34 = 5.9 %). Furthermore, there was an increased worsening of renal function (measured by increased blood creatinine) in the satavaptan group (8/49 = 16.3 %) compared to placebo (4/34 = 11.8 %). Regarding the first event, it could be speculated if the aquaretic effect of satavaptan is too high for the doses used in this patient population.

Baseline serum sodium categories:
Euvolemic dilutional hyponatremia (SIADH):
The majority of the common TEAEs occurred in patients with serum sodium level at baseline between 125 and 130 mmol/L. No tendency of increased incidence of common events was observed in the subgroup with serum sodium concentration below 125 mmol/l.
Cirrhotic ascites:
The cirrhotic patient population suffer from hyponatremia due to their hypervolemic condition, but do in fact have normal or high total body sodium. The threshold for treating this hyponatremic condition is way below the level of hyponatremia studied in these cirrhotic studies and would normally be around 110-115 mmol/l depending on symptoms. It is therefore, of great concern that the incidence of AE´s in these cirrhotic patients increases by decreasing serum sodium. Of particular interest is the high incidence of hyperkalemia and impaired renal function in patients with serum sodium < 125 mmol/l (amounting to 28/50 = 56.0 % and 15/50 =30 % respectively) compared to placebo (amounting to 5/24 = 20.8 % and 4/24 =16.7 % respectively).
Congestive heart failure:
No detailed overview is given for the CHF patient population why no conclusions can be made. However, the Applicant states that the majority of the common TEAEs occurred in patients with serum sodium level at baseline of at least 135mmol/L in the satavaptan group.

Safety related drug-drug interactions and other interactions

- CYP3A4 inhibitors:

It is known from the pharmacological studies that CYP3A inhibitors (erythromycin and ketoconazol) in healthy subjects highly increase the exposure of satavaptan. No pharmacokinetic data have been given on patients treated with satavaptan concomitantly with CYP3A4 inhibitors. This is of great concern in relation to the following safety issues: 1) satavaptan is mainly metabolised by CYP3A4, 2) satavaptan induces QTc interval prolongation, 3) satavaptan induces hyperkalemia and renal impairment in cirrhotic patients and patients with CHF, 4) patients with moderate to severe cirrhosis who receive satavaptan have higher mean C_{max} compared to healthy subjects.

Euvolemic dilutional hyponatremia (SIADH):

- Double-blind periods (study DFI4488 and EFC4489)
For weak, moderate and strong CYP3A inhibitors no final conclusions can be drawn on any unfavourable influences (with respect to adverse events) of concomitant administration with satavaptan. The number of patients and number of events for the single subgroups of the SOCs were too low.
- Open-label periods (Studies DFI4488 OL/LTS5066, EFC4489 OL, SFY5904)
Weak CYP3A inhibitors
For weak inhibitors similar adverse event rates were reported for patients concomitantly treated and not concomitantly treated. *For moderate or strong CYP3A inhibitors the* number of patients and events were too low to allow any conclusions.

Hypervolemic hyponatremia associated with cirrhosis:
Pooled double-blind and single-blind studies (DFI4521/LTS5634, DFI4522/LTS5635, DFI5563)
Weak CYP3A inhibitors
Overall, patients concomitantly treated with weak CYP3A inhibitors (satavaptan: 344/502, 68.5%, placebo: 142/185, 76.8%) had a lower reporting rate of TEAEs as compared with patients not concomitantly treated. However, again the number of events for the single subgroups of the SOCs is low, which makes conclusions difficult
Moderate or strong CYP3A inhibitors
Only few satavaptan treated patients were concomitantly treated with moderate or strong CYP3A inhibitors which limits any conclusions regarding AE rates.

Congestive heart failure studies:
No detailed information (i.e. tables) can be found for study EFC5816, TEAE´s associated with satavaptan treated patients concomitantly treated with CYP3A inhibitors, thus, the following data regarding study EFC5816 is only a summary of the statements in the dossier.

EFC5816 CHF patients - double-blind period:
Weak CYP3A inhibitors
The incidences of TEAEs were comparable between satavaptan treated patients concomitantly treated and not concomitantly with weak CYP3A inhibitors.
Moderate or strong CYP3A inhibitors
Few patients were concomitantly treated with moderate (2 patients) CYP3A inhibitors without any AEs, or serum sodium >145mmol/L. No patients were concomitantly treated with strong CYP3A inhibitors.
EFC5816 CHF patients
– open-label period:
Weak CYP3A inhibitors
Overall, satavaptan patients concomitantly treated with weak CYP3A inhibitors (63%) did not report more TEAEs than patients without concomitant treatment. However, 2 cases of ventricular tachycardia, 1 case of cardiac arrest and 1 case of syncope occurred in a patient concomitantly treated with a weak CYP3A inhibitor, as well as 4 cases of renal impairment. Four patients experienced serum sodium>145 mmol/L or AE of hypernatremia while concomitantly treated with weak CYP3A inhibitor, versus none in patients not concomitantly treated.
Moderate or strong CYP3A inhibitors
Few patients were concomitantly treated with moderate (4 patients) and strong (1) CYP3A inhibitors without any AEs of interest.

- Drugs known to increase serum potassium:

Euvolemic dilutional hyponatremia (SIADH)
- Double-blind periods (study DFI4488 and EFC4489):
The number of patients in each treatment group (placebo, 25 and 50 mg, 13-24 patients in each) and the number of the different events for the single subgroup of SOCs (1 or 2 events) were low making conclusions impossible.
- Open-label periods (study DFI4488 OL/LTS5066, EFC4489 OL and SFY5904):

In the OL periods, comparable incidences of TEAEs in patients concomitantly treated (97/166, 58.4 %) vs. in patients not concomitantly treated were observed. Hyperkalemia were reported with a higher frequency in patients (3.1% vs. 1.4%) concomitantly treated. Of serious TEAEs 4 cases of ventricular arrhythmia related events (3 sudden deaths and 1 cardiac arrest) were reported in patients concomitantly treated vs. 0 in patients non-concomitantly treated.

Hypervolemic hyponatremia associated with cirrhosis:
Pooled double-blind and single-blind studies (DFI4521/LTS5634, DFI4522/LTS5635, DFI5563):
Only few patients treated with satavaptan (15/502, 3.0 %) were not concomitantly treated with drugs known to increase serum potassium, making comparisons impossible.

Hypervolemic hyponatremia not associated with cirrhosis/SIADH:
- Study EFC5816 (CHF patients):
Only few patients both in the double-blind period (3 satavaptan treated patients) and open label period (4 satavaptan treated) were not concomitantly treated with drugs known to increase serum potassium, thus, making comparisons between concomitantly vs. non-concomitantly treated satavaptan patients impossible.

- Drugs known to increase QT

Euvolemic dilutional hyponatremia (SIADH)
Both in the DB-blind periods (study DFI4489 and EFC4489) and the open-label periods (study DFI4488 OL/LTS5066, EFC4489 OL and SFY5904) the satavaptan treated patients concomitantly treated with drugs known to increase QTc reported more TEAEs than patients non-concomitantly treated. No increased incidences of ventricular arrhythmia were observed in the groups concomitantly treated.

Hypervolemic hyponatremia associated with cirrhosis:
Pooled double-blind and single-blind studies (DFI4521/LTS5634, DFI4522/LTS5635, DFI5563):
The frequency of overall TEAEs were higher in the concomitant treated group (162/200, 81%) compared to the non-concomitant treated group (209/302, 69%). No increased incidence of clinical ventricular arrhythmia-related events was observed in the group concomitantly treated.

Hypervolemic hyponatremia not associated with cirrhosis/SIADH:
- Study EFC5816:
The Applicant states that for both the DB period and open-label period all clinical ventricular arrhythmia related events were reported in patients concomitantly treated with drugs known to prolong QTc. No incidences have been given.

Discontinuations due to adverse events

It can be summarised that in the SIADH program, about one third of patients discontinued satavaptan due to AEs, and in patients with cirrhotic ascites, more patients discontinued satavaptan than placebo; renal impairment, infections, increased kalemia, and ventricular-arrhythmia-related events being the main causes of satavaptan discontinuation as compared with placebo group.
In CHF patients, in the placebo-controlled DFI4510 study, there were more cases of congestive cardiac failure, dry mouth, thirst, and ventricular-arrhythmia-related events leading to satavaptan discontinuation.
A detailed overview over discontinuations is presented in the following paragraphs:

Pharmacology studies:
7 patients discontinued, of which 4 patients had been treated with satavaptan. Reasons for discontinuation were: influenza, rash papular, Quincke oedema (coadministration with digoxin) and neutropenia (coadministration with omeprazole).

Overall, the majority of the clinical studies had very short duration of the DB treatment (in the range of 3-5 days for the main studies). For longer term treatment in the relevant patient populations only uncontrolled data is available. Discontinuations in these longer term periods were very frequent. It must be

stated that the safety of satavaptan is not assessable without any control groups and stress the need for further safety studies in satavaptan treated patients.

Euvolemic hyponatremia studies:
In the pooled DB studies (DFI4488 and EFC4489, 4-5 days duration) 4 TEAEs led to permanent discontinuation: 1 non-serious TEAE (1.3%) in the satavaptan 25 mg group (severe thirst) versus 3 serious events in the placebo group (8.3%) (bronchopulmonary aspergillosis, pulmonary vasculitis, and cryoglobulinemia).
In the pooled satavaptan population (DFI4488/LTS5066, EFC4489, and SFY5904), 49 (29.2%) patients discontinued study drug due to TEAEs. The most frequently reported TEAEs were in the following SOC: neoplasms benign, malignant and unspecified (6.0%). In addition, with an incidence ≥ 2%, were, by decreasing order of frequency: ventricular arrhythmias related events (5.4%) and septic shock (2.4%).
As can be seen, discontinuations due to AEs were frequent in the long term studies and included potentially serious adverse events. The safety data, however, in these studies are inconclusive due to lack of control groups.

Hypervolemic hyponatremia associated with cirrhotic ascites:
TEAEs leading to study drug discontinuations in the hypervolemic hyponatremic patients (pooled combined DB and SB studies: DFI4521/LTS5634, DFI4522/LTS5635, and DFI5563) were reported in 33/117 (28.2%) of placebo patients and 83/281 (29.5%) of satavaptan patients.
Renal impairment was a more frequent reason for discontinuation in satavaptan patients than in placebo patients (7.5% vs. 2.6%), as well as also infections and infestations (5.3% versus 1.7%), hyperkalemia (3.2% versus 1.7%), and ventricular arrhythmias related events (2.8% versus 1.7%).

Hypervolemic hyponatremia not associated with cirrhotic ascites/SIADH:
In study EFC5816 (all patients, DB period) discontinuations due to AEs were clearly dose-dependently higher for satavaptan patients (3/35 (8.6%) for 25 mg, 7/42 (16.7%) and 2/45 (4.4%) placebo), with ventricular arrhythmias related events being the most frequently reported cause of discontinuation (25 mg, 5.7%; 50 mg, 4.8%; versus placebo, 0%). Also bleeding events and increased natremia were more frequent reasons for discontinuation in satavaptan patients (2.6% each vs. 0% in placebo). Considering the pooled satavaptan population (uncontrolled open label period) a total of 9.6% (11/114) discontinued due to ventricular arrhythmia-related events. This is of great concern and underlines the necessity of further meticulous evaluation of this issue and of controlled long term data.

OVERALL SAFETY CONCLUSION:

Considering the prevalence of hyponatremia in the conditions investigated (SIADH, cirrhosis of the liver and CHF) and considering that at least cirrhosis of the liver and CHF are very common diseases, the safety database is too small and the exposure to the drug too short and without controlled long term data to provide proper safety data on the treatment with satavaptan in these patient categories.
Special safety concerns relate to QTc prolongation, ventricular arrhythmias and an increased mortality rate in satavaptan treated patients.
Keeping in mind that the target population consist of patient already in risk of arrhythmias and that a considerable risk of accumulation of satavaptan exists, satavaptan's potential for QTc prolongation and ventricular arrhythmia is of great concern. This risk could be even more pronounced given the increase of exposure of satavaptan upon concomitant administration of CYP3A4 inhibitors.
In the liver cirrhosis patients the mortality rate was almost twice as high in the satavaptan group compared to the placebo group (7.4% vs. 4%), and even higher in hyponatremic liver cirrhosis patients in these studies compared to placebo (13.2% vs. 2%). Noteworthy in this hyponatremic patient population is also the development of hyperkalaemia and renal impairment.

Pharmacovigilance system

The Rapporteurs consider that the Pharmacovigilance system as described by the Applicant fulfils the requirements and provides adequate evidence that the Applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management plan

Exposure to satavaptan has been obtained only during pre-marketing clinical trials so far. In addition to clinical pharmacology studies including healthy subjects, clinical studies with satavaptan have been performed in patients with dilutional hyponatremia: either euvolemic hyponatremia [syndrome of inappropriate antidiuretic hormone secretion (SIADH)], or hypervolemic hyponatremia [cirrhotic ascites (CAS), congestive heart failure (CHF)] as well as patients without dilutional hyponatremia: [patients with cirrhotic ascites, CHF, and hypertension (HTN)].

The safety evaluation of satavaptan was based on results of:

- Two double-blind placebo-controlled studies in the SIADH population with a duration of 4 to 5 days;
- Three double-blind, placebo-controlled studies in the cirrhotic ascites population with a median duration of 14 days;
- Study DFI4510 in the CHF population and in a CHF subgroup of study EFC5816.

These studies were limited in term of number of patients followed and time for duration. The long-term safety evaluation of satavaptan was based on the results from the open-label extension of these studies that limits the interpretation of long term safety data.

Important identified risks are:

- Overly rapid correction of hyponatremia
- Increased natremia
- Increased kalaemia
- Renal impairment
- Interaction with moderate and potent CYP3A inhibitors

Important potential risks are:

- Ventricular-arrhythmia related events
- Off-label use in adults
- Birth defects and adverse effects on growth

Important missing information:

- Experience in children and adolescent
- Experience in Black and Asian patients
- Effect on lactation

Epidemiology of identified or potential risks in the indications reveal that there is very limited information is available in the published studies on the prevalence of hyperkalaemia in hyponatremia patients, in particular with SIADH, liver cirrhosis, and CHF.

IV. ORPHAN MEDICINAL PRODUCTS

N/A

V. BENEFIT RISK ASSESSMENT

V.1 Benefits

The Applicant seeks marketing authorisation for the indications euvolemic and hypervolemic dilutional hyponatremia.
Dose-finding studies and pivotal studies are not differentiated. At best, it is differentiated between studies and supportive efficacy data.

EUVOLEMIC DILUTIONAL HYPOVOLAEMIA
Appropriate dose-findings studies have not been performed.
Study EFC4489B is the only phase III study. A total of 77 patients were enrolled, 25 patients each in the 25mg and 50mg dose groups and 27 in the placebo group. The applied doses have not been sufficiently justified, lower doses may have been appropriate. Patients with SIADH of any origin (including drug-induced SIADH limited to carbamazepin and derivates and antidepressants) and with serum sodium between 115 and 132 mmol/L, urine osmolality >200 mosm/kgH_2O, and urine sodium >30mmol/L were enrolled.
It should be noted that patients were neither required to be symptomatic with respect to hyponatremia, nor is it stated whether they suffered from acute or chronic hyponatremia which would have impact on the correction rate, nor were the chosen serum sodium limits justified. Patients were treated for up to 4 days in a DB manner and continued thereafter in a non-comparative open label period (on-going) for up to1012 days with the possibility to adjust the satavaptan dose from 5-50 mg od.
The primary endpoint was percentage of serum sodium responders at the end of the DB period (responders were defined as achieving a serum sodium concentration ≥135 mmol/L and/or with increased serum sodium concentration (from baseline) ≥5 mmol/L, for at least 24 hours.) Secondary endpoints included mostly other laboratory parameters (such as serum osmolality, urine osmolality), urine volume, body weight, daily fluid intake, thirst index, hormonal assessments, quality of life etc.
The results of the primary endpoint: responders in the placebo group: 11.5%, in the satavaptan 25mg group 84.0%, in the 50 mg group 88.0%.
The open label period was without control group which limits a proper assessment.

HYPERVOLEMIC DILUTIONAL HYPONATREMIA
This condition was subdivided with respect to clinical studies in hypervolemic dilutional hyponatremia associated with cirrhotic ascites and hypervolemic dilutional hyponatremia not associated with cirrhotic ascites or SIADH. The subpopulation of patients with CHF was retrospectively defined in the study submitted in support of latter condition.
For hypervolemic dilutional hyponatremia associated with cirrhotic ascites two phase II studies, DFI4521 and LTS5634 were submitted.
Study DFI4521 was a DB, placebo controlled dose ranging study with satavaptan doses 5mg, 12.5mg or 25mg od with comparison vs. placebo not within different satavaptan dose groups. This treatment was given on top of suboptimal diuretic therapy with spironolactone 100mg daily.
The treatment period was 14 days. The primary endpoints were change in body weight, measured from the baseline to the end of the study treatment period and change in serum sodium, measured from the baseline to the Day 5 assessment (or to the day of discharge, if the patient was discharged from hospital within 5 days). It should be noted that an assessment of ascites or oedema were not part of the body weight assessment, and that fluid restriction was recommended but not controlled. It should also be noted that laboratory evaluations were done locally, not centrally, which may hamper the comparability. Sample size calculations were performed based on the first co-primary endpoint only: Change in body weight from baseline to the end of study treatment period. Overall, 110 patients were included, 28 in the placebo group, and 28 in the 5mg satavaptan group, 26 in the 12.5 mg satavaptan group and 28 in the 25 mg satavaptan group. Baseline data were not well balanced.
For the endpoint change in body weight a change in kg at the end of the treatment period of mean (SD) 0.49 (4.99) in the placebo group, 0.15 (4.23) for the 5mg dose group, -1.59 (4.60) in the 12.5mg dose

group and -1.68 (4.98) in the 25 mg dose group was noted. None of these changes was statistically significant in the comparison to placebo.
The coprimary endpoint change in serum sodium from baseline to day 5 (or to hospital discharge, if sooner) in mmol/L was mean (SD) 1.3 (4.2) in the placebo group, 4.5 (3.5) in the 5mg satavaptan group, 4.5 (4.8) in the 12.5mg satavaptan group, and 6.6 (4.3) in the 25 mg group.
Secondary endpoints included among others ascites worsening, 24-h-urinary volume, urine osmolality, urinary electrolytes excretion. Clinically or statistically significant differences were not observed. Thirst increased in all active treatment groups and appeared to be dose related. A dose dependent increase in the change from baseline plasma vasopressin concentrations was observed in the satavaptan groups.
Study LTS5634 (single blind, placebo controlled randomised satavaptan : placebo =2:1) was designed as an optional long-term extension to study DFI4521, however, after an amendment, patients with cirrhotic ascites and serum sodium<130 mmol/L could also enter directly into this study without having participated in DFI4521. This 2-year study started in April 2004 and is on-going, an interim report including data up to 1 September 2006 was provided. Satavaptan was initiated at 5 mg once daily, and could be increased depending on response to treatment, after an amendment the increase was limited to 12.5mg od. The primary objective of the study was the demonstration of safety. Secondary efficacy criteria included serum sodium, episodes of hyponatremia, number of paracenteses, ascites symptoms and others. A total of 140 patients were randomised, 73 ex-DFI patients and 67 direct entry patients. 139 patients were exposed, 47 to placebo and 92 to satavaptan. Only 10/47 placebo patients and 28/92 satavaptan patients completed 1 year of treatment, the main reasons for discontinuation were adverse events (46.8% in the placebo group, 34.8% in the satavaptan group), and more than twice as many patients in the satavaptan group discontinued due to lack of efficacy or disease progression.
Efficacy analyses were made for direct entry patients only. The provided results are thus based on 19 patients in the placebo group and 44 in the satavaptan group on day 2, decreasing gradually to 4 and 12 patients, respectively at week 52. As the study is very heterogenous with respect to entry criteria (imbalances for direct entry patients vs. DFI patients and for satavaptan vs. placebo groups for various baseline parameters/demographic characteristics), and to concomitant diuretic treatment, and considering the small number of patients completing 1 year of treatment (38/139) valid conclusions are not possible.

For hypervolemic dilutional hyponatremia associated with congestive heart failure, one phase III study, EFC5816, was provided. The study was a randomised, DB, placebo controlled trial evaluating two doses of satavaptan, 25mg and 50mg, which have been insufficiently justified, on serum sodium in patients with dilutional hyponatremia due to other than known SIADH or cirrhosis. The trial consisted of a 4-day DB period with a 1-year open label uncontrolled extension period. For the open label period, all patients started to receive satavaptan 25mg with the possibility to adjust the dose between 12.5mg and 50 mg. After an amendment, however, satavaptan was to be administered at a dose of 12.5mg in the open label period with the possibility to increase the dose to 25mg, maintain at 12.5 mg or discontinue treatment. Apart from the change in dosing, many changes were made during the study including major changes such as primary endpoint, sample size, and statistical procedures. The primary endpoint was responder rate for serum sodium concentration (defined as percentage of patients reaching serum sodium >135 mol/L and/or having an increase of serum sodium >5 mmol/L relative to baseline for 2 consecutive measurements at least 24 hours apart) at the end of the DB period. A total of 118 patients were included in the study, 42 patients in the placebo group, 35 patients in the satavaptan 25 mg group, and 41 patients in the 50 mg group. 105 patients completed the DB period (there were 17 discontinuations in the satavaptan groups and 6 discontinuations in the placebo group), most of the discontinuations were due to AEs in the satavaptan groups. A total of 101 patients entered the open-label period of the trial, 2 patients completed, 34 are ongoing and 65 discontinued (mostly due to AEs and recovery).
The result of the primary endpoint (26.8% responders in the placebo group, 48.6% in the satavaptan 25mg group and 61.0% in the 50mg group) was not statistically significant for the satavaptan 25mg dose, which is the only relevant dose according to the SPC proposal. For the (post-hoc) subgroup of CHF patients both doses were statistically significant in comparison to placebo (responder rates of 23.5%, 53.6% and 57.1% for placebo, 25mg and 50mg).
Efficacy results for the open label are not assessable due to the lack of a comparator and the fact that the majority of patients had discontinued during the study.

In summary, no clinically relevant benefits have been demonstrated for satavaptan.

V.2 Risks

Most of the safety evaluation of satavaptan was based on very short treatment duration; 4 - 5 days to 2 weeks in the main studies. The safety database included 615 healthy subjects and a total of 1422 patients, 1091 of whom were exposed to satavaptan. Of those exposed to satavaptan, only 594 patients were hyponatremic patients in the settings of the 2 indications applied for and even fewer patients were exposed to the doses proposed to be used.
Thirst was an AE occurring for all patients groups.
Of concern for the hyponatremic liver cirrhosis patients are the AEs hyperkalaemia (placebo 7.8%, satavaptan 5mg 9.4%, satavaptan 12.5 mg 12.0%, satavaptan 25mg 14.3%.), hepatic encephalopathy (placebo 3.9%, satavaptan 5mg 9.4%, satavaptan 12.5 mg 8.0%, satavaptan 25mg 12.5%.), renal failure (placebo 0%, satavaptan 5mg 5.7%, satavaptan 12.5 mg 4.0%, satavaptan 25mg 7.1%.). With respect to hyperkalemia and its relationship to renal impairment it should be remembered that these patients usually are concomitantly treated with the potassium sparing spironolactone and other diuretics, however, as spironolactone therapy probably was not optimal and diuretic therapy not standardised in the liver cirrhosis studies there is room for even worse outcomes.
Of concern in the non-cirrhosis/non-SIADH (→CHF) population are ventricular arrhythmia related events (25 mg, 5.7%; 50 mg, 4.8%; versus placebo, 0%).
In this regard it must be underlined that satavaptan in the clinical studies had a clear QTc prolonging effect which had not been appropriately investigated before enrollment of patients into the "main" clinical studies. The Applicant has presented a very little transparent evaluation of the QTc prolongation issue which makes final conclusions difficult. The highest incidence of QTc prolongation was found in the study EFC5816 (Hypervolemic hyponatremia not associated with cirrhosis/SIADH) where 19% of patients presented with QTc prolongation.
The most frequently occurring SAEs in the liver cirrhosis studies were infections (placebo 0%, satvaptan groups 7.5% in the treatment period), hepatic encephalopathy related events (placebo 2.0% vs. satavaptan groups 6.3% in the treatment period) and renal impairment (placebo 0% vs. satavaptan groups 6.3% in the treatment period. SAEs in the other patient groups were not so frequent, perhaps due to the very short DB treatment period in these trials, and cannot be evaluated. The same is true for the evaluation of deaths. They were, however, in the DB studies in liver cirrhosis patients almost twice as high in the satavaptan group compared to the placebo group and even higher for the hyponatremic liver cirrhosis patients (13% in the satavaptan groups vs. 2% in the placebo groups). Most patients died from hepatic impairment, followed in frequency by infections/infestations, renal impairment, and bleeding events. Liver function was not evaluated during the (short) DB periods of the trials, therefore no comparison with placebo is available. Some liver enzyme elevations in the open label periods were noted in SIADH and CHF patients, but are difficult to assess due to the lack of a control group. In view of the observed hepatotoxicity in preclinical studies and the suspicion of accumulation in the liver of Wistar rats of one metabolite of satavaptan (for details please refer to the preclinical part of the AR), this issue requires further evaluation in humans.
Considering the prevalence of the proposed conditions the safety database is too small. Considering further the intended chronic (or at least repeated) administration of the drug, the exposure to satavaptan is too short and the absence of uncontrolled long term data not acceptable.

V.3 Balance

Satavaptan is a vasopressin 2 (V2) receptor antagonist and belongs thus to a potentially interesting new class of drugs.
The proposed indications are treatment of euvolemic and hypervolemic dilutional hyponatremia. For these conditions, no guidelines exist and no drugs have been authorised previously.

The indication euvolemic hyponatremia comprises patients with SIADH of different origin.
Despite statistically significant results of the primary and several of the secondary endpoints in the phase

III trial submitted in support of the proposed indication euvolemic hyponatremia, efficacy conclusions for the proposed indication cannot be drawn. Problems relate to the very low patient numbers (25 patients in the proposed dosing group 25mg– as mentioned previously, lower doses might have been suitable) and particularly the different aetiologies of SIADH included in the trial, which indeed hampers the interpretation of the results. It should also be noted that patients were neither required to be symptomatic with respect to hyponatremia, nor is it stated whether they suffered from acute or chronic hyponatremia which would have impact on the correction rate, nor were the chosen serum sodium limits justified. Furthermore, the clinical relevance of the chosen laboratory endpoints and the demonstrated effect of satavaptan on sodium concentration remain to be shown. Other clinical parameters, e.g. hospitalisations, morbidity and mortality, would have been relevant. The submitted uncontrolled long-term data is insufficient in light of the intended chronic administration of the drug.

In overall terms, it can be questioned whether the Applicant's approach to treat hypervolemic dilutional hyponatremia, not being a disease but a manifestation of several disorders, is appropriate.
Hyponatremia in the setting of an extracellular volume expansion is a very common manifestation of conditions with oedematous states such as liver cirrhosis, congestive heart failure or nephrotic syndrome. In these disorders hyponatremia is the final result of a decrease in the circulating arterial volume resulting in thirst, increasing AVP levels and a stimulation of the renin-angiotensin-aldosteron system. It should be remembered, however, that these conditions actually are associated with an increased total body natrium.
The indication hypervolemic dilutional hyponatremia was by the Applicant differentiated by its relationship to liver cirrhosis, and non-liver cirrhosis/non SIADH (a CHF population was defined post-hoc).
A phase III study in patients with liver cirrhosis and hyponatremia is not available, only a phase II dose ranging study. The appropriateness of the inclusion criterion of serum sodium ≤130 mmol/L is questionable. Patients with liver cirrhosis tend to develop hyponatremia gradually and the correction of hyponatremia is therefore not as urgent as for hyponatremia with rapid origin. Any treatment for this hyponatremia, apart from water restriction, would currently not be initiated unless serum sodium falls below 110-115 mmol/L.
In support of the hypervolemic dilutional hyponatremia indication in non-liver cirrhosis and non-SIADH patients (retrospectively a population of CHF patients was defined) a small (N=118, 2 satavaptan dose groups and placebo) and short term (4 day DB) study was submitted, which also had major flaws.
Endpoints in all studies focussed on laboratory parameters. Primary endpoints were change in serum sodium concentration or responders for serum sodium. However, the upper inclusion criteria limits of serum sodium concentrations were too high, i.e. patients would in clinical practice hardly be considered for treatment of their hyponatremia. From a patient perspective it would have been important to include clinically relevant endpoints such as symptoms of the disease, hospitalisations or mortality, at least short term. Few controlled data beyond these very short term DB periods are available (only for the phase II liver cirrhosis study); these are of very poor methodological quality and of no relevant value. The remaining long term data are uncontrolled. Due to the intended chronic/repeated administration of the drug this is completely unacceptable.

In summary, no clinically relevant benefit has been demonstrated with satavaptan.

There are, in turn, numerous risk associated with satavaptan.
The pharmacological investigation of the drug in the target population is completely insufficient: Bioavailability cannot be assessed, the accumulation of drug is not sufficiently described, and the pharmacokinetics of satavaptan is extensively influenced by CYP3A4 inhibitors but this has not been investigated in the target population. No relationship between pharmacodynamic effect and serum concentration of satavaptan has been demonstrated in healthy subjects or in the target population. The QT prolonging potential has not been investigated in accordance with the guideline on Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhytmic Drugs (CHMP/ICH/2/04). Ventricular arrhythmia related events are of major concern especially in the non-cirrhosis/non-SIADH (→CHF) population and cannot be sufficiently evaluated in the remaining patient groups due to very short term treatment in a controlled manner and due to very low patient numbers.

The higher incidences of hyperkalaemia and renal failure in the satavaptan groups are of special interest in the light of the already existing risk of developing hepatorenal syndrome in this fragile patient population. The higher incidence of hepatic encephalopathy is also grieving. Mortality appears to be higher for satavaptan treated patients, at least for the hyponatremic patients with liver cirrhosis.
Considering the prevalence of the proposed conditions the safety database is too small. Considering further the intended chronic (or at least repeated) administration of the drug, the exposure to satavaptan is too short and the absence of uncontrolled long term data not acceptable.

V.4 Conclusions

The overall quality of the existing data is extremely poor and the overall benefit risk balance of Aquilda in the treatment of euvolemic and hypervolemic dilutional hyponatremia is negative.