



European Medicines Agency
Evaluation of Medicines for Human Use

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CHMP ASSESSMENT REPORT

FOR

Samsca

International Nonproprietary Name: **tolvaptan**

Procedure No. EMEA/H/C/000980

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

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Otsuka Pharmaceutical Europe Ltd. submitted on 28 January 2008 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Samsca, through the centralised procedure under Article 3(2)(a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 July 2007.

The legal basis for this application refers to:

A - Centralised / Article 8(3) / New active substance.

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The applicant applied for the following indication:

- Treatment of patients with symptoms of worsening heart failure as add-on to standard of care such as diuretics, beta-blockers, angiotensin II antagonists, ACE-inhibitors, and digitalis.
- Treatment of euvolemic and hypervolemic hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion [SIADH], heart failure, and liver cirrhosis.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status:

A new application was filed in the following countries: United States

The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: **Ian Hudson**

Co-Rapporteur: **Antonio Addis**

1.2 Steps taken for the assessment of the product

- The application was received by the EMA on 28 January 2008.
- The procedure started on 27 February 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 19 May 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 20 May 2008.
- During the meeting on 26 June 2008 the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 26 June 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 27 October 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 2 February 2009.
- During the CHMP meeting on 19 February 2009, the CHMP agreed on a List of Outstanding Issues to be addressed in writing and in an oral explanation by the applicant.
- Written explanations were provided by the applicant on 20 March 2009.
- During the CHMP meeting on 22 April 2009, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 5 May 2009.
- During the meeting on 26- 29 May 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a

Marketing Authorisation to Samsca on 28 May 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 20 May 2009.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

A number of disorders, including congestive heart failure (CHF), liver cirrhosis, and syndrome of inappropriate antidiuretic hormone (SIADH) secretion, are associated with increased arginine vasopressin (AVP) secretion. Increased AVP levels lead to excessive water retention accompanied by electrolyte imbalances, in particular hyponatraemia. Conventional therapy to treat these patients often exacerbates hyponatraemia and other electrolyte imbalances by promoting a loss of water together with electrolytes. A selective vasopressin V₂ receptor antagonist could neutralize the effects of the increased AVP levels and reduce water retention without disturbing electrolytic balance.

Tolvaptan (OPC-41061) is a vasopressin antagonist that blocks the binding of AVP at the V₂ receptors of the distal portions of the nephron, thereby inducing free water clearance (aquaresis) without depletion of electrolytes. The clinical development of tolvaptan was initiated in 1994 with early healthy subject trials conducted in Japan and has since been investigated extensively in hyponatraemia and heart failure patients. There is some overlap between the 2 indications that were originally filed in this application, and these 2 complementary tolvaptan programs have proceeded in parallel.

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 were not requested.

The claimed indication for Samsca was:

- Treatment of patients with symptoms of worsening heart failure as add-on to standard of care such as diuretics, beta-blockers, angiotensin II antagonists, ACE-inhibitors, and digitalis.
- Treatment of euvolemic and hypervolemic hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion [SIADH], heart failure, and liver cirrhosis.

The approved indication is the following:

- Treatment of adult patients with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH).

2.2 Quality aspects

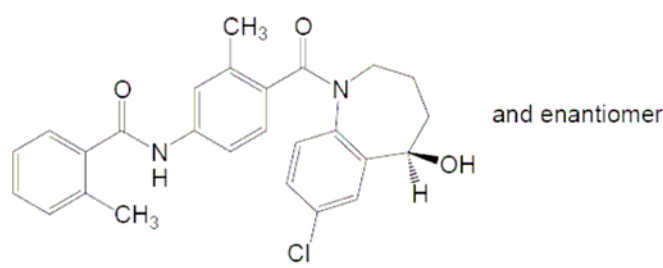
Introduction

Tolvaptan is a new active substance used as a Vasopressin (V₂) antagonist. The medicinal product is formulated as an immediate release tablet containing either 15mg or 30 mg of active substance.

Other ingredients are lactose monohydrate, maize starch, microcrystalline cellulose, hydroxypropylcellulose, low-substituted hydroxypropylcellulose, magnesium stearate and indigo carmine (E 132) aluminum lake. Tablets are coloured in blue and packed in PVC/Aluminum foil blisters.

Active Substance

Tolvaptan or '(±) 4'-[(7-chloro-2,3,4,5-tetrahydro-5-hydroxy-1*H*-1-benzazepin-1-yl) carbonyl]-*o*-tolu-*m*-toluidide' is a new active substance with the following structure (molecular weight of 448.94):



The molecule has an asymmetric centre and can exist as two enantiomers. Tolvaptan active substance has been developed as a racemate and exhibits no optical rotation.

It is a non hygroscopic, white crystalline powder; physical characterisation demonstrated that this substance shows only one crystalline configuration. Solubility investigations indicated that tolvaptan is soluble in benzyl alcohol and methanol but practically insoluble in water and hexane across a wide range of pH.

- **Manufacture**

The proposed commercial manufacturing process for the preparation of tolvaptan active substance consists of three steps which have been described in detail with reference to an ASMF. Controls of the starting materials and critical intermediates are sufficient to ensure the quality of the final compound. Potential impurities, including genotoxic impurities, have been discussed in relation to their origin and potential carry-over into the final finished product.

- **Specification**

The active substance specification includes tests for description, identity (IR, UV and HPLC), melting point, heavy metals, related substances (HPLC), residual solvents (GC), loss on drying, sulphated ashes, assay (HPLC) and test for specific optical rotation.

Analytical methods are performed in line with common pharmacopoeia technique and sufficient details have been provided. Validation reports have been provided when relevant. Impurity limits in the specification are justified by toxicological studies.

- **Stability**

Stability studies were performed according to ICH conditions. 36 months long-term and 6 months accelerated data is provided on three production scale batches of active substance manufactured by the commercial synthetic route.

The active substance was tested for description, identification (IR and HPLC), melting point, impurities (HPLC), assay (HPLC) and loss on drying. Tolvaptan was also exposed to various stress conditions, i.e. exposure in the solid state to elevated temperature and/or humidity, and to light irradiation. In general the proposed retest period is justified based on the stability studies results.

Medicinal Product

- **Pharmaceutical Development**

The main concern for the formulation development was the low bioavailability linked to the fact that tolvaptan active substance is practically insoluble in water, and that no pH dependence of solubility is observed. In order to improve the dissolution and thereby enhance the bioavailability, amorphous powder is used in the tablet formulation. Also, the capability of conversion to crystalline form from amorphous tolvaptan is a critical point of pharmaceutical development and pharmaceutical process because a solid state transition can significantly affect dissolution and bioavailability; this is controlled during manufacture by X-ray diffraction. Then the in vitro dissolution method included in the specification is used as a Quality Control and also as an indirect method of evaluating any crystallisation of the drug substance. The data provided suggest that no amorphous crystalline

conversion occurs during manufacture or storage. Thus, the physical characteristics (particle size, crystalline configuration...) of the neat drug substance do not have any direct impact on the tablet formulations. Studies to optimise the process are described. The 15 mg tablet is a direct scale down from the 30 mg tablet.

A number of formulations were used during development and a series of bioavailability studies have been presented to summarise the clinical/formulation development and to compare the bioequivalence (BE) of those formulations used in Phase I/II/III studies. With the exception of the colorant, the 30 mg tablet used in phase II & III studies is the same as the commercial formulation.

The excipients were chosen based on previous long-term pharmaceutical technological experience of the applicant with the same dosage form. These are: lactose monohydrate (diluent), maize starch (diluent), microcrystalline cellulose (diluent), hydroxypropylcellulose (binder), low-substituted hydroxypropylcellulose (disintegrant), magnesium stearate (lubricant) and indigo carmine (E 132) aluminum lake (colorant).

All excipients used are compendial grade except for the colorant which conforms to EC Directive 95/45/EC. Magnesium stearate used in the formulation is of vegetal origin. A satisfactory BSE/TSE statement from the supplier of lactose is provided.

Tolvaptan tablets are packaged in polyvinyl chloride (PVC)/aluminium blisters. The components of the composite film material and the aluminium foil comply with current EU guidelines; moreover, no interaction between the tablets and the chosen immediate packaging material, PVC/Aluminium blisters have been observed during stability studies.

The packaging components for the market packages are almost identical to those employed to package the primary stability batches; comparability has been demonstrated (structure, composition and moisture and oxygen barrier).

- **Manufacture of the Product**

Manufacture of tolvaptan tablets is composed of two stages: The granulation is common for both strength. Flow chart valid for all strength of tablets has been provided.

The manufacturing process does not involve novel processes but several steps are considered as critical to ensure the solubility and hence, the bioavailability of the active substance: granulation/drying, lubrication/final blending and compression.

The critical steps of the manufacturing process are adequately defined and controlled by suitable in-process controls with acceptable limits.

The data generated demonstrates that the manufacturing processes are adequately controlled, reproducible and justified. The manufacture process is considered as standard and therefore, validation will be completed before marketing according to the process validation plan provided.

- **Product Specification**

The product specification includes description, identification (HPLC), impurities/degradation products (HPLC), uniformity of dosage units (HPLC), dissolution, assay HPLC and microbial limits (Ph.Eur.). In-house analytical methods have been developed and are described in detail; all methods have been fully validated.

Data on 3 commercial scale batches of each strength is provided and all the batches comply with the proposed specifications. Moreover, batch data from clinical trial and bioequivalence batches is also provided as supporting information.

The specification reflects all relevant quality attributes of the active substance and was found to be adequate to control the quality of the active substance.

The limit for total degradation product is based on data generated from batches of the new drug product and its stability characteristics.

- Stability of the Product

Stability studies according to ICH guidelines have been completed through 36 months under long term conditions and through 6 months under accelerated studies. Stress studies have also been performed. Stability studies were also conducted on production-scale tolavaptan 15mg and 30-mg bulk tablets. The following parameters, tests for identification, assay, impurities/degradation products, and dissolution are the same as those proposed in the regulatory specifications. The primary stability protocols also include tests for friability, disintegration, water content, hardness, and microbial limit.

Based on available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant provided a Letter of Undertaking and committed to resolve these issues as Follow Up Measures after opinion within an agreed timeframe.

2.3 Non-clinical aspects

Introduction

The non-clinical development of tolavaptan has been designed in accordance EU/ICH guidelines. In general the pivotal safety pharmacology and toxicology studies were conducted in compliance with the GLP regulations and in accordance with guidance that was current at the time the studies were conducted. However, none of the safety pharmacology studies on the CNS in mice were performed under GLP compliance. The studies were conducted in 1992, before CPMP/ICH/539/00 was issued in June 2001. Some of the dose-range finding studies were not conducted in compliance with GLP either but this is not considered to affect the validity of the results.

There has been no formal CHMP scientific advice for the tolavaptan development programme.

Pharmacology

- Primary pharmacodynamics

A series of *in vitro* studies looked at the antagonistic effects of tolavaptan, its optical isomers, intermediates and metabolites at human, dog and rat V₂, V_{1a} and V_{1b} receptors. Tolavaptan demonstrated selectivity for V₂ over V₁ receptors in rat, dog and human *in vitro*, with inhibition constants at the V₂ receptor of 1.33±0.26, 0.66±0.09 and 0.43±0.06 nM, respectively. Selectivity was shown for human V₂ receptors over human V_{1a} receptors, but tolavaptan had no affinity for human V_{1b} receptors even at 10⁻⁴M. The optical isomers were no different from each other or from the racemate in their ability to antagonise the binding of [³H]- AVP (Arginine vasopressin) to V₂ receptors in HeLa cells. In dogs, the isomers were also equipotent at V₂ receptors, but S-(-) appeared to be more potent than R-(+)-tolavaptan at rat V₂ receptors. Metabolites were less potent than the parent compound.

Tolavaptan, its optical isomers and metabolites had no agonist activity in HeLa cells expressing human vasopressin V₂-receptors.

Tolavaptan had little or no affinity for a range of other ion channels and receptors, with a weak effect only at adenosine and oxytocin receptors which is not considered to be of clinical relevance.

In vivo, tolvaptan produced dose-related increases in urine volume and decreases in urine osmolality in conscious rats, mice, rabbits and dogs following single oral doses of up to 10 mg/kg. Excretion of electrolytes was not affected in dogs over a 6 hour period post-dose and in rats over 24 hours, although there was an initial increase in Na, K, Cl, creatinine and urea excretion during the first 4 hours post-dose in rats. In mice, there was also an increase in urinary Na, creatinine and urea nitrogen in the 0-4 h post-dose period, and in rabbits, an increase in urinary Na and Cl excretion at 10 mg/kg. Serum osmolality increased at 10 mg/kg in mice, rats and rabbits.

Repeated oral doses of tolvaptan at 1 or 10 mg/kg for 4 weeks in rats produced an aquaretic effect that was maintained for the duration of the study. Tolvaptan increased the excretion of AVP in this study but had no effect on serum or pituitary AVP levels, nor on the number of AVP receptors in the liver or kidney and may have resulted from increased AVP secretion from the pituitary.

An agonistic effect of tolvaptan was not seen in water-loaded, alcohol-anaesthetised rats, but tolvaptan antagonised the antidiuretic effect of AVP when administered intravenously (ED₅₀ 13 µg/kg). Tolvaptan also inhibited AVP-induced platelet aggregation (IC₅₀ 1.28µM), but did not itself induce platelet aggregation, therefore showing no V_{1a}-agonist activity.

In heart failure models in dogs, tolvaptan at 1 to 10 mg/kg induced aquaresis as in normal dogs, without any significant increases in urinary electrolyte excretion or changes in the renin-angiotensin-aldosterone system or stimulation of the sympathetic system. At 10 mg/kg it reduced cardiac preload but did not affect cardiac afterload or renal function. Plasma vasopressin was increased in this study. However the effect of tolvaptan at 10 mg/kg on serum osmolality varied between the studies. This difference was likely to have resulted from differing experimental conditions, with dogs in one study allowed free access to water and showing no change in serum osmolality, whilst those in the other study did not have access to water and had increased serum osmolality.

Tolvaptan increased survival in rats with acute progressive hyponatraemia from a dose of 1 mg/kg, and in an ischemia/reperfusion-induced model of myocardial infarction in SIADH rats, a dose of 10 mg/kg improved plasma sodium levels and osmolality to normal levels and significantly reduced infarct size.

A comparison of dietary vs. gavage administration in rats showed a more constant change in urine volume and osmolality when tolvaptan was administered in the diet. With gavage dosing, increasing the dose or the frequency of dosing prolonged the duration of the pharmacological effects.

- Secondary pharmacodynamics

In secondary pharmacology studies, tolvaptan has shown some potentially beneficial effects in animal models of human autosomal dominant polycystic kidney disease.

- Safety pharmacology programme

A core battery of safety pharmacology studies as indicated in CPMP/ICH/539/00 Note for Guidance was conducted. Those studies conducted after publication of the guidance were carried out in compliance with GLP.

Tolvaptan at oral doses of up to 1000 mg/kg had no effects on the central nervous system in mice, that is, no proconvulsive, analgesic or sedative effects, or effects on general behaviour, motor activity, or body temperature.

Cardiovascular effects were studied *in vivo* and *in vitro*. In anaesthetised dogs, heart rate and respiration rate increased and blood pressure decreased at 10 mg/kg intravenously, but these parameters were unaffected in conscious dogs following oral doses up to 1000 mg/kg, at which dose the serum C_{max} for tolvaptan was 2.83 µg/ml. T-wave amplitude of the ECG decreased at this dose, and following a 10 mg/kg intravenous dose in anaesthetised animals. *In vitro* studies in guinea pig papillary muscle and CHO-K1 cells stably transfected with the hERG channel showed tolvaptan had

no effect on action potential parameters or hERG current at concentrations up to 3×10^{-5} M and 2×10^{-6} M, respectively.

There were no effects on gastrointestinal motility *in vivo* or *in vitro* at clinically relevant concentrations.

Metabolites DM-4103 and DM-4107 were tested for respiratory and cardiovascular effects in dogs, behavioural effects in mice and inhibition of the hERG current *in vitro*. The only finding was an increased ST segment in the ECG in dogs with DM-4107 following an intravenous dose of 10 mg/kg (serum concentration 70.1 µg/ml).

- Pharmacodynamic drug interactions

Pharmacodynamic studies in normal rats and dogs and in congestive heart failure (CHF) dogs with tolvaptan and furosemide suggest that the aquaretic effect of tolvaptan is still evident when co-administered with furosemide.

Pharmacokinetics

Pharmacokinetic studies were conducted in rats, dogs and rabbits at oral doses up to 1000 mg/kg.

High performance liquid chromatography with ultraviolet detection (HPLC/UV) and liquid chromatography with tandem mass spectrometry (LC/MS/MS) methods were developed for the measurement of concentrations of tolvaptan and/or its metabolites in serum/plasma, urine, and/or tissues of mice, rats, rabbits, dogs, monkeys, and guinea pigs.

The methods were validated and the lower limit of quantitation (LLQ) for tolvaptan in serum by the HPLC/UV method was 2.5 to 100 ng/ml and the LLQ for each of the metabolites ranged from 20 to 100 ng/ml. The LLQ for tolvaptan in serum by the LC/MS/MS method was 1 to 5 ng/ml and the LLQ for the metabolites ranged from 1 to 5 ng/ml.

Stability of the samples under various collection/storage conditions was also investigated. Radioactivity was measured by liquid scintillation counting.

Initial studies used jet-milled tolvaptan. Absorption was relatively rapid (T_{max} ranging from 0.25h to 3.3h), as was elimination half-life (0.3 to 4.1h). C_{max} and AUC increased dose-dependently, but the increases were generally not linear, possibly due to high first-pass metabolism. The presence of food reduced C_{max} and AUC in male rats and dogs and delayed T_{max} in dogs compared with the values in fasted animals.

In fasted rats, exposure (C_{max} and AUC) to tolvaptan was greater in females than in males after a single oral dose. Following oral administration of [14 C]-tolvaptan, the proportion of unchanged tolvaptan to radioactivity in the serum was much smaller in males than in females, therefore male rats metabolise tolvaptan to a greater extent than females. Repeated oral administration of [14 C]-tolvaptan to male rats resulted in blood concentration of radioactivity increasing to steady state by day 12, which was 3.6 to 4.6 times higher than the blood level on day 1.

In comparison with the jet-milled tolvaptan, a spray-dried (SD) formulation produced higher C_{max} and AUC values for tolvaptan when administered orally to rats and dogs. Bioavailability of a 30 mg oral dose of jet-milled oral spray-dried tolvaptan was calculated to be 0.63% and 16% in male rats, respectively, and in male dogs, 2.0% and 14.6% respectively. Bioavailability is higher in humans (56%), but the animal species used for toxicology studies were generally exposed to tolvaptan and its principal metabolites (DM-4103 and DM-4107) to a greater extent than humans.

In fasted female rats, tolvaptan concentrations in the kidney were four times higher than in serum, but followed a similar pharmacokinetic time course.

In vitro and *ex vivo* plasma protein binding were high (>97% and >93%, respectively) in rat, dog, mouse, rabbit and human and independent of concentration over the ranges tested (0.1 to 10 µg/ml).

Furosemide, spironolactone, propranolol, disopyramide, lidocaine and warfarin had little effect on plasma protein binding of tolvaptan and its metabolites DM-4103 and DM-4107 and similarly, tolvaptan and DM-4103 had little effect on the binding of propranolol, lidocaine and spironolactone to human plasma proteins *in vitro*. Therefore the potential for interactions resulting from displacement of plasma protein binding is low.

Tissue distribution studies with [¹⁴C]-tolvaptan showed radioactivity mainly distributed to liver, GI tract and kidney, with little crossing the blood brain barrier (BBB) or into skin or eyes in male albino rats. In comparison, there were a larger number of tissues in female albino rats that had higher levels of radioactivity than serum, although there was again little crossing the BBB or in skin or eyes. A subsequent distribution study in male Long-Evans rats showed that the ratio of radioactivity in eyeballs and in skin to that in serum was similar to that in the albino rats, confirming that tolvaptan or its metabolites in the rat do not have a particular affinity for melanin and that there is little likelihood of it being distributed into the skin and eyes in pigmented animals.

Transfer of radioactivity across the placenta has been demonstrated in pregnant rats following oral administration of [¹⁴C]-tolvaptan, with highest levels in foetal liver. The ratio of radioactivity in foetal tissue to that in maternal plasma did not exceed 0.8 during the 48h post-dose period. Radioactivity was also present in milk when [¹⁴C]-tolvaptan was administered orally to lactating rats on day 14 post-partum. Levels in milk were higher than those in plasma, peaking at 8h post-dose. Section 4.6 of the Summary of Product Characteristics (SCP) reflects this information.

Tolvaptan is extensively metabolised in all species investigated. *In vitro* studies with rat liver supernatant produced a number of metabolites of tolvaptan. Hydroxylation of the benzazepine ring produced metabolites DM-4110, DM-4111 and DM-4119. Cleavage of the bond between the 1 and 2 positions of the benzazepine ring produced metabolites DM-4103, DM-4104, DM-4105 and DM-4107. Oxidation of the hydroxyl group at the 5 position in the benzazepine ring produced MOP-21826.

Human liver microsomes incubated with tolvaptan produced DM-4103, DM-4104, DM-4105, DM-4107, DM-4110, DM-4111, MOP-21826 and 3 unknowns. When incubated with the optical isomers of tolvaptan, there were some quantitative differences in metabolism. Both R-(+)-tolvaptan and S-(-)-tolvaptan produced DM-4103, DM-4104, DM-4105, DM-4107, DM-4110, DM-4111, DM-4119, DM-4120, MOP-21826 and an unknown, but the major metabolite from R-(+)-tolvaptan was DM-4104 and that from S-(-)-tolvaptan was DM-4110.

In vitro studies with recombinant human cytochrome P450 isozymes showed tolvaptan to be a substrate for CYP3A4, and an inhibitor of the metabolism of other CYP3A4 substrates as well as of CYP2C9. In this study, incubation with R-(+)-tolvaptan (DM-4101) produced DM-4111, MOP-21826 and DM-4119. S-(-)-tolvaptan (DM-4102) produced DM-4110, MOP-21826 and DM-4119. Therefore DM-4110 and DM-4111 were produced stereo-selectively in this assay.

Further *in vitro* studies demonstrated that DM-4103 is produced from MOP-21826 by way of DM-4105 in human liver supernatant (S9) fraction, and that DM-4128 is produced in the presence of β-NADPH and microsomal CYP3A4 and CYP1A1.

In vivo metabolism was investigated by analysing serum from rats, dogs, rabbits and mice following oral administration of tolvaptan or [¹⁴C]-tolvaptan.

Following a single oral dose of spray-dried tolvaptan (30 mg/kg), 6 metabolites (DM-4103, DM-4104, DM-4105, DM-4107, DM-4110 and DM-4111) were detected in serum of male dogs and male rats. In addition, MOP-21826 was detected in female rats. The ratio of serum concentration of the metabolites to that of the parent compound varied between rat and dog and between male and female rats. The metabolites in female rat serum were present at lower levels than was tolvaptan, whereas DM-4103, DM-4107 and DM-4110 were present in male rat serum at levels greater than the parent compound.

The rank order of serum radioactivity concentration two hours after oral administration of 30 mg/kg [¹⁴C]-tolvaptan to male mice, rats, rabbits and dogs was evaluated. The rank order in rat bile was also

investigated. There were at least 11 metabolites in the serum, and 28 in rat bile, some of which were not identified. Tolvaptan and the identified metabolites accounted for 75.5%, 85.3%, 57.6% and 58.1% of the serum radioactivity in mice, rats, rabbits and dogs, respectively. In rat bile, unidentified metabolites accounted for 39.1% of the radioactivity.

Therefore there were quantitative differences between the species but metabolism was qualitatively similar. The species chosen for the toxicity studies (rat and dog, and mice and rabbits for carcinogenicity and reproductive toxicity studies), were appropriate. There were no unique human metabolites.

Administration of the racemate to rats and male rabbits produced higher levels of R-(+)-tolvaptan than S-(-)-tolvaptan in the serum. The reverse was true in dogs. S-(-)-tolvaptan was not converted to R-(+)-tolvaptan in dogs, and R-(+)-tolvaptan was not converted to S-(-)-tolvaptan in rats. As the affinity of the isomers for the V₂ receptor is similar, any differences in the proportions of the isomers between the non-clinical species are unlikely to affect the interpretation of the results of the toxicity studies.

Repeated dosing of female rats reduced systemic exposure to tolvaptan. Analysis of the serum samples for metabolites DM-4103 and DM-4107 revealed increases in the concentrations of these metabolites following repeated dosing, and explained the reduction in serum tolvaptan concentrations. Furthermore, tolvaptan was shown to induce hepatic drug-metabolising enzymes (cytochrome b5 content and aminopyrine N-demethylase activity) in female rats after 7 days dosing at 300 mg/kg/day. Tolvaptan was both a substrate for, and inhibitor of, MDR1-mediated transport.

In rats and dogs, radioactivity was predominantly (90-95%) eliminated in the faeces. This was also the case in humans although a substantial quantity (about 40% of the dose) was also excreted in the urine, mainly as metabolites. As these metabolites are reported to have no activity at the levels found, and renal effects were not increased in the tolvaptan group compared with those on placebo, there would appear to be no clinically relevant effects on target organs as a result of the higher urinary excretion seen in man. In the animal species as well as man, tolvaptan clearance was mainly by metabolism.

Toxicology

- **Single dose toxicity**

Tolvaptan had low acute toxicity when administered to rats and dogs at 2000 mg/kg, the only findings being the presence of white material in the faeces and reduced food consumption.

- **Repeat dose toxicity (with toxicokinetics)**

Findings in the repeated dose toxicity studies in rats and dogs were generally related to the pharmacological effect of tolvaptan and consisted of increased urine volume, decreased urine osmolality and increased water consumption. Decreased body weight was also seen, and alterations in haematological parameters (decreased haemoglobin, erythrocyte count, haematocrit) and clinical chemistry parameters (including increased cholesterol, and changes in triglyceride and phospholipids, albumin/globulin ratios and electrolytes), which were reversible during a recovery period. There were no obvious target organs in either species, although there may have been a minimal effect on the adrenal cortex in dogs in the 52-week study resulting from enhanced cortisol production in response to tolvaptan-induced increases in plasma levels of AVP.

In the 26-week rat study, females had a higher systemic exposure to tolvaptan than males throughout the study. Re-analysis of the samples for metabolite concentrations confirmed that the metabolic rate was higher in males than females. Exposure to tolvaptan and to the metabolites increased with dose at each time point, but exposure to tolvaptan decreased later in the study compared with week 0, and metabolite exposure increased.

For the chronic dog study, AUC increased in proportion with dose except for the mid-dose females, where there was a supra-proportional increase. The C_{max} and AUC of the metabolites DM-4103 and DM-4107 increased with dose at week 52 in both sexes and were less than the values of the parent

compound. Unlike the rat, there appeared to be no sex differences in toxicokinetics, and values at week 52 were similar to those on day 1.

At the NOAEL in the 26-week rat study, the AUC in males and females was 4-times and 6.5 times, respectively, the AUC in humans following a 60 mg dose. The corresponding exposure margins at the NOAEL in the 52-week dog study were 9.8 and 13.2-times in males and females, respectively.

In male and female rats, metabolite DM-4103 was not toxic up to the maximum dose of tolvaptan tested in males (1000 mg/kg/day) and at a dose of 100 mg/kg/day in females. Due to the long half-life of DM-4103, exposure to this metabolite at steady state in humans was not measured, but, with the exception of female rats in the 26-week study, exposure to DM-4103 in the chronic rat studies was greater than that in humans on day 10 following daily doses of 60 mg tolvaptan.

- Genotoxicity

The battery of genotoxicity studies were conducted appropriately and yielded negative results. Previous studies have demonstrated exposure to both jet-milled and spray-dried tolvaptan at the doses used in the *in vivo* studies. Tolvaptan is not considered to be genotoxic.

- Carcinogenicity

Two-year studies in mice and rats were conducted. In neither study was there an indication of increased incidence of neoplastic lesions in relation to treatment with tolvaptan at doses up to 60 or 100 mg/kg/day in male and female mice, respectively, or up to 1000 mg/kg/day in rats. At the high doses in these studies, the AUC was 0.9- and 1.3- times that in man in male and female mice, respectively, and 3.9- and 10.4-times that in man in male and female rats, respectively. Therefore only in the rat study did serum levels of the parent compound exceed those in humans. However, despite the absence of safety margins in exposure in the mouse study, given the negative results of the genotoxicity and carcinogenicity studies, overall tolvaptan is not considered to be carcinogenic.

- Reproduction Toxicity

Two fertility studies in rats showed effects on the parental generation (decreased food consumption and body weight gain, salivation), but tolvaptan did not affect reproductive performance in males and there were no effects on the foetuses. In females, abnormal oestrus cycles were seen in both studies. The NOAEL for effects on reproduction in females (100 mg/kg/day) was about 16-times the maximum human recommended dose on a mg/m² basis.

A series of studies in pregnant rats and rabbits showed developmental toxicity in the rat foetuses (decreased body weight and delayed ossification) at a dose of 1000 mg/kg/day, and in rabbits (increased incidences of embryo-foetal death, microphthalmia, open eyelids, cleft palate, brachymelia and fused phalanx), also at 1000 mg/kg/day. There were abortions at the lower dose of 300 mg/kg/day in rabbits. Further studies in pregnant rabbits showed that the sensitive period for these effects was from days 6 to 11 of gestation, particularly between days 9 and 11. However, the mechanism of this effect was not clarified, despite investigations into the effects of water restriction and biotin deficiency.

Dosing from days 9 to 11 of gestation in pregnant rabbits at 300 mg/kg/day did not produce teratogenic effects and at this dose on day 11, AUC was 5.3 times that in humans after a 60 mg dose. Using a value of 8.117 µg.h/ml, obtained from a toxicokinetic study in which pregnant rabbits were dosed from day 6 to day 18 of gestation at 300 mg/kg/day, the exposure margin is only 2.5-times the human exposure.

According to the "Discussion paper on contraindications in pregnancy concerning sections 4.3, 4.6 and 5.3 of the summary of product characteristics" (CPMP/3833/03, June 2004) and the "Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling" (EMA/CHMP/203927/2005), when there is insufficient or no experience in human, the contraindication may be justified if there are pharmacological properties known to cause direct or indirect embryo-foetal damage which have to be considered as a strong signal and provided that other safer treatment options are available or treatment can be avoided or delayed until the pregnancy has ended.

The applicant has discussed the non-clinical evidence for teratogenicity. The period of particular sensitivity in the rabbit equates to around day 30 in a pregnant woman, who may at that stage be unaware that she is pregnant. As the safety margin is small, a contraindication in pregnancy seems warranted if safer alternatives are available. The applicant further discussed the availability of alternative, safer treatments during pregnancy for patients with symptoms of worsening heart failure and patients with euvolemic and hypervolemic hyponatraemia. In both cases, the options for management during pregnancy include conservative approaches, correcting the underlying causes and using treatments for which there is experience of use during pregnancy in those cases when there is an urgent need or the symptoms are severe. Such treatments may include beta-blockers, anti-arrhythmics or loop diuretics, depending on the condition requiring treatment. Therefore alternative treatments are available and the contraindication during pregnancy is accepted.

In the pre- and post-natal study, the NOAEL for the offspring was 100 mg/kg/day. Tolvaptan is excreted in the milk of lactating rats and the levels are higher than those in maternal plasma. The product is contraindicated in breastfeeding and this appears to be a suitably cautious approach. This is reflected in section 4.3 of the SPC.

There are no paediatric data currently for this product and no studies in the paediatric population have been planned or proposed. Juvenile animal studies have not been conducted or their absence discussed. There were perinatal deaths and reduced pup weight in the pre- and post-natal developmental study and tolvaptan may have adverse effects if administered to children. The applicant plans to prepare a Paediatric Investigation Plan (PIP) or PIP waiver prior to any future development of the product that involves the paediatric population.

- Toxicokinetic data

The major human metabolites DM-4103 and DM-4107 showed no significant toxicity when administered subcutaneously to male rats. Toxicokinetic analysis demonstrated that suitable exposures were achieved. Neither metabolite had mutagenic potential in *in vitro* tests.

The optical isomers of tolvaptan appeared to be more toxic than the racemate when administered as a single oral dose to female rats. Toxicokinetic analysis revealed that this was due to a greater systemic exposure when the single isomers were administered. It is considered that this greater exposure was due to a smaller particle size of the isomers when compared with that of the racemate. Both isomers were negative in *in vitro* genotoxicity studies.

- Local tolerance

Tolvaptan was not a dermal or ocular irritant, nor was it antigenic in guinea pigs. Repeated dosing of rats for 4 weeks with tolvaptan at doses up to 1000 mg/kg/day did not affect the humoral immune response to sheep red blood cell antigen.

- Other toxicity studies

In vitro phototoxicity studies showed tolvaptan and metabolite DM-4107 to have weak or very little phototoxic potential. Tolvaptan did not show any phototoxicity *in vivo* in guinea pigs and rabbits following repeated oral doses of up to 2000 mg/kg and 1000 mg/kg, respectively. Metabolite DM-4103 did show phototoxic potential *in vitro* however. The concentrations of the metabolites as well as of the parent compound were measured in the tissues in the *in vivo* studies. DM-4103 was present at < 0.125 µg/g in the guinea pig study, but up to about 6 µg/g in the rabbit study. The *in vivo* studies provide some reassurance that phototoxicity might not occur as a result of exposure to DM-4103, and the distribution study in partially pigmented Long-Evans rats showed that tolvaptan and its metabolites have little affinity for melanin. Consequently, the potential for phototoxicity reactions occurring in man is considered to be low.

Ecotoxicity/environmental risk assessment

The phase I calculation of Predicted Environmental Concentration (PEC) produced a value (0.3 µg/L) that was greater than the action limit of 0.01 µg/L, and therefore a Phase II Tier A assessment was

conducted. The outcome of the Tier A fate and effects analysis led to the conclusion that potential for bioaccumulation (because the Kow of 9000 exceeds the 1000 trigger value) and the effects on sediment dwelling organisms (because tolvaptan is not readily biodegradable and the results from the water sediment study demonstrate shift from water to sediment where >10% remains after 14 days) should be evaluated in Tier B. Data on bioaccumulation in fish (OECD 305) are being collected, and the report will be submitted as a post-authorisation commitment. On the basis of the data available so far, tolvaptan does not appear to present a risk to the environment.

2.4 Clinical aspects

Introduction

A number of disorders, including congestive heart failure (CHF), liver cirrhosis, and syndrome of inappropriate antidiuretic hormone (SIADH) secretion, are associated with increased AVP secretion. Increased AVP levels lead to excessive water retention accompanied by electrolyte imbalances, in particular hyponatraemia. Conventional therapy to treat these patients often exacerbates hyponatraemia and other electrolyte imbalances by promoting a loss of water together with electrolytes. A selective vasopressin V₂ receptor antagonist could neutralize the effects of the increased AVP levels and reduce water retention without disturbing electrolytic balance.

Tolvaptan (OPC-41061) is a vasopressin antagonist that blocks the binding of arginine vasopressin (AVP) at the V₂ receptors of the distal portions of the nephron, thereby inducing free water clearance (aquaresis) without depletion of electrolytes. The clinical development of tolvaptan was initiated in 1994 with early healthy subject trials conducted in Japan and has since been investigated extensively in hyponatraemia and heart failure patients. There is some overlap between the 2 indications that were originally filed in this application, and these 2 complementary tolvaptan programs have proceeded in parallel.

The tolvaptan clinical program for hyponatraemia and heart failure can be found in the Clinical Efficacy section.

The claimed indication for Samsca was:

- Treatment of patients with symptoms of worsening heart failure as add-on to standard of care such as diuretics, beta-blockers, angiotensin II antagonists, ACE-inhibitors, and digitalis.
- Treatment of euvolemic and hypervolemic hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion [SIADH], heart failure, and liver cirrhosis.

The approved indication and posology are the following:

- Treatment of adult patients with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Posology

“Treatment with tolvaptan should be initiated at a dose of 15 mg once daily. The dose may be increased to a maximum of 60 mg once daily as tolerated to achieve the desired level of serum sodium. During titration, patients should be monitored for serum sodium and volume status (see section 4.4). In case of inadequate improvement in serum sodium levels, other treatment options should be considered, either in place of or in addition to tolvaptan. For patients with an appropriate increase in serum sodium, the underlying disease and serum sodium levels should be monitored at regular intervals to evaluate further need of tolvaptan treatment. In the setting of hyponatraemia, the treatment duration is determined by the underlying disease and its treatment. Tolvaptan treatment is expected to last until the underlying disease is adequately treated or until such time that hyponatraemia is no longer a clinical issue.”

No scientific advice that is relevant to this application was given by CHMP. However scientific advice meetings were held with several National Competent Authorities.

The hyponatraemia development programme included CHF patients with hyponatraemia. Additionally a trial in hyponatremic patients with liver cirrhosis and Child-Pugh score less than 10 (156-96-203) was performed. Patients with significant/severe renal impairment were excluded from the development programme and therefore the information in this group is limited.

GCP

The CHMP requested a GCP inspection of the clinical study 156-03-236 EVEREST. Two investigator sites and the sponsor site in the USA were inspected in this routine GCP inspection. Although there was one critical finding at the Sponsor site, the Inspectors did not find evidence that the deficiencies found had impact on the overall validity and credibility of the data reported in this clinical trial and therefore deemed the inspected clinical trial as valid for use in the assessment of the marketing authorisation application for Samsca.

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

Tolvaptan drug substance is practically insoluble in water (0.00005 w/v% at 25°C), and the solubility is pH independent. In order to address the concern for low absorption the development proceeded with the SD powder formulation for further clinical studies.

Three specific biopharmaceutical studies were conducted in order to address the issues relating to the development of the tablet/capsule formulation in addition to one 'absolute bioavailability' study.

The PK studies in the dossier included:

- Single dose healthy volunteer studies (dose ranging from 15-480mg);
- Single dose in patients;
- Multiple dose study in healthy volunteer;
- Multiple dose study in patients with heart failure or hyponatraemia 5-60mg;
- Interaction studies (CYP3A4 inhibitors/inducers, substrates and transporters such as P-gp)

The analytical methods described included dissolution methods. Four different analytical methods were used for analysis of tolvaptan and metabolites and almost all used plasma as the matrix of the measurement. For absolute bioavailability studies the HPLC-tandem MS method with high sensitivity was used. Most studies assessed the following parameters; C_{max} (ng/ml), T_{max} (h), AUC_{∞} (ng.h/ml), $t_{1/2}$ and z (h). The comparisons were carried out using geometric mean ratios of C_{max} and AUC. Additionally, AUC_t , clearance (CL) and bioavailability (F) and a ratio of CL/F were estimated in different studies.

A population PK model for tolvaptan to estimate the model parameters, assess inter-subject variability and evaluate effects of covariates using two core data sets one for heart failure and another for patients with hyponatraemia of any aetiology was developed. An additional hyponatraemia analysis that included those with hyponatraemia at baseline from either trial set (HypoNa or CHF) was also performed. The covariates investigated for all patients included:

- demographics (age, gender and race),
- body metrics (body weight, lean body mass, BMI),
- liver function,
- renal function (calculated creatinine clearance),
- concomitant medications (diuretics, CYP3A4 inhibitors or inducers and P-gp interactions)

and for hyponatraemia patients:

- the severity of hyponatraemia,
- disease association and
- volume status.

A covariate modelling approach emphasizing parameter estimation rather than stepwise hypothesis testing was implemented for this population PK analysis. Where appropriate a bootstrap procedure was used to estimate the uncertainty of the parameter estimates.

- Absorption

Although tolvaptan is poorly soluble in water, following single dose of 30-480 mg, it is absorbed rapidly with a median time to peak plasma concentrations of about 2 hours (range of 1-12 hours) in healthy subjects. The mean (SD) of elimination half life is 7.8 (4.9) hours. C_{max} increases linearly with dose ranging from 30 to 300 mg and a plateau is noted at doses >300mg. The AUC increases linearly over the clinical dosing range (15-60mg doses) although at higher doses the C_{max} increase is not dose proportional.

The absolute bioavailability is ~56% with close relative bioavailability between different dose strengths. Food has little effect on the tolvaptan tablet formulations as evidenced by studies using both the high fat meal (FDA recommended: >50% of calorie content from fat) or the Japanese standard meal. Both high fat meal and a Japanese standard meal have similar effects, with no significant or clinically relevant food effect.

- Distribution

Tolvaptan primarily resides in the plasma rather than red blood cells. Protein binding was extensive at 98.6% for ^{14}C -labelled tolvaptan obtained from *in vitro* studies using human materials. In the plasma, it was bound mainly to serum albumin and α_1 -acid glycoprotein. The mean unbound fraction was higher in patients with liver disease.

The commercially available form is a racemate with R and S enantiomers and both enantiomers are stable in plasma. Both enantiomers were found to be equally potent at the V_2 receptor in *in vitro* binding studies. Following single doses, the concentrations of S (-) enantiomer is consistently higher in the plasma. Tolvaptan exhibits a low level of intra-subject variability in healthy volunteers.

- Elimination

After IV administration, a half-life was estimated to be 3.5 hours, but it is suggested that this value most likely represents a distribution half-life and not a true elimination half-life. There is high variability for terminal half-life values, mainly because the number of points in the terminal elimination phase was often insufficient, particularly with the lower doses.

Tolvaptan is metabolised extensively in humans by the CYP3A4/5 system with seven metabolites (DM-4103, DM-4104, DM-4105, DM-4107, DM-4110, DM-4111, DM-4119) detected in the plasma, urine, and faeces of all subjects in a ^{14}C mass balance study. After administration of [^{14}C]-tolvaptan, 13 metabolites were identified in human plasma. Tolvaptan and identified metabolites accounted for about 70% of administered radioactivity. The predominant metabolite, with >50% of the total dose using the mass balance approach was DM-4103. The terminal elimination half-life of DM-4103 is ~183 hours and after multiple dosing DM-4103 shows accumulation by day 28, but this appears pharmacologically inactive in the concentrations achieved using clinically relevant doses. Only 3% of the radioactivity was due to unchanged tolvaptan in the plasma.

Data from the mass-balance study show that about 40% of the administered dose was excreted with urine as unchanged tolvaptan plus metabolites; the parent drug was only ~0.2% of the administered dose. The major analyte in urine was DM-4107, which accounted for 23% of the excreted radioactivity, followed by DM-4111, which accounted for 14.09% of the radioactivity. Tolvaptan and several metabolites were also detected in the faeces. Metabolites identified in faeces accounted for about 19% for the administered dose. Therefore, this value estimates the approximate fraction of the absorbed dose excreted with the faeces. Renal clearance of tolvaptan is negligible.

- Dose proportionality and time dependencies

Overall, there is good dose-proportionality in the range of therapeutic doses. With higher doses, absorption rate and BA may decrease, probably due to the limited solubility of the drug.

The data of both healthy subjects and heart failure patients indicate that there is no or minimal accumulation of tolvaptan following multiple administration. Drug clearance also showed no time dependency.

- Special populations

In the target population the PK parameters C_{max} and AUC increased linearly with dose for single doses 10-60 mg of tolvaptan and were higher compared to healthy volunteers. In CHF mean C_{max} values are 1.19 to 1.85-fold higher and mean AUC values are 1.73 to 3.3 fold higher. In liver disease patients (HypoNa) a small increase in C_{max} (1.07 to 1.65 fold) and a larger increase for AUC (1.56 to 2.75 fold) are noted with single dosing. After multiple dosing (13 days), tolvaptan concentrations also appear to accumulate 1.7- to 1.8-fold.

The applicant used the child-Pugh scoring system in assessing patients with liver disease. Dosing in those patients with severe hepatic impairment should be cautious and as experience with Child–Pugh Class C is limited; this is reflected in the SPC.

Tolvaptan PK is not affected by age and gender in humans in the studies submitted (although in animal models a gender difference was noted). The gender variation of this metabolite seen in study 156-98-202 can be attributed to high variability. Patients with renal impairment have not been studied systematically although there are some studies in those with adult polycystic kidney disease. This is important missing information as both PK and PD could be different of tolvaptan could be different in these subjects. This further discussed in the PD section. The applicant has committed to further studying this as a post-authorisation commitment.

- Pharmacokinetic and pharmacodynamic interaction studies

Tolvaptan showed an expected level of interaction with CYP3A4 inhibitors and inducers as well as P-gp substrates-digoxin. Inhibition by ketoconazole caused a 5-fold increase in tolvaptan AUC, a 3-fold increase in C_{max} , and a 50% increase in half-life. Grapefruit juice increased tolvaptan C_{max} by 86% and AUC by 56%. Consistently, it was found that the CYP inducer rifampicin decreased tolvaptan C_{max} and AUCt by 83% and 87%, respectively. The effect of CYP3A4 inhibition or induction on the PK parameters varied among metabolites because some of them are also metabolised by CYP3A4.

No relevant interaction was noted between statins, amiodarone and warfarin with tolvaptan. Caution is necessary when digoxin is administered concomitantly (1.3-fold increase in digoxin maximum observed plasma concentration). Tolvaptan also increased the mean trough serum concentrations of digoxin at steady state and decreased digoxin renal clearance by 59%. As such patients receiving digoxin should be evaluated for excessive digoxin effects when treated with tolvaptan. Finally, the PK and PD interactions between tolvaptan and furosemide or hydrochlorothiazide were also studied with no significant findings. Tolvaptan has not demonstrated a clear interaction with antiplatelet agents (Please see safety section for details).

Metabolite DM-4103 does not have potential for interaction at steady-state concentrations.

- Pharmacokinetics using human biomaterials

Although no true *in vitro* studies assessed the drug interactions of tolvaptan this is compensated by the *in vivo* studies which have been performed.

Pharmacodynamics

The pharmacodynamic properties of tolvaptan were investigated in:

- four single dose trials with healthy subjects,
 - two single dose trials in patients with stable heart failure,
 - two multiple dose trials in healthy subjects and,
 - three multiple dose trials in patients with hyponatraemia secondary to liver disease and stable heart failure.
- Mechanism of action

Tolvaptan (OPC-41061) is a vasopressin antagonist that blocks the binding of arginine vasopressin (AVP) at the V_2 receptors of the distal portions of the nephron. Animal pharmacology studies indicated that tolvaptan should increase excretion of water without increasing excretion of electrolytes (aquaresis) and thus offer a means of correcting serum sodium concentration by inducing excretion of water without loss of serum electrolytes. Tolvaptan is about 29 times more selective for V_2 receptors than for V_{1a} receptors with virtually no binding to V_{1b} receptors.

- Primary and Secondary pharmacology

Tolvaptan increased urine excretion at concentrations as low as 25–40 ng/mL; urine volumes for 0 to 2 hours post-dose following 1 hour IV infusion of tolvaptan are about 66% higher compared to placebo. A maximal increase in urine excretion rate (3–5 times greater than baseline) appears to be reached when tolvaptan concentrations are greater than 150 ng/mL. The offset of tolvaptan action also appears to be rapid. Following 60 to 120 mg doses, urine excretion rate returns to baseline values by 26 hours post-dose as plasma concentrations drop below 25 ng/mL. Marked elevations of tolvaptan plasma concentrations, much above those achieved with a 60 mg dose produce a sustained, but not a greater magnitude of response, as active concentrations of tolvaptan are present for longer periods of time. Following 28 multiple dosings, mean plasma AVP concentrations were 2–4 pg/mL higher for tolvaptan-treated subjects compared to placebo. On Day 1, mean 0–24 hour urine volumes were 4825, 5419 and 2256 mL for the 30 mg, 60 mg and placebo groups, respectively; on Day 7, the volumes were 3974, 4807 and 1342 mL, respectively.

Similar effects were seen in patients with heart failure and hyponatraemia. Following multiple oral doses of 10 to 120 mg tolvaptan to subjects with stable heart failure, 24-hour urine output on Days 2 and 3 was about 20% less than observed on Day 1 for the 60, 90 and 120 mg doses. In patients with hyponatraemia no dose response was seen for increases in 24-hour fluid volume. Following a single dose, 5 mg produced no changes in 24-hour urine volume and doses of 10 to 60 mg appeared to increase urine volume 1.33- to 2-fold.

In patients with hyponatraemia secondary to liver disease the increases in plasma sodium concentration and increases in urine volume were roughly dose-related over the 5–60 mg/day dose range. Only the 30 and 60 mg/day doses caused weight losses consistently greater than placebo. In the majority of cases, tolvaptan-treated patients showed lower urine osmolality than placebo-treated patients.

Tolvaptan significantly increased the effective renal plasma flow (9%) and renal blood flow (10%) compared to placebo and furosemide. There were also increase in glomerular filtration rate (GFR) (1.37ml/min) and decrease in renal vascular resistance.

The fluid balance following tolvaptan in all subjects (healthy volunteers, CHF or liver disease) tended to be negative by day 2. However, the response showed large variability without dose response, especially in healthy volunteers:

- Dose dependent increase in ‘Free water clearance’- in healthy volunteers and CHF with the magnitude following the same pattern as urine volume (plateau and fall).
- Mean AVP concentrations increase variably in the range 2 to 9 pg/mL after single oral doses (30 to 480 mg) and the increases were highly variable and not dose-dependent.
- After single oral dose of tolvaptan (60 to 480 mg), changes in plasma renin activity (PRA) and plasma aldosterone were small, highly variable and not dose dependent.
- Changes in plasma norepinephrine concentrations were highly variable and were similar to placebo after single oral dose of tolvaptan ranging from 60 to 480 mg.

Plasma/ Serum sodium:

Single oral doses of tolvaptan ranging from 60 to 480 mg, increased serum Na⁺ concentrations approximately 4 to 6 mEq/L at 4 h post-dose and the increase was maintained for at least 24 hours. These were not dose-dependent (similar to urine volume). The changes in serum sodium in patients with heart failure were assessed in 7 clinical trials including the long-term outcome trial that is discussed in the efficacy section. In all trials serum sodium concentrations increased with correction of hyponatraemia. Using a pooled analysis of phase-2 studies (4 trials), short term effects on sodium at days 1 and 6 and weeks 1 and 2 were similar with increases in serum sodium compared to baseline.

Short term haemodynamic effects were noted in those with CHF. Short term antagonism of the V₂ vasopressin receptor produces favourable haemodynamic effects in advanced heart failure. Pulmonary capillary wedge pressure (PCWP), RAP and PAP were reduced compared to placebo while no effect on cardiac index, systemic vascular resistance (SVR) or pulmonary vascular resistance (PVR) were

noted. The reduction in PCWP did not show dose dependence but was associated with dose dependent increase in urine output and free water clearance.

Tolvaptan exhibits only a partial relationship between concentration and effect. The explanations may include: a down regulation of the V_2 receptors or a negative fluid balance after first day of administration. Irrespective of the explanations, the clinical relevance of this is that the optimal clinical dose range varies from 15-60 mg. A maximal increase in urine excretion rate appears to be reached when tolvaptan concentrations are greater than 150 ng/mL. It should be noted that although plasma concentrations are still greater than 150 ng/mL at 24 hours following doses of or greater than 180 mg, urine output is considerably less from 24 to 48 hours than compared to the first 24 hours.

As would be anticipated, there is some pharmacodynamic interaction between tolvaptan and diuretics. An increase in free water clearance and urine volume were higher, but urine osmolality lower. Free water clearance was increased following tolvaptan administration alone and in combination with either furosemide or hydrochlorothiazide (HCTZ). Co-administration with furosemide or HCTZ did not change the effect of tolvaptan. There does not appear to be any clinically relevant, unexpected potentiation, permitting the concomitant use of tolvaptan with these agents. Tolvaptan appeared to augment the increase in PRA elicited by furosemide, but not that elicited by HCTZ. It is considered that tolvaptan increases K^+ excretion but affects PRA minimally. Data from pivotal trials did not show any clinically relevant reduction in dose, frequency of administration of either loop diuretics or antimineralocorticoid diuretics. This is surprising given the aquaretic effect of tolvaptan, but is likely to have been influenced by the fact that diuretic doses were investigator determined.

Patients with renal impairment have not been studied systematically although there are some studies in those with adult polycystic kidney disease. Data from the EVEREST trial (Efficacy of Vasopressin antagonism in heart failure: outcome Study with Tolvaptan) show that the efficacy parameters did not differ in this study based on the classification of subjects in accordance to GFR values of >60 ml, 60-30 ml and <30 ml. Based on the data from pivotal trials, the effect of tolvaptan shows a decreasing trend in most parameters (free water excretion, urine osmolality change and change in serum sodium) as renal function decreases. This analysis is limited due to the fact that there were few subjects in the pivotal trials who had severe renal dysfunction (GFR <30 ml/min).

Similar findings were seen in relation to the adverse event rates. However, the small numbers ($n=286$) make definitive conclusion difficult. Those with GFR <30 ml show a trend towards less effect in most parameters or numerically worse outcome. In the safety analysis, a comparison of parameters between GFR <50 ml and 30-60 ml is made and here, blood urea nitrogen (BUN) rose considerably in those with GFR 30-60 ml in both heart failure and cirrhosis. Cirrhotic subjects showed a greater increase in potassium in the same GFR subgroup. It stands to reason that in chronic kidney disease there is a reduction in nephron numbers (and consequently the distal tubule) and consequently there is likely to be a reduction in V_2 receptor density. As stated above the applicant agrees on the need to study those with severe renal impairment in a PK-PD study as a post-authorisation follow up measure.

Clinical efficacy

The tolvaptan clinical program for hyponatraemia consists of 6 trials:

- two placebo-controlled phase 3 trials,
- three placebo-controlled phase 2 trials and,
- one open-label phase 3 trial.

The efficacy of tolvaptan in the treatment of hyponatraemia was evaluated in three phase 3 hyponatraemia trials:

- pivotal trials (156-02-235 and 156-03-238),
- one open-label trial (156-03-244)

and two phase 2 hyponatraemia trials (156-96-203 and 156-97-204).

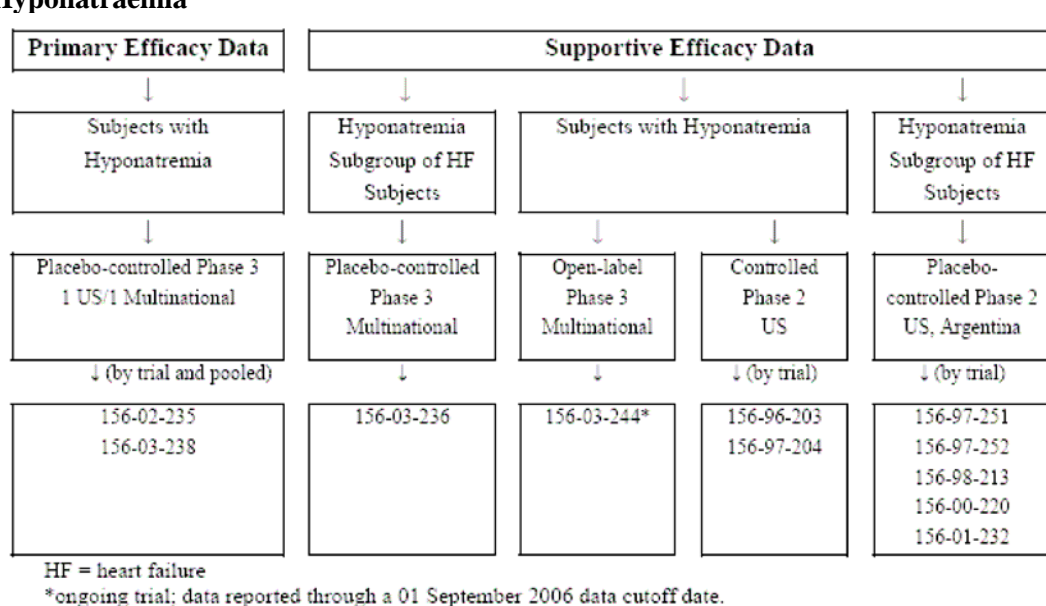
The tolvaptan doses investigated in hyponatraemia subjects were fixed doses of 5, 10, 15, 30, and 60 mg QD and titrated doses among 10, 15, 30, 45, and 60 mg QD. In all but 2 of the hyponatraemia trials (156-96-201 and 156-96-203), tolvaptan doses were titrated based on serum sodium response.

There were 6 heart failure trials having subpopulations of hyponatraemic subjects:

- one phase 3 heart failure trial (156-03-236) and
- five phase 2 heart failure trials (156-97-251, 156-97-252, 156-00-220, 156-01-232, 156-98-213).

The hyponatraemic subgroup from the heart failure trials were evaluated as supportive data. A phase 2 hyponatraemia trial (156-96-201) was stopped due to lack of enrolment and this trial is not included because it evaluated a dose lower than the range of interest. With the exception of the open-label phase 3 hyponatraemia trial (156-03-244) and an open-label active-controlled (fluid restriction with placebo) phase 2 hyponatraemia trial (156-97-204); all of these trials were of a randomized, double-blind, multiple dose, placebo-controlled design. The figure and table below lists the clinical efficacy trials for tolvaptan for hyponatraemia in further detail.

Organization of Trials for Hyponatraemia



List of Clinical Efficacy Trials of Tolvaptan for Hyponatraemia

Protocol # Trial Location Trial Phase # Trial Sites	Trial Objective Trial Duration	Trial Design and Choice of Control	Trial Drug Dose, Route, and Regimen	Subjects By Arm Entered/ Completed	Gender (%) Race (%) Mean Age (Range) (years)	Diagnosis Main Inclusion Criteria	Primary Efficacy
156-02-235 United States Phase 3 42 sites	Efficacy, safety, and PK 30 days	R, DB, PC, Parallel	Tol PO QD (15 mg start dose, titrated as needed 15, 30, or 60 mg) PLA QD (titrated)	102/75 103/62	44.4% F 71.7% Caucasian; 14.6% Black; 10.7% Hispanic; 1.5% Asian; 1.5% Other 60 (18-90)	Serum Na+ < 135 mEq/L. ~ 50% subjects w/serum Na+ of < 130 mEq/L at baseline w/CHF, cirrhosis, SIADH, etc;	Average daily AUC Na+ concentrations up to Days 4 and 30.

156-03-238 Multinational Phase 3 72 sites	safety, and PK 30 days	DB, PC, Parallel	TOL PO QD (15 mg starting dose, titrated as needed among to 30, or 60 mg) PLAQD (titrated)	123/89 120/85	39.1%F 93.4% Caucasian; 1.6% Black; 3.7% Hispanic; 0.4% Asian 0.8% Other 63 (27- 100)	Na serum < 135 mEq/L at baseline. ~ 50% of subjects had serum Na < 130 mEq/L at baseline. CHF, cirrhosis, SIADH, etc;	AUC change from BL serum Na+ concentrations up to Day 4 or 30.
156-96-203 United States Phase 2 7 sites	Efficacy, safety, and PK 13 days	R(2:1), DB, , PC, sequential- cohort, ascending- dose	Tolvaptan Tablets PO QD: 5 mg 10 mg 15 mg 30 mg 60 mg Placebo QD	6/2 6/4 6/4 6/4 15/9	28.9% female 71.1% Caucasian; 24.2% Hispanic; 2.2% Black; 2.2% Other 52 (37-73)	liver disease ≥30 days, Child-Pugh score < 10. Plasma Na+125-135 mEq/L. Plasma K+3.4-5.0 mEq/L Peripheral edema and/or ascites.	Plasma sodium concentrations
156-96-201 United States Phase 2 3 sites	Efficacy, safety, PK Up to 9 days	R, DB, PC, Sequential dose- ranging	TOL PO 5 mg QD 10 mg QD 15 mg QD 30 mg QD PLA QD	6/5 3/3	44.4% female 77.8% Caucasian; 22.2% Hispanic Tolvaptan: 56 Placebo: 57	Hospitalized adults w/ hyponatremia secondary to CHF.	Plasma sodium concentrations
156-97-204 United States Phase 2 24 sites	Efficacy safety, and dosing characteristics Up to 26 days	Rand (2:1), O-L, A-C (PLA with fluid restriction), dose titration	Tablets PO 10 mg, 15 mg, 30 mg, 45 mg, and 60 mg QD (titrated to effect) Placebo QD	17/6 11/2	42.9% female 78.6% Caucasian; 14.3% Black; 7.1% Hispanic 67 (41-88)	Serum Na < 135 mEq/L, normal ECF or evidence of extracellular volume expansion.	Serum Na concentrations

The heart failure programme included a total of 7 multiple-dose placebo-controlled safety and efficacy trials:

- six phase 2 trials and
- one pivotal phase 3 trial

plus 1 supportive phase 2 single-dose haemodynamics trial. The tabulated list is shown below.

Summary table of heart failure programme

Study ID	No. of centres / locations	Design	Study Posology	Study Objective	Subjs by arm	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
Pivotal Study									
03-236	Multi	R, DB, PI Embedded	T30 Vs PLA	Mort/Morb	2072/2061	Min 60 days	3075/1058, 60y	CHF	Mort, morb
Supportive studies									
01-232	US, 38	R,DB, PC	T30, PIA	Card Remodel	120/arm	54 wks	196/44 64 y	CHF/LVD	LV vol reduction
98-213	US, Arg, 46	R,DB, PC	T30-90, P	Phs-2; Eff	61 days		224/95 62 y	CHF III-IV	LVF Worsening
00-220	US, Arg, 67	R,DB,PC	T15-60, P	Phs-2: Eff	82/arm	169 days	223/107, 65 y	CHF II-III	Clinical status
00-222	US 18	R,DB,PC & Furo	T30, PL, Fu 80	Phs-2; Eff	20/arm	7 days	67/16, 59 y	CHF +HyperVol	Chng in BW
00-251	US 10	R(2:1), DB, PC,	T10-120, PL,	Dose ranging	6 /arm	13 days	34/21, 64y	CHF	BW chng day 1 & 3
97-252	US 30	R,DB,PC	T30-60	Dose ranging	64/arm	25 days	163/91, 67	CHF	BW on day 14
04-257	Multi 48	R,DB,PC	T15-60	Haemo	44/arm	SD	144/37, 60y	CHF	PCWP, 3-8 hrs
Additional study									
96-201	US	R (2:1),DB, PC, Seq	T5, 10, 15, 30	Eff- Hypo in CHF	6 + 3	4 days		CHF + hypo	Clinical + Na+

- Dose response studies

In the heart failure programme there were two main dose response studies and one haemodynamic study forming the basis of the dose recommendation in the pivotal study and for the proposed clinical use.

Study 97-252

Four groups of 60 subjects were randomly assigned to receive 30, 45, or 60 mg of tolvaptan or placebo daily for 25 days in this dose defining trial. The primary efficacy variable was the change from baseline in body weight.

Mean decreases from baseline in body weight, were observed on Day 1 of tolvaptan treatment at all doses and were maintained throughout the trial. These changes (mean decreases of 0.35 to 1.02 kg) were statistically significantly different from that of placebo (mean increases of 0.32 to 0.59 kg). All three tolvaptan doses decreased urine osmolality at all time points with statistically lower ($p < 0.05$) urine sodium concentrations. Tolvaptan at all three doses produced small, but significant ($p < 0.05$) increases (< 4 mEq/L) in mean serum sodium concentrations. Neither the QoL assessment nor the cardiovascular assessment scores showed differences between the tolvaptan dose groups and the placebo group.

Study 00-251

Six groups of subjects were randomized in the following order: 10, 15, 30, 60, 90, and 120 mg. In each treatment group, 6 subjects received tolvaptan and 3 subjects received placebo except for the 10 and 120 mg groups. The primary efficacy variable was the change from baseline in body weight, while urine osmolality, urine volume, and urine sodium excretion were the secondary efficacy variables.

Overall mean decreases from baseline were observed in the tolvaptan treatment groups at doses of 15 to 120 mg (body weight; -0.1 to -2.9 kg) and in the placebo group (-0.2 to -1.9 kg) during the treatment period.

Study 04-257 (haemodynamic study)

In this study doses of 15, 30 and 60 mg were compared in ~180 subjects (44 in each arm) with baseline PCWP > 18 mm Hg. Haemodynamic measurements and PK samples were obtained for 8 hours (and optionally for up to 24 hours). The main outcome measures included PCWP, right arterial

pressure (RAP), pulmonary arterial pressure (PAP), cardiac index and systemic vascular resistance in addition to urine volume, urine osmolality, and free water clearance.

The primary statistical analysis for the overall comparison among the treatment groups of placebo and of 30 and 60 mg tolvaptan approached statistical significance (F-test, $p = 0.0563$). The pair-wise comparisons of 15, 30, and 60 mg tolvaptan versus placebo each showed a statistically significant decrease in peak change in PCWP from 3 to 8 hours post-dose ($p = 0.0027$, $p = 0.0443$, and $p = 0.0328$, respectively). No significant differences between the tolvaptan doses were seen with respect to the magnitude of the peak change in PCWP relative to placebo. The absence of a reduction in peripheral resistance and cardiac index suggests that the favourable effect of tolvaptan on filling pressures is secondary to the enhanced urine output.

The conclusion from the dose response studies is that they provide a rather limited evidence for dose response and doses studied. Some evidence that 30 and 60 mg doses produce an effect is shown although the dose response slope is likely to be flat. This is evidenced best in the haemodynamic study where the reduction in PCWP or RAP and PAP were not dose dependent. Tolvaptan has a clear effect on urine volume, serum sodium and osmolality with potential for benefit in those 'difficult to treat patients' with heart failure.

In general the dose response studies in the hyponatraemia programme are similar to heart failure programme. As previously highlighted, with single oral doses of tolvaptan ranging from 60 to 480 mg, serum Na^+ concentrations increased approximately 4 to 6 mEq/L at 4 h post-dose and the increase was maintained for at least 24 hours. Most hyponatraemia studies used the dose titration scheme.

All hyponatraemia trials evaluated tolvaptan doses between 15 and 60 mg in subjects having baseline serum sodium concentrations < 135 mEq/L. Lower doses were also evaluated in two phase 2 trials (5 and 10 mg in Trial 156-96-203 and 10 mg in Trial 156-97-204). Fixed doses of 5, 10, 15, 30, and 60 mg were used in one phase 2 trial (156-96-203).

Study 156-96-203

This study was designed to assess the efficacy, safety, and pharmacokinetic characteristics of daily doses of up to five dosage levels of tolvaptan in subjects with hyponatraemia secondary to liver disease. Five groups of 9 subjects were randomized on Day 1 into the following dose groups: 5, 10, 15, 30, and 60 mg. In each treatment group, 6 subjects received tolvaptan QD and 3 subjects received a matching placebo QD. The subjects were hospitalized during the first four days of treatment. Dose escalation was evaluated at the completion of each dose group.

The conclusion obtained from the hyponatraemia dose finding studies is that tolvaptan, at doses of 5, 10, 15, 30, and 60 mg QD resulted in higher mean increases in plasma sodium compared to placebo. Tolvaptan at doses of 30 and 60 mg was associated with consistently greater body weight loss compared to placebo; however, at doses of 5, 10, and 15 mg was associated with inconsistent body weight loss.

- Main studies

HYPONATRAEMIA PROGRAMME

Pivotal Studies: SALT 1 and SALT 2

- Study 156-02-235: Multicenter, randomized, double-blind, placebo-controlled, efficacy and safety study of the effects of titrated oral tolvaptan tablets in patients with hyponatremia. "SALT 1 TRIAL" (Sodium Assessment with Increasing Levels of Tolvaptan in Hyponatremia 1)
- Study 156-03-238: International, multicenter, randomized, double-blind, placebo controlled, efficacy and safety study of the effects of titrated oral tolvaptan tablets in patients with hyponatremia. "SALT 2 TRIAL" (Sodium Assessment with Increasing Levels of Tolvaptan in Hyponatremia 2)

METHODS

Study Participants

Subjects were males or females 18 years of age or older. In both trials, the subjects enrolled had non-acute euvolemic or hypervolemic hyponatraemia, defined as serum sodium <135 mEq/L (mmol/L) irrespective of aetiology (including CHF, liver disease or Syndrome of inappropriate ADH secretion [SIADH]).

Among other exclusion criteria, subjects were excluded if they were hypovolemic; had hyponatraemia due to head trauma, post-operative state, medicinal therapy that could be safely withdrawn (e.g. thiazide diuretics), laboratory artefacts or psychogenic polydipsia; received other treatment for hyponatraemia (demeclocycline, lithium carbonate or urea); or required intravenous saline for severe hyponatraemia.

Treatments

Subjects are initially randomized to tolvaptan 15 mg once daily or placebo. The dose was individually optimized for each subject: the initial dose of tolvaptan could be increased to 30 mg and then 60 mg, if the response to the previous dose was inadequate (i.e. if the change in serum sodium level from the previous measurement was < 5 mEq/L and if the sodium concentration remained < 135 mEq/L).

Objectives

These two pivotal phase 3 trials were identical in design. The primary objective was to demonstrate that tolvaptan is a safe, effective, and useful agent for achieving and maintaining increased serum sodium for the treatment of non-hypovolemic hyponatraemia arising from a variety of aetiologies over a 30-day treatment period in both trials.

Outcomes/endpoints

The primary endpoint was the change from baseline in mean daily AUC of serum sodium concentration. AUC provided a more complete picture than a single point measurement.

Secondary end-points include other serum sodium parameters and clinical endpoints such as body weight change (for hypervolemic subjects), health status (SF-12 questionnaire), percentage of subjects requiring fluid restriction 24 hour urine volume, 24 hour fluid intake, hyponatraemia disease specific survey, neurological examination and symptoms and signs, and percentage of treatment failures requiring saline infusion.

Sample size

It was calculated that a sample of 100 patients per group would yield more than 90% power (with a two-sided significance level of 0.025) to detect a mean (\pm SD) between-group difference of 1.99 ± 2.7 mmol of sodium per liter in the change from baseline to day 4 and of 3.00 ± 3.28 mmol of sodium per liter from baseline to day 30. With similar assumptions, the inclusion of 50 patients with marked hyponatraemia in each group would yield 90% power (with a two-sided significance level of 0.05).

Randomisation

Subjects satisfying the study entry criteria were randomized at Day 1. Randomization was performed in a 1:1 ratio (tolvaptan 15 mg or placebo). Randomization was stratified based on the subject's baseline serum sodium level (< 130 mEq/L and 130-134 mEq/L) with a target of 50% of the subjects having a serum sodium value of < 130 mEq/L.

The second stratification was based on the subject's underlying disease state (CHF or non-CHF) with no aetiology representing more than 50% of the subjects.

Blinding (masking)

Subjects received tolvaptan or matching placebo in a randomized, double-blinded fashion. Study medication was supplied for each subject in monthly kits per randomization number, each labeled with a two-panel double-blind disclosure label specifying the treatment assignment in the concealed portion of the label. The study drug was packaged so that each subject received an identical number of tablets regardless of the treatment group assignment. All tablets were identical in appearance.

Statistical methods

The change in the average daily AUC for the serum sodium concentration from baseline to day 4 and from baseline to day 30 (the two primary end points) was calculated as the AUC for each patient, divided by the observation period (4 or 30 days), minus the baseline value. The sodium changes in the two study groups were compared with an analysis of covariance (ANCOVA) model in which the group assignment and baseline stratification factors were covariates.

Serum sodium concentrations were compared between study groups with the use of the ANCOVA model and the covariates noted above. The percentage of patients in whom serum sodium concentrations normalized (>135 mmol per liter) or fluid restriction was used was analyzed with the Cochran–Mantel–Haenszel test and the baseline stratification factors. Shifts comparison in the categorical change in hyponatraemia in the two groups with the use of the Cochran–Mantel–Haenszel mean score test, was performed by using a modified riddit score (van Elteren test), with cause as a stratification factor.

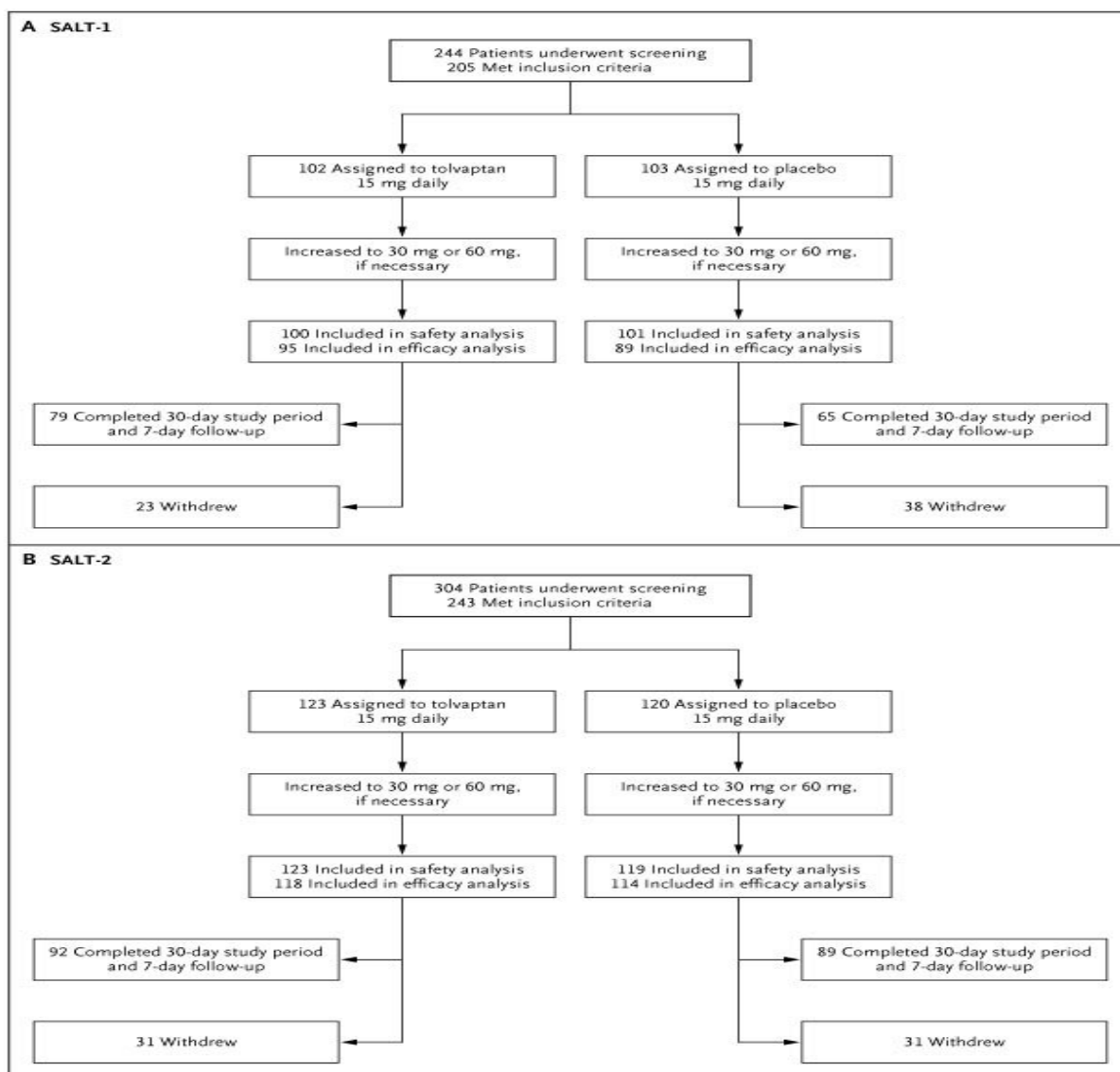
This analysis was performed separately for subgroups of patients classified at baseline as having mild hyponatraemia (a serum sodium concentration of 130 to 134 mmol per liter) or marked hyponatraemia (<130 mmol per liter). Categories after treatment were defined as normal, mild, and marked, as described above, with the range for mild conservatively extended to a serum sodium concentration of 135 mmol per liter for this analysis.

The time to normalization of the serum sodium concentration was analyzed with the use of a log-rank test. Fluid loss, fluid intake, and fluid balance (total intake minus total output) on day 1 were evaluated with the use of an analysis-of-variance model, with the assigned study group and baseline stratification factors as covariates.

The Physical Component Summary (PCS) and Mental Component Summary (MCS) scales of the SF-12 Health Survey (ranges, 5 to 69 for the physical component and 8 to 73 for the mental component, with higher scores indicating better functioning) were derived with the use of weights provided in the SF-12 Health Survey manual. The SF-12 Health Survey was chosen as a patient-reported outcome for overall health status because it has been validated in numerous clinical studies. The physical component assesses physical functioning, bodily pain, physically limited accomplishment, and general health, and the mental component assesses vitality, social functioning, emotionally limited accomplishment, calmness, and sadness. The absolute shift from baseline of 5 units was considered a clinically important difference. Changes from baseline scores were analyzed in the pooled database of the SALT-1 and SALT-2 trials with an ANCOVA model, with the assigned study group, baseline stratification factors, and baseline scores as covariates. All reported P values are two-sided.

RESULTS

Participant flow



Recruitment

SALT 1:

Date of first signed informed consent: 11 Apr 2003

Date of last study observation: 20 Dec 2005

SALT 2:

Date of first signed informed consent: 20 Nov 2003

Date of last study observation: 06 Jul 2005

Conduct of the study

There were 3 amendments to the protocol, with multiple changes in primary end point, exclusion criteria, clarification about patient population (e.g. diabetic patients) and procedures. It is noted that these changes were made early in the study and it is likely that these changes improved the accuracy and quality of the results. There is no evidence to suggest these changes biased the results or had an impact on the integrity of the study.

Baseline data

In general the baseline characteristics were sufficiently balanced between two groups. For the pooled data, there were more men (59%) than women (42%), and the average age of subjects was 62 years. The table below gives further details on the demographic and baseline characteristics of the patients in the SALT 1 and SALT 2 studies.

Characteristic	SALT-1		SALT-2		P Value		SALT-1 and SALT-2
	Tolvaptan (N = 102)	Placebo (N = 103)	Tolvaptan (N = 123)	Placebo (N = 120)	SALT-1	SALT-2	
Age — yr							
Mean	60±14	60±13	62±15	63±14	0.94	0.66	0.72
Range	18–86	35–90	27–92	28–100			
Female sex — no. (%)	50 (49)	41 (40)	48 (39)	47 (39)	0.21	1.00	0.39
Race — no. (%)					0.26	0.47	0.56
White	71 (70)	76 (74)	118 (96)	109 (91)			
Black	13 (13)	17 (17)	1 (1)	3 (2)			
Hispanic	13 (13)	9 (9)	3 (2)	6 (5)			
Other	5 (5)	1 (1)	1 (1)	2 (2)			
Mean body weight — kg	78±23	75±22	73±19	75±21	0.44	0.39	0.96
Mean height — cm	167±10	170±11	168±11	167±9	0.02	0.42	0.14
Fluid status — no. (%)					0.38	0.80	0.70
Euvoletic	61 (60)	67 (65)	63 (51)	60 (50)			
Hypervolemic	41 (40)	34 (33)	58 (47)	60 (50)			
Cause of hyponatremia — no. (%)					0.63	0.96	0.70
Chronic heart failure	35 (34)	33 (32)	36 (29)	34 (28)			
Cirrhosis	25 (25)	21 (20)	38 (31)	36 (30)			
SIADH and other	42 (41)	49 (48)	49 (40)	50 (42)			
Mean serum sodium — mmol/liter	128.7±4.5	128.8±4.1	129.5±3.5	129.1±4.5	0.85	0.37	0.60
Degree of hyponatremia — no. (%)					0.89	1.00	0.93
Mild	49 (48)	51 (50)	64 (52)	62 (52)			
Mean serum sodium — mmol/liter	132.4±1.5	132.1±1.3	132.3±1.6	132.4±1.3	0.37	0.56	0.88
Marked	53 (52)	52 (50)	59 (48)	58 (48)			
Mean serum sodium — mmol/liter	125.4±3.5	125.5±3.2	126.6±2.5	125.5±3.8	0.84	0.07	0.26
Mean score on SF-12 Health Survey†							
Physical Component Summary	33.4±10.7	33.9±10.5	33.0±10.6	33.1±10.8	0.78	0.95	0.81
Mental Component Summary	42.4±11.6	44.7±11.9	44.3±11.9	44.9±11.6	0.15	0.89	0.30

* Mild hyponatremia was defined as a baseline serum sodium concentration of 130 to 134 mmol per liter. Marked hyponatremia was defined as a serum sodium concentration of less than 130 mmol per liter. SIADH denotes syndrome of inappropriate antidiuretic hormone secretion. Race was self-reported. Plus-minus values are means ±SD.

† Scores on the Physical Component Summary of the SF-12 range from 5 to 69, and those on the Mental Component Summary range from 8 to 73, with higher scores indicating better functioning.

The pooled data for the 2 pivotal trials were analyzed according to 3 subject groups: CHF, cirrhosis, and SIADH/other.

Aetiology	Percentage of Total Population		
	SALT-1	SALT-2	Pooled
CHF	32.1%	28.6%	30.2%
Cirrhosis	23.2%	31.2%	27.6%
SIADH/other	40.2%	40.2%	42.2%

SIADH - Syndrome of inappropriate antidiuretic hormone secretion; CHF - Congestive heart failure

Numbers analysed

Of the 424 randomized subjects in the 2 trials (216 tolvaptan, 208 placebo) with data, 311 (73%) completed the trials (164 tolvaptan, 147 placebo) and 113 (52 tolvaptan, 61 placebo) were withdrawn prior to completion.

There are no important differences between treatment groups in either the reasons for or the timing of withdrawals.

Outcomes and estimation

In both trials and the pooled analysis, serum sodium concentrations improved significantly for all 3 disease groups when compared to placebo. Serum sodium normalized (>135 mEq/L) in more than 50% of subjects treated with tolvaptan. The results were similar in subjects with mild and severe hyponatraemia. The biggest difference compared to placebo was seen for the SIADH/Other subjects. Increased serum sodium AUC was seen both on day 4 and day 30 irrespective of the volume status. The overall magnitude of change was greater for the euvolemic subjects and this stands to reason (hypervolemic subjects likely to have different extracellular fluid [ECF] and intracellular fluid [ICF] sodium distribution with dilutional effect in the ECF). Understandably those with severe hyponatraemia had a slower response (less change from baseline in comparison to mild group on the same time point). The serum sodium changes based on aetiology can be found in the table below:

Table-2: Serum Sodium changes based on aetiology

Visit	Treatment Group	N	Mean (SD)	Estimated Treatment Effect	95% CI	P-value ^a
SIADH/Other						
Up to Day 4	Tolvaptan	85	4.76 (2.81)	4.70	3.93 - 5.47	< 0.0001
	Placebo	88	0.19 (2.62)			
Up to Day 30	Tolvaptan	85	7.42 (3.75)	6.15	5.19 - 7.11	< 0.0001
	Placebo	88	1.53 (3.55)			
CHF						
Up to Day 4	Tolvaptan	65	3.52 (2.97)	2.98	2.12 - 3.85	< 0.0001
	Placebo	61	0.51 (1.99)			
Up to Day 30	Tolvaptan	65	6.58 (4.12)	4.05	2.75 - 5.35	< 0.0001
	Placebo	61	2.38 (4.21)			
Cirrhosis						
Up to Day 4	Tolvaptan	63	3.50 (2.41)	3.15	2.32 - 3.99	< 0.0001
	Placebo	54	0.42 (2.32)			
Up to Day 30	Tolvaptan	63	4.18 (3.40)	2.83	1.65 - 4.01	< 0.0001
	Placebo	54	1.46 (3.37)			

In hypervolemic subjects, there was a clinically relevant and statistically significant improvement in fluid balance in both trials. The urine output was consistently and statistically significantly greater in the tolvaptan group than the placebo group in the pooled analysis, regardless of aetiology. Fluid intake was also greater in the tolvaptan group compared with placebo in the pooled analysis; however, the difference from placebo was not as large and was statistically significant for subjects with cirrhosis (554 mL; $p = 0.0030$), but not for those with CHF or SIADH/other. Statistically significant greater mean decreases in body weight were observed in hypervolemic subjects at Days 2, 3, and 4 for the tolvaptan group compared with the placebo group in SALT-1 and in the pooled analysis ($p \leq 0.0311$). A sustained effect was not observed beyond Day 4 in SALT-1 or in the pooled analysis, and no statistically significant differences in body weight were observed between the tolvaptan and placebo groups in SALT-2.

Table-3: Volume status and Serum sodium AUC

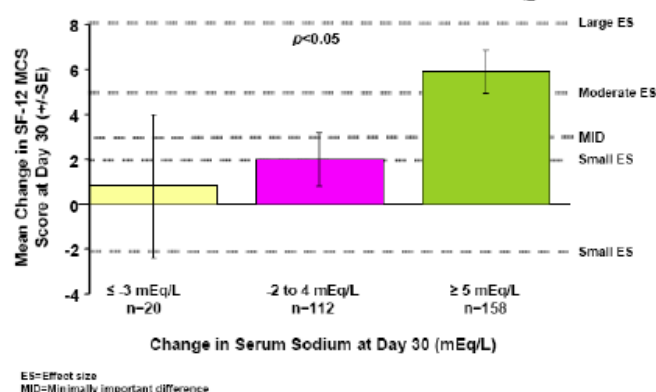
Average Daily AUC up to Day 4 and Day 30 of Mean Change From Baseline in Serum Sodium Concentration (mEq/L) by Volume Status in the Pooled Placebo-controlled Phase 3 Hyponatremia Trials; Restricted Intent-to-treat Dataset						
Visit	Treatment Group	N	Mean (SD)	Estimated Treatment Effect	95% CI	P-value ^a
Euvolemia						
Up to Day 4	Tolvaptan	117	4.37 (2.78)	4.35	3.71 - 4.99	< 0.0001
	Placebo	117	0.15 (2.46)			
Up to Day 30	Tolvaptan	117	6.90 (3.85)	5.37	4.51 - 6.22	< 0.0001
	Placebo	117	1.82 (3.81)			
Hypervolemia						
Up to Day 4	Tolvaptan	94	3.53 (2.75)	2.73	2.02 - 3.43	< 0.0001
	Placebo	86	0.62 (2.20)			
Up to Day 30	Tolvaptan	94	5.36 (4.06)	3.39	2.35 - 4.42	< 0.0001
	Placebo	86	1.69 (3.61)			

The 'fluid balance status' results suggest favourable effects of tolvaptan in comparison to placebo. The fluid balance, urine output and fluid intake were all significantly different in both SALT-1 and SALT-2 trials between placebo and tolvaptan, as shown above. The small differences between different

aetiologies notwithstanding, the overall results suggests that tolvaptan favourably influences the sodium and fluid balance across aetiologies and across varied volemic states. The lack of statistical significance of fluid intake in euvolemic subjects is based on the physiological differences in reasons for hyponatraemia. The body weight data are inconsistent and thus do not support the assertion that all secondary analysis are in line with the clinical relevance of correction of serum sodium.

Mental status was assessed using the Mental Component Summary of the SF-12 Health Survey, evaluated at Day 30 compared to baseline. The analyses of these results were pre-specified as combined analyses on the pooled data from the SALT trials. The results provide evidence that improvements in SF-12 MCS scores related to and were associated with changes in serum sodium (see figure below). The overall group (all 3 aetiologies) when pooled showed that MCS score suggested improvement and the effect size was greater than the MID (minimally important difference; published by Ware et al or Cohen & colleagues independently). Similar results were seen across different volume states (euvolemic or hypervolemic) in comparison to placebo. When the three aetiologies were analysed separately (although these were not individually powered to find a difference), there were statistically significant improvements in mental status (MCS) on Day 30 for tolvaptan compared to placebo ($p = 0.0129$) for subjects with SIADH/Other in the pooled analysis. Similar results were found in those with cirrhosis for the ITT populations using the LOCF approach or all inclusive approach. In those with CHF the survey results were not statistically significant but showed a trend. This has been argued to be due to baseline imbalances noted with the MCS score in those with CHF and the method of analysis (using ANCOVA) assuming a linear relationship between baseline findings and effect size. Different statistical methodologies used to analyse this effect size appear to show that the effect size in CHF is of the similar magnitude here as in SIADH or Cirrhosis.

Figure-1;- Changes in SF12 MCS score associated with change in serum sodium concentrations (pooled SALT population).



Source; Section 5.3.5.3 Summary of Efficacy.

Table-4: Effect sizes for SF-12 MCS at D-30 using various statistical models (Pooled SALT population)

Statistical model	Effect size (p-value)		
	CHF	SIADH/Other	Cirrhosis
ANCOVA (linear relationship)	1.24 (0.5825)	2.95 (0.0886)	4.22 (0.0339)
ANOVA (no adjustment)	4.25 (0.1076)	2.78 (0.1658)	4.70 (0.0442)
ANCOVA (quadratic relationship)	1.34 (0.5547)	2.86 (0.1010)	4.35 (0.0276)
ANCOVA (baseline categories ^a)	2.69 (0.3033)	4.12 (0.0481)	3.09 (0.1551)

a - Baseline MCS groups: <25, 25-<30, 30-<35, 35-<40, 40-<45, 45-<50, 50-<55, 55-<60, >60.

In CHF and cirrhosis, assessment of mental status might be limited by a number of confounding factors such as poor circulation in severe heart failure and accumulation of toxic metabolites associated with liver disease. In SALT-2 an additional analysis of the Hyponatraemia Disease-specific Survey (HDS) was performed. The findings support the SF-12 Health Survey, i.e., significant improvement in questions focusing on mental functioning, which was particularly evident on

correction of severe hyponatraemia, and a lesser effect on physical (strength/endurance) symptoms. The HDS survey has not been validated in any other study and thus its value here was considered limited.

The major issue with the hyponatraemia indication was assessed as being the lack of clear patient oriented benefit related to correction of serum sodium values as there were a number of difficulties with the MCS analysis and HDS provided. This concern was considered a major objection during the procedure and was addressed in an oral explanation. The applicant argued that tolvaptan effect is consistent across the aetiologies for normalisation of sodium, for urine output and for overall fluid balance (primary and secondary efficacy parameters). Similar results were seen across different volume states in comparison to placebo. The applicant further argues that the improvements in SF-12 MCS scores related to and were associated with changes in serum sodium in the pooled analysis. However, it was considered that there was not sufficient evidence available that correction of hyponatraemia is of clinical relevance in all the populations studied. The applicant's analysis suggests that tolvaptan treated subjects had less worsening of sodium overtime within the study and such preventive measures could be important in the patient groups under discussion. A clear withdrawal effect is noted suggesting that underlying disease and co-morbidity play a significant role in the clinical picture of hyponatraemia. Additionally, the Nervous system effects were not assessed objectively.

The MCS analysis (especially in CHF and to a lesser extent in cirrhosis) is confounded by the factors mentioned and also by statistical analysis problems. Firstly, a multiplicity issue: MCS by (SF12) was not specified in the statistical analysis plan as a key secondary end point but was one of several. Some of these secondary end points showed benefit and others, such as physical component score-PCS, did not. The lack of such specification limits its use as a key secondary end point that shows benefit as a direct correlate or consequence of increase in serum sodium values. The second difficult aspect is that the effect size in CHF is smaller than the other two aetiologies (SIADH and Cirrhosis). The applicant claimed that the secondary endpoints are only supportive and not intended to support specific claims. As stated above, additional analyses showed the possibility that the effect size may have been similar in all three aetiologies (see table above). In terms of the multiplicity issues surrounding the MCS endpoint, even though the vast majority of secondary endpoints showed significant effects in favour of tolvaptan, it cannot be accepted that the interpretation of the results are not affected by multiplicity. Due to the fact that a hierarchy was not put in place to test the secondary endpoints it cannot formally be concluded that a statistically significant effect has been demonstrated on the MCS endpoint.

Additional benefit of Tolvaptan in CHF

An additional post-hoc analysis of the hyponatraemia subset from the EVEREST trial (outcome of trial discussed in Heart Failure Programme) was performed in order to support the hyponatraemia indication in this subgroup. In patients with hyponatraemia at baseline, there was a general trend for tolvaptan to be better than standard care (SC) alone for “time to all-cause mortality”, “time to first occurrence of cardiovascular mortality or heart failure hospitalisation”, and “time to first occurrence of CV mortality or CV morbidity”. With respect to time to first occurrence of CV mortality or morbidity the beneficial effects of tolvaptan in patients with serum sodium <130mEq/L achieved statistical significance ($p=0.04$). In hyponatraemic patients with worsening heart failure, tolvaptan as add-on to SC clearly demonstrated improvements in serum sodium levels that were statistically superior to SC alone for up to 40 weeks. Similar results were noted for normalisation of sodium in the same groups. In addition, tolvaptan ($n=203$) resulted in greater percentages of patients achieving “less worsening” in serum sodium levels compared to SC ($n=176$) alone (22.2 vs. 37.5%; $p<0.01$). Tolvaptan as add-on to SC treatment demonstrated greater improvements in the “Kansas City Cardiomyopathy Questionnaire” (KCCQ) score. Again, as was the case for mortality/morbidity, greater effects were observed in those patients with more severe hyponatraemia at baseline (serum sodium levels <130 mEq/L). For the KCCQ treatment effect, there were improvements in KCCQ that met or exceeded the thresholds for small and moderate improvements (according to Cohen) in clinical change at each of the assessment time points.

Although these additional analyses appear to favour tolvaptan use in CHF+ hyponatraemic population, the differences are based on small populations/subgroups ($n=92$, Serum Na <130mEq/L) and are of

limited value in establishing its utility in the overall population without restriction of serum sodium level.

Long term effects (Duration of treatment with tolvaptan) - SALTWATER trial - 156-03-244

The benefits of tolvaptan treatment achieved in the SALT trials were maintained in all 3 disease aetiology groups for durations exceeding 1 year in an open-label long-term follow-up trial (SALTWATER). In the SALT trials, the dose was titrated from 15 to 30 mg up to a maximum of 60 mg as per protocol based on subject's serum sodium. The majority normalised serum sodium by day 7. Serum sodium levels dropped after the discontinuation of tolvaptan at the end of the SALT trials, but they rapidly were restored to normalised levels when tolvaptan treatment was re-started. The SALTWATER trial reflects the effect of tolvaptan with chronic therapy. The proportions of patients with the 3 disease aetiologies in SALTWATER were generally comparable to the SALT trial except that there were somewhat more SIADH and fewer cirrhosis patients who restarted treatment in the SALTWATER trial (SALT: 28% Cirrhosis, 30% CHF, 42% SIADH; SALTWATER: 18% Cirrhosis, 30% CHF, 52% SIADH).

This is an ongoing extension trial and is yet to be completed. The applicant has submitted an abbreviated clinical report with a data cut-off of 01 February 2007. A number of these subjects have been followed up to 106 weeks. There were 33 CHF, 20 Cirrhosis and 58 with SIADH. Of these, 13, 5 and 35 respective aetiologies are continuing in the trial while 19, 15 and 16 respectively discontinued for variable reasons. Up to the cut-off date there have been no deaths. Overall, the numbers of cirrhosis and CHF patients followed long-term are small. This especially is true for cirrhosis and thus the long-term effect of tolvaptan in this difficult population remains to be established.

HEART FAILURE PROGRAMME

The "worsening of heart failure (HF)" indication was withdrawn during the procedure, the evaluation of the data are included however as they are considered relevant and of public interest.

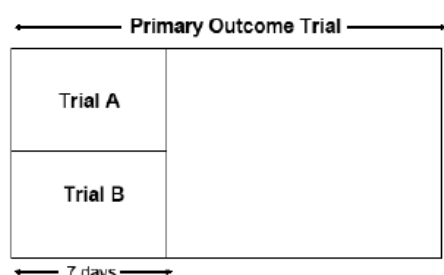
Pivotal study EVEREST

- Trial 156-03-236: EVEREST trial - Efficacy of Vasopressin antagonism in hEart failure: outcome Study with Tolvaptan. Phase 3, multicentre, double-blind, placebo-controlled pivotal trial to compare the efficacy of tolvaptan 30 mg daily versus placebo in conjunction with optimal (as determined by the investigator) current therapy in adult subjects hospitalized with worsening CHF. This forms the pivotal study for heart failure and utilized a 3-in-1 design, consisting of a Long-term Outcome Trial and 2 distinct Short-term Clinical Status Trials (Trials A and B) using the same population.

METHODS

Study Participants

Patients >18 years or older with reduced LV function or CHF and signs of volume expansion, NYHA III-IV symptoms who were hospitalised of no more than 48 hours were eligible for entry. Among the main exclusion criteria were cardiac surgery within 60 days of enrolment, cardiac mechanical support, biventricular pacemaker placement within the last 60 days, co-morbid conditions with an expected survival of less than 6 months and acute myocardial infarction at the time of hospitalization.



Source: Section 5.3.5.3 Summary of Efficacy.

Treatments

Subjects were randomized to receive either 30 mg tolvaptan or matching placebo in addition to SC and assigned to either Trial A or Trial B by a pre-defined algorithm.

All patients received standard HF therapy including diuretics, digoxin, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, aldosterone blockers, hydralazine, and/or nitrates, at the discretion of the treating physician.

The trial was planned to continue enrolment until 1065 deaths (event driven) would be reached and all enrolled subjects have been followed for a minimum of 60 days. Patients still in the trial at that point would continue until the last patient enrolled had been treated for 60 days.

Objectives

The primary objectives of the primary outcome trial were to compare the effects of tolvaptan + SC to placebo + SC on the time to all-cause mortality in subjects with worsening HF and on the time to first occurrence of cardiovascular (CV) mortality or hospitalization for heart failure.

Patients with advanced CHF suffer greatly due to clinical symptoms of congestion like dyspnoea and experience serious restrictions to their daily lives and so 2 short-term, clinical status trials, A and B, were performed within the primary outcomes trial, to evaluate the effect of tolvaptan + SC on short-term clinical signs and symptoms. This design was used to maximize clinical information from the large subject population in the primary outcome trial.

Outcomes/endpoints

The primary efficacy endpoint was a composite endpoint of change from baseline in patient-assessed global clinical status (using a visual analogue scale, VAS) and change from baseline in body weight at inpatient Day 7 or discharge, if earlier. Secondary efficacy variables included changes in global clinical status at Day 7; body weight reductions at Days 1 and 7; frequency of dyspnoea at Day 1 and the frequency of oedema at Day 7.

The co-primary endpoints of the primary outcome trial were all-cause mortality and the composite of cardiovascular death or heart failure hospitalisation analyzed as time-to-first-event and tested for superiority and non-inferiority. Secondary efficacy variables in the primary outcome trial included the time to first occurrence of cardiovascular mortality/morbidity; incidence of cardiovascular mortality; incidence of clinical worsening of heart failure; short-term changes from baseline in body weight, serum sodium (in subjects with baseline values <134 mEq/L), oedema score, and dyspnoea (in subjects with dyspnoea at baseline); and change from baseline in quality of life assessments.

Sample size and statistical methods

The sample size for this trial was estimated based on the number of events (1065 deaths, event driven trial) required to provide 90% power to compare all-cause mortality at alpha 0.009 under the following assumptions. For the purpose of sample size estimation, the rates of all-cause mortality for the placebo + SC group were assumed to be 10%, 25%, and 35% at 2 months, 6 months, and 1 year, respectively.

Beyond 1 year, an annual mortality rate of 30.5% was assumed. A proportional hazards model was assumed such that tolvaptan reduced the 6-month mortality rate by 20% (to 20%, hazard ratio [HR] = 0.776), which resulted in mortality rates in the tolvaptan group of 7.8%, 20.0%, and 28.4% at 2 months, 6 months, and 1 year, respectively. It was also assumed that the discontinuation rate at 18 months would be 15% with treatment discontinuations uniformly distributed over the follow-up time.

With these assumptions, an estimated 1065 deaths were needed for this trial, after accounting for interim analyses by the Data Safety Monitoring Board. Using S+ SeqTrial software for proportional hazards model, 1065 deaths provided 90% power for the HR of 0.8132 with alpha = 0.0402 (2-sided), and HR of 0.7865 with alpha = 0.009 (2-sided).

If there were no treatment difference, testing for non-inferiority was planned at a power of more 94% for demonstrating non-inferiority at the 95.98% ($= 1 - 0.0402$) confidence level. The ITT for the outcomes evaluation represents all subjects who were randomized to the trial.

It was projected that the target number of deaths could be observed with 3600 subjects recruited uniformly over an 18-month period with an additional 2 months of treatment, for an entire trial duration of 20 months.

The EVEREST trial was designed with an overall alpha of 0.05. Among this 0.01, 0.0008 was assigned to the primary endpoint of Trial A and Trial B (so that each Trial would have an alpha of 0.04 ($0.04 \times 0.04 / 2 = 0.0008$) for its primary endpoint), and 0.009 was assigned to the co-primary endpoints of the Primary Outcome Trial.

Randomisation

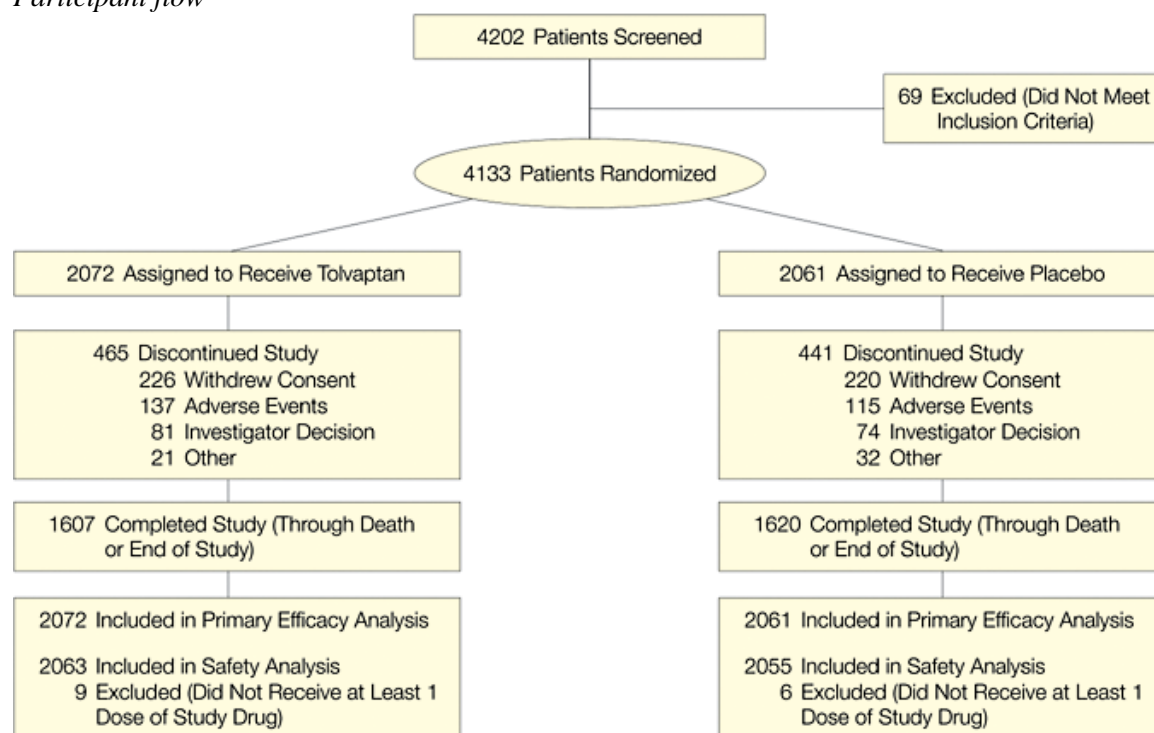
Subjects satisfying the trial entrance criteria were assigned a randomization number on inpatient Day 0. Within each center, subjects were randomized in a 1:1 ratio to either tolvaptan 30 mg or placebo according to a blocked randomization schedule.

Blinding (masking)

Subjects received tolvaptan 30 mg or matching placebo in a randomized, double-blind fashion. The trial drug was packaged so that each subject received an identical number of tablets regardless of the treatment group assignment. Tolvaptan and placebo tablets were identical in appearance.

RESULTS

Participant flow



Source: Konstam, M. A. et al. JAMA 2007;297:1319-1331.

Recruitment

Date of first signed informed consent: 07 Oct 2003

Trial Termination Date: 17 Apr 2006

Date of last trial observation: 05 Jul 2006

Conduct of the study

There were 3 amendments to the protocol, of which 2 were considered major as they modified the primary end-points. Amendments were performed in one case prior to randomization of the first patient, and in the other before the database were locked, and therefore were not considered post-hoc.

Baseline data

Both groups were similar in terms of sex, age and race. There were more men (74%) than women (26%), and the average age of subjects was 65 years. There is no obvious imbalance between the treatment groups. Interestingly, beta-blocker use was only in ~70% in both groups. It was clarified that the combinations did not produce higher degree of electrolyte imbalance in any of the combinations of angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs) and antimineralocorticoids. There were 2960 patients (1469 tolvaptan + SC; 1491 SC alone) in the EVEREST trial with concomitant antimineralocorticoid therapy and 1173 patients (603 tolvaptan + SC; 570 SC alone) that did not receive antimineralocorticoid therapy. A comparison of efficacy parameters between tolvaptan + SC and SC alone in patients with and without concomitant antimineralocorticoid therapy shows that there is no difference in the treatment effect of tolvaptan. The entire population was one of moderate to severe CHF, more towards the severe end of the

spectrum with ~50% exhibiting orthopnoea. About 17% of subjects had pacemakers and about 14% had defibrillators; it is unclear if these were biventricular pacemakers for heart failure. The groups were evenly matched for these characteristics. About 40% of the patients had atrial fibrillation in both groups. The applicant has clarified that all subjects with AF received anticoagulation and that there were no relevant differences in the incidence of stroke in the EVEREST trial (for further discussion See safety aspects). There is a small but consistent presence of those with some renal impairment despite the exclusion criteria of serum creatinine value of >3.5mg. Whilst a population with greater gender and ethnicity distribution might have shown different characteristics, the current cohort could be considered part representative although this is insufficient to provide any confidence that tolvaptan is effective in those with chronic kidney disease.

Characteristics	Tolvaptan (n = 2072)	Placebo (n = 2061)
Age, mean (SD), y	65.9 (11.7)	65.6 (12.0)
Male	1520 (73.4)	1555 (75.4)
Race		
White	1767 (85.3)	1766 (85.7)
Black	161 (7.8)	149 (7.2)
Other†	144 (7.0)	146 (7.1)
Systolic blood pressure, mean (SD), mm Hg	120.8 (19.9)	120.2 (19.4)
Ejection fraction, mean (SD), %	27.5 (8.0)	27.5 (8.2)
Ischemic heart failure etiology	1332 (65.1)	1340 (65.9)
Previous hospitalization for heart failure	1642 (79.2)	1608 (78.1)
NYHA class		
III	1218 (60.1)	1186 (58.7)
IV	801 (39.5)	821 (40.6)
Medical history		
Hypertension	1468 (70.8)	1464 (71.1)
Diabetes mellitus	824 (39.8)	774 (37.6)
Atrial fibrillation	902 (43.6)	888 (43.2)
Chronic renal insufficiency	549 (26.5)	558 (27.1)
Valvular disease, mitral	646 (31.2)	658 (31.9)
Baseline therapy		
ACE inhibitors/ARBs	1746 (84.3)	1733 (84.1)
β-Blockers	1468 (70.8)	1435 (69.6)
Diuretics	2012 (97.1)	1990 (96.6)
Aldosterone blockers	1110 (53.6)	1127 (54.7)
Baseline cardiovascular assessment		
Dyspnea, frequent/continuous	1839 (90.9)	1840 (91.1)
Orthopnea, frequent/continuous	1081 (53.5)	1089 (54.1)
Rales	1642 (81.0)	1653 (81.8)
Pedal edema, slight/moderate/marked	1607 (79.3)	1602 (79.3)
Jugular venous distention ≥10 cm	544 (27.0)	538 (26.9)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NYHA, New York Heart Association.

*Data are expressed as No. (%) unless otherwise indicated.

†Defined as Asian, unknown, and other. The "other" category was used when the patient did not meet one of the other specified categories.

Numbers analysed

Of the 4133 randomized subjects (2072 tolvaptan + SC, 2061 SC), 2466 (59%) completed the trial and 1667 (841 tolvaptan + SC, 826 placebo + SC) were withdrawn prior to completing the trial. About 20% of subjects discontinued treatment prior to trial termination for reasons other than death, mostly due to withdrawal of consent, and there were no relevant differences between tolvaptan + SC and placebo + SC. The proportion of subjects who received trial drug for up to 10 days was greater than 99% for both treatment groups. Approximately 89% of subjects in each group received trial drug for up to 2 months, 72% for up to 6 months, and 42% for up to 12 months.

Outcomes and estimation

The EVEREST trial was designed to allow the sequential testing of superiority and non-inferiority of tolvaptan + SC compared to placebo + SC. Treatment with tolvaptan + SC demonstrated statistical non-inferiority to placebo + SC for the primary endpoints: time to all-cause mortality, CV death or HF hospitalization. Although the hazard ratios were all close to 1.0, there were fewer events of all-cause mortality in the tolvaptan + SC group (537, 25.9%) compared to the placebo + SC group (543, 26.3%) whereas the CV death or HF hospitalization (co-primary end point) was numerically higher for tolvaptan + SC (871) than for placebo + SC (829). The analysis of time to first occurrence of CV

mortality or hospitalisation for heart failure also shows similar rates in both groups although the rate was slightly higher in the tolvaptan group. This appears to be due to higher incidence of stroke in the tolvaptan group (discussed in the safety section).

Whilst tolvaptan has been shown to be non-inferior to placebo in the EVEREST trial, some questions arose due to the differences in mortality in the supportive studies (Positive effect in Meteor 156-01-232; but a negative effect in 156-00-220 especially in NYHA-II or III subjects) with the caveat that these may not have been powered to detect differences in mortality. To address this concern the applicant provided a pooled analysis of all heart failure trials that does not regard mortality and neither a negative nor positive effects were seen. The applicant also provided further analysis of the hyponatraemic subset for EVEREST trial. These analysis however, based on a total of 92 subjects with serum sodium <130mEq/L are only of limited value given the overall numbers with hyponatraemia (sodium <135mEq/L; n=203) or the entire EVEREST population (n=4130) where such differences with placebo were not seen.

Short term trials

Trials A and B included a total of 2048 (trial A) and 2085 (trial B) patients hospitalized with heart failure and congestion.

The results suggest that short-term treatment with tolvaptan 30 mg in combination with standard therapy has a favourable effect on the composite of change in patient-assessed clinical global status and change in body weight at inpatient day 7 or discharge, compared with placebo (p = 0.0005 in Trial A, p < 0.0001 in Trial B and p < 0.0001 in the Long-term Outcome Trial). The main contributor to the positive composite result was body weight (Trial A: -3.53 kg tolvaptan + SC; -2.73 kg placebo + SC, p<0.0001 and Trial B: -3.69 kg tolvaptan + SC; -2.79 kg SC, p<0.0001). As VAS was only measured after 7 days or discharge, no statistically significant difference between the treatment groups could be demonstrated (Trial A: 18.25 mm tolvaptan + SC; 17.73 mm SC, p<0.5131 and Trial B: 18.72 mm tolvaptan + SC; 18.28 mm SC, p<0.5188). The positive effect on the composite end point was due primarily to the statistically greater decrease in body weight demonstrated for tolvaptan 30 mg relative to placebo. Improvements of other signs and symptoms were also observed during short-term treatment, including oedema, fatigue, rales and orthopnoea.

While a statistical difference for the primary analysis and for a range of sensitivity analyses has been noted, the clinical relevance of this difference is difficult to quantify from the above analyses.

The applicant has further analysed the significance of these short term findings and in response to questions raised has provided the following.

- ▲ There is an association between body weight change and physician assessed signs and symptoms on day 1,
- ▲ A statistically significant difference between tolvaptan and placebo groups was noted for dyspnoea in both trials (% improvers/responders); 76.5 vs 70.6 % (p =0.0004) in trial A and 72.1 vs 65.3% (p=0.0002) in trial B.
- ▲ A van Elteren analysis to show overall effect (see table below)

Table-6; Overall effect analysis, Van Elteren Test of physician assessed symptoms in EVEREST trial; Difference from Std Care.

Symptom	van Elteren p-value of statistical comparison of tolvaptan +SC vs. SC alone								
	Hospitalized							After discharge	
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Week 1	Week 4
Dyspnea	0.006	0.001	0.019	0.044	0.163	0.403	0.773	0.748	0.626
Pedal edema	0.001	0.003	0.001	0.004	0.004	<0.001	0.003	0.003	0.006
Rales	0.031	0.073	0.006	0.019	0.228	0.190	0.167	0.089	0.013
Orthopnea	0.011	0.006	0.032	0.055	0.128	0.306	0.130	0.346	0.058
JVD	0.026	0.010	0.002	0.069	0.064	0.099	0.274	0.998	0.556
Fatigue	0.187	0.071	0.016	0.034	0.011	0.016	0.062	0.335	0.887

Note: shaded values are statistically significant differences (p <0.05) for tolvaptan + SC vs. SC alone;
Source: Module 5, CSR 156-03-236, Table CT - 1.17.3.4.

In summary, tolvaptan demonstrated some short term effects on parameters such as patient assessed dyspnoea, body weight, reduction in jugular venous distension, and qualitative reduction in pedal

oedema between day 1 and 7. The association between dyspnoea and body weight is explained easily as a similar relation can be demonstrated with the use of any diuretic. The benefit appears to be predominantly on day 1 and 2 and sustained effect is not seen even with continued treatment. Notwithstanding these analysis and arguments, there are important considerations. Pharmacodynamically, the aquaresis is marked in the first 24 hours but subsequently it is less marked and hence the clinical effect is maximal on days 1-2. The re-analyzed data on clinical evidence, driven largely by change in body weight, only suggests weak improvement on signs and symptoms as dyspnoea and oedema. Notably, there is no direct comparison of diuretics and tolvaptan as both groups received standard care. There are other limitations of the dataset: use of vasodilators such as nesiritide showed that in those receiving nesiritide, effect of tolvaptan was less prominent in terms of sodium correction and pedal oedema but better for dyspnoea and body weight. There is dissociation between pedal oedema and other claimed benefits (dyspnoea and body weight) which lends little support to the overall picture. No clear advantages of tolvaptan administration have been identified with respect to choice of the diuretic, frequency/dose of furosemide on days other than day 4 and 5 (a difference of 35 mg furosemide dose on day 4 between tolvaptan and SC groups; background dose 180 mg), length of hospital stay, alterations in renal function or repeated hospitalisations. Thus the effects demonstrated are considered small and the clinical utility of tolvaptan in all patients with heart failure is not clear. While it is true that hyponatraemia occurs in 20-30% of patients with severe heart failure and that it may be poor prognostic indicator, in the EVEREST trial only 8% of such subjects were included. Analysis of these subgroups in the EVEREST trial did not provide evidence of increased benefit although some differences were seen. CV mortality/morbidity were better with tolvaptan treatment in those with serum sodium <130meq/L. The difference in dyspnoea responders was also better but the numbers are extremely limited for both these analysis. The other parameters (body weight and pedal oedema) however appear to move in the opposite direction (see hyponatraemia section for more details of these).

Overall, the evidence to support an indication in heart failure was considered small and CHMP considered that they will require further study/data. In view of this the applicant decided not to pursue the heart failure indication.

- Clinical studies in special populations

There were no specific studies performed in special populations.

- Supportive studies

Hyponatraemia

All supportive studies examined the level of serum sodium attained after treatment with tolvaptan. Some heart failure studies also act as supportive studies for use of tolvaptan in patients with heart failure. Approximately 12% of subjects in this trial (N = 243 on tolvaptan 30 mg QD, 232 on placebo QD) were found to have hyponatraemia at baseline, as defined by serum sodium concentrations < 135 mEq/L. Although these have not been analyzed separately, they form a fairly specific subset to assess the long term treatment set for hyponatraemia with tolvaptan.

Study 97-204

This was a multi-centre, randomised, open label, active controlled (fluid restriction with placebo), dose titration study in both euvolemic and hypervolemic states. After a placebo baseline (days 0 & 1) tolvaptan was individually titrated (from 10, to 15, 30, 45 and 60 mg). Male and female patients >18 years with hyponatraemia (sodium <135mEq/L) before randomisation of any aetiology were included. The primary outcome measure was serum sodium concentrations while urine osmolality, urine volume, urine sodium concentration, body weight, total fluid intake, free water clearance and thirst assessment were the secondary variables.

During the titration phase, tolvaptan group had higher mean increases from baseline in serum sodium levels than the fluid restriction group (mean increase of 5.73 vs. 1.00 mEq/L at the last visit respectively).

Mean urine sodium concentrations decreased (by 1.33 to 20.40 mEq/L) in the tolvaptan group while they increased (by 9.67 to 34.44 mEq/L) in the fluid restriction group. Urine potassium levels showed

similar changes. Serum osmolality increased in both groups but were generally higher in the tolvaptan group (mean increase by 9.38 mOsm/kg vs. 3.0 mOsm/kg). Statistically significant differences in the mean total daily fluid balance were seen between the two groups. The mean thirst scale scores were 81.50 and 42.11 for the fluid restriction and OPC-41061 groups, respectively.

The supportive studies including those in CHF population where few subjects had hyponatraemia provide some evidence of the effect of tolvaptan on enhanced urine output, selective aquaresis, and correction of hyponatraemia. The numbers from CHF trials are limited and hence offer only minimal support for efficacy. Study 00-204 albeit in a small population, does offer evidence that tolvaptan increases serum sodium levels that are not achieved by fluid restriction alone.

Cardiac Function

The METEOR (156-01-232) trial was designed to evaluate the effect of long-term administration of tolvaptan + SC at a dose of 30 mg/day on the reduction in left ventricular end-diastolic volume compared to placebo + SC in subjects with heart failure and left ventricular systolic dysfunction. A total of 240 subjects underwent quantitative radionuclide ventriculography (RVG) at baseline, repeated after 1 year of treatment with tolvaptan + SC or placebo + SC, and repeated again approximately 1 week after withdrawal of tolvaptan. The primary endpoint was prospectively defined as the change from baseline in left ventricular end diastolic volume (adjusted for body surface, i.e., LV EDV index) at the week 54 Visit.

In the placebo + SC group, there was no change in LV EDV index over the year of follow-up (change of 0.0 ± 10.0 mL/m²), while in the tolvaptan + SC group, there was a small reduction in LV volumes (decrease of 1.8 ± 10.7 mL/m²; $p=0.21$). There was also no difference in the change of volumes from baseline at the week-55 assessment. Un-adjudicated outcomes of mortality and heart failure hospitalizations were reported by investigators (who were blinded to randomization treatment assignment). Over the course of the trial, there were 6 deaths (5%) and 21 heart failure hospitalizations (18%) for tolvaptan + SC, compared with 11 deaths (9%) and 34 heart failure hospitalizations (28%) placebo + SC. In a post hoc, time-to-event analysis, there was significant favourable effect of tolvaptan on the composite of mortality or heart failure hospitalization ($p<0.03$ by log-rank test).

Trial 156-00-220

This was a multicenter, randomized, double blind, placebo-controlled, parallel group trial to assess the efficacy and safety of 6 months of treatment with 3 doses of tolvaptan or placebo in conjunction with conventional therapy in adult subjects with CHF. Four groups of 80 subjects were randomized to receive 15, 30, or 60 mg of tolvaptan or placebo once daily for 169 days. All subjects continued to receive conventional therapy. A total of 330 subjects were randomized to trial drug and 329 subjects were treated. A total of 260 subjects completed the trial.

The primary end point, clinical status at 6 months was not statistically significant different between the tolvaptan 15, 30, and 60 mg treatment groups and placebo. In a post-hoc subpopulation analysis of subjects with oedema at screening or baseline, tolvaptan produced some improvements in NYHA class and CHF symptoms. For secondary efficacy variables, the incidence of death and hospitalization for heart failure was statistically significantly greater for the tolvaptan 15 mg group vs. placebo ($p<0.05$). There were no other statistically significant differences between treatment groups for death, hospitalization for heart failure, or unscheduled visit. The data from this trial suggest that subjects with stable chronic heart failure (NYHA Class II and III) on standard optimal background therapy did not demonstrate an improvement in outcomes when exposed to once daily dosing of tolvaptan for up to 6 months. However, possible additional symptomatic and outcome benefit may be present in the subset of subjects with evidence of congestion (oedema at baseline).

Trial 156-00-222

Tolvaptan was compared to 80 mg furosemide in a multicenter, randomized, double blind, placebo-controlled, parallel group trial to assess the efficacy and safety in adult subjects with CHF over a period of 7 days of trial drug dosing. Four groups of 20 subjects were to be randomly assigned to receive 30 mg tolvaptan, 80 mg of furosemide, 30 mg of tolvaptan and 80 mg of furosemide, or placebo daily for 7 days stratified by baseline furosemide dose levels (≤ 80 mg/day or >80 mg/day). The primary efficacy variable was the change from baseline in body weight at Day 8. The secondary efficacy variables were the changes from baseline in urine volume, plasma renin activity (PRA), brain

natriuretic peptide (BNP), atrial natriuretic peptide (ANP), arginine vasopressin (AVP), aldosterone, norepinephrine (NE), oedema, JVD, rales, hepatomegaly, dyspnoea, orthopnoea, and serum electrolytes (sodium, potassium, and magnesium).

Tolvaptan, at a dose of 30 mg, significantly ($p<0.05$) reduced body weight (mean decreases of 0.41 kg to 1.38 kg), when compared with placebo (mean increases of 0.41 kg to 1.21 kg, with the exception of the Day 2 visit, which showed a mean decrease of 0.31 kg) at all time points throughout the trial. In summary, tolvaptan, when given at doses of 30 mg once daily either alone or in combination with furosemide for up to 7 days was effective and safe as an aquaretic agent in subjects with NYHA class II or III CHF.

Clinical safety

Tolvaptan has been investigated clinically in Japan since 1994 and in Europe and the US since 1996. The safety dataset consists of 3294 subjects treated with any dose of tolvaptan and 2738 subjects treated with placebo from a total of 14 clinical trials. The combined population contains safety data for 1,870 subject years (683,036 days) of exposure to tolvaptan and 1,796 subject/years (656,651 days) of exposure to placebo. Overall there were 817 subjects treated with tolvaptan in placebo-controlled trials for 1 year or more.

- **Patient exposure**

More than 4000 subjects have been exposed to oral doses of tolvaptan in the 57 trials conducted in the US, Europe, Brazil and Argentina: 527 healthy volunteers, 2982 subjects in trials for CHF, 497 subjects in trials for hyponatraemia, and 45 subjects in trials for autosomal dominant polycystic kidney disease (ADPKD). The exposure of subjects to tolvaptan in the heart failure and hyponatraemia programme is adequately representative to assess the adverse event profile. Whether this is adequate exposure to assess all events including those of the very rare group is open to questions. However, the size of the heart failure dataset is similar to a number of other agents but this does not truly compare with those agents (for example ACE inhibitors / AT-II receptor antagonists) that were used for hypertension first and subsequently heart failure as the use in heart failure was preceded by a significant safety database arising out of hypertension trials. Whether the size of the data set and duration of treatment (exposure) is adequate to assess mortality is questionable. Only ~800 subjects are exposed to tolvaptan for over 1 year and this considered to a limitation.

The demographic characteristics for the subjects with heart failure and hyponatraemia were comparable between the treatment groups. The majority of subjects were Caucasian and male. The mean age in both treatment groups was 65 years, with approximately 55% of subjects in both treatment groups being 65 years or older. The other ethnic groups formed a small percentage.

The areas of safety concern relate to the following;

1. **Excess aquaresis leading to**

- Thirst and dry mouth affecting ability to restrict fluid
- Hypotension
- Dehydration
- Massive electrolyte shifts including hypo or hyperkalaemia
- Coagulation and thrombotic risk
- Arrhythmias
- Renal function

- **Adverse events**

Adverse events (AEs) were classified based on frequency by organ class and subsequently all treatment emergent adverse events (TEAEs) occurring in >5% of subjects. The following were the most frequent possibly related TEAEs: thirst, ~18% in tolvaptan group [~2.5% in SC group], dry mouth (8.5 vs. 2.1%), pollakiuria (frequent day time urination: 5.4 vs. 0.9%), fatigue (2.3 vs. 0.9%), polyuria (3.3% vs. 0.6% SC) and ventricular tachycardia (0.9% vs. 0.3% SC). Cardiac disorders occupied the highest frequency. Further classification based on individual AEs revealed that a clear distinction in the number and type of adverse events as detailed with thirst, dry mouth, fatigue, pollakiuria showed clear differences from the placebo group. All other AEs/TEAEs had a similar distribution in both tolvaptan and placebo groups. Interestingly, hypokalaemia (6.3% T vs. 7.9% SC)

upper abdominal pain (1.8 %T vs. 3.2% SC) and muscle spasms (2.9% T vs. 3.9% SC) were more frequent in the placebo group. Tolvaptan was associated with a slightly higher incidence of increases in serum creatinine concentrations in the HF population (tolvaptan 3.6%, placebo 3.0%). This slight difference was not associated with increased frequencies of TEAEs associated with renal function (renal failure, renal failure acute, renal failure chronic) or increased all-cause mortality. Acute renal failure occurred in >2% of subjects in the overall population and was marginally higher in the placebo group (3.2%T vs. 4.1% SC). Hyperkalaemia occurred in 6.6% (n=219) in the tolvaptan group and 5.8% in the placebo group. A few other events showed numerical differences between groups but were not of large magnitude but all in favour of placebo; dizziness (9.1 vs. 8.2%), constipation (8.6 vs. 7.9%), and increased uric acid (2.9 vs. 2.1%). In tolvaptan-treated hyponatraemia patients the number of TEAE reports related to glucose elevations was slightly above the placebo group (hyperglycaemia 3.8% vs. 3.1%, diabetes mellitus 2.0% vs. 0.8%). An apparent signal exists for modest hyperglycaemia associated with tolvaptan treatment in the hyponatraemia subgroup only but not heart failure.

- Serious adverse event/deaths/other significant events

TEAEs occurred in both groups with higher numerical values in the placebo group (47% vs. 51%). Cardiac disorders formed the highest proportion (32.1% vs. 34.6%) of these. Overall cardiac failure (15% for tolvaptan vs. 17% SC) and congestive cardiac failure (=12% in both) were the most common serious TEAEs. With the exception of pneumonia (2.6% for both groups), ventricular tachycardia (2.2% for tolvaptan and 1.8% for placebo), and acute renal failure (2.0% for tolvaptan and 2.7% for placebo), all other serious TEAEs were reported at frequencies less than 2%. The serious TEAEs of special interest (including ventricular tachycardia [VT], cardiac arrest, hyperkalaemia, cerebrovascular accident, renal failure, and hypotension) all occurred with differences of $\leq 1\%$ between the tolvaptan and the placebo groups. Among all the heart failure and hyponatraemia subjects, 17.2% in the tolvaptan group and 20.0% in the placebo subjects died during the on-treatment period. A total of 567 (17%) tolvaptan and 547 (20%) placebo subjects died and the types of events were similar for the 2 treatment groups. Most deaths (331 [10%] tolvaptan subjects and 285 [10%] placebo subjects) were due to events of the cardiac disorders system organ class. Of interest is the fact that both hyperkalaemia and cardiac arrest were numerically higher in the tolvaptan group. The applicant provided an explanation that the tables reflected different groups of patients and reanalysis did not show any difference. This explanation was accepted. The applicant confirmed that the firing rate from the automatic implantable cardioverter/defibrillator (AICDs) and VT /cardiac arrest events were not related, but as the AICD firing rates were not systematically collected and thus a definitive conclusion is not possible.

A larger number of hospitalisations were adjudicated as due to stroke in the tolvaptan + SC group (42) compared to placebo + SC (25, $p=0.0116$ for the difference). Increased frequencies for hospitalisations due to stroke were observed for tolvaptan-treated patients in the EVEREST trial (2.2% tolvaptan + SC; 1.2% placebo + SC). A more detailed analysis, demonstrated that this difference resulted from a significantly larger number of hospitalizations due to ischemic events in the tolvaptan + SC group (38/2063, 1.8%) compared to the placebo + SC group (18/2055, 0.9%; $p=0.0100$). Overall, no statistically significant difference was seen between the tolvaptan + SC and placebo + SC groups in the incidences of death due to ischemic stroke $p=0.6066$). The analysis of the overall distribution of stroke showed that there were also no statistically significant differences between tolvaptan + SC and placebo+ SC for: time to first stroke, time to first cardiovascular event, time to multiple strokes, and time to multiple cardiovascular events. The applicant provided a reanalysis of stroke/ events in all subgroups in order to analyse any interaction between antiplatelet agents and tolvaptan. The most interesting finding of this re-analysis is that the group which received a combination of warfarin+antiplatelet agents and tolvaptan had more ischaemic events. This is contrary to the expectation and is likely to be a chance finding.

Some events occurred rarely and these included neutropenia related events with a total incidence for all subjects of 0.4% (14/3294) for tolvaptan and 0.3% (9/2738) for placebo.

- Laboratory findings

Tolvaptan did not influence the renal function parameters in a small population of patients with CHF. The occurrence of abnormal blood urea nitrogen in most combinations varied between 28-42% in the

tolvaptan group while it ranged between 33-49% in the standard care group. In the cirrhosis population these were 20-48% for tolvaptan and 27-52% for standard care respectively. For acute renal failure the figures varied as follows: in all trials the ranges were 7-22% for tolvaptan and 8-22% for standard care; in the cirrhosis population the ranges were 0-33% for tolvaptan 7-35% for standard care. It should be noted that although some gradation was seen depending on the number of agents in each combination, the numbers were small in each subgroup and thus are unlikely to indicate a particular predisposition for tolvaptan to increase renal complications. These figures are only for occurrence of change in laboratory parameters and not discontinuations. To conclude, there are no concerns regarding the laboratory findings, therefore no restrictions are necessary in the SPC except serum sodium and potassium monitoring.

- **Safety in special populations**

The data presented thus far has not revealed any specific concern relating to use in the over 65 year population, or changes relating to ethnic origins although Caucasians formed the majority. Tolvaptan has not been studied in children and thus, no safety issues are identified but use will be restricted to those older than 18 years. The safety aspects did not differ in the special populations between tolvaptan and placebo groups although some differences between aetiologies of hyponatraemia are evident.

As regards pregnancy, tolvaptan should not be used in pregnancy or lactation firstly due to its teratogenicity and secondly due to absence of any experience with pregnant or lactating women. The contraindication is supported as other treatment options are available during pregnancy.

- **Safety related to drug-drug interactions and other interactions**

The applicant has analysed the interaction in the EVEREST trial for the following commonly administered agents in heart failure; digoxin, amiodarone and warfarin. No significant interaction was evident although in the placebo group those who did not receive amiodarone had more events and higher rate of death, which is not unexpected. Such a difference was not seen in the tolvaptan group with or without amiodarone. Further information on drug interactions can be found in the Pharmacokinetics section.

- **Discontinuation due to adverse events**

The majority of discontinuations were due to cardiac disorders. Of particular concern during the procedure was the occurrence of acute renal failure. The applicant provided a reanalysis of the events such as occurrence of renal failure in different subsets including pre-disposing factors to address this concern. This included an analysis of combination therapies for agents acting on the RAS (ACEI, ARBs and antimineralocorticoid agents). From the assessment it was concluded that tolvaptan does not appear to have major safety concerns.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan

Table Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Renal toxicity	Routine PhV	<ul style="list-style-type: none"> • Contraindication in Section 4.3 of the SPC for subjects with volume depletion and subjects who cannot perceive thirst • Contraindication in Section 4.3 of the SPC for subjects with anuria • Warning in Section 4.4 of the SPC that subjects should have access to water and be able to drink sufficient amounts of water • Warning in Section 4.8 of the SPC that increases in blood creatinine, pollakiuria and polyuria are common undesirable effects
Volume depletion and dehydration	Routine PhV	<ul style="list-style-type: none"> • Contraindication in Section 4.3 of the SPC for subjects with volume depletion and subjects who cannot perceive thirst • Warning in Section 4.4 of the SPC that subjects should have access to water and be able to drink sufficient amounts of water. • Warning in Section 4.8 of the SPC that thirst and dehydration are very common undesirable effects
Acute urinary retention (patients with urinary outflow obstruction)	Routine PhV	<ul style="list-style-type: none"> • Contraindication in Section 4.3 of the SPC for subjects with anuria • Warning in Section 4.4 of the SPC that urinary output must be secured and that “subjects with partial obstruction of urinary outflow, for example subjects with prostatic hypertrophy or impairment of micturition, have an increased risk of developing acute retention and require careful monitoring”
Electrolyte shifts	Routine PhV	<ul style="list-style-type: none"> • Contraindication in Section 4.3 of the SPC for subjects with hypernatraemia • Warning in Section 4.4 of the SPC that rapid changes in serum sodium: {Trade

		<p>name} may cause rapid increases in serum sodium; therefore after initiation of treatment, subjects should be carefully monitored for serum sodium and volume status. Particular care should be applied in subjects at risks for demyelination syndromes (e.g. hypoxia, alcoholism, malnutrition)</p> <ul style="list-style-type: none"> Warning in Section 4.8 of the SPC that hypernatraemia and hyperkalaemia are common undesirable effects.
Cardiac arrhythmias	Routine PhV	Not required.
Rapid rise of serum sodium and neurologic sequelae	Routine PhV	<ul style="list-style-type: none"> Contraindication in Section 4.3 of the SPC for subjects with volume depletion and subjects who cannot perceive thirst Warning in Section 4.4 of the SPC that subjects should have access to water and be able to drink sufficient amounts of water and that fluid and electrolyte status should be monitored in all patients and particularly in those with renal and hepatic impairment.
Gastrointestinal bleeding in patients with liver cirrhosis	Routine PhV	<ul style="list-style-type: none"> Gastrointestinal bleeding events in cirrhotic patients will be placed under close monitoring and analysed appropriately in the PSUR.
Hyperglycaemia, diabetes mellitus	Routine PhV	<ul style="list-style-type: none"> Warning in Section 4.8 of the SPC that hyperglycaemia is a common undesirable effect.
Hyperuricaemia and gout	Routine PhV	<ul style="list-style-type: none"> Warning in Section 4.8 of the SPC that hyperuricaemia is a common undesirable effect.
Hypercoagulability and stroke	Routine PhV	Not required
Post-treatment myocardial ischaemia	Routine PhV	Not required
Dyspnoea	Routine PhV	Not required
Lack of paediatric data	<ul style="list-style-type: none"> Routine PhV Capture of paediatric off-label use in a Non-interventional study 	<ul style="list-style-type: none"> Statement in Section 4.2 of the SPC that there is no experience in children and adolescents under the age of 18 years.
Teratogenicity, Lack of pregnancy data	Routine PhV	<ul style="list-style-type: none"> Contraindication in Section 4.3 that tolvaptan shall not be used during pregnancy Adequate contraceptive practice requirements in Section 4.6.
Lack of Breastfeeding	Routine PhV	<ul style="list-style-type: none"> Contraindication in Section 4.3 of the SPC in breastfeeding

experience		<ul style="list-style-type: none"> Warning in Section 4.6 of the SPC that tolvaptan is contraindicated during breastfeeding
Hepatic-impaired	Routine PhV	<ul style="list-style-type: none"> Warning in SPC section 4.4 that fluid and electrolyte status should be monitored in all patients and particularly in those with renal and hepatic impairment.
Interaction with CYP3A4 inhibitors	Routine PhV	<ul style="list-style-type: none"> Warning in SPC Section 4.5 of increased tolvaptan plasma concentrations after the administration of strong CYP3A4 inhibitors and after intake of grapefruit juice Warning in SPC Section 4.5 that patients taking tolvaptan should avoid ingesting grapefruit juice.
Interaction with CYP3A4 inducers	Routine PhV	<ul style="list-style-type: none"> Warning in SPC Section 4.5 of decreased tolvaptan plasma concentrations after the administration of CYP3A4 inducers.
Interaction tolvaptan and serum potassium concentration-increasing substances	Routine PhV	Not required
Interaction tolvaptan with combined administration of warfarin and antiplatelet agents	Routine PhV	Not required
Off-label use	<ul style="list-style-type: none"> Routine PhV Non-interventional study 	Not required

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are a number of unresolved minor quality issues but these do not have a negative impact on the benefit/risk balance.

Non-clinical pharmacology and toxicology

Overall the primary PD studies provided adequate evidence that tolvaptan has demonstrated selectivity for V₂ over V₁ receptors in rat, dog and human in vitro, and selectivity for human V₂ receptors over human V_{1a} receptors, but tolvaptan had no affinity for human V_{1b} receptors. Metabolites were less potent than the parent compound. *In vivo*, this was seen to produce dose-related increases in urine

volume and decreases in urine osmolality. Repeated oral doses of tolvaptan at 1 or 10mg/kg for 4 weeks produced an aquaretic effect that was maintained for the duration of the study. The aquaretic effect is not accompanied by significant urinary electrolyte excretion. The safety pharmacology programme did not reveal any findings of concern for humans.

From the PK point of view, the disposition characteristics were generally similar across the species tested showing tolvaptan to have a relatively rapid absorption, with C_{max} and AUC increasing dose-dependently, but the increases were generally not linear, possibly due to high first-pass metabolism. The presence of food reduced C_{max} and AUC. *In vitro* and *ex vivo* plasma protein binding were high (>97% and >93%, respectively). Therefore the potential for interactions resulting from displacement of plasma protein binding is low. Tissue distribution studies showed radioactivity mainly distributed to liver, GI tract and kidney, with little crossing the blood brain barrier (BBB) or into skin or eyes in male albino rats. Tolvaptan or its metabolites in the rat do not have a particular affinity for melanin and therefore there is little likelihood of it being distributed into the skin and eyes in pigmented animals. Transfer of radioactivity across the placenta has been demonstrated in pregnant rats. Section 4.6 of the Summary of Product Characteristics (SCP) reflects this information. Tolvaptan is extensively metabolised in all species investigated, being the metabolism was qualitatively similar. There were no unique human metabolites. In rats and dogs, radioactivity was predominantly (90-95%) eliminated in the faeces. This was also the case in humans although a substantial quantity (about 40% of the dose) was also excreted in the urine, mainly as metabolites. There appear to be no clinically relevant effects on target organs as a result of the higher urinary excretion seen in man. In the animal species as well as man, tolvaptan clearance was mainly by metabolism.

Toxicology studies showed that tolvaptan had low acute toxicity. Findings in the repeated dose toxicity studies in rats and dogs were generally related to the pharmacological effect of tolvaptan and it is accepted that there were no obvious target organs in either species studied. Tolvaptan is not considered to be genotoxic or carcinogenic.

A series of studies in pregnant rats and rabbits showed developmental toxicity in the rat fetuses. This was a point of major concern. The availability of alternative, safer treatments during pregnancy was discussed and it was accepted that there are other options for management during pregnancy which include conservative approaches such as correcting the underlying causes and using treatments for which there is experience of use during pregnancy in those cases when there is an urgent need or the symptoms are severe. In view of the availability of alternative treatments a contraindication during pregnancy is accepted.

Tolvaptan was not a dermal or an ocular irritant, and the potential for phototoxicity reactions occurring in man is considered to be low.

On the basis of the data available so far, tolvaptan does not appear to present a risk to the environment.

Efficacy

Hyponatraemia

Tolvaptan treatment significantly improved serum sodium concentrations for all 3 disease groups (SIADH, CHF and cirrhosis) when compared to placebo. The results were similar in subjects with mild and severe hyponatraemia, with the biggest difference compared to placebo seen for the SIADH population (effect size for: SIADH 4.70 and 6.15 for Day 4 and Day 30 respectively; CHF 2.98 and 4.05 for Day 4 and Day 30 respectively; Cirrhosis 3.15 and 2.83 Day 4 and Day 30 respectively). This improvement was irrespective of the volume status (hypervolemic or euvolemic).

The urine output was consistently and statistically significantly greater in the tolvaptan group than the placebo group in the pooled analysis, regardless of aetiology. Fluid intake was also greater in the tolvaptan group compared with placebo in the pooled analysis; however the difference from placebo was only statistically significant for subjects with cirrhosis. Statistically significant greater mean decreases in body weight were observed in hypervolemic subjects at Days 2, 3, and 4 for the tolvaptan group compared with the placebo group in SALT-1 and in the pooled analysis.

Mental status was assessed using the Mental Component Summary of the SF-12 Health Survey, evaluated at Day 30 compared to baseline. Improvements in SF-12 MCS scores related to and were associated with changes in serum sodium. These results were seen across different volume states in comparison to placebo. When the three aetiologies were analysed separately (although these were not

individually powered to find a difference), there were statistically significant improvements in mental status (MCS) on Day 30 for tolvaptan compared to placebo ($p = 0.0129$) for subjects with SIADH/Other in the pooled analysis. However, different statistical methodologies appear to show that the effect size in CHF could be of similar magnitude here as in SIADH or cirrhosis. The MCS analysis is also confounded by a multiplicity issue: MCS by (SF12) was not specified in the statistical analysis plan as a key secondary end point but was one of several, and therefore it cannot formally be concluded that a statistically significant effect has been demonstrated on the MCS endpoint.

A post-hoc analysis of results in the hyponatraemic subgroup from the EVEREST trial shows that in the subgroup with hyponatraemia+CHF, the tolvaptan group had a trend to lower CV mortality/morbidity, shorter hospital stay (1.5 days), better KCCQ score and greater impact on dyspnoea and normalisation of sodium. These additional analyses appear to favour tolvaptan use in CHF+ hyponatraemic population, however the differences are based on small populations/subgroups ($n=92$, Serum Na $<130\text{mEq/L}$) but not clear in the larger population of those with serum sodium $<135\text{mEq/L}$.

The major issue with the hyponatraemia indication is lack of clear patient oriented benefit related to correction of serum sodium values and this has been shown for the SIADH population.

Worsening of heart failure

Symptomatic benefit has been shown in the short term 1-7 days with the majority of the benefit restricted to days 1-3. Dyspnoea reduction is noted on day 1-3. Pedal oedema was different in the two groups for a longer period. Tolvaptan did not have negative effect on mortality in the EVEREST trial but the number followed up were only 800 up to 12 months. In the heart failure population, the lack of any medium to long-term effect was considered a significant deficiency. A clear benefit over and above that of use of diuretics was hypothesized but not clearly demonstrated. The demonstrated effect sizes are small and the Van-Elteren analyses were post-hoc. In view of the concerns of the CHMP the applicant withdrew this indication during the procedure.

Safety

No major safety concerns have been identified with tolvaptan, except for the teratogenicity. The most frequent possibly related treatment emergent adverse events were: thirst, ~18% in tolvaptan group [$\sim 2.5\%$ in SC group], dry mouth (8.5 vs. 2.1%), pollakiuria (frequent day time urination: 5.4 vs. 0.9%), fatigue (2.3 vs. 0.9%), polyuria (3.3% vs. 0.6% SC) and ventricular tachycardia (0.9% vs. 0.3% SC). For a large number of other adverse events, there was no difference between the two groups.

The serious TEAEs of special interest (including ventricular tachycardia [VT], cardiac arrest, hyperkalaemia, cerebrovascular accident, renal failure, and hypotension) all occurred with differences of $\leq 1\%$ between the tolvaptan and the placebo groups. Among all the heart failure and hyponatraemia subjects, 17.2% in the tolvaptan group and 20.0% in the placebo subjects died during the on-treatment period. A total of 567 (17%) tolvaptan and 547 (20%) placebo subjects died and the types of events were similar for the 2 treatment groups. Most deaths (331 [10%] tolvaptan subjects and 285 [10%] placebo subjects) were due to events of the cardiac disorders system organ class.

An imbalance in the number of strokes in the EVEREST trial is noted and the applicant argues that a specific analysis of 'hypercoagulable state' (stroke, arterial occlusion or myocardial infarction, etc) did not show differences between tolvaptan and placebo.

No cases of demyelination have been identified in the clinical programme; however, a warning is included in section 4.4 of the SPC as this is considered a potential risk.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

The results of the user consultation are acceptable. The package leaflet (PL) is presented in line with the QRD template and articles 59(3) and 61(1) of directive 2001/83/EC. Lay language is generally used throughout the PL and the information is considered to be clear and understandable.

Risk-benefit assessment

Some aspects of benefit in heart failure are included below as they may be of relevance; a detailed analysis of benefit risk in this population is not considered necessary however. The applicant was ultimately only seeking the hyponatraemia indication patients with SIADH.

Benefits

- Demonstrated benefits

In the hyponatraemia population, tolvaptan undoubtedly improves serum sodium balance for the duration of therapy and prevents progressive lowering of sodium. There is clear evidence of an effect on the serum sodium levels and the secondary parameters including urine output, fluid intake and overall fluid balance. Serum sodium increases from start of therapy that is titrated in order to achieve best results and persists up to day 30 in the two pivotal studies. There is a theoretical advantage over currently available therapies that hyponatraemia is not common and prevented. The MCS component of the SF12 questionnaire showed advantages of tolvaptan therapy over standard care in the SIADH and cirrhosis populations albeit with some statistical limitations (see Uncertain benefits). The effect on serum sodium is consistent across the aetiologies (SIADH, CHF & Cirrhosis) for normalisation of sodium, for urine output and for overall fluid balance (primary and secondary efficacy parameters). Similar results were seen across different volume states (euvolemic or hypervolemic) in comparison to standard care.

The applicant presents a post-hoc analysis of results in the hyponatraemic subgroup from the EVEREST trial. The post-hoc analysis argues that in the subgroup with hyponatraemia+CHF, tolvaptan group had a trend to lower CV mortality/morbidity, shorter hospital stay (1.5 days), better KCCQ score and greater impact on dyspnoea and normalisation of sodium. Of note, these were mainly in the small group that had serum sodium <130mEq/L but not clear in the larger population of those with serum sodium <135mEq/L.

In heart failure clinical programme, symptomatic benefit has been shown in the short term 1-7 days with the majority of the benefit restricted to days 1-3, although a small but significant difference is noted on day 7 or discharge and to a maximum of 2 weeks on some parameters. Dyspnoea reduction is noted on day 1-3 and no further. Pedal oedema was different in the two groups for a longer period while orthopnoea was not. Tolvaptan did not have negative effect on mortality in the EVEREST trial but the number followed up were only 800 up to 12 months. In the heart failure population, the lack of any medium to long-term effect was considered a significant disadvantage. A clear benefit over and above that of use of diuretics hypothesized but not clearly demonstrated. The demonstrated effect sizes are small and the Van-Elteren analyses were post hoc. The CHMP concerns regarding the indication of worsening of heart failure lead the applicant to withdrawn this indication although some of the discussion is considered relevant to the hyponatraemic population.

- Uncertain benefits

In the hyponatraemia population, there are difficulties with the lack of correction of multiplicity of secondary parameters such as MCS and the effect size in CHF+hyponatraemia subset is smaller than the other two groups (SIADH and cirrhosis). While the effect size on MCS was smaller than the other two aetiologies after correction of hyponatraemia, the applicant has provided reanalysis of this subgroup in the EVEREST trial; but these effects were not seen in the major subgroup of those with serum sodium <135mEq/L. Severe hyponatraemia population was not included in the trial, as such section 4.4 of the SPC includes a warning stating that for patients that may require rapid correction of serum sodium alternative treatment should be considered.

There is a lack of long-term data in cirrhosis patients as only few patients were followed up for 100 weeks in the SALTWATER trial.

Risks

The safety dataset is of reasonable size for the indications sought although the larger studies have been conducted in heart failure patients. There are no major safety concerns related to tolvaptan except for the teratogenicity. It is questionable however whether the size of the data set and duration of treatment (exposure) is adequate to assess mortality. Only ~800 subjects are exposed to tolvaptan for over 1 year and this may be a limitation especially given the assumptions regarding mortality in this long symptomatic patient group with CHF. It is reassuring to note that for a large number of other adverse events there was no difference between the two groups. Although overall numbers showed some differences for hyperkalaemia, hypokalaemia and others, these differences are not sustained in the “possibly related TEAEs”. The groups did not differ in terms of the type and number of serious TEAEs. An imbalance in the number of strokes in the EVEREST trial is noted and the applicant argues that a specific analysis of “hypercoagulable state” (stroke, arterial occlusion or myocardial infarction, etc.) did not show differences between tolvaptan and placebo.

- Demonstrated risks

The demonstrated risk remains one of excess dehydration and the lack of clarity regarding use of tolvaptan in association with fluid restriction especially in patients with heart failure. Teratogenicity has been identified in animal studies; this is addressed by a contraindication in pregnancy. There is also a contraindication in breastfeeding.

- Potential risks

Serious hypernatraemia and consequent CNS effects are a potential risk but based on the doses used in clinical studies this has not been seen; as a potential risk a warning is included in section 4.4 of the SPC regarding this point. The lack of a clear effect on clinical outcome measures could be considered as another risk as a longer follow-up might have revealed a negative effect on mortality. These however remain hypothetical (or only potential risks).

Long-term follow-up and effect especially in the cirrhosis population is of interest. The SALTWATER trial provides some reassurance that there have been no serious adverse events reported as of the date of this report. Conclusions based on this will be limited as the numbers were small.

Risk-benefit balance

There is clear evidence of an effect on the serum sodium levels and the secondary parameters including urine output, fluid intake and overall fluid balance. The applicant however has not provided sufficient evidence that correction of hyponatraemia is of clinical relevance in all the populations studied. Whilst a number of limitations of the data provided have been identified including lack of definition of crucial secondary end points, the applicant has argued that there is tangible benefit in this difficult condition to treat. The important consideration here is that serum sodium improvement has been very well demonstrated in all three aetiologies. The changes in MCS and SF12 have their limitations but do provide a validated assessment of the subtle signs of changes brought about by chronic hyponatraemia. These changes in MCS are likely to be most obvious in those with severe hyponatraemia, a group of subjects usually excluded from clinical trials for reasons of patient safety and other reasons (poor recruitment, ethical reasons etc). Tolvaptan is not to be used where rapid correction of serum sodium is required. Based on the data presented thus far and based on the applicant's explanations to CHMP, the general view is that a clear effect has been shown for correction of sodium and patient related benefit in SIADH population. In the CHF and cirrhosis populations some questions remain due to insufficient data and low patient numbers. The SALT trials were not powered to detect significance in each aetiology, for the secondary end points. The central issue therefore is whether “correction of hyponatraemia offers clinically relevant effect” and this has been shown for the SIADH population.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns. No additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Samsca in the treatment of adult patients with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH) was favourable and therefore recommended the granting of the marketing authorisation.