Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Tolvaptan

Proprietary Product Name: Samsca

Sponsor: Orphan Australia Pty Ltd

October 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of Submission	New Chemical Entity
Decision:	Approved
Date of Decision:	15 March 2012
Active ingredient(s):	Tolvaptan
Product Name(s):	Samsca
Sponsor's Name and Address:	Orphan Australia Pty Ltd
	300 Frankston-Dandenong Road
	Dandenong VIC 3175
Dose form(s):	Tablet
Strength(s):	15 and 30 mg
Container(s):	PVC/Aluminium foil blister
Pack size(s):	10 and 30 tablets
Approved Therapeutic use:	Samsca is indicated for the treatment of clinically significant hypervolemic or euvolemic hyponatremia (serum sodium less than 125 mmol/L, or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction) including patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).
Route(s) of administration:	Oral
Dosage:	15 mg once daily (maximum 60 mg)
ARTG Number (s)	15 mg: AUST R 176602
	30 mg: AUST R 176601

Product background

This AusPAR describes an application by the sponsor, Orphan Australia Pty Ltd, to register Samsca (Tolvaptan), a product licensed from Otsuka Pharmaceutical Co Ltd, Japan. The proposed indication for which approval is sought is:

> *"Treatment of clinically significant dilutional hyponatremia including patients with heart failure, cirrhosis, and Syndrome of Inappropriate Antidiuretic Hormone (SIADH)."*

The application documents were originally written for both indications of hyponatremia and heart failure. However, during the evaluation period, Otsuka Pharmaceuticals had withdrawn the heart failure indication from the European and US submissions. Only the hyponatremia indication is approved in both the US and EU. Accordingly, only the treatment of hyponatremia is proposed in the Australian submission.

Tolvaptan is a selective vasopressin V_2 receptor antagonist for oral administration. Tolvaptan acts by blocking arginine vasopressin (AVP) binding to V_2 receptors of the distal nephron resulting in electrolyte free water secretion without significantly changing total electrolyte excretion.

The clinical development of Tolvaptan was initiated in 1994 with early healthy subject trials conducted in Japan, and it has since been investigated extensively in hyponatremia and heart failure subjects with volume overload. Given that some subjects with advanced heart failure may also have hyponatremia and that hyponatremia can occur in other hypervolaemic states, there is some overlap between the two indications, and these two complementary Tolvaptan programs have proceeded in parallel.

Regulatory status

By August 2009, Samsca was approved in the US and EU (30 countries including UK, France, Germany, Spain and Italy) for 'treatment of hyponatremia'. The approved indication in the US is:

> *"Samsca is indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium < 125 mEqL or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure, cirrhosis, and SIADH."*

The approved indication in the EU is:

> *"Treatment of adult patients with hyponatremia secondary to SIADH."*

The international regulatory status of Samsca as of 30 November 2011 is summarised in Table 1.

Table 1: Summary of international regulatory status of Samsca.

Country	Pharmaceutical Form	Strength (mg)	Date of Approval	Indication
Canada	tablet	15, 30, 60	25/07/11	Samsca (Tolvaptan) is indicated for the treatment of clinically important, non hypovolemic hyponatremia, for example, serum sodium <130 mEq/L, or symptomatic hyponatremia.
China	tablet	15, 30	23/09/11	Tolvaptan is indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure, cirrhosis, and SIADH.
EU*	tablet	15, 30	03/08/09	Treatment of adult patients with hyponatremia secondary to SIADH.
Hong Kong	tablet	15, 30	06/08/10	Samsca is indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium <125 mEq/L or less

Country	Pharmaceutical Form	Strength (mg)	Date of Approval	Indication
				marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure, cirrhosis, and SIADH.
Indonesia	tablet	15, 30	01/11/11	Treatment of adult patients with hyponatremia secondary to SIADH. Treatment of clinically significant hypervolume hyponatremia that has resisted correction with fluid restriction (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic in patients with heart failure).
Japan	tablet	15	27/10/10	Volume overload in heart failure when adequate response is not obtained with other diuretics (for example, loop diuretics).
Korea	tablet	15, 30	01/09/11	The treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium <125 mEq/L or hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure, cirrhosis, SIADH, etc.
Taiwan	tablet	15, 30	23/11/10	Samsca is indicated for the treatment of patients with hyponatremia secondary to SIADH.
US	tablet	15, 30, 60	19/05/09	Samsca is indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure,

Country	Pharmaceutical Form	Strength (mg)	Date of Approval	Indication
				cirrhosis, and SIADH.

* EU: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Estonia, Greece, Finland, France, Hungary, Iceland, Ireland, Italy, Liechtenstein, Lithuania, Luxembourg , Latvia, Malta, Netherlands, Norway, Poland, Portugal, Romania, Sweden, Slovenia, Slovakia, Spain and United Kingdom.

Product Information

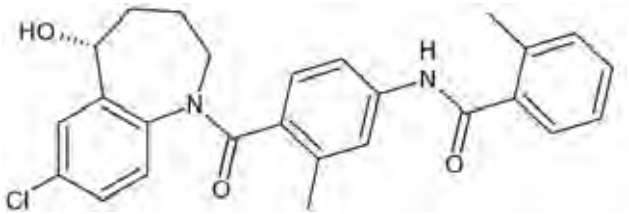
The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Drug substance (active ingredient)

Tolvaptan, $C_{26}H_{25}ClN_2O_3$ Molecular Weight 448.94, has one chiral centre but is presented as a racemate (Figure 1).

Figure 1: Chemical structure of Samsca (Tolvaptan); one enantiomer is shown.

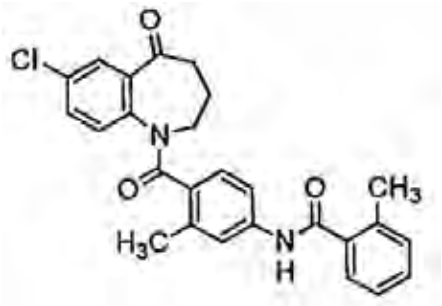


Tolvaptan is a white crystalline powder. No polymorphic forms have been identified (but the drug is dissolved during tablet manufacture).

Aqueous solubility is very low, independent of pH (< 0.1 mg/250 mL).

The specification includes a specific optical rotation test to demonstrate that the batch is racemic. The only nominated impurity in the specification is the intermediate, and benzylic oxidation product, SFO-41019 (Figure 2).

Figure 2: Benzylic oxidation product, SFO-41019.



The drug substance is dissolved during tablet manufacture, so that particle size is not relevant.

Stress stability data are noted in the evaluation; the mass balance in these studies will also be queried.

Drug product

The tablets are made via wet granulation. The strengths are direct scales (17.2% drug w/w). Both tablets are blue, unscored, uncoated, but they are differentiated by both embossing and tablet shape (triangular/round).

III. Nonclinical findings

Introduction

The overall quality of the submitted studies was high. All pivotal safety related studies were Good Laboratory Practice (GLP) compliant with the exception of a set of safety pharmacology studies examining potential effects of Tolvaptan on central nervous system (CNS) function (in mice). The non GLP studies were nevertheless adequately documented, and were conducted in established laboratories.

Pharmacology

AVP is a peptide hormone synthesised in the hypothalamus and released from the pituitary. It exerts an antidiuretic effect by promoting water reabsorption in the kidneys, primarily through activation of V_2 receptors (G protein coupled). AVP can also cause vasoconstriction via V_{1a} receptors. Patients with various disorders, including congestive heart failure, liver cirrhosis and SIADH, are at risk of experiencing excess water retention or inadequate water disposal due to increased vasopressin secretion. Electrolyte imbalances with unclear aetiologies, in particular hyponatremia, often occur in such patients. Conventional diuretics may exacerbate hyponatremia (and other electrolyte imbalances) through promotion of inappropriate loss of electrolytes, potentially leading to neurological and/or cardiac complications. A selective V_2 receptor antagonist, to promote free water loss without disturbing electrolyte balance (that is, an aquaretic), was envisaged to be clinically useful for the treatment of disease states associated with hyponatremia or fluid excess.

Antagonism of V_2 receptors by Tolvaptan was demonstrated *in vitro* in binding and functional experiments. Racemic Tolvaptan inhibited ^{3}H AVP binding to human vasopressin V_2 receptors with a Ki (inhibition constant) of 0.43 nM (~1.8 times more potent than AVP) and inhibited AVP induced cAMP (cyclic adenosine monophosphate)

production in HeLa cells expressing the human V_2 receptor with an IC_{50} (concentration of drug producing 50% inhibition) of 8.0 nM. These compare favourably with the peak free plasma concentrations of Tolvaptan obtained in patients at the proposed clinical doses (~6.5-28 nM). The S- and R-enantiomers displayed equivalent potency. No agonist activity was observed for Tolvaptan in the cell based functional assay. Affinity of Tolvaptan for rat and dog V_2 receptors was also demonstrated (3 and 1.5 times lower, respectively, compared with the human isoform). The major metabolites of Tolvaptan, DM-4103 and DM-4107, displayed no or negligible affinity for the V_2 receptor (human, rat and dog). Certain other metabolites (DM 4110, DM 4111 and MOP 21826) were found to have some activity at the V_2 receptor (~2-4 fold lower compared with Tolvaptan in binding assays and 5-15 fold lower in the functional assay). Based on potency and pharmacokinetic (PK) data, they are not predicted to contribute meaningfully to efficacy in patients.

In the *in vivo* studies, increases in urine volume (statistically significant and dose dependent) were consistently seen with Tolvaptan at oral doses ≥1 mg/kg in mice and dogs and ≥3 mg/kg in rats and rabbits. Urine osmolality was also significantly decreased in these studies at ≥0.3 mg/kg in mice, rats and dogs, and at ≥1 mg/kg in rabbits. In the toxicity studies, these findings were generally accompanied by decreased urine specific gravity and electrolyte concentrations (where measured). Tolvaptan increased free water clearance to positive levels in mice and rats at 10 mg/kg, in rabbits at ≥3 mg/kg, and in dogs at ≥1 mg/kg.

Tolvaptan increased urinary sodium excretion in mice, rats and rabbits, but not in dogs. Despite this, serum sodium concentration was elevated increased in rats and rabbits, as well as in dogs. Serum AVP was increased in rats and dogs following Tolvaptan administration. Tolvaptan did not enhance serum renin activity or elevate plasma aldosterone concentration in either rats or dogs and did not affect plasma adrenaline or noradrenaline concentrations in dogs. The AVP content of the pituitary gland was unchanged and there was no effect on the number or affinity of AVP receptors of the kidney in rats following once daily oral administration of Tolvaptan at up to 10 mg/kg/day for 4 weeks. The increase in sodium excretion induced by Tolvaptan was typically smaller than that induced by furosemide. Aquaresis with Tolvaptan was retained with concomitant admin of furosemide in rats and dogs; an additive increase in urine volume was shown in dogs.

Normalisation of plasma sodium concentrations was demonstrated with Tolvaptan (escalated to 8 mg/kg/day PO [oral administration]) in a rat model of SIADH secretion.

Secondary pharmacodynamics and safety pharmacology

Receptor binding experiments indicated 29 fold selectivity for Tolvaptan at V_2 compared with V_{1a} receptor subtypes in humans, and even greater selectivity in the laboratory animal species (259 fold in rats; 61 fold in dogs). Consistent with this, Tolvaptan inhibited platelet aggregation induced by AVP in human blood (mediated by the V_{1a} receptor) with an IC50 of 1.3 µM; ADP (Adenosine Diphosphate) induced aggregation was unaffected. Affinity of the drug for the human V1b receptor appears negligible, with no significant inhibition of ^3H AVP binding seen with Tolvaptan at 100 nM (>230 times its Ki at the V_2 receptor). Tolvaptan's affinity for the human oxytocin receptor was ~1000 times weaker than for the V_2 receptor. The drug's major metabolites (DM-4103 and DM-4107) were devoid of activity at human V_{1a} and V_{1b} receptors. Further screening assays showed no notable activity for Tolvaptan, DM-4103 or DM-4107 at muscarinic, adenosinergic, adrenergic, angiotensin II, bradykinin, calcitonin gene related peptide, dopamine, endothelin, epidermal growth factor, histamine, opioid, serotonin, somatostatin and vasoactive intestinal peptide receptors, or calcium, potassium and sodium channels.

Specialised safety pharmacology studies examined potential effects of Tolvaptan on the CNS, cardiovascular, respiratory and gastrointestinal systems.

Tolvaptan had no significant effects in CNS investigations in mice (≤1000 mg/kg PO). Effects of PO Tolvaptan on cardiovascular and respiratory function in dogs were transient and minor (≤1000 mg/kg). Significant effects of Tolvaptan were seen after intravenous (IV) administration at 10 mg/kg in dogs, comprising increased heart rate, decreased blood pressure, and changes to the respiratory rate relative to the vehicle control (100% DMSO). However, interpretation was confounded by effects of the vehicle itself. Tolvaptan did not inhibit the hERG K+ channel in vitro (≤20 μM), nor affect action potentials in isolated guinea pig papillary muscles (≤30 μM). Some inhibition of the hERG K+ current was seen with DM-4103, but this was very weak (IC50, >100 μM). IV administration of DM-4103 and DM-4107 transiently affected respiratory rate, heart rate, blood pressure and some ECG (electrocardiogram) parameters in dogs, but at concentrations considerably greater than anticipated in humans at the maximum recommended dose. No ECG changes were seen in the repeat dose toxicity studies conducted in dogs (≤1000 mg/kg/day PO).

Tolvaptan suppressed acetylcholine, histamine and Ba^{2+} induced contractions of the isolated guinea pig ileum at 10-30 μM, but was without effect at 3 μM. Gastrointestinal motility was unaffected in mice at ≤1000 mg/kg PO and rats at ≤3 mg/kg IV. Decreased volume and increased pH of the gastric juice were noted in rats at 1000 mg/kg PO, but doses ≤100 mg/kg had no effect.

Pharmacokinetics

Tolvaptan was rapidly absorbed following oral administration in the laboratory animal species, with T_{max} (time to reach maximum plasma concentration following drug administration) values typically 1-1.5 h post dose in mice, rats, rabbits and dogs (though ~4 h at high doses in dogs). T_{max} in patients was comparable (generally 2-4 h). The initial formulation of Tolvaptan (jet milled powder) showed poor oral bioavailability in rats and dogs (0.63% and 2%, respectively). This led to the development of a fine granule spray dried formulation, which showed improved oral bioavailability (16% and 14.6% in the respective species, compared with 56% in humans). Exposure to Tolvaptan following single oral administration was approximately dose proportional in mice, rats, rabbits and dogs, as it is in humans over the proposed clinical dose range. A sex difference was apparent in rats, with exposure to Tolvaptan ~10 times higher in females compared with males. Meanwhile, exposure to metabolite DM-4103 was found to be considerably higher in males in the species, suggesting that differences in the rate of metabolism were largely responsible for the finding. Accumulation of Tolvaptan with repeat daily dosing was not observed in the laboratory animal species.

Volume of distribution was moderate to high in rats and dogs. Accordingly, radioactivity was found to be widely distributed to tissues in rats following oral administration of ^{14}C Tolvaptan. Outside of the GI (gastrointestinal) tract, ^{14}C Tolvaptan derived radioactivity was highest in the liver, adrenal gland and kidney (peaking at 10.3, 2.4 and 1.8 times the serum C_{max} (maximum plasma drug concentration) in males, and 13.0, 6.3 and 3.1 times in females, respectively). Tissue levels of radioactivity generally declined in parallel with serum, though somewhat slower for the liver. There was no evidence of accumulation in any tissue. Penetration across the blood:brain barrier was low (peak levels in the cerebrum and cerebellum were 3–8% of the serum C_{max}). Distribution to reproductive tissues was low in males (Cmax in testis, 13% of that for serum) and greater in females (C_{max} in ovary, 1.7 times the serum C_{max}). A specialised renal distribution study with unlabelled Tolvaptan, conducted in female rats, revealed similar findings: peak and overall exposure to the unchanged compound in the kidney were both ~4 times higher than for serum; T_{max} and half life were similar. Plasma protein binding by Tolvaptan *in vitro* was high in humans (≥98.0%) and all of the laboratory animal species examined (mouse, rat,

rabbit and dog; ≥97.2%). The major metabolites of Tolvaptan (DM-4103 and DM-4107) were also found to be highly protein bound in human plasma (98.3-99.8%). ^{14}C Tolvaptan was not significantly distributed to red blood cells in rats and dogs.

Tolvaptan was extensively metabolised in all laboratory animal species investigated as well as in humans. Metabolism primarily involved dehydrogenation, hydroxylation and deamidation. All metabolites found in humans were also formed in the species used in toxicology studies (mice, rats, rabbits and/or dogs), although there were quantitative differences. DM-4103 (a derivative with a cleaved benzapine ring) was the dominant circulating species in humans, rats and rabbits, present in serum at levels well above that of unchanged drug. CYP3A4 was identified as the P450 isoform chiefly responsible for the metabolism of Tolvaptan in the *in vitro* experiments; a role for CYP1A1 was also identified. Following oral administration of Tolvaptan, serum concentrations of the (S)-(-)- optical isomer were higher compared with the (R)-(+)-isomer in humans and dogs; the reverse was true for rats and rabbits. Some transformation from (S)- to (R)-isomers was observed in rats, and (R)- to (S)- in dogs, *in vivo* (but not in the other direction).

Metabolic clearance was the predominant mechanism of elimination of Tolvaptan in all species. Excretion of radioactivity following oral dosing with ^{14}C Tolvaptan was primarily via the faeces in all species examined (rats, dogs and humans). In humans, a greater proportion of the dose was eliminated via urine (40%) than in the laboratory animal species (up to 8%). This may reflect the higher bioavailability of the drug in humans. Biliary excretion was demonstrated in the rat.

Comparisons of the PK profiles of Tolvaptan in the laboratory animal species used in the toxicity studies indicate that sufficient similarities exist to allow them to serve as appropriate models of Tolvaptan toxicity in humans.

PK drug interactions

Given the major role of CYP3A4 in the metabolism of Tolvaptan, co administered drugs that inhibit this isoform can be expected to increase exposure to Tolvaptan.

Tolvaptan itself was found to act as a competitive inhibitor of CYP3A4 and also 2C9 in experiments with recombinant human enzymes; Ki values were ≥5.4 μM and 7.8 μM, respectively (= 2424 and 3502 ng/mL). These are ~3.5 and 5 times higher than the peak serum concentration of Tolvaptan expected in hyponatremia patients at the maximum recommended human dose of 60 mg/day (713 ng/mL in Study 156-96-203), suggesting the potential for some inhibition *in vivo*, but likely only slight at most. DM-4103 and DM-4107 displayed no significant inhibitory activity against human CYPs 1A1/2, 2C8/9, 2C19, 2D6, 2E1 and 3A4. Hepatic CYP450 induction was observed in rats treated with Tolvaptan at 300 mg/kg/day PO for 7 days, but not at doses ≤100 mg/kg/day.

The concomitant presence of furosemide, spironolactone, propranolol, dispyramide, lidocaine or warfarin did not significantly affect human plasma protein binding by Tolvaptan, DM-4103 or DM-4107 *in vitro*, suggesting that drug displacement interactions are unlikely. Tolvaptan was both a substrate and an inhibitor of P glycoprotein (IC50, 15.9 μM [= 7.1 μg/mL)), indicating potential for interactions with other P glycoprotein substrates.

Toxicology

Acute toxicity

Single dose toxicity studies were conducted with Tolvaptan by the oral route in mice, rats and dogs, and by the IV route in rats and cynomolgus monkeys. While individual studies

did not fully comply with the relevant ICH (International Conference on Harmonisation) guideline [3BS1a] (for example, dogs were not subjected to necropsy, group sizes were sometimes very small, and an observation period shorter than the recommended 14 day period was used in two studies), as a package the studies are considered adequate. Maximum non lethal doses of spray dried Tolvaptan by the oral route were 300 mg/kg in mice and 2000 mg/kg in rats and dogs, indicating a low order of acute toxicity for the drug. No mortality was observed in the IV studies (≤1 mg/kg in rats and ≤0.333 mg/kg in monkeys).

No overt toxicity was observed in male rats following SC (subcutaneous) administration of either DM-4103 or DM-4107 (≤500 mg/kg).

Repeat dose toxicity

Studies of up to 13 weeks duration were conducted in mice, 26 weeks in rats and 52 weeks in dogs. All involved once daily oral administration. The spray dried formulation was used in the longest studies in each species, as well as in 4 week studies in rats and dogs. The duration of the pivotal studies, the species used (rats and dogs), group sizes and the use of both sexes were consistent with ICH guidelines.

Relative exposure

Exposure ratios have been calculated based on animal:human serum/plasma $AUC_{0\text{-}24\ h}$ (area under the plasma concentration-time curve within time span 0 to 24 h) values for Tolvaptan and (where data were available) its major human metabolites (Table 2). Human reference values are for the maximum recommended daily dose of 60 mg in patients with hyponatremia secondary to liver disease for Tolvaptan (Study 156-96-203) and at the same dose in healthy human subjects for the metabolites (Study 156-97-202). Multiples of the human dose adjusted for body surface area (BSA) are also tabulated.

Table 2: Exposure ratios for Tolvaptan – mouse, rat, dog.

Species	Study	Sex	Dose (mg/kg /day); PO	$AUC_{0\text{-}24h}$ (µg.h/mL)			Exposure ratio			
							based on AUC			based on BSA#
				Tolvaptan	DM-4103	DM-4107	Tolvaptan	DM-4103	DM-4107	
Mouse ($B6C3F_1$)	13 weeks (013773)	♂	100	8.30	3.80	–	0.85	0.09	–	7.6
		♀		9.31	15.2	7.20	0.95	0.34	4.6	
	2 years (014252)	♂	10	0.43	0.59	0.14	0.04	0.01	0.09	0.8
			30	1.38	1.43	0.42	0.14	0.03	0.27	2.3
			60	2.86	6.07	1.22	0.29	0.14	0.78	4.5
		♀	10	0.18	1.03	0.30	0.02	0.02	0.19	0.8
			30	0.90	4.41	1.51	0.09	0.10	0.97	2.3
			100	4.33	72.9	11.7	0.44	1.6	7.5	7.6
Rat (SD)	6 months (013774)	♂	30	2.21	6.28	4.82	0.23	0.14	3.1	4.5
			100	7.76	71.6	28.6	0.79	1.6	18	15
			1000	12.7	581	298	1.3	13	191	152
		♀	30	15.9	1.7	4.34	1.6	0.04	2.8	*as above*
			100	20.7	12.3	20.3	2.1	0.28	13	
			1000	33.4	–	–	3.4	–	–	
	2 years (014253)	♂	300	7.78	254	63.4	0.79	5.7	41	45
		♀		24.7	90.9	61.9	2.5	2.0	40	
Dog (Beagle)	52 weeks (012707)	♂	30	9.79	1.19	0.39	1.0	0.03	0.25	15
			100	31.5	6.36	1.48	3.2	0.14	0.95	51
			1000	271	16.2	7.40	28	0.36	4.7	505
		♀	30	6.77	3.10	0.68	0.69	0.07	0.44	*as above*
			100	42.3	9.16	2.63	4.3	0.21	1.7	
			1000	228	34.6	22.0	23	0.78	14	
Human	156-96-203; 156-97-202	♂/♀	[60 mg]	9.81	44.5	1.56	–	–	–	–

BSA adjusted doses have been calculated using mg/kg to mg/m^2 conversion factors of 3, 6, 20 and 33 in mice, rats, dogs and humans (50 kg) respectively.

While high doses (on a BSA basis) were used, animal:human exposure ratios for Tolvaptan were low in rodents. Exposure margins for one or both of the major metabolites were more substantial. These findings are considered to reflect the much greater metabolic clearance in mice and rats compared with humans. A large multiple of the human AUC for Tolvaptan was obtained at the high dose level in the pivotal dog study.

Major findings

Increased water consumption and urine volume, and an associated decrease in urine osmolality, were seen in all of the studies in rats and dogs, and are consistent with the drug's pharmacological action (these parameters were not assessed in the study in mice). In most studies there was evidence of at least transient body weight loss and/or a reduction in body weight gain, which was accompanied by a transient reduction in food consumption, and probably related to dehydration.

The only treatment related histopathological findings observed in the repeat dose toxicity studies were thymic atrophy and enlargement of the renal proximal tubular epithelium nuclei in dogs treated at 1000 mg/kg/day PO for 4 weeks and reduced vacuolisation of adrenal cortical cells and increased width of the adrenal cortex (with increased adrenal weight) in dogs at ≥100 mg/kg/day PO for 52 weeks (relative exposure, 3.2-28). These were graded as minimal to at most slight severity. The changes seen in the pivotal study

are consistent with stress rather than a direct effect of Tolvaptan, and were demonstrated to be reversible following treatment withdrawal. The microscopic findings in the 4 week dog study were not reproduced in the pivotal study (involving 52 weeks treatment at the same dose level); notably too, the kidney finding was not degenerative in nature. Increased adrenal and decreased thymic weights (without accompanying histopathological changes) were seen in rats treated at 1000 mg/kg/day PO for 26 weeks, and again are consistent with stress (non specific toxicity). The pivotal studies establish NOAELs (no observed adverse effect levels) of 100 mg/kg/day PO in dogs (relative exposure, ~3-4) and female rats (relative exposure, 2), and 1000 mg/kg/day PO in male rats (relative exposure, 1.3).

In a set of additional studies conducted with the individual isomers of Tolvaptan, single oral doses of ≥500 mg/kg (R)-(+)-Tolvaptan and ≥1000 mg/kg (S)-(-)-Tolvaptan produced mortality and clinical signs in rats, with histopathological changes seen in the brains of decedents. The microscopic findings (ischaemic change and spongy deterioration) were attributed to the exaggerated diuretic action of the isomers and the resultant dehydration or impairment of blood flow. Toxicokinetic analyses revealed exposure levels much higher than that obtained with the racemate. The nonclinical overview reports that this was considered to be due to the smaller particle size of the isomer powders compared with racemic Tolvaptan powder.

Coagulation parameters were slightly prolonged in rats at ≥300 mg/kg/day (activated partial thromboplastin time [APTT]) or 1000 mg/kg/day (prothrombin time [PT]) in the 4 week study. The activities of factors II, VII, VIII, IX and X were reduced. A slight increase in APTT was also observed in male rats treated at 1000 mg/kg/day in the 26 week study. An investigative study found that prolonged PT and APTT were linked to decreased vitamin K obtained in the diet: the changes in coagulation parameters were attenuated in rats treated with Tolvaptan that were not fasted prior to blood collection and were normalised in animals that received vitamin K supplementation. Given the absence of effects on coagulation in dogs, and as humans can utilise both vitamins K1 and K2, the PT and APTT prolongation observed in Tolvaptan treated rats is considered unlikely to be of clinical significance.

Genotoxicity

The potential genotoxicity of Tolvaptan was investigated in the standard battery of tests, comprising assays for mutagenicity in bacterial and mammalian cells, and for chromosomal aberrations *in vitro* (Chinese hamster lung fibroblasts) and *in vivo* (rat bone marrow micronucleus test). Concentrations/doses used were appropriate and limited by cytotoxicity/solubility or feasibility of administration. The spray dried formulation (≤2000 mg/kg/day PO) and animals of both sexes were used *in vivo*. All assays were appropriately validated and returned negative results. The individual isomers and major metabolites of Tolvaptan (DM-4103 and DM-4107) also returned negative results for mutagenicity in bacterial and mammalian cells.

Carcinogenicity

The carcinogenic potential of Tolvaptan was investigated in 2 year studies in mice and rats, conducted with the spray dried formulation and by the oral route. Group sizes were consistent with ICH guidance.[1] Dose selection was appropriate (up to 60 mg/kg/day in male mice, 100 mg/kg/day in female mice and 1000 mg/kg/day in rats), limited by

[1] European Medicines Agency, "Note for Guidance on Carcinogenic Potential", 25 July 2002, Web, accessed 2 July 2012 <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003258.pdf>.

adverse effects on body weight. However, relative exposure to Tolvaptan was low in both species (up to 0.3-0.4 in mice and 1.3-3.4 in rats; with higher exposure in females). Large multiples of the human exposure were obtained for the major human metabolites in some cases (namely, for DM-4103 in male rats, and for DM-4107 in female mice and rats of both sexes). Survival was unaffected. No treatment related increase in the incidence of neoplastic or preneoplastic lesions was observed in either species.

Reproductive toxicity

Reproductive toxicity studies covered all stages (fertility and early embryonic development, embryofoetal development and pre/postnatal development). Numbers of animals, the timing and duration of treatment, and the range of species (rat/rabbit) were appropriate. All studies involved oral administration. The spray dried formulation was used in all of the studies in rabbits and in the definitive studies in rats.

Relative exposure

Exposure ratios have been calculated based on animal:human serum/plasma AUC_{0-24h} values for Tolvaptan and (where data were available) its major human metabolites (Table 3).

Table 3: Exposure ratios for Tolvaptan – rat, rabbit.

Species	Study; (day of sampling)	Dose (mg/kg /day); PO	AUC_{0-24h} (µg.h/mL)			Exposure ratio based on AUC			Exposure ratio based on BSA#
			Tolvaptan	DM-4103	DM-4107	Tolvaptan	DM-4103	DM-4107	
Rat (SD)	012903 (GD17)	100	28.7	22.7	12.0	2.9	0.5	7.7	15
		1000	113.8	203.6	192.5	12	4.6	123	152
Rabbit (NZW)	012779 (GD18)	100	3.9	259.9	35.3	0.4	5.8	23	30
		300	8.1	471.6	101.7	0.8	11	65	91
		1000	16.9	1601.6	408.5	1.7	36	262	303
	013578 (GD11)	300	17.0	325.0	87.9	1.7	7.3	56	91
		1000	48.3	831.9	327.3	4.9	19	210	303
Human	156-96-203; 156-97-202	[60 mg]	9.81	44.5	1.56	–	–	–	–

BSA adjusted doses have been calculated using mg/kg to mg/m^2 conversion factors of 6, 12 and 33 in rats, rabbits and humans (50 kg) respectively; GD = gestation day.

Placental transfer of Tolvaptan and/or its metabolites was demonstrated in the rat. Peak levels of ^{14}C Tolvaptan derived radioactivity in the whole foetus and the foetal liver were 27% and 54%, respectively, of the maternal serum C_{max}. Tolvaptan, DM-4103 and DM-4107 were also detected in the embryo of rabbits after oral administration of the drug. Tolvaptan and/or its metabolites were readily excreted in milk in lactating rats, with the peak concentration of ^{14}C Tolvaptan derived radioactivity almost 12 times higher in milk compared with in blood.

Male and female fertility were unaffected in rats treated with Tolvaptan at ≤1000 mg/kg/day PO (relative exposure based on AUC, 1.3 and 3.4 in the respective sexes). However, a significant increase in the incidence of altered oestrus cycles (prolonged diestrus) was observed at ≥300 mg/kg/day (relative exposure, ≥2.5). Slight (~10%), but statistically significant, reductions in the mean number of corpora lutea and the number of implantations were seen at 1000 mg/kg/day compared with concurrent controls. These were in line with historical control values, though; they are therefore not considered to be treatment related.

Adverse effects on embryofoetal development were observed in both species tested. In rats, decreased foetal weight and impaired ossification were observed at 1000 mg/kg/day PO (relative exposure based on AUC, 12); this was a maternotoxic dose (maternal body weight gain over the treatment period was 27% lower compared with controls). More severe effects, including teratogenicity, were seen in rabbits. General toxicological effects (decreased maternal body weight gain and food consumption) were evident at ≥30 mg/kg/day PO, and abortions occurred at ≥300 mg/kg/day (on Gestation Day [GD] 25-27; relative exposure, 0.8). Treatment at 1000 mg/kg/day PO was associated with increased post implantation loss (early resorptions), decreased live litter size and foetal malformations (microphthalmia, open eyelids, cleft palate, brachymelia and bent radius, tibia and fibula). A follow up study identified GD9-11 as the period of maximum sensitivity to teratogenicity by Tolvaptan in the rabbit. Exposure to Tolvaptan declined with ongoing treatment. Based on data for GD11, exposure to Tolvaptan at this dose in rabbits was 4.9 times that of patients at the maximum recommended dose (60 mg/day). In further studies in rabbits investigating the mechanism for teratogenicity, dehydration and plasma electrolyte changes (through water restriction) were not associated with malformations. Noting that biotin deficiency has been linked to similar teratogenic effects in other species (mouse and hamster; though not previously the rabbit), the sponsor demonstrated that treatment with Tolvaptan at 1000 mg/kg/day markedly decreased maternal plasma biotin levels and significantly reduced the biotin concentration of the whole embryo (to ~35% of control levels) in pregnant rabbits. Exposure ratios for Tolvaptan at the NOAELs for embryofoetal toxicity in the rat and rabbit (100 and 300 mg/kg/day, respectively) are low (2.9 and 0.8 times the clinical AUC).

Tolvaptan had no effect on pre/postnatal development in the rat at doses up to ≤100 mg/kg/day PO. Reduced perinatal survival and decreased postnatal body weight gain (during the lactation period and after weaning), but no effects on other developmental parameters, were observed in the offspring at 1000 mg/kg/day (a maternotoxic dose).

Pregnancy classification

The sponsor has proposed Category C; this appears to have been based on the category for the US. Under the Australian categorisation scheme, Category C is for "drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations". Given the demonstration of teratogenicity in the rabbit, and the failure to establish a direct pharmacological basis for the adverse effects, this category is not appropriate for Tolvaptan. Teratogenicity and embryofoetal lethality in rabbits at low or reasonably low exposure margins justify placement in **Category D** instead ("Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.").

Paediatric use

The draft PI notes that safety and efficacy of Samsca in children have not been established. No specific studies in juvenile animals were submitted in this application. Data from nonclinical toxicology studies were being acquired at the time of submission "in order to satisfactorily ensure safety prior to initiating a paediatric clinical programme".

Antigenicity and immunotoxicity

Tolvaptan demonstrated no antigenic potential in guinea pigs. There was no evidence of toxicity to the T cell mediated humoural immune response to sheep red blood cells in rats (≤1000 mg/kg/day PO for 4 weeks).

Phototoxicity

Weak phototoxic potential for Tolvatan, and more significant phototoxic potential for metabolite DM-4103, were identified in an *in vitro* assay using BALB/3T3 cells. However, Tolvaptan was not phototoxic in female guinea pigs or female rabbits treated with oral doses up to 2000 or 1000 mg/kg/day for 7 or 3 days, respectively. Serum concentrations of Tolvaptan in both species were equivalent to or greater than that the peak level anticipated in patients at the maximum recommended clinical dose. Skin concentrations of Tolvaptan were similar or higher compared with its concentration in serum; DM-4103 and DM-4107 were present in skin at significantly lower concentrations than in serum.

Nonclinical summary and conclusions

Summary

- Orphan Australia Pty Ltd has applied to register Tolvaptan (as Samsca tablets) for the treatment of clinically significant dilutional hyponatremia. The maximum recommended clinical dose if 60 mg/day PO.
- The sponsor has conducted adequate nonclinical studies on the pharmacodynamics (PD), PK and toxicity of Tolvaptan according to the relevant guidelines. All pivotal safety related studies were conducted under GLP conditions or were otherwise of an acceptable standard.
- Tolvaptan acts as a vasopressin V_2 receptor antagonist with nanomolar potency. It is a racemate, with its S- and R-enantiomers having equivalent affinity for the target receptor; the drug's major human metabolites (DM-4103 and DM-4107) have no significant V_2 receptor affinity. Water reabsorption in the kidneys is promoted by activation of V_2 receptors by endogenous arginine vasopressin. Oral administration of Tolvaptan was shown to increase urine volume, decrease urine osmolality and increase serum sodium concentrations in laboratory animal species.
- Secondary pharmacodynamic studies revealed high selectivity for Tolvaptan at human V_2, compared with V_{1a} receptor subtypes and negligible affinity for the V_{1b} receptor. No significant activity for Tolvaptan or its major metabolites was apparent at other receptors or ion channels. Safety pharmacology studies covered the CNS, cardiovascular, respiratory and gastrointestinal systems. Significant effects were only observed with IV administration. The hERG K+ channel was not inhibited by Tolvaptan, and only very weakly by DM-4103. ECG abnormalities were not observed in dogs treated with Tolvaptan PO.
- PK studies indicated rapid absorption in all species (mice, rats, rabbits, dogs and humans). Oral bioavailability was significantly lower in rats and dogs (~15–16%) compared with humans (56%). Exposure was approximately dose proportional. Wide tissue distribution of radiolabelled Tolvaptan was seen after oral dosing in rats. Plasma protein binding was high in humans (≥98.0%) and the laboratory animal species. Tolvaptan was extensively metabolised, with CYP3A4 identified as the P450 isoform chiefly responsible. Excretion was principally by the faecal route in humans, rats and dogs.
- Tolvaptan displayed a low order of acute oral toxicity in laboratory animal species.
- Pivotal repeat dose toxicity studies were conducted by the oral route in rats (26 weeks) and dogs (52 weeks). Significant findings were consistent with exaggerated pharmacology and non specific toxicity (stress) only. The highest doses without adverse effect were established to be 100 mg/kg/day PO in dogs and female rats, and 1000 mg/kg/day PO in male rats.

- A full battery of tests indicated no evidence of genotoxicity for Tolvaptan. Two year oral carcinogenicity studies revealed no evidence of carcinogenicity in either mice or rats.
- Placental transfer (rats and rabbits) and excretion in milk (rats) of Tolvaptan and/or its metabolites were shown. Fertility was unaffected in male and female rats, although altered oestrus cycling was observed. In embryofoetal development studies, Tolvaptan impaired ossification and decreased foetal weights in rats, and caused abortions, embryofoetal lethality and teratogenicity in the rabbit. The offspring of treated rats showed reduced perinatal survival and decreased postnatal body weight gain.

Conclusions

- The nonclinical dossier contained no major deficiencies.
- Primary pharmacology studies, demonstrating an aquaretic effect of Tolvaptan and its ability to increase serum sodium concentrations, support the drug's use for the proposed indication.
- Secondary pharmacodynamic and safety pharmacology studies revealed no effects considered to be clinically significant.
- Adverse findings in the repeat dose toxicity studies were confined to effects attributable to exaggerated pharmacology or general stress (that is, involving dehydration). Supporting safety, there was no evidence of histopathological changes directly caused by Tolvaptan in dogs at a high margin of the human exposure (up to 28 times the clinical AUC at 60 mg/day).
- While the mouse and rat carcinogenicity studies were negative, these studies suffer from the inability to obtain high multiples of the clinical exposure to Tolvaptan in rodent species. The AUC for Tolvaptan at the highest dose in the mouse study was less than half that of patients at the maximum recommended human dose, and only 1.3-3.4 times that of patients in rats. Universally negative findings in the assays for genotoxicity, the additional absence of pre neoplastic lesions in the rodent carcinogenicity studies, as well as the absence of hyperplastic changes in the 52 week dog study (relative exposure, ≤28), however, lend support to the view that Tolvaptan is unlikely to pose a particular risk of carcinogenicity in patients.
- Findings of embryofoetal lethality and teratogenicity in rabbits at low or relatively low exposure margins (1.7-4.9), albeit in conjunction with maternotoxicity, warrant placement of Tolvaptan in Pregnancy Category D (rather than C as the sponsor has proposed) and strengthening of the warning against use in pregnancy in the PI document.
- There are no nonclinical objections to the registration of Samsca for the proposed indication, conditional on the sponsor's acceptance of the recommended changes relating to use in pregnancy.

IV. Clinical findings

Introduction

The clinical studies were conducted in compliance with local regulations and guidance, the ICH Guidelines and Good Clinical Practice (GCP) regulations. Subjects were accorded all rights granted by the Declaration of Helsinki. All protocols received approval by the appropriate governing investigational review board, ethics committee, or similar

authority. Standard research methodology was utilised for the conduct and performance of each clinical study under consideration.

Pharmacokinetics

Introduction

The PK section of this evaluation included 25 PK studies (excluding population PK) conducted in 523 male and 185 female subjects (including patients). These included studies in healthy subjects as well as studies involving 54 patients with mild to moderate congestive heart failure, 45 patients with hyponatremia secondary to liver disease and 22 patients with a history of arrhythmia.

Methods

Analytical methods

Several analytical methods were used to determine the plasma concentrations of Tolvaptan and its metabolites. The HPLC (high performance liquid chromatographic) method for analysis of Tolvaptan in human plasma was used for the comparative bioavailability trial (Study 156-96-301): gelatin capsule versus tablet. This method was also used for several clinical pharmacology and the Phase 2 trials. Tolvaptan and the internal standard OPC-41100 were extracted from plasma using a liquid-solid phase extraction procedure, followed by reversed phase HPLC. Linearity was established over the calibration curve range of 5-1000 ng/mL using 0.5 mL plasma. The lower limit of quantitation (LLQ) of the HPLC assay for Tolvaptan was 5 ng/mL based on 0.50 mL of plasma. The HPLC method for the determination of Tolvaptan in human plasma was validated over the range from 5-1000 ng/mL using 0.50 mL of plasma.

An increased sensitivity HPLC/MS/MS method was developed and validated for the analysis of Tolvaptan and DM-4103 in human plasma. This method was used for the absolute bioavailability trial of the Tolvaptan 30 mg oral tablet (Study 156-05-254). Tolvaptan, DM-4103, and the internal standard (OPC-41100) were extracted from plasma using solid phase extraction. The LLQ for Tolvaptan and DM-4103 were 1.00 ng/mL and 2.50 ng/mL, respectively, based on 0.25 mL of plasma and the assay was validated over the range from 1.00 to 200 ng/mL for Tolvaptan and over the range from 2.50 to 500 ng/mL for DM-4103 using 0.25 mL of plasma.

The HPLC/MS/MS method for analysis of Tolvaptan and metabolites DM-4103 and DM-4107 in human plasma was used for the absolute bioavailability trial of the Tolvaptan 30 mg oral tablet (Sudy 156-05-254) and for the comparative bioavailability food effect trial of the Tolvaptan 60 mg tablet (Study 156-05-256). The LLQ were 5.00 ng/mL for Tolvaptan and 12.5 ng/mL for DM-4103 and DM-4107, based on 0.25 mL of human plasma and the assay was validated over the range from 5-1000 ng/mL for Tolvaptan and over the range from 12.5 to 2500 ng/mL for DM-4103 and DM-4107 using 0.25 mL of plasma.

PK data analysis

In general, plasma concentration-time data were analysed using noncompartmental methods and PK calculations and their descriptive statistics were performed with WinNonlin Pro, Versions 1.1 to 3.1 (Pharsight Corporation, Mountain View, CA).

Statistical analysis

Descriptive statistics including the number of subjects (n), mean, standard deviation (SD), coefficient of variation (%CV), minimum, median, and maximum, were provided for all PK parameter estimates, except T_{max} for which only median, minimum, and maximum were

determined. Tests of statistical significance for the PK parameters were via pair wise comparison of treatment regimens using Student's t-test or analysis of variance (ANOVA). All tests were conducted at the 0.05 significance level unless otherwise specified. The software used for the statistical analyses included WinNonlin Professional, Version 1.5, SAS (SAS Institute Inc., Cary, NC 27513) version 6.12 with Proc-Stat Xact (Cytel Software Corn., Cambridge, MA 02139) and Microsoft Excel 2000.

Absorption

Bioavailability

A single centre, open label, sequential administration study (Study 156-05-254) examined the absolute bioavailability of Tolvaptan following IV Tolvaptan and single dose 30 mg PO Tolvaptan tablets in 14 healthy subjects (7 female), aged 19 to 44 years. On Day 1, subjects received a single IV Tolvaptan infusion equivalent to a 1 mg Tolvaptan dose (1 mg/10 mL) diluted with 250 mL 5% dextrose in water and infused over 1 h. The subjects were then administered a 30 mg tablet on Day 8.

The median T_{max}, $t_{1/2}$ (elimination half life), C_{max} and AUC_{inf} (area under the plasma concentration-time curve from time zero to infinity) of Tolvaptan following the 1 mg IV infusion was 1.00 h, 3.5 h, 32.7 ng/mL and 106 ng.h/mL, respectively, whereas following administration of the 30 mg tablet these values were 2 h, 6.7 h, 231 ng/mL and 1731 ng.h/mL, respectively (Table 4). The mean absolute bioavailability (F) of Tolvaptan tablet was 56%, range 42-80%. Following end of the 1 mg IV infusion, Tolvaptan concentrations dropped rapidly in a biphasic manner.

Table 4: Mean (SD) plasma PK parameters for Tolvaptan following a 1 h constant rate IV infusion of Tolvaptan 1 mg or a single PO tablet dose of Tolvaptan 30 mg to normal healthy subjects.

Parameter	Tolvaptan 1 mg IV (N = 14)	Tolvaptan 30 mg PO (N = 14)
C_{max} (ng/mL)	32.7 (6.95)	231 (81.3)
t_{max} (h)[a]	1.00 (0.75 - 1.00)	2.00 (1.50 - 6.00)
AUC_t (ng·h/mL)	96 (28)	1611 (693)
AUC_∞ (ng·h/mL)	106 (30)[b]	1731 (694)[c]
$t_{1/2,z}$ (h)	3.5 (1.0)[b]	6.7 (2.6)[c]
CL or CL/F (mL/min/kg)	2.34 (0.78)[b]	4.46 (1.54)[c]
F (%)	—	56 (10)[d]

SD = standard deviation.
[a]Values are median (range).
[b]N = 11.
[c]N = 13.
[d]N = 10.

Bioequivalence

An open label, three period, randomised, crossover study (Study 156-96-301) examined the relative bioavailability of three different formulations of Tolvaptan at doses of 30 mg: 2 x 15 mg hard gelatin capsules (Treatment A), 2 x 15 mg tablets (Treatment B), and 6 x 5 mg tablets (Treatment C) in six healthy, Caucasian males, aged 20 to 31 years. The C_{max} for Treatments A, B and C were 260, 235 and 233 ng/mL, respectively, and the AUC_{inf} were 1231, 1090 and 1105 ng.h/mL, respectively (Table 5). The ratio of least square means of C_{max} and AUC ranged from 0.82 to 1.09; however, possibly due to the small sample size none of the treatments were bioequivalent. The investigators concluded that as the tablet

had adequate bioavailability, any further clinical development of Tolvaptan (including all Phase 2 and 3 trials) would be conducted with tablets.

Table 5: Serum PK parameters (mean ± SD).

Parameter	Treatment A (N=6)	Treatment B (N=6)	Treatment C (N=6)
C_{max} (ng/mL)	260.29±66.34	235.83±74.02	223.62±98.43
Ln C_{max}	5.54±0.25	5.42±0.30	5.34±0.42
C_{max} (ng/mL) Geomean	253.43	226.71	207.37
t_{max} (h)[a]	1.5	1.5	1.8
AUC_{0-t} (ng•h/mL)	1188.2±316	1057.7±290	1038.93±467.9
Ln AUC_{0-t}	7.04±0.31	6.93±0.30	6.88±0.46
AUC_{0-t} (ng•h/L) Geomean	1146.89	1020.7	972.72
$AUC_{0-\infty}$ (ng•h/L)	1230.8±332	1090.04±288	1104.9±471.4
Ln $AUC_{0-\infty}$	7.08±0.31	6.96±0.29	6.93±0.44
$AUC_{0-\infty}$ (ng•h/L) Geomean	1187.03	1055.04	1021.03
CL/F (L/h/kg)	6.41±2.33	7.22±2.5	7.72±3.45
CL/F (L/h/kg) Geomean	6.07	6.83	7.06
Vd/F (L/kg)	2.09±1.12	1.57±0.41	2.35±0.92
Vd/F (L/kg) Geomean	1.86	1.52	2.19
K_d (h^{-1})	0.23±0.15	0.29±0.11	0.24±0.16
K_d (h^{-1}) Geomean	0.20	0.27	0.19
$t_{1/2}$ (h)	4.27±2.76	2.77±1.19	4.30±2.56
$t_{1/2}$ (h) Geomean	3.55	2.58	3.58

[a] The values reported are the median values for t_{max}
Treatment A = 2 x 15 mg capsule
Treatment B = 6 x 5 mg tablet
Treatment C = 2 x 15 mg tablet

An open label, three period, randomised, six sequence, crossover study (Study 156-01-233) examined the PK of Tolvaptan following sequential administration of different combinations of Tolvaptan tablets (60 mg dose on each day) and following a single 60 mg Tolvaptan tablet coadministered with 80 mg lovastatin in Period 4 in 30 healthy subjects (7 female), aged 19 to 44 years. The C_{max} and AUC were similar for each of the tablet combinations and the treatments of 4 x 15 mg tablets, 2 x 30 mg tablets, and the 1 x 60 mg tablet were bioequivalent for all comparisons.

Influence of food

An open label, two period, two treatment, crossover study (Study 156-00-002) examined the effects of food on the PK of a 30 mg dose of Tolvaptan in 16 healthy Japanese males, aged 20 to 40 years. The C_{max}, T_{max}, and AUC_t (mean ± standard deviation) of Tolvaptan were 208.46 ± 79.72 ng/mL, 3.21 ± 1.24 h, and 1419.29 ± 667.68 ng.h/mL, respectively, following administration in the fasted state, and 319.29 ± 79.44 ng/mL, 2.36 ± 0.89 h, and 1335.39 ± 417.74 ng.h/mL for a fed state. The 90% CI (confidence interval) for the mean ratios for AUC_t ratio was 0.885-1.132, which was within the range of the specified criteria for bioequivalence (0.8-1.25). By contrast, the 90% CI for the C_{max} ratio was 1.372-1.889, which was not within the range of the specified criteria (0.7-1.43), and it was therefore concluded that the PK of Tolvaptan are affected by food, that is, although the overall exposure to Tolvaptan was not affected, the rate of absorption was increased with food.

This was again confirmed in the randomised, open label, crossover study (Study 156-05-256) which examined the effect of food (FDA [US Food and Drug Administration] high fat meal [HFM]) on the PK of Tolvaptan and its metabolites (DM-4107 and DM-4103) following oral administration of 60 mg Tolvaptan tablets in 14 healthy subjects (5 female), aged 18 to 45 years. Only a synopsis was provided for Study 156-05-256 in the evaluation material. The C_{max} was 430 ng/mL and 603 ng/mL in the fasted and fed states respectively, whereas the AUC_t was 3500 and 3670 ng.h/mL in the two states, respectively (Table 6). AUC_{inf} values could not be compared as this parameter could not be determined for many

of the study's participants. The geometric mean ratios and 90% CIs for Tolvaptan C_{max} and AUC_t were 1.40 (1.17-1.67) and 1.06 (0.97-1.16), respectively.

Table 6: Mean (SD) Tolvaptan plasma PK parameters following a single oral 60 mg dose of Tolvaptan in either the fasted state or immediately following a high fat meal to normal healthy subjects.

Parameter	Fasted (n = 14)	Fed (n = 14)
C_{max} (ng/mL)	430 (150)	603 (223)
t_{max} (h)[a]	2.00 (1.50 - 4.00)	2.00 (1.00 - 4.00)
AUC_{0-24h} (ng·h/mL)	3470 (1260)	3590 (1340)
AUC_t (ng·h/mL)	3500 (1440)	3670 (1440)
$t_{1/2,z}$ (h)	7.1 (2.6)[b]	4.3 (1.3)[c]
AUC_∞ (ng·h/mL)	3980 (1260)[b]	3880 (1750)[c]
CL/F (mL/min/kg)	3.35 (1.09)[b]	4.23 (2.72)[c]

[a] Values are median (range).
[b] N=7.
[c] N=9.

Distribution

A single centre, single dose, open label study (Study 156-97-202) examined the absorption, distribution, metabolism, and excretion of radioactivity and intact drug following a single 60 mg ^{14}C-OPC-41061 radioactive (100 µCi total radioactivity) in 12 healthy, Caucasian males, aged 25 to 37 years. The mean C_{max} for radioactivity was 1064 ng equiv/mL occurring at 3.0 h post dose (T_{max}), with $t_{1/2}$ of 209 h and plasma radioactivity levels were generally below the level of detection by 648 h post dose. Radioactivity in blood reached a mean C_{max} of 588 ng equiv/mL at a T_{max} of 4.0 h. The mean values for the blood to plasma radioactivity concentration ratio ranged from 0.51 to 0.65 at 0.5 to 456 h post dose. In human plasma, ^{14}C Tolvaptan was bound mainly to serum albumin and α1-acid glycoprotein.[2] For Tolvaptan, C_{max}, AUC_{inf}, $t_{1/2}$, CL/F (apparent total clearance of the drug from plasma after oral administration) and V/F (apparent volume of distribution after non IV administration) were 259.4 ng/mL, 2574.9 ng.h/mL, 9.3 h, 6.0 ml/min/kg and 4.33 l/kg, respectively.

Elimination

Excretion

In Study 156-97-202, a total of 98.9% of the administered radioactivity was recovered with 40.2% in urine and the remaining 58.7% recovered in the faeces. About 80% of the cumulative urine ^{14}C excretion occurred during the first 36 h and approximately 65% of radioactivity was recovered in the faeces within the first 72 h. However, radioactivity could be detected in the faeces for up to 960 h post dose.

[2] Kudo S, et al. Binding of 14C-OPC-41061 to human plasma proteins. Otsuka Study No. 011100, Otsuka Report No. 009473, 1995.

Metabolism

In vitro

In human liver microsomes, the following metabolites were produced following incubation with 3 or 30 µM Tolvaptan: DM-4103; DM-4104; DM-4105; DM-4107; DM-4110; DM-4111; MOP-21826; as well as three unknown metabolites. Formation and elimination of most metabolites was mediated by CYP3A4/5.[3] In microsomes from cells expressing human cytochrome P450s (CYPs) it was identified that CYP3A4 and CYP1A1 were responsible for formation of DM-4128.[4] DM-4107 was produced from DM-4104, whereas, DM-4103 was produced from DM-4105.[5]

Further *in vitro* studies using microsomes from the AHH-1 TK+/- cell line that expressed either CYP3A4, CYP2C9 or CYP2C9-Arg, showed that Tolvaptan competitively inhibited CYP2C9- mediated metabolism of tolbutamide 4-hydroxylation (Ki=6.7 µM, 3.0 µg/mL) and the CYP3A4 mediated metabolism of warfarin 10-hydroxylation (Ki=5.4 µM, 2.4 µg/mL), quinidine N-oxidation (Ki=7.8 µM, 3.5 µg/mL), and amiodarone N-deethylation (Ki=10.4 µM, 4.7 µg/mL).[6] However, the Tolvaptan concentrations required to inhibit these *in vitro* systems were many fold higher than the Tolvaptan plasma concentrations seen following multiple dosing with 60 mg (mean [SD] C_{max} of 60 mg dose was 884 [237] ng/mL in stable heart failure subjects).

In vivo

Tolvaptan and seven metabolites (DM-4103, DM-4104, DM-4105, DM-4107, DM-4110, DM-4111 and DM-4119) were identified in the plasma of all subjects. Tolvaptan and these metabolites accounted for 60.4% of the total plasma radioactivity (based on mean AUC-INF). DM-4103 alone accounted for 52.5% of the plasma radioactivity, whereas, unchanged Tolvaptan accounted for 2.8% and the other metabolites combined accounted for 5.1%.

Tolvaptan and the identified metabolites accounted for 71.2% of the radioactivity excreted in urine for up to 36 h. The major analyte in urine was DM-4107, which accounted for 23.28% of the radioactivity, followed by DM-4111, which accounted for another 14.09%. Tolvaptan and the other metabolites together accounted for 35.29% of the radioactivity. The balance of radioactivity excreted in urine was due to the presence of other minor unidentified metabolite(s), none of which alone accounted for more than 5% of the radioactivity. No glucuronide conjugates of the parent compound or the identified metabolites were detected. Tolvaptan and identified metabolites accounted for 74.66% of the radioactivity excreted in the faeces, based on specimens collected during the first 96 h post dose. Tolvaptan accounted for 31.91% of radioactivity, followed by DM-4107, which accounted for another 20.55%, whereas the other metabolites combined accounted for 22.38% of the radioactivity. The balance of radioactivity excreted in faeces was due to the presence of other unidentified minor metabolite(s), none of which alone accounted for more than 2% of the radioactivity.

[3] Kudo S. Study of metabolism of OPC-41061 using microsomes derived from human livers. Otsuka Report No. 011240, 1997.

[4] Okada K, Kudo S, Umehara K. Involvement of cytochrome P450 in the formation of DM-4128 from OPC-41061. Otsuka Study No. 015387, Otsuka Report No. 014276, 2002.

[5] Furukawa M. In vitro metabolism of MOP-21826, DM-4104, DM-4105 and DM-4107 using human liver supernatant fraction (S9). Otsuka Study No. 020769, Otsuka Report No. 016298, 2004.

[6] Kudo S. In vitro study of metabolism of OPC-41061 enantiomers using microsomes derived from human AHH-1TK+/- cells expressing human cytochrome P450s in livers. Otsuka Report No. 010760, 1997.

Interconversion

Not applicable

PK of metabolites

The PK of Tolvaptan and its metabolites following a 60 mg dose of ^{14}C-OPC41061 were assessed. The major metabolite identified in plasma, DM-4103, had a C_{max}, AUC_{inf} and $t_{1/2}$ of 220.0 ng/mL, 54022.3 ng.h/mL and 183 h, respectively, whereas the major metabolite in urine and faeces, DM-4107, had a C_{max}, AUC_{inf} and $t_{1/2}$ of 100.2 ng/mL, 1725.2 and 12.4 h, respectively.

The effect of combinations of different strength Tolvaptan tablets to a dose of 60 mg (4 x 15 mg, 2 x 30 mg and 1 x 60 mg) on the PK of DM-4103 from Study 156-01-233 was also assessed. For the different combinations of tablets, the C_{max} and AUC_t were similar and ranged from 494 to 513 ng/mL and 28101 to 29587 ng.h/mL, respectively.

Influence of food on metabolites

Study 156-05-256 examined the effect of food on the PK of Tolvaptan and its metabolites (DM-4107 and DM-4103) following oral administration of 60 mg Tolvaptan tablets in healthy subjects. The values of C_{max}, T_{max} and AUC_t for DM-4017 were similar in the fed and fasted state. Due to the long half life of DM-4103, values of C_{max}, T_{max} and AUC_t (t=72 h) were evaluated on Day 1 only for the 7 subjects in the fasted state and 7 subjects in the fed state; values were similar for both treatment groups.

DDI on metabolites

Study 156-01-233 also examined the effect on the PKs of DM-4103 following coadministration of 60 mg Tolvaptan and 80 mg lovastatin. When lovastatin was coadministered, the median T_{max} of Tolvaptan was halved (from 24 to 12 h) and mean C_{max} and AUC_t increased from 492 to 734 ng/mL and from 28566 to 57231 ng.h/mL, respectively, compared to when Tolvaptan was administered alone.

Consequences of possible genetic polymorphism

Although no studies examined the effects of CYP mutations on the PK of Tolvaptan it should be assumed, as Tolvaptan is primarily metabolised by CYP3A4/5, that patients with known mutations in this isoenzyme may require dose adjustment.

Dose proportionality and time dependency

Dose proportionality

A single blind Study 156-00-001 investigated the PK and pharmacodynamics of a single oral dose of Tolvaptan at 15-120 mg in a fasting state in 56 healthy Japanese males, aged 20 to 40 years.

However, only a synopsis is provided for this study. Following administration of Tolvaptan at 15-120 mg, large individual differences in plasma PK were observed. The main metabolite of Tolvaptan identified was DM-4103. Of the metabolites, the plasma concentration of MOP-21826 was below the lower limit of quantification at all sampling points during the study period in all subjects in the 60 and 90 mg groups. The AUC_t and C_{max} of Tolvaptan increased almost dose dependently, and no visually apparent non linearity was observed. Statistical analysis of linearity indicated dose proportionality for AUC_t but not for C_{max}. For Tolvaptan, the percentage of the administered dose excreted in cumulative urine plateaued within 48 h following dosing in all subjects. The fe_{48h} (Fraction of the Systemically Available Drug Excreted into the Urine to 48 h) of Tolvaptan was less than 1% in all subjects and the urinary excretion quantity (percentage of the administered dose) in the elimination phase of Tolvaptan was considered to be small. Among the metabolites, the urinary concentrations of DM-4103, DM- 4105, and MOP-21826 were

below the lower limit of quantification at all sampling points during the study period in all subjects in the 60 and 90 mg groups.

Two single centre, double blind, randomised, placebo controlled, ascending single dose trials (156-98-210 and 156-01-229) were conducted to determine the PK/PD and safety of Tolvaptan in healthy male and female subjects.

In Study 156-98-210, 8 subjects (6 active/2 placebo) were enrolled into each dose group and received 60, 90, 120, 180 or 240 mg Tolvaptan or placebo as 15 mg tablets, for a total number of subjects of 40 (11 females), aged from 18 to 44 years. On Day 1, subjects were dosed and post-dose fluid intake for 0 to 72 h was limited to fluid volume replacement only (that is, the volume of water subjects were allowed to consume was limited to the volume of urine excreted – Period 1). On Day 8, subjects received the same study medication as on Day 1 but fluid intake was unrestricted (that is, the subjects could drink ad lib – Period 2). Following each dose, plasma samples were obtained for determination of Tolvaptan and metabolite PK for 168 h post dose. Non compartmental PK analysis was performed using plasma concentrations of Tolvaptan, DM-4103, DM-4104, DM-4105, DM-4107, DM-4110, DM-4111, and DM-4119. Plasma concentrations of MOP-21826 were quantifiable (5.24 ng/mL) in a single sample following the 240 mg dose.

During Period 1, in which the subjects were allowed fluid replacement, C_{max} values increased with dose, but the increase was not dose proportional as indicated by the negative slope obtained when dose normalised C_{max} was plotted versus dose. In addition, log-log regression analysis of C_{max} versus dose showed that the 95% CI of the slope did not include one. By contrast, AUC_{inf} values increased proportionally with dose and log-log regression analysis of AUC_{inf} versus dose showed that the 95% CI of the slope included one. The median T_{max} values ranged from 2.0-3.0 h for all five dose groups (Table 7). Linear regression analysis of CL/F versus dose and $t_{1/2,z}$ versus dose indicated that CL/F and $t_{1/2,z}$ were independent of dose ($p>0.05$); although $t_{1/2,z}$ showed a trend of increasing with increasing doses. Similarly in subjects without volumetric fluid replacement (Period 2), C_{max} values increased with dose, but not proportionally. As in Period 1, the AUC_{inf} values increased dose proportionally. Median T_{max} values ranged from 2.3-4.0 h for all five dose groups. Linear regression analysis of CL/F versus dose and $t_{1/2,z}$ versus dose indicated that $t_{1/2,z}$ and CL/F were independent of dose ($p>0.05$); although once again $t_{1/2,z}$ showed a trend of increasing with increasing doses.

Table 7: Mean PK parameters of Tolvaptan (OPC-41061) in subjects with volumetric fluid replacement.

Period 1:

	t_{max} (h)	$t_{½,z}$ (h)	C_{max} (ng/mL)	AUC_{∞} (ng·h/mL)	CL/F (mL/min/kg)
60 mg (n=6)	2.00	5.98	374.39	2788.91	4.40
90 mg (n=6)*	2.99	6.23	417.65	3112.50	5.93
120 mg (n=6)*	3.01	7.32	568.88	6244.70	3.58
180 mg (n=6)	2.00	15.74	576.65	7528.04	4.79
240mg (n=6)	2.50	12.58	915.66	13181.48	4.34

* For $t_{1/2,z}$, AUC_{∞} and CL/F, n=5 for those doses.

Period 2:

Median Pharmacokinetic Parameters of OPC-41061 in Subjects Without Volumetric Fluid Replacement (Period 2)

	t_{max} (h)	$t_{½,z}$ (h)	C_{max} (ng/mL)	AUC_{∞} (ng·h/mL)	CL/F (mL/min/kg)
60 mg (n=6)	2.25	6.71	399.44	3216.11	3.84
90 mg (n=6)	3.0	7.74	427.78	3809.22	5.75
120 mg (n=6)	3.03	10.29	530.38	5490.29	4.60
180 mg (n=5)	3.0	13.6	845.37	9309.01	3.77
240mg (n=5)	4.0	12.35	969.14	13289.44	3.67

In Study 156-01-229, 8 or 9 subjects (6 active/3 placebo) were enrolled in each group and received 180, 240, 300, 360, 420, or 480 mg Tolvaptan or placebo as 60 mg tablets, for a total of 59 subjects (9 female), aged 19 to 51 years. Fluid intake was unrestricted. Plasma and urine PK and PD sampling for this trial was similar to Trial 1; however, samples were not analysed for metabolite levels. Urine samples were analysed for Tolvaptan to determine the fraction of dose excreted unchanged. Following single dose oral administration of 180, 240, 300, 360, 420, and 480 mg Tolvaptan, median plasma Tolvaptan concentrations increased with increasing dose (Table 8). However, the 95% CI of the slope obtained from log regression of log C_{max} versus log dose did not include 1, indicating that the increase in C_{max} was not dose proportional. This result was consistent with the negative slope obtained when dose normalised C_{max} was plotted versus dose. By contrast as in the previous study, AUC_{inf} increased dose proportionally and the log regression analysis log AUC_{inf} versus log dose showed that the 95% CI of the slope included 1. In this study, the PK parameters $t_{1/2,z}$ and CL/F were independent of dose administered and the slopes of the regression line generated when these parameters were plotted against dose were not significantly different from zero ($p>0.05$). Median $t_{1/2,z}$ values ranged from 8.9 h (360 mg dose) to 10.8 h (420 mg dose).

Table 8: Median (range) Tolvaptan PK parameters following single dose oral administration of 180, 240, 300, 360, 420 or 480 mg Tolvaptan to healthy male and female adult subjects.

Dose	t_{max} (h)	C_{max} (ng/mL)	AUC_{∞} (ng·h/mL)	$t_{1/2,z}$ (h)	CL/F (mL/min/kg)
180 mg (n=5)	4.00 (1.00-8.00)	618 (356-1129)	10478 (6050-13689)	9.5 (5.0-17.1)	3.80 (3.32-5.52)
240 mg (n=6)	2.75 (1.00-12.00)	682 (406-1282)	11628 (9105-22835)	10.5 (6.0-20.4)	4.27 (1.99-5.93)
300 mg (n=6)	2.25 (1.00-4.00)	820 (742-1747)	14770 (10800-17737)	10.2 (6.0-32.1)	4.75 (3.70-6.21)
360 mg (n=6)	3.50 (1.50-12.00)	887 (510-1730)	14570 (7330-15667)	8.9 (5.5-19.8)	6.43 (4.09-10.48)
420 mg (n=5)	4.00 (3.00-6.00)	1357 (831-1617)	22202 (19069-45282)	10.8 (5.4-19.9)	3.99 (1.68-5.17)
480 mg (n=6)	3.50 (2.00-6.00)	1035 (808-1380)	24299 (16227-38534)	9.4 (8.9-12.2)	3.69 (2.26-7.18)

Multiple dose studies

It is important to note that only synopses were provided for Studies 156-00-003 and 156-05-001.

A double blind Study 156-00-003 examined the PK of Tolvaptan after single and multiple doses of 30 mg and 60 mg in healthy males, aged 20 to 40 years. Mean C_{max} and AUC_{24h} (area under the plasma concentration-time curve from time zero to 24 h) following 7 day repeated oral administration of Tolvaptan (Day 9) was slightly lower than those following single oral administration (Day 1) in the 30 mg group (Table 9); however, there were no

differences in mean C_{max} and AUC_{24h} between Day 1 and Day 9 in the 60 mg group. In both the 30 mg and 60 mg groups, the mean $t_{1/2,z}$ for Day 9 was shorter than that for Day 1. Mean CL/F for Day 9 was higher than that for Day 1 in the 30 mg group, but the values for Days 1 and 9 were similar in the 60 mg group. Mean Vz/F (apparent volume of distribution during terminal phase after non IV administration) for Day 9 tended to be greater than that for Day 1 in the 30 mg group, while the value for Day 1 tended to be greater than that for Day 9 in the 60 mg group. However, these differences in PK parameters were not considered notable, and the pattern of change in parameters varied among subjects. C_{max} and AUC_{24h} values for Days 1 and 9 in the 60 mg group were approximately double the values in the 30 mg group, suggesting that the PK parameters increased dose proportionally following repeated administration. The mean accumulation index, calculated by dividing the AUC_{24h} for Day 9 by that for Day 1, was 0.82 in the 30 mg group and 0.98 in the 60 mg group.

Table 9: Key PK parameters of Tolvaptan following single and 7 day repeated dosing.

	Group (n)	Statistics	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2,z}$ (h)	CL/F (mL/min)	V_z/F (L)	AUC_{24h} (ng·h/mL)
Day 1	30 mg (n=6)	Mean	198.45	2.25	3.33	467.47	125.65	1192.68
		SD	31.68	1.08	0.93	156.46	23.82	412.92
	60 mg (n=5)	Mean	401.30	2.10	4.00	433.86	149.28	2347.42
		SD	79.01	0.89	1.01	75.30	43.30	501.74
Day 9	30 mg (n=6)	Mean	161.55	2.75	2.95	568.52	143.30	931.22
		SD	56.78	1.67	0.90	137.32	53.38	258.17
	60 mg (n=5)	Mean	380.22	2.40	3.32	461.22	124.76	2367.00
		SD	114.42	1.14	1.00	130.15	24.94	907.08

Urine samples were collected up to 48 h post dose on Days 1 and 9 and up to 24 h post dose on Days 3 to 8. Blood samples for PD were collected pre dose and up to 24 h post on Days 1 and 9, and 6 h after administration on Days 4 and 6. The amount and the time of fluid intake were recorded from Day 1 to 11.

A single blind Study 156-05-001 investigated the PK of Tolvaptan following 7 day repeated oral administration of 90 or 120 mg, or placebo in 18 healthy males, aged 20 to 40 years. Although Tolvaptan C_{max} was similar for both doses between Days 1 and 9, there was a decrease in AUC_{24h} on Day 9 compared to Day 1 for both doses, AUC_{24h} on Days 1 and 9, e.g. for the 90 mg dose, were 4635 and 3590 ng.h/mL, respectively. In addition, the AUC_{24h} of DM-4103 on Day 9 was 8-10 times that on Day 1 and increased with each administration and did not reach a steady state during 7 days of repeated administration. By contrast, all of the other metabolites reached steady state during the 7 day repeated administration period.

A double blind, parallel, placebo controlled Study 156-95-305 examined the PK of Tolvaptan following multiple doses of Tolvaptan (30 mg and 60 mg dose groups) or placebo administered once daily for 28 days in 24 healthy Caucasian males, aged from 20 to 39 years. Nine, eight, and seven subjects were randomised to the 30 mg, 60 mg, and placebo dose groups, respectively. On Day 1, mean C_{max} values for the 30 and 60 mg doses were 308 and 560 ng/mL respectively, and on Day 28 the values were 327 and 547 ng/mL respectively. On Day 1, AUC_{24h} values for the 30 and 60 mg doses were 1709 and 3688 ng.h/mL, respectively, and on Day 28 the values were 1931 and 3703 ng.hr/mL, respectively. Mean T_{max} was approximately 2 h for both dose levels on Days 1 and 28. The mean $t_{1/2}$ of Tolvaptan was approximately 5.2 h. The mean accumulation ratios for the 30 mg and 60 mg doses were 1.26 and 1.00, respectively. This indicated that there is no accumulation of the drug in the serum for up to 28 days.

Time dependency

Study 156-05-001 states that diurnal changes in metabolite plasma concentrations were great following multiple doses of 90 and 120 mg Tolvaptan. However, as only a synopsis is provided for this study, it is impossible to determine the exact nature of these changes.

Intra and inter individual variability

The inter subject variability for C_{max}, AUC and CL/F was similar for healthy subjects, subjects with stable heart failure and subjects with hyponatremia secondary to liver disease, with %CV ranging from 20 to 75%; values in the range of 35-50% were the most frequently observed. The large inter subject variability in Tolvaptan PK parameters is consistent with other known weak substrates for CYP3A4. For healthy subjects, Study CSR 156-98-210 states that in a comparison of C_{max} and AUC_{inf} from Day 1 and Day 8, the intra subject variability of Tolvaptan is approximately 21%.

Population PK Study 156-01-224 indicated that between patient variability and residual error were high [CV 61-66% (CL/F), 42-49% (V/F), 114-124 % (KA) and 51-62% (random residual error)].

PK in target population

A single centre, open label, randomised, single dose, placebo controlled, crossover design Study 156-00-221 examined the effects of a single dose of Tolvaptan and furosemide (Lasix) on renal function and renal haemodynamics in 14 patients with mild to moderate congestive heart failure, NYHA Class II-III (4 female), aged 45 to 70 years. Following a single dose of 30 mg Tolvaptan in patients with mild to moderate CHF (congestive heart failure), the median T_{max}, mean C_{max}, AUC_t, $t_{1/2}$, CL/F and V_zF were 2 h, 277 ng/ml, 2758 ng.h/mL, 9.4 h, 2.66 mL/min/kg and 1.41 L/kg, respectively. Compared to the PK results following a single 30 mg dose of Tolvaptan in healthy subjects (Study 156-00-003), the C_{max} and AUC_t and $t_{1/2}$ were significantly increased in patients with CHF (Table 10). Similar results were observed in Study 156-01-231 in patients with mild to moderate CHF (Table 11). It must also be noted that the Tolvaptan C_{max} and AUC were significantly higher following a single 30 mg QD tablet than following a single day's treatment with 15 mg tablets BID in subjects with mild and moderate CHF. However, following seven days treatment with the two regimens (QD and BID), the C_{max} and AUC were more similar.

Table 10: Key PK parameters following a single 30 mg dose of Tolvaptan in patients with congestive heart failure.

Subject status	Mean Cmax *(ng/mL)*	Mean AUC_t *(ng.h/mL)*	Mean $t_{1/2}$ *(hours)*
Mild to moderate CHF[a]	277	2758	9.4
Mild to moderate CHF[b]	306	2614	9.4
Healthy[c]	198	1193	3.3

[a] – Study 156-00-221
[b] – Study 156-01-231
[c] – Study 156-00-003

Table 11: Mean (SD) Tolvaptan PK parameters for the two dosing regimens.

Pharmacokinetic Parameters	30 mg QD	15 mg BID
Day 1		
C_{max} (ng/mL)	306 (96)	194 (77)
t_{max} (h)[#]	1.10, 0.98-4.00	9.99, 1.00-16.05
AUC_{24} (ng·h/mL)	2614 (1289)	2205 (875)
Day 7		
C_{max} (ng/mL)	283 (138)	240 (85)
t_{max} (h)[#]	2.00, 1.00-6.03	9.63, 1.00-11.95
$t_{1/2,z}$ (h)	9.4 (4.6)	9.3 (5.6)
AUC_τ (ng·h/mL)	3087 (2464)	3001 (1375)
$C_{min,ss}$ (ng/mL)	48 (69)	60 (50)
$C_{avg,ss}$ (ng/mL)	129 (103)	125 (57)
$V_{z,ss}/F$ (L/kg)	1.76 (0.76)	ND
CL_{ss}/F (mL/min/kg)	2.73 (1.87)	ND
$R_{ac}(AUC_\tau)$	1.19 (0.34)	1.35 (0.41)
$R_{ac}(C_{max})$	0.94 (0.36)	1.32 (0.42)

[#] For t_{max} the median and range are given.
SD = standard deviation, ND = not determined.

Special populations

Children

No studies examined the PK of Tolvaptan in children.

Elderly and gender

An open label, single/multiple-dose Study 156-98-202 examined the PK of orally administered Tolvaptan (60 mg) in 26 healthy adults (age of 18-45 years) and in 25 elderly (age ≥65 years) male and female subjects. Tolvaptan C_{max} was significantly higher on Day 1 in females compared to males, whereas no significant gender differences were observed on Day 10. However, analysis of covariance including weight as a covariate indicated that the observed gender differences in C_{max} were related to differences in body weight, not physiologic differences due to gender. The PK parameters of all Tolvaptan metabolites on Day 1 and Day 10 were comparable in all male and female subjects. Statistical analysis comparing Days 1 and 10 did not identify any significant age differences in Tolvaptan PK, except for CL/F (mL/min/kg) on Day 1, which was lower in elderly subjects (Table 12). Analysis of covariance with weight as a covariate once again indicated that the observed age differences in CL/F were related to differences in body weight. The PK parameters of all Tolvaptan metabolites on Days 1 and 10 were comparable in male and female, young and elderly subjects. Two elderly subjects were withdrawn from treatment because of mild TEAEs (treatment emergent adverse event) (asymptomatic atrial fibrillation and dizziness). All TEAE were mild to moderate in severity. The most commonly reported TEAE (≥ 15%) were thirst (90.2%), dry mouth (60.8%), asthenia (21.6%), and headache (19.6%). In general, similar incidences of TEAE were found between men and women in the adult population and in the elderly subjects. No subjects had AEs (adverse events) due to abnormal changes from baseline in laboratory test values or vital signs.

Table 12: Summary [mean (SD)] and statistical comparison of Tolvaptan PK parameters on Day 10 following multiple dose oral administration of 60 mg Tolvaptan as tablets (4 x 15 mg) daily from Days 4 to 10 in young and elderly, male and female subjects.

	Cmax (ng/mL)	tmax (h)	AUC_τ (ng•h/mL)	CL/F (mL/min/kg)	$t_{1/2}$ (h)	Rac (Cmax)	Rac (AUC)
Young Males n=12	525 (230)	2.46 (0.92)	4356 (2375)	4.212 (3.001)	8.20 (3.00)	1.455 (0.576)	1.477 (0.677)
Young Females n=12	507 (155)	1.96 (1.16)	3773 (1444)	5.447 (2.495)	8.40 (5.09)	1.223 (0.324)	1.383 (0.345)
Elderly Males n=11	474 (140)	2.32 (0.84)	4047 (1224)	3.247 (1.335)	10.78 (8.71)	1.192 (0.133)	1.280 (0.175)
Elderly Females n=12	538 (223)	2.65 (1.14)	5015 (2512)	3.762 (1.846)	10.49 (4.99)	1.082 (0.254)	1.276 (0.211)
p-values: Age	0.859	0.310	0.426	0.053	0.171		
Gender	0.685	0.659	0.741	0.195	0.978		
Age•Gender	0.466	---	0.188	0.591	0.882		

p values for t_{max} determined using Cochran-Mantel-Haenszel Tests.
--- No sample or not determined.

Weight

In the previous Study 156-98-202, it was determined that differences in body weight were responsible for the significantly higher C_{max} identified in female compared to male subjects and the significantly lower CL/F in elderly compared to young subjects.

Race

As Tolvaptan was also being investigated for the Japanese market, a bridging trial comparing Japanese and Caucasian male subjects was conducted; this Study 156-03-242 also evaluated the effects of a high fat meal and a high sodium (Japanese standard) meal following a 30 mg dose. A parallel arm, randomised, open label, three period, six sequence, crossover study examined the PK effects of a FDA HFM and a standard Japanese meal (JSM)[7] compared to administration of Tolvaptan in the fasted state following single oral 30 mg tablet doses of Tolvaptan in 22 Japanese and 24 Caucasian men, aged 20 to 40 years. In Japanese and Caucasian subjects following a HFM, mean C_{max} and AUC_{inf} values of Tolvaptan were modestly increased (~15%) compared to the fasted state (Tables 13-14). In Japanese subjects following a JSM, Tolvaptan exposure was similar to that following a HFM; in Caucasian subjects following a JSM, Tolvaptan exposure was similar to that following the fasted state (Table 15).

[7] For the JSM, fat accounted for 20.8% of total calories (approximately 125 calories). Protein and carbohydrate accounted for approximately 106 and 383 calories, respectively. The meal contained 2.1 g of sodium and 5.5 g of sodium chloride.

Table 13: Mean ± SD Tolvaptan plasma PK parameters following a single oral 30 mg dose of Tolvaptan in either the fasted state or immediately following a high fat meal or Japanese standard meal to Japanese subjects (n=24).

	Treatment		
Parameter	Fasted	High-fat Meal	Japanese Standard Meal
C_{max} (ng/mL)	273 ± 80.7	320 ± 129	335 ± 157[d]
t_{max} (h)[a]	2 (1-3)	3 (0.5-6)	3 (1-6)[d]
AUC_t (ng·h/mL)	1605 ± 716	1870 ± 876	1855 ± 1016[d]
$t_{1/2,z}$ (h)	4.5 ± 1.9[c]	4.1 ± 1.2[c]	4.0 ± 1.6[b]
AUC_∞ (ng·h/mL)	1729 ± 761[c]	2036 ± 909[c]	2018 ± 1025[c]
AUC_{24h} (ng·h/mL)	1666 ± 675[d]	1963 ± 814[d]	1957 ± 942[c]
AUC_{48h} (ng·h/mL)[b]	1668 ± 697	1970 ± 829	1949 ± 993[d]
CL/F (mL/min/kg)	5.36 ± 2.09[c]	4.64 ± 1.98[c]	4.83 ± 2.03[c]
V_z/F (L/kg)	1.92 ± 0.85[c]	1.50 ± 0.49[c]	1.50 ± 0.61[c]
CL/F (mL/min)	338 ±133[d]	289 ± 122[d]	297 ± 126[c]
V_z/F (L)	119 ± 44.7[c]	93.5 ± 26.7[c]	94.3 ± 41.0[c]

SD = standard deviation

[a] Values are median (range)

[b] AUC determined by including first time point with plasma concentrations below quantifiable limit after time points with measurable concentrations

[c] n = 20

[d] n = 22

[e] n = 21

Table 14: Mean ± SD Tolvaptan plasma PK parameters following a single oral 30 mg dose of Tolvaptan in either the fasted state or immediately following a high fat meal or Japanese standard meal to Caucasian subjects (n=24).

	Treatment		
Parameter	Fasted	High-fat Meal	Japanese Standard Meal
C_{max} (ng/mL)	247 ± 71	319 ± 175	273 ± 113
t_{max} (h)[a]	2 (1-6)	3 (0.5-8)	3.55 (1-6)
AUC_t (ng·h/mL)	1528 ± 834	1596 ± 713	1504 ± 694
$t_{1/2,z}$ (h)	4.1 ± 1.6[c]	3.3 ± 0.9[d]	3.5 ± 1.3[e]
AUC_∞ (ng·h/mL)	1443 ± 455[c]	1713 ± 712[d]	1576 ± 722[e]
AUC_{24h} (ng·h/mL)	1511 ± 671	1703 ± 668[e]	1565 ± 675[f]
AUC_{48h} (ng·h/mL)[b]	1585 ± 817	1683 ± 699	1580 ± 665
CL/F (mL/min/kg)	5.14 ± 1.85[c]	4.65 ± 2.23[d]	5.19 ± 2.49[e]
V_z/F (L/kg)	1.69 ± 0.49[c]	1.22 ± 0.42[d]	1.36 ± 0.34[e]
CL/F (mL/min)	384± 129[c]	346 ± 152[d]	388 ± 178[e]
V_z/F (L)	126 ± 32.7[c]	91.3 ± 31.8[d]	102 ± 25.0[e]

SD = standard deviation

[a] Values are median (range)

[b] AUC determined by including first time point with plasma concentrations below quantifiable limit after time points with measurable concentrations

[c] n = 19

[d] n = 17

[e] n = 21

[f] n = 22

Table 15: Geometric mean ratios (90% CI) comparing Japanese to Caucasian Tolvaptan PK parameters.

Parameter	Treatment		
	Fasted	High-fat Meal	Japanese Standard Meal
C_{max}	1.105 (0.845 - 1.443)	1.046 (0.801 - 1.368)	1.196 (0.913 - 1.566)[a]
AUC_{∞}	1.345 (1.043 - 1.554)[a]	1.136 (0.833 - 1.549)[a]	1.267 (0.950 - 1.744)[a]
AUC_{24h}	1.069 (0.788 - 1.451)[a]	1.100 (0.827 - 1.615)[a]	1.215 (0.894 - 1.652)[a]

CI=confidence interval

[a] Not equivalent based on confidence interval within the range (0.69-1.45)

Impaired renal function

No studies examined the effects of Tolvaptan in subjects with impaired renal function as the applicant indicates <1% of Tolvaptan is excreted unchanged. However, they propose that Tolvaptan be contraindicated in subjects with anuria and subjects undergoing dialysis. Furthermore, it is important to note that subjects with severe renal failure (serum creatinine >3.5 mg/dL) were excluded from the Phase 3 trials.

Impaired hepatic function

A Phase 2, multicentre, randomised, double blind, placebo controlled, dose ranging Study 156-96-203 examined the PK of Tolvaptan in 45 patients with hyponatremia secondary to liver disease. Subjects with stable heart failure or with a history of congestive heart failure were specifically excluded from the trial. Following a single dose oral administration of 5, 10, 15, 30 and 60 mg of Tolvaptan, the median values of Tolvaptan C_{max} and mean AUC_t increased with dose and log-log regression analysis of C_{max} versus dose showed that the 95% CI of the slope included one (Table 16). By contrast, CL/F was independent of dose (p=0.75), whereas, $t_{1/2,z}$ increased with dose (p=0.05). The median T_{max} values ranged from 2.86 to 5.09 h across the five dose groups. Similarly, on Day 13, following multiple dose oral administration of 5, 10, 15, 30 and 60 mg Tolvaptan, a visual inspection of scatter plots for C_{max}, AUC_t and $CL_{ss/F}$ (apparent clearance of drug from plasma) indicated that C_{max} and AUC_t increased with dose and clearance was independent of dose. Protein binding of Tolvaptan was determined at concentrations of 160 ng/mL and 400 ng/mL. The median fraction unbound at a concentration of 160 ng/mL ranged from 1.28 to 2.37 and at 400 ng/mL from 1.59 to 1.85 across the five dose groups.

Table 16: Mean ± SD [n] Tolvaptan C_{max} and AUC values following 30 and 60 mg doses of Tolvaptan, healthy subjects and subjects with hyponatremia/liver disease.

Dose Regimen/Population	C_{max} or $C_{ss,max}$ (ng/mL)	AUC_{0-24h} or AUC_{τ} (ng·h/mL)	AUC_{∞} (ng·h/mL)
Single 30 mg Dose			
Healthy[a]	235 ± 90 [133]	1650 ± 661 [85]	1620 ± 713 [81]
Hyponatremia/Liver Disease[b]	280 ± 141 [6]	2930 ± 733 [6]	4330 ± 1900 [3]
Single 60 mg Dose			
Healthy[c]	594 ± 136 [135]	3590 ± 1440 [78]	3630 ± 1610 [119]
Hyponatremia/Liver Disease[b]	423 ± 248 [6]	3270 ± 1940 [6]	10000 ± 7280 [2]
Multiple 30 mg Dose			
Healthy[d]	238 ± 104 [41]	1800 ± 730 [28]	Not applicable
Hyponatremia/Liver Disease[b]	392 ± 131 [4]	4070 ± 830 [4]	Not applicable
Multiple 60 mg Dose			
Healthy[e]	512 ± 188 [47]	4500 ± 1980 [47]	Not applicable
Hyponatremia/Liver Disease[b]	713 ± 390 [4]	9815 ± 4600 [3]	Not applicable

[a] CSR 156-96-205, CSR 156-98-201, CSR 156-03-242, CSR 156-03-245, CSR 156-05-254.

[b] CSR 156-96-203.

[c] CSR 156-95-202, CSR 156-98-210 (dose Period 2), CSR 156-01-233 (60 mg as single tablet), CSR 156-01-234, CSR 156-03-240, CSR 156-05-256.

[d] CSR 156-03-245.

[e] CSR 156-98-202.

Evaluator's overall comments on PK in special populations

- No studies examined the PK of Tolvaptan in children.
- Age and gender had no affect on Tolvaptan PK.
- Weight affected Tolvaptan PK, whereby, lower weight was associated with higher C_{max} and CL/F.
- No studies examined the effects of Tolvaptan in subjects with impaired renal function.
- Hyponatremia/Liver Disease had a similar affect on the PK of Tolvaptan to mild and moderate CHF, that is, it increased C_{max} and AUC compared to healthy subjects.

Interactions

In vitro PK interactions

Diazepam, digitoxin and warfarin had no effect on the human serum albumin binding of Tolvaptan. Furosemide, spironolactone, propranolol, disopyramide, lidocaine, and warfarin did not affect the plasma protein binding of Tolvaptan, DM-4103, or DM-4107. Tolvaptan and DM-4103 did not affect human plasma protein binding of propranolol, lidocaine, and spironolactone.[8]

[8] Kudo S, et al. Binding of 14C-OPC-41061 to human plasma proteins. Otsuka Study No. 011100, Otsuka Report No. 009473, 1995; Furukawa M. Interaction of protein binding in human plasma between OPC-41061 metabolites and concomitant drugs in vitro: Method validation and protein binding measurement. Otsuka Study No. 021987, Otsuka Report No. 017335, 2005; Furukawa M. Effects of OPC-41061 and DM-4103 on human plasma protein binding of concomitant drugs (in vitro). Otsuka Study No. 019946, Otsuka Report No. 015892, 2004.

In vivo pharmacokinetic interactions

CYP3A4 inhibitors

A placebo controlled, randomised (4 active:1 placebo), sequential treatment Study 156-98-201 examined the effect of ketoconazole (a potent CYP3A4 inhibitor) on Tolvaptan PK in 24 healthy subjects (5 female), aged 19 to 45 years. Tolvaptan, 30 mg, or placebo was given alone on Day 1. Ketoconazole, 200 mg once daily, was given on Days 4, 5 and 6. On Day 5, a second 30 mg dose of Tolvaptan or placebo was administered. Blood samples for PK analysis were taken up to 72 h post dose. Coadministration of ketoconazole significantly inhibited the metabolism of Tolvaptan and the C_{max}, AUC_t, AUC_∞, $t_{1/2}$ and CL_r (renal clearance of the drug from plasma) of Tolvaptan were all increased in the presence of ketoconazole, whereas, CL/F decreased. Following coadministration with ketoconazole, the C_{max} and AUC_{inf} of Tolvaptan increased by 3.48 and 5.6 fold, respectively, and CL/F decreased by 83%. CYP3A4 activity, as measured by erythromycin breath testing (ERBT), was unchanged following administration of Tolvaptan, whereas, it was significantly decreased by an average of 49% ± 15% and 63% ± 12% ($p<0.05$) following administration of 200 mg ketoconazole on Day 4 and 200 mg ketoconazole + Tolvaptan on Day 5, respectively.

CYP3A4 also plays a role in the formation and elimination of Tolvaptan metabolites and following coadministration of Tolvaptan with ketoconazole, Tolvaptan metabolite concentrations DM-4104, DM-4105, DM-4107, DM-4110, DM-4111 and DM-4119 were significantly reduced; mean C_{max} values decreased 37 to 73% with DM-4105 concentrations becoming undetectable.

An open label, randomised, two period crossover Study 156-03-240 examined the effect of grapefruit juice (an inhibitor of CYP3A4 in the gastrointestinal tract) on Tolvaptan PK following single doses of Tolvaptan 60 mg administered in the presence and absence of grapefruit juice in 20 healthy subjects (5 female), aged 19 to 45 years. Doses were separated by a 72 h washout and blood samples for determination of Tolvaptan and DM-4103 PK were collected for 72 h postdose. Coadministration of grapefruit juice with Tolvaptan significantly increased the C_{max} and AUC_{inf} of Tolvaptan compared to when it was administered alone, whereas, it had little effect on T_{max} or $t_{1/2}$ (Table 17). The geometric mean ratios for Tolvaptan+grapefruit juice/Tolvaptan alone for C_{max} and AUC were 1.86 and 1.56, respectively (Table 18).

Table 17: Mean (SD) plasma PK parameters for Tolvaptan following a single oral 60 mg dose with water or grapefruit juice to normal healthy subjects.

Parameter	60 mg Tolvaptan + Water	60 mg Tolvaptan + Grapefruit Juice
C_{max} (ng/mL)	320 (77.5)	602 (175)
t_{max} (h)[a]	3.00 (2.00-4.00)	3.00 (1.00-3.03)
AUC_∞ (ng·h/mL)	2540 (849)[b]	4402 (1780)[b]
$t_{1/2,z}$ (h)	5.1 (1.1)[b]	5.7 (2.3)[b]
CL/F (mL/min/kg)	6.22 (2.49)[b]	3.69 (1.73)[b]

SD = standard deviation.
[a] Values are median (minimum -maximum)
[b] n=15

Table 18: Geometric mean ration (90% CIs) for Tolvaptan with grapefruit juice versus tolvaptan alone.

Parameter	Tolvaptan With Grapefruit Juice Versus Tolvaptan Alone
C_{max}	1.86 (1.67-2.06)
AUC_∞	1.56 (1.40-1.74)

CYP3A4 inducers

An open label, sequential treatment Study 156-03-239 examined the effect of rifampin (a potent inducer of CYP3A4 and P-gp) on Tolvaptan PK in 15 healthy subjects (6 female), aged 18 to 42 years. Tolvaptan, 240 mg, was administered in the fasted state alone on Day 1 and with rifampin on Day 9. On Days 3 through 10, rifampin was given 600 mg QD (once daily); on Days 3 to 8 and on Day 10, rifampin was dosed 1 h prior to breakfast. Blood samples were taken up to 48 h post dose for PK determination. Rifampin administration decreased Tolvaptan C_{max} and AUC_t by 83% and 87%, respectively (Table 19), possibly resulting from the increased metabolism of Tolvaptan following the induction of CYP3A4 by rifampin and a decrease in Tolvaptan bioavailability caused by induction of P-glycoprotein in the intestine. Rifampin administration increased DM-4017 C_{max} by 153%, but only increased AUC_t by 10%. Due to the long half life of DM-4103 (~180 h), significant amounts of DM-4103 were still present on Day 9; the mean concentration was 480 ng/mL. Due to the short duration of sampling, no effect of rifampin on the half-life of DM-4013 could be determined.

Table 19: Plasma PK parameters for Tolvaptan following a single oral 240 mg dose of Tolvaptan alone or with Rifampin at steady state (600 mg QD) in normal healthy subjects.

Parameter	Tolvaptan (N = 15)	Tolvaptan + Rifampin (N = 15)
C_{max} (ng/mL)	1000 (436)[a]	168 (73.5)
t_{max} (h)[b]	2.52 (1.00-12.00)	3.00 (1.50-6.02)
AUC_t (ng·h/mL)	11600 (4060)[a]	1470 (686)
$t_{1/2,z}$ (h)	7.7 (3.9)[c]	ND
AUC_∞ (ng·h/mL)	12100 (4140)[c]	ND
CL/F (mL/min/kg)	5.23 (1.97)[c]	ND
C_{max} ratio[d]	—	0.17 (0.05)
AUC_t ratio[d]	—	0.13 (0.04)

ND = Not determined.
[a]Values significantly higher as determined by paired t-test, $p < 0.0001$.
[b]Values are median (minimum -maximum).
[c]N = 12.
[d]Tolvaptan + Rifampin/ Tolvaptan alone.

CYP3A4 substrate

An open label, three period, sequential treatment Study 156-01-223 examined the effect of Tolvaptan administration on the PK of lovastatin (a weak CYP3A4 substrate) and its metabolite lovastatin β-hydroxy acid in 15 healthy subjects (6 female), aged 22 to 44 years. The PK of lovastatin were not statistically different when coadministered with 60 mg or 90 mg of Tolvaptan compared to lovastatin given alone, with the except of the fact that AUC_t of lovastatin following coadministration with Tolvaptan 60 and 90 mg was significantly higher (1.4-fold, p=0.02) (Tables 20-21). Coadministration of Tolvaptan with lovastatin, resulted in a higher Tolvaptan C_{max} (113% for the 60 mg dose and 166% for the 90 mg dose) and AUC_{inf} (126% and 90 % for the 60 mg and 90 mg dose of Tolvaptan, respectively) (Table 22) compared to when 60 mg and 90 mg Tolvaptan were administered alone in Study 156-98-210. By contrast, the median T_{max} and $t_{1/2,z}$ values were similar when Tolvaptan was coadministered with lovastatin and when Tolvaptan was given alone.

Table 20: Mean (SD) PK parameters of Lovastatin.

Parameter	Lovastatin 80 mg (N=11) [a]	Lovastatin 80 mg + 60 mg tolvaptan (N=9) [a]	Lovastatin 80 mg + 90 mg tolvaptan (N=12) [a]
C_{max} (ng/mL)	15.91 (7.35)	21.61 (11.11)	21.38 (13.3)
t_{max} (h)[b]	2.00 (0.50-3.00)	2.00 (1.00-3.00)	2.00 (1.00-4.00)
$t_{1/2,z}$ (h)	12.19 (7.58)	10.13 (4.9)	9.75 (4.74)
AUC_{∞} (ng·h/mL)	134.69 (64.01)	189.40 (84.85)	187.74 (70.75)
CL/F (mL/min/kg)	144.36 (56.93)	107.38 (58.10)	107.19 (53.42)

[a] N for $t_{1/2,z}$, AUC_{∞}, CL/F; N for C_{max} and t_{max} is 15 for the lovastatin 80 mg group and lovastatin 80 mg + 90 mg tolvaptan group, and 14 for the lovastatin 80 mg + 60 mg tolvaptan group.

[b] t_{max} values are median (range).

Table 21: Mean (SD) PK parameters of Lovastatin b-hydroxy acid.

Parameter	Lovastatin 80 mg (N=7) [a]	Lovastatin 80 mg + 60 mg tolvaptan (N=7) [a]	Lovastatin 80 mg + 90 mg tolvaptan (N=12) [a]
C_{max} (ng/mL)	18.97 (14.54)	22.96 (17.60)	19.34 (14.76)
t_{max} (h)[b]	4.00 (2.00-24.00)	3.00 (2.00-4.17)	3.00 (2.00-8.00)
$t_{1/2,z}$ (h)	13.89 (5.2)	16.10 (12.35)	17.41 (16.07)
AUC_{∞} (ng·h/mL)	217.8 (139.8)	191.1 (187.5)	208.4 (169.7)

[a] N for $t_{1/2,z}$, AUC_{∞} ; N for C_{max} and t_{max} is 15 for the lovastatin 80 mg group and lovastatin 80 mg + 90 mg tolvaptan group, and 14 for the lovastatin 80 mg + 60 mg tolvaptan group.

[b] t_{max} values are median (range).

Table 22: Summary of Tolvaptan PK parameters following a single oral administration of either 60 or 90 mg of Tolvaptan coadministered with 80 mg of Lovastatin.

Treatment: Lovastatin 80 mg + Tolvaptan 60 mg

	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2,z}$ (h)	AUC_t (ng·h/mL)	AUC_∞ (ng·h/mL)	CL/F (mL/min/kg)	V_z/F (L/kg)
N	14	14	12	14	12	12	12
Mean	919.63	—	7.11	6693.22	6846.25	2.12	1.21
SD	323.77	—	2.03	2015.04	2162.19	1.14	0.46
Median	903.29	2.00	6.30	7179.59	7269.58	1.73	1.04
%CV	35.21	—	28.56	30.11	31.58	53.80	37.65

— not determined.
Source: ST-16

Treatment: Lovastatin 80 mg + Tolvaptan 90 mg

	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2,z}$ (h)	AUC_t (ng·h/mL)	AUC_∞ (ng·h/mL)	CL/F (mL/min/kg)	V_z/F (L/kg)	% f_u^a	% f_u^b
N	15	15	12	15	12	12	12	15	6
Mean	1251.21	—	7.28	9499.67	10212.76	2.08	1.30	0.90	0.94
SD	454.56	—	1.44	3130.33	3276.27	0.79	0.56	0.10	0.21
Median	1146.43	2.00	7.51	8881.5	10707.44	1.84	1.13	0.87	0.90
%CV	36.34	—	19.73	32.95	32.08	37.97	42.86	11.59	22.49

— not determined.
[a] protein binding determined at 160 ng/mL of OPC-41061
[b] protein binding determined at 600 ng/mL of OPC-41061.

Warfarin

An open label, randomised, placebo controlled, crossover Study 156-01-225 examined the effect of steady state Tolvaptan administration on warfarin PK in 24 healthy subjects (4 female), aged 20 to 40 years. Tolvaptan had no statistically significant effect on the plasma concentrations of any warfarin analyte following warfarin administration.

Amiodarone

A four centre, open label, three period, sequential treatment Study 156-01-226 examined the effect of Tolvaptan administration on steady state amiodarone (AMI), and its metabolite desethylamiodarone (DEA), in 22 subjects with a history of arrhythmia and on oral amiodarone maintenance therapy of 200 mg/day for at least 10 months (11 female), aged 49 to 80 years. With the exception of arrhythmia, subjects were otherwise healthy. Of 21 subjects with complete Tolvaptan concentration profiles, only 17 were found to be evaluable because 4 subjects had positive concentrations of Tolvaptan in the first pre dose sample and concentration profiles not consistent with other subjects, which indicated that some substance was possibly interfering with the assay of Tolvaptan. Coadministration of 30 mg and 90 mg Tolvaptan did not significantly affect AMI or DEA concentrations compared with when AMI was given alone.

P-gp substrates

An open label, sequential treatment Study 156-01-234 examined the interaction between single and multiple doses of Tolvaptan and steady state digoxin (a P-gp substrate) in 14 healthy subjects (5 female), with an average age of 31.4 years. Following multiple oral doses of Tolvaptan, digoxin concentrations were significantly increased (Table 23). The digoxin + Tolvaptan/digoxin alone ratio (Day 16/Day 11) for digoxin mean C_{max} and AUC_t values were 1.30 and 1.18, respectively. Digoxin renal clearance was decreased 59%. Following a single oral dose of Tolvaptan with digoxin (Day 12), the amount of digoxin excreted in the urine (Ae,u) was unchanged compared to digoxin alone (Day 11); mean values of Ae,u were 100.5 and 99.6 µg for Days 11 and 12.Tolvaptan concentrations were not significantly affected by coadministration with digoxin. The digoxin + single dose Tolvaptan/Tolvaptan alone ratio (Day 12/Day 1) for Tolvaptan mean C_{max} and $AUC_{0\text{-}24h}$ values were 1.10 and 1.02, respectively. The ratios for digoxin + steady state Tolvaptan/Tolvaptan (Day 16/Day 11) were 1.07 and 1.02, respectively.

Table 23: Summary of Digoxin PK parameters following multiple oral administrations of 0.25 mg Digoxin QD alone (Day 11) or with multiple oral 60 mg doses of Tolvaptan QD (Day 16) to healthy men and women.

Parameters	Statistics	Day 11	Day 16
t_{max} (h)	N	14	14
	Median	1.00	1.25
	Range	0.50-3.00	1.00-3.00
$C_{ss,max}$ (ng/mL)	N	14	14
	Geo Mean	1.76	2.25
	Mean	1.80	2.34
	CV%	19.7	29.0
AUC_τ (ng·h/mL)	N	14	14
	Geo Mean	19.7	23.2
	Mean	19.9	23.4
	CV%	14.4	13.7
$A_{e,0\text{-}24}$ (ng)	N	9	13
	Mean	83236	54767
	CV%	58.9	41.7
CL_F (mL/min/kg)	N	8	8
	Mean	1.05	0.43[a]
	CV%	49.9	45.6

Geo Mean = Geometric mean.

[a] Statistically significantly lower than that on Day 11, $p < 0.05$ (ANOVA with treatment and subject as factors)

Other Diuretics

A single centre, randomised, open label, parallel arm, three period cross over Study 156-96-205 examined the PK interaction between Tolvaptan and furosemide or hydrochlorothiazide (HCTZ) in 12 healthy Caucasian men, aged 18 to 29 years. No clinically significant changes were noted in the PK profiles of Tolvaptan and furosemide, or Tolvaptan and HCTZ, when coadministered.

Evaluator's overall comments on pharmacokinetic interactions:

- The CYP3A4 inhibitor, ketoconazole significantly increased Tolvaptan C_{max} (3.48 fold) and AUC (5.4-fold).
- Grapefruit juice (containing naringinine, a CYP3A4 inhibitor in the gastrointestinal tract) also increased Tolvaptan C_{max} (188%) and AUC_{inf} (173%) but elimination halflife was unchanged.
- Rifampicin (a potent inducer of CYP3A4), at 600 mg, once daily statistically significantly decreased the Tolvaptan C_{max} by 83% and AUC_t by 87%; therefore, an increase in Tolvaptan dose may be required if the two drugs are to be coadministered.
- As a weak CYP3A4 substrate, Tolvaptan had no effect on amiodarone (in subjects with cardiac arrhythmias), warfarin or lovastatin (or its β-hydroxy acid metabolite).
- However, lovastatin coadministration increased both Tolvaptan C_{max} (113% for the 60 mg dose and 166% for the 90 mg dose), and AUC_{inf} (126% and 90 % for the 60 mg and 90 mg dose of Tolvaptan).
- Steady state digoxin C_{max} and AUC_t were elevated 1.3 fold and 1.2 fold, respectively, following coadministration of Tolvaptan 60 mg daily. Digoxin renal clearance was also significantly lowered by coadministration with Tolvaptan (decrease of 59%).
- However, coadministration of digoxin did not affect Tolvaptan PK. Due to the changes in digoxin PK, patients receiving digoxin should therefore be evaluated for excessive digoxin effects when treated with Tolvaptan.
- Coadministration of hydrochlorothiazide had no effect on Tolvaptan PK and furosemide increased the Tolvaptan Cmax (8%) and AUC (10%) only slightly.
- Tolvaptan did not affect the PK of HCTZ or furosemide.

Population PK analysis

Study 156-01-224 represented an integrated Tolvaptan population pharmacokinetic analysis in subjects with hyponatremia or heart failure with and without hyponatremia. The objectives of this analysis were to develop and evaluate a population PK model of Tolvaptan, estimate model parameters, inter subject variability and evaluate the effects of covariate factors on Tolvaptan PK, and to provide individual estimates of Tolvaptan exposure for subsequent PK/PD analyses.

Two core PK datasets were created, one including patients with hyponatremia of any origin enrolled in the hyponatremia trials and one including patients with heart failure with or without hyponatremia enrolled in the heart failure trials. The core PK data file for the hyponatremia analysis contained 1486 plasma samples from 213 patients enrolled in three hyponatremia trials, a Phase 2 trial in patients with liver disease, and two phase 3 trials in patients with hyponatremia of any origin. The heart failure analysis contained 10200 plasma samples of 2392 patients from five heart failure trials, four Phase 2 trials and the Phase 3 trial. A separate hyponatremia analysis included patients with hyponatremia at baseline enrolled in either the hyponatremia or heart failure trials, the dataset contained 2716 plasma samples from 490 patients.

Covariates investigated in both heart failure and hyponatremia analysis included demographics (age, race sex), size metrics (for example, body weight, lean body weight, body mass index), liver function (Child-Pugh Classification), renal function (creatinine clearance calculated from the Cockroft-Gault equation) and concomitant medications (loop, potassium sparing, and thiazide diuretics, CYP3A4 inhibitors and CYP3A4 inducers, and drugs that interact with P-glycoprotein). In addition, the hyponatremia analysis included disease association (CHF, cirrhosis, or SIADH/other), hyponatraemic severity (mild or severe) and volume status (euvolemic or hypervolemic), whereas the heart failure analysis also included NYHA class and drug classes associated with this population (ACE [angiotensin converting enzyme] inhibitors, beta blockers, vasodilators, angiotensin receptor antagonists [ARBs], inotropes, and antacids).

Hyponatremia analysis

A covariate modelling approach emphasising parameter estimation rather than stepwise hypothesis testing was implemented for this analysis. First, pre defined covariate parameter relationships were identified based on scientific interest, mechanistic plausibility or prior knowledge, and a full model was constructed with care to avoid correlation or collinearity in predictors. Model parameters were estimated and assessment of any remaining trends was conducted by graphical inspection of all covariate effects. Inferences about clinical relevance of parameters were based on the parameter estimates of the full model and measures of estimation precision. Individual PK parameters were also estimated, and derived exposure parameters such as AUC_t and C_{max} and fraction of time above certain concentration levels were calculated for the subsequent PK/PD analysis. A bootstrap procedure was used to estimate the uncertainty of the parameter estimates. Predictive check and posterior predictive check methods were used to assess the performance of the final model and parameters. In addition, an exploratory parallel covariate analysis based on screening of covariates using the objective function change was conducted in association with the analysis of the hyponatremia population enrolled in hyponatremia and heart failure trials. Covariates that were deemed important based on the objective function drop from the base model were included into the alternative covariate model. Model parameters were estimated and assessment of any remaining trends was conducted by graphical inspection of all covariate effects. The alternative covariate model was used to confirm results of the full model approach and generate hypothesis concerning possible drug interactions.

Heart failure analysis

In light of the size, noise, and imbalance of the heart failure database, the PK modelling process was limited to a simple base model search. Model selection was guided by model stability, minimum objective function value and various 'goodness of fit' plots. The precision of the estimates was assessed by a stratified bootstrap procedure, the standard error of parameter estimates from successful runs out of a total 200 runs was calculated. Random effects versus covariates were plotted and examined for trends.

Findings

The population PK of Tolvaptan in both hyponatremia and heart failure were best described by a one compartment model with first order absorption, random effects on CL/F, V/F, and KA, and exponential residual error.

- Tolvaptan oral clearance mildly increased with weight while apparent volume was proportional to weight.
- Child-Pugh Class was identified as a predictor of oral clearance (19 and 24% increase for Class B and C, respectively) and volume (50% increase for Class C) in the core hyponatremia dataset. The expanded hyponatremia dataset showed a mild increase in oral clearance for Class B and C and a 50% increase in volume for Class C. The heart

failure analysis showed no strong trend for Class B (25% of the patients in the database with Class B) and mild trends for Class C V/F and CL/F (1.2% of the database). The clearance results are not inconsistent with the hyponatremia/liver disease Study 156-96-203.

- Renal impairment (as estimated by the normalised creatinine clearance calculated from the Cockroft-Gault equation) had no effect on Tolvaptan clearance in the hyponatremia analysis.
- Coadministration of CYP3A4 inducers resulted in a 45% (7%, 84 % [95% CI]) increase in Tolvaptan oral clearance, based on data from only five patients in the core hyponatremia analysis and a 75% (44%, 124% [95% CI]) increase from 11 patients in the expanded hyponatremia analysis (hyponatremia trials and patients with hyponatremia enrolled in heart failure trials). The heart failure database included only 17 patients reporting concomitant administration with CYP3A4 inducers; however, plots of random effects versus concomitant CYP3A4 inducer showed an effect. This effect of inducers is consistent with that seen in the rifampin interaction Study 156-03-239.
- Hyponatremia severity, concomitant administration of diuretics, CYP3A4 inhibitors, heart failure concomitant medications, and P-gp inhibitors did not have a meaningful influence on Tolvaptan PK for the patient populations investigated.

Exposure relevant for safety evaluation

Hyponatremia/Liver Disease had a similar affect on the PK of Tolvaptan to mild and moderate CHF, that is, it increased C_{max} and AUC compared to healthy subjects.

The CYP3A4 inhibitor, ketoconazole significantly increased Tolvaptan C_{max} by 3.48 fold and AUC by 5.4 fold. Similarly, grapefruit juice also significantly increased Tolvaptan C_{max} (188%) and AUC_{inf} (173%). By contrast, 600 mg rifampicin QD (a potent inducer of CYP3A4) significantly decreased Tolvaptan C_{max} by 83% and AUC_t by 87%; therefore, an increase in Tolvaptan dose may be required if the two drugs are to be coadministered.

Lovastatin coadministration increased both Tolvaptan C_{max} (113% for the 60 mg dose and 166% for the 90 mg dose), and AUC_{inf} (126% and 90 % for the 60 mg and 90 mg dose of Tolvaptan).

Evaluator's overall conclusions on pharmacokinetics

- The median T_{max}, $t_{1/2}$, C_{max} and AUC_{inf} of Tolvaptan following oral administration of a 30 mg tablet were 2 h, 6.7 h, 231 ng/mL and 1731 ng.h/mL, respectively. The mean absolute bioavailability (F) of Tolvaptan tablet was 56%.
- Although the overall exposure to Tolvaptan was not affected, the rate of Tolvaptan absorption increased with food.
- Following a 60 mg dose of ^{14}C-OPC-41061 radioactive, the CL/F and V/F were 6.0 ml/min/kg and 4.33 l/kg, respectively. A total of 98.9% of the administered radioactivity was recovered with 40.2% in urine and the remaining 58.7% recovered in the faeces. About 80% of the cumulative urine ^{14}C excretion occurred during the first 36 h and approximately 65% of radioactivity was recovered in the faeces within the first 72 h. However, radioactivity could be detected in the faeces for up to 960 h post dose.
- Tolvaptan and seven metabolites (DM-4103, DM-4104, DM-4105, DM-4107, DM-4110, DM-4111 and DM-4119) were identified in the subject's plasma. Tolvaptan and its metabolites accounted for 60.4% of the total plasma radioactivity. DM-4103 alone

accounted for 52.5% of the plasma radioactivity, whereas, unchanged Tolvaptan accounted for 2.8% and the other metabolites combined accounted for 5.1%

- In vivo studies indicate that the formation and elimination of Tolvaptan and most of its metabolites occurs via CYP3A4/5. Therefore, although no studies specifically examined the effects of CYP mutations on the PK of Tolvaptan it should be assumed that patients with known mutations in this isoenzyme may require dose adjustment.
- No studies examined the PK of Tolvaptan in children or in subjects with impaired renal function.
- Age and gender had no affect on Tolvaptan PK, whereas, lower weight (kg) was associated with higher C_{max} and CL/F.
- Hyponatremia/Liver Disease had a similar affect on the PK of Tolvaptan to mild and moderate CHF, that is, it increased C_{max} and AUC compared to healthy subjects.
- The CYP3A4 inhibitor, ketoconazole significantly increased Tolvaptan Cmax by 3.48 fold and AUC by 5.4 fold. Similarly, grapefruit juice also significantly increased Tolvaptan C_{max} (188%) and AUC_{inf} (173%). By contrast, 600 mg rifampicin QD (a potent inducer of CYP3A4) significantly decreased Tolvaptan C_{max} by 83% and AUC_t by 87%; therefore, an increase in Tolvaptan dose may be required if the two drugs are to be coadministered.
- Lovastatin coadministration increased both Tolvaptan C_{max} (113% for the 60 mg dose and 166% for the 90 mg dose), and AUC_{inf} (126% and 90 % for the 60 mg and 90 mg dose of Tolvaptan).
- Steady state digoxin C_{max} and AUC_t were elevated 1.3 fold and 1.2 fold, respectively, following coadministration of Tolvaptan 60 mg daily. Digoxin renal clearance was also significantly lowered by co-administration with Tolvaptan (decrease of 59%). By contrast, coadministration of digoxin did not affect Tolvaptan PK. Due to the changes in digoxin PK, patients receiving digoxin should therefore be evaluated for excessive digoxin effects when treated with Tolvaptan.
- Coadministration of HCTZ had no effect on Tolvaptan PK, whereas, furosemide increased the Tolvaptan Cmax (8%) and AUC (10%) only slightly.
- Tolvaptan had no effect on the PK of amiodarone (in subjects with cardiac arrhythmias), warfarin, lovastatin (or its β-hydroxy acid metabolite), HCTZ or furosemide.
- PK population modelling indicated that: the PK of Tolvaptan in both hyponatremia and heart failure were best described by a one compartment model with first order absorption, random effects on CL/F, V/F, and KA, and exponential residual error.
- Tolvaptan oral clearance mildly increased with weight while apparent volume was proportional to weight.
- Child-Pugh Class was identified as a predictor of oral clearance (19 and 24% increase for Class B and C, respectively) and volume (50% increase for Class C) in the core hyponatremia dataset. The expanded hyponatremia dataset showed a mild increase in oral clearance for Class B and C and a 50% increase in volume for Class C.
- Renal impairment (as estimated by the normalised creatinine clearance calculated from the Cockroft-Gault equation) had no effect on Tolvaptan clearance in the hyponatremia analysis.
- Coadministration of CYP3A4 inducers resulted in a 45% (7%, 84 % [95% CI]) increase in Tolvaptan oral clearance, based on data from only five patients in the core hyponatremia analysis and a 75% (44%, 124% [95% CI]) increase from 11 patients in

the expanded hyponatremia analysis (hyponatremia trials and patients with hyponatremia enrolled in heart failure trials).

- Hyponatremia severity, concomitant administration of diuretics, CYP3A4 inhibitors, heart failure concomitant medications, and P-gp inhibitors did not have a meaningful influence on Tolvaptan PK for the patient populations investigated.

Pharmacodynamics

Introduction

The evaluation materials contained 19 studies with information on the PD of Tolvaptan conducted in 736 male and 133 female subjects (including patients). As part of this work, studies examined Tolvaptan in 54 patients with mild to moderate congestive heart failure and 45 patients with hyponatremia secondary to liver disease.

Mechanism of action

Tolvaptan is a selective vasopressin V_2 receptor antagonist with an affinity for the human V_2 receptor that is 1.8 times that of native AVP. Tolvaptan is approximately 29 fold more selective for V_2 receptors than for V1a receptors and has an even lower affinity for V_{1b} receptors. Animal pharmacology studies indicate that Tolvaptan increases excretion of water without increasing the excretion of electrolytes (aquaresis). Therefore, the selection of PD endpoints for the human trials were based on possible physiological changes that might occur based on this mechanism of action: urine volume, fluid intake, fluid balance, body weight, serum or plasma Na+, K+, Mg++, Ca++ and Cl- concentrations and osmolality, urinary excretion of Na+, K+ and osmoles, urine Na+ and K+ concentrations and osmolality, plasma AVP, aldosterone, and norepinephrine concentrations, plasma renin activity and systolic and diastolic blood pressure (standing, supine).

Primary pharmacology

The absolute bioavailability Study 156-05-254 also examined the effects of Tolvaptan 1 mg IV and 30 mg Tolvaptan oral tablet PO on urine osmolality and urine volumes. Following IV Tolvaptan, the effect of Tolvaptan on urine osmolality (Figure 3) and volume (Figure 4) lasted less than 6 h and by the 4-6 h interval, these parameters had returned to placebo levels. Following Tolvaptan 30 mg PO, Tolvaptan concentrations were sufficient in all subjects to suppress urine osmolality for the entire sampling interval, 0-24 h. By contrast, there was no change from baseline (Placebo IV) in 24 h urine volume or fluid balance. The study suggested that Tolvaptan concentrations of approximately 25-44 ng/mL were able to produce a detectable reduction in urine osmolality and an increase in urine volume.

Figure 3: Mean urine osmolality plotted at the end time of the collection interval following a 1 h constant rate IV infusion of placebo or Tolvaptan 1 mg or a single oral tablet dose of Tolvaptan 30 mg to normal healthy subjects (n=14).

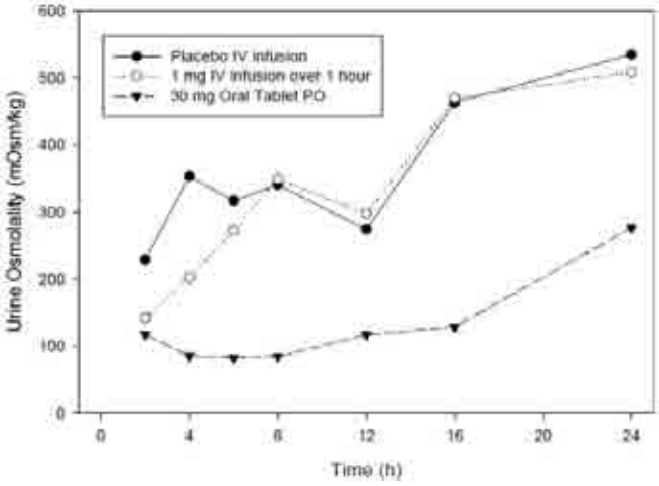
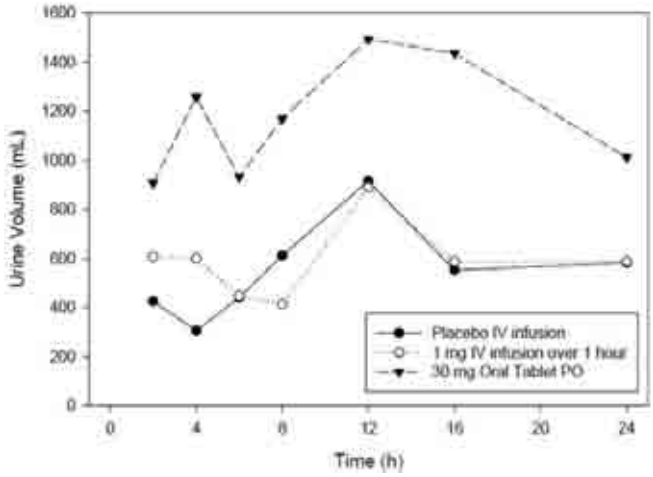


Figure 4: Mean urine volume plotted at the end time of the collection interval following a 1 h constant rate IV infusion of placebo or Tolvaptan 1 mg or a single oral tablet dose of Tolvaptan 30 mg to normal healthy subjects (n=14).



Bioequivalence Study 156-01-233 also examined the PD effects of Tolvaptan following sequential administration of different combinations of Tolvaptan tablets (60 mg dose on each day). Changes from baseline of urine output and fluid balance were similar following all treatments. The mean change in urine output on Day 1 was ~7000 mL and returned to baseline during the 24-48 h interval. Mean fluid balance was approximately -1500 mL for the first 24 h following drug administration and was slightly positive for the 24-48, 48-72 and 72-96 h collection intervals.

Effect of food

Study 156-00-002 examined the effects of food on the plasma AVP following a 30 mg dose of Tolvaptan. Plasma AVP concentrations (mean ± SD) following administration in a fasting and a fed state were 1.1 ± 0.5 and 1.1 ± 0.8 pg/mL, respectively, at baseline and increased to 6.2 ± 5.1 and 4.2 ± 2.2 pg/mL, respectively, at 24 h post dose (Table 25).

Table 25: Descriptive statistics of plasma AVP concentrations.

Treat-ment	Timepoint	Measured Value (pg/mL)						Change From Baseline (Postdose Value Minus Predose Value)					
		N	Mean	SE	Min	Median	Max	N	Mean	SE	Min	Median	Max
Fasting	Predose	14	1.056	0.467	0.50	0.940	2.05						
	24 h Postdose	14	6.199	5.066	1.76	3.785	20.40	14	5.142	4.963	0.67	2.835	19.28
Fed	Predose	14	1.119	0.796	0.32	1.030	3.39						
	24 h Postdose	14	4.182	2.195	1.84	3.580	9.73	14	3.063	1.875	0.99	2.625	8.19

Ascending dose studies

Study CSR 156-00-001 investigated the pharmacodynamics of a single oral dose of Tolvaptan at 15-120 mg in a fasting state in healthy Japanese males. The 24 h cumulative urine volume increased dose dependently with a urine volume in the highest dose group (120 mg) of 11945.8 mL compared to 2585 mL (Table 26). Urine excretion rates for each 2 h period up until 8 h post dose increased to approximately 700 to 800 mL/h in the 60-120 mg groups. Although the urine excretion rates tended to decrease by 8 h post dose, in the 60-120 mg groups the diuretic action of Tolvaptan continued until 24 h post dose. By contrast, there were no significant changes in quantity of Na+ excreted in 24 h cumulative for all doses, whereas, the quantity of K+ excreted in 24 h cumulative urine was greater in the higher Tolvaptan dose groups. Urine osmolality decreased during 0-2 h periods post dose and hyposthenuria[9] was observed. Free water clearance was positive following Tolvaptan administration and was higher than pre dose values. The high dose groups showed a longer lasting aquaretic effect. Plasma AVP concentrations began increasing shortly following Tolvaptan administration and remained greater than the baseline values 24 h post dose. Although increases in serum Na+ concentration were also seen after administration, the changes were within the range of physiological fluctuation. No significant changes in serum K+ concentration were observed. Fluid balance 0-2 h following Tolvaptan administration was negative and dose dependent. Fluid balance improved on the second day after administration.

[9] Excretion of urine of low specific gravity due to an inability of the tubules of the kidneys to produce concentrated urine.

Table 26: Summary of PK parameters of Tolvaptan.

Dose	Parameter	24-Hour Cumulative Urine Volume (mL)	24-Hour Cumulative Na^+ Excretion (mEq)	24-Hour Cumulative K^+ Excretion (mEq)
15 mg	N	6	6	6
	Mean	3018.5	91.00	56.93
	SD	729.9	31.38	6.53
30 mg	N	12	12	12
	Mean	5722.9	94.94	62.38
	SD	643.2	26.64	10.35
45 mg	N	6	6	6
	Mean	6209.8	106.49	66.39
	SD	1749.1	20.24	6.63
60 mg	N	6	6	6
	Mean	8751.5	129.29	85.06
	SD	1280.6	36.33	11.81
90 mg	N	6	6	6
	Mean	9936.2	111.53	99.45
	SD	1163.1	25.24	10.68
120 mg	N	6	6	6
	Mean	11945.8	155.12	91.51
	SD	1822.6	24.09	9.13
Placebo	N	14	14	14
	Mean	2584.5	95.58	44.11
	SD	1298.4	22.98	12.64

Population for pharmacodynamic analysis: N = 56

An ascending single dose Study 156-98-210 examined PD of Tolvaptan of 60, 90, 120, 180 and 240 mg in healthy subjects under conditions of volumetric fluid replacement (Period 1) and no volumetric fluid replacement (Period 2). For the 0-24 h interval following administration of Tolvaptan, serum K+, creatinine clearance, and urinary excretion of Na+ and K+ were similar to the placebo group. Mean urine volume excretion increased dose dependently only in Period 2. However, it reached a plateau after the 180 mg dose in subjects with and without volumetric fluid replacement. There appeared to be no dose proportional increase or decrease in the pharmacodynamic parameters of serum sodium, serum potassium, AVP, plasma renin activity, urine sodium and urine potassium. Mean free water clearance was negative for subjects administered placebo and was positive for subjects administered Tolvaptan. In both periods, the free water clearance at 24 h post dose was similar for the 60, 90, and 120 mg dose groups, increased at the 180 mg dose, and was similar for the 180 and 240 mg dose groups.

A final ascending dose trial Study 156-01-229 examined the PD in healthy subjects following single doses of 180, 240, 300, 360, 420, or 480 mg Tolvaptan or placebo. Urine collections occurred up to 144 h post dose on Days -1, 1, 2, and 3 for all dose groups and additionally on Days 4, 5, and 6 for the 480 mg dose group only. Similar maximum urine excretion rate and free water clearance values occurred within 8 h following drug administration for all doses. These results indicated that urine excretion rate and free water clearance plateaued at the 180 mg dose. Positive free water clearance values in subjects who received Tolvaptan indicated the formation of hypotonic urine compared with subjects administered placebo. Following administration of Tolvaptan creatinine clearance values were similar to baseline values suggesting little to no effect on glomerular filtration. Following increasing doses of Tolvaptan, total urine volume for 72 h post dose increased, but not proportionally with dose.

Multiple dose studies

Study 156-00-003 examined the PD of Tolvaptan following single and multiple doses of 30 mg and 60 mg in healthy males. Cumulative urine was collected up to 48 h after administration on Days 1 and 9; and up to 24 h after administration on Days 3 through 8. In addition, the volume and time of each fluid intake on Days 1 through 11 were documented. Plasma AVP concentration and serum osmolality increased markedly

following administration of both the 30 mg and 60 mg doses of Tolvaptan. In both groups, the increases observed following 7 day repeated oral administration (Day 9) were smaller than those observed following single administration on Day 1. For serum electrolytes (Na+, K+, Cl-, and Mg++), although post-dose increases in serum Na+ and Cl- concentrations were seen, the increases observed for Day 9 were smaller than those observed for Day 12. No significant changes in serum K+ and Mg++ concentrations were observed following either single or repeated administration. On Days 1 and 9, the quantity of K+ excreted in 24 h cumulative urine was greater in the Tolvaptan treated subjects than in the placebo group. For instance, on Day 1, the quantity of K+ excreted in 24 h cumulative urine was approximately 2 fold higher in the Tolvaptan treated subjects than in the placebo group. By contrast, the quantities of Cl- and Mg++ excreted in 24 h cumulative urine were only slightly greater in the Tolvaptan treated subjects than in the placebo group. All increases in urinary electrolyte excretion following a single dose decreased following repeated administration, with electrolyte quantities on Day 9 similar to those in the placebo group. There were no significant changes in the quantity of Na+ excreted in 24 h cumulative urine following administration of Tolvaptan, and the quantities in the Tolvaptan treated subjects and the placebo group remained similar throughout the treatment period. The quantities of all electrolytes excreted following administration were similar between the 30 mg and 60 mg groups. Urine osmolality markedly decreased following single and repeated administration of Tolvaptan. Mean free water clearance was positive in subjects administered Tolvaptan, and urine electrolyte parameters (particularly the K excretion rate and the quantity of K excreted in 24 h cumulative urine) were increased on both Days 1 and 9, although the increases for Day 9 were smaller than those for Day 1. Cumulative urine volume, urine excretion rate, and cumulative fluid intake increased markedly in the Tolvaptan treated subjects compared to placebo and the degree of increase was similar following both single and repeated administration. Following repeated administration (Days 3 through 9), 24 h cumulative urine volume was 6440.8 to 9014.0 mL in the 30 mg group and 7245.4 to 10629.4 mL in the 60 mg group. Fluid balance per unit time showed notably negative values following dosing, but returned to positive values by 24 h post dose. The 24 h cumulative fluid balance showed negative values of below -1000 mL on Days 1 and 3, but the negative values tended to become less significant from Day 4 (second day of repeated administration).

Study CSR 156-05-001 investigated Tolvaptan PD following repeated oral administration of 90 or 120 mg, or placebo in healthy males. Plasma AVP concentration increased following Tolvaptan administration and the values for the 120 mg dose group were twice that of the 90 mg group on both Days 1 and 9, whereas, although serum Na+ and Cl- concentrations increased following Tolvaptan administration, they were similar for both Tolvaptan dosage groups. Serum osmolality also increased following Tolvaptan administration. The quantity of Na+ excreted in 24 h cumulative urine in the Tolvaptan treated subjects was slightly greater than that of the placebo group. Urine osmolality was greatly decreased in the Tolvaptan treated subjects and the extent of decrease did not change following repeated administration. The 24 h cumulative urine volume during the repeated administration period was 7693.0-9193.7 mL for the 90 mg group, 9035.2-11590.0 mL for the 120 mg group and 2824.2-4227.6 mL for the placebo group.

Study 156-95-305 examined the PD effects following once daily administration of 30 and 60 mg Tolvaptan for 28 days compared to placebo in healthy males. On Days 1, 7, and 28, urine was collected over intervals up to 24 h post dosing. Increases in fluid intake and urine volume output were apparent in subjects dosed with Tolvaptan, with the 60 mg dose group showing larger increases than the 30 mg dose group. A dose dependent decrease in urine osmolality was apparent. Compared to placebo, the decrease in urine osmolality in the 60 mg dose group was larger than that in the 30 mg dose group. There was no accumulation of the drug in the serum in either dose group for up to 28 days.

Pharmacodynamic studies in patients

Study 156-00-221 examined the effects of a single dose of Tolvaptan and furosemide (Lasix) on renal function and renal haemodynamics in subjects with mild to moderate congestive heart failure, NYHA Class II-III. The primary efficacy criteria examined were: glomerular filtration rate (GFR); proximal fractional reabsorption of sodium (PFRNa+); distal fractional reabsorption of sodium (DFRNa+); effective renal plasma flow (ERPF); renal blood flow (RBF); and renal vascular resistance (RVR). Tolvaptan significantly increased EPRF by 9% (to 42.56 mL/min) compared to placebo, whereas compared to placebo, furosemide significantly decreased EPRF by 7% (to 34.68 mL/min) (Table 27). Similarly, RBF increased by 74.62 mL/min (10%) post Tolvaptan, whereas, furosemide decreased RBF by 97.33 mL/min (13%) ($p = 0.0362$ and $p = 0.0010$, respectively). For the other primary variables, there was a trend toward improvement in GFR following 30 mg Tolvaptan (increase of 1.37 mL/min over placebo) and a deterioration of GFR with furosemide 80 mg (decrease of 3.26 mL/min over placebo). In addition, Tolvaptan decreased RVR (-1.54 mmHg/dL compared to placebo), whereas, furosemide increased RVR (0.12 mmHg/dL compared to placebo). Both Tolvaptan and furosemide treatment decreased PFRNa+ and DFRNa+ compared to placebo (-0.62% and -2.44%, and -1.53% and -11.03%, respectively). Significant differences were seen in Tolvaptan versus furosemide ($p = 0.0233$) and placebo versus furosemide ($p = 0.0056$) for DFRNa+. Additional variables of Na+ and K+ clearance, urine, Na+ and K+ excretion rates, and MAP (mean arterial pressure) were also analysed longitudinally. The significant increases in Na+ and K+ excretion rates and clearance induced by furosemide were not seen with Tolvaptan. Although, Tolvaptan increased Na+ excretion rate by 1.28 mmol/h (23%) and clearance by 0.22 mL/min (35%) compared to placebo, but it did not induce significant depletion of these electrolytes compared to furosemide. In contrast to furosemide, Tolvaptan did not significantly affect K+ excretion rate and clearance. However, the rates of urine excretion compared to placebo were similar following administration of Tolvaptan and furosemide in ($p = 0.0001$ and $p < 0.0001$, respectively). The differences in MAP for the treatment comparisons were not significant. The analysis of the secondary variables did not reveal any significant treatment differences based on the mean changes from baseline at 2.5 h post dose.

Table 27: Tolvaptan and placebo treatment comparisons[a] for the renal function parameters.

	OPC-41061	Placebo			
	LS Mean (SD)	LS Mean (SD)	Delta (SD)	% Change[c]	P-value[d]
GFR	95.59 (49.35)	94.22 (55.01)	1.37 (69.19)	1.45	0.7092
ERPF	515.38 (345.85)	472.82 (269.78)	42.56 (392.24)	9.00	0.0437
RBF	854.96 (579.59)	780.34 (461.71)	74.62 (661.77)	9.56	0.0362
PFRNa+	76.14 (72.67)	76.76 (15.73)	-0.62 (73.84)	-0.81	0.8797
DFRNa+	93.15 (11.03)	94.67 (6.75)	-1.53 (12.33)	-1.61	0.1404
RVR[b]	17.15 (12.89)	18.69 (12.68)	-1.54	-8.24	0.2182[e]
MAP	100.45 (14.20)	100.25 (12.66)	0.21 (18.67)	0.20	0.8838
Clearance of Na^+	0.88 (1.54)	0.65 (0.63)	0.22 (1.62)	35.38	0.0800
Clearance of K^+	11.86 (9.05)	11.73 (11.71)	0.14 (14.36)	1.11	0.8967
Urine Excretion Rate	610.93 (726.14)	458.70 (319.05)	152.24 (778.25)	33.19	0.0001
Na^+ Excretion Rate	6.82 (11.88)	5.54 (5.22)	1.28 (12.64)	23.10	0.0705
K^+ Excretion Rate	3.33 (2.99)	3.24 (3.39)	0.09 (4.39)	2.78	0.6975

[a] Comparisons between OPC-41061 and placebo were made using sequence, subject within sequence, period, treatment as fixed effect, and time points within a day with autoregression(1) variance structure.

[b] Based on the LS means of the daily averages. Daily average of RVR = 100*(daily average weighted average MAP)/(daily weighted average RBF).

[c] Percent change = delta/LS means of placebo*100.

[d] Performed two-sided with a significance level of 0.05.

[e] P-values were derived from ANOVA with factors sequence, subject (sequence), treatment, and period for comparison of OPC-41061 and placebo.

Study 156-01-231 assessed the pharmacodynamic effects of Tolvaptan 30 mg QD versus Tolvaptan 15 mg BID in patients with CHF Class II-III. In this study, no clinically significant differences in any of the studied pharmacodynamic variables were identified (Table 28). Although the exploratory analysis showed that there was a difference in the mean change from baseline at Day 7 in serum sodium between the two dosage regimens, this result was not considered clinically relevant due to the lack of consistent response in the other observed PD parameters.

Table 28: Mean (SD) change from baseline at Day 1 (urine parameters) or Day 2 (serum parameters and body weight) and Day 7.

Pharmacodynamic Parameters	30 mg QD		15 mg BID	
	Day 1 or 2	Day 7	Day 1 or 2	Day 7
Body weight (kg)	-1.44 (2.57)	-0.13 (1.61)	-1.04 (1.32)	1.11 (2.55)
Urine volume (mL)[a]	4278 (2360)	3524 (1634)	4197 (3392)	3067 (1928)
Urine Excretion Rate (mL/min)[b]	2.97 (1.64)	2.45 (1.13)	2.92 (2.36)	2.13 (1.34)
Serum Sodium (mEq/L)	2.52 (2.52)	0.95 (2.14)[c]	3.84 (3.00)	3.53 (2.78)[c]
Serum Potassium (mEq/L)	0.00 (0.35)	-0.06 (0.57)	0.17 (0.39)	0.01 (0.45)
Serum Magnesium (mEq/L)	0.09 (0.13)	-0.02 (0.14)	0.14 (0.14)	0.06 (0.21)
Serum Osmolality (mOsm/kg)	2.43 (7.41)	-1.40 (8.44)	5.58 (10.35)	1.58 (11.77)
Urine Osmolality (mOsm/kg)[a]	-325 (168)	-326 (167)	-247 (222)	-323 (276)
Creatinine Clearance (mL/min)[a]	-16 (39)	-11 (31)	-6 (24)	-12 (27)

[a] Day 1 and 7 values are truncated to integers from source tables.
[b] Values not statistically compared.
[c] Value from 15 mg BID compared to 30 mg QD was found to have a p = 0.0028.

Study 156-96-203 examined the PD of a range of Tolvaptan doses (5, 10, 15, 30, and 60 mg) in patients with hyponatremia secondary to liver disease and this has been discussed in the 'Efficacy' section below.

Intrinsic factors

Age and gender

Study 156-98-202 (Table 11) examined the pharmacodynamics of orally administered Tolvaptan (60 mg dose) in healthy adults (age of 18-45 years) and in elderly (age ≥65 years) male and female subjects. Blood and urine samples were collected up to 72 h post dosing on Days 1 and 10 for the assessment of pharmacodynamics. There were no significant age/gender interactions for the pharmacodynamic parameters AVP, plasma renin activity, and urine osmolality on Days 1 and 10. Pairwise comparison of AUC values for AVP showed a significant difference ($p<0.05$) only on Day 1 for young males versus elderly females. Pairwise comparison of AUC values for urine osmolality showed a significant gender difference ($p<0.05$) in both age groups (young male versus young female, young male versus elderly female, young female versus elderly male, and elderly male versus elderly female) on Day 1 and Day 10. Pairwise comparison of AUC values for plasma renin activity showed a significant age and gender difference ($p<0.05$) except for elderly male versus elderly female on Day 1, and young female versus elderly male and elderly male versus elderly female on Day 10.

Secondary pharmacology

A single centre, parallel arm, double blind, placebo and positive controlled, multiple dose Study 156-03-245 of 30 mg or 300 mg doses of Tolvaptan and 400 mg doses of moxifloxacin on QT interval in 172 healthy subjects (84 female), aged 18 to 45 years. The mean change from baseline in QT_{cI} (individually corrected QT) was not statistically

significantly different in healthy subjects taking multiple oral doses of either 30 mg or 300 mg Tolvaptan compared to healthy subjects taking placebo (Table 29). By contrast, the mean change from baseline in QT_{cI} was statistically significantly lower in healthy subjects taking a single oral dose of either 30 mg or 300 mg Tolvaptan compared to healthy subjects taking placebo. For both single and multiple oral doses of moxifloxacin, the mean change from baseline in QT_{cI} was statistically significantly higher than in healthy subjects taking placebo.

Table 29: Mean change in QT_{cI} from mean baseline and 95% CIs.

	Mean	95% CI	P-value[a]
Day 5 Treatment			
30 mg tolvaptan	-5.02	-7.02 to -3.03	0.1151
300 mg tolvaptan	-0.74	-3.65 to 2.18	0.3786
400 mg moxifloxacin	8.20	5.89 to 10.50	<0.0001
Placebo	-2.21	-4.43 to 0.02	
Day 1 Treatment			
30 mg tolvaptan	-6.31	-8.04 to -4.58	0.0036
300 mg tolvaptan	-6.26	-8.21 to -4.30	0.0032
400 mg moxifloxacin	3.79	2.21 to 5.36	<0.0001
Placebo	-2.67	-4.23 to -1.12	

QTcI = individually corrected QT; CI = confidence interval; ANCOVA = analysis of covariance.
[a]Derived from ANCOVA with factors of treatment group and gender, and covariate baseline for least squares mean difference from placebo.

Relationship between plasma concentration and effect

In general, there was no correlation between Tolvaptan exposure ($AUC_{0\text{-}24h}$) and urine volume for 24 h post dose, and there was no correlation between Tolvaptan $AUC_{0\text{-}24h}$ and the duration that urine osmolality remained less than 300 mOsm/kg.

In Study 156-03-239, following a single oral 240 mg dose of Tolvaptan with rifampin at steady state, Tolvaptan C_{max} values were comparable to those for a 15 mg dose and AUC_t values were comparable to a 30 mg dose, but PD responses were similar to those for a 60-mg dose.

In the QT Study 156-0-245, no concentration dependence was seen for any ECG parameter following administration of Tolvaptan.

In Study 156-01-231, following 30 mg QD (once daily) and 15 mg BID (twice daily) doses of Tolvaptan tablets in patients with CHF Class II-III, there were no clinically significant differences between the two dosing regimens with regards to PD outcomes.

Pharmacodynamic interactions with other medicinal products or substances

CYP3A4 inducers

Study 156-03-239 examined the effect of 600 mg rifampin on urine volume, fluid balance and urine osmolality following a single oral 240 mg dose of Tolvaptan alone. Following a single oral 240 mg dose of Tolvaptan alone, urine volumes for 0 to 24 and 24 to 48 h post dose, fluid balance for 0 to 24 h post dose, and urine osmolality were similar to values reported previously. When rifampin was coadministered with Tolvaptan the Tolvaptan-induced changes in urine volume and fluid balance decreased compared to when Tolvaptan was given alone, and the PD parameters were similar to those reported for a single oral 60 mg dose of Tolvaptan (Table 31). For the 240 mg dose of Tolvaptan alone, urine volume excretion was maximal for all intervals from 0 to 24 h post dose, whereas,

urine volume excretion was only maximal from 0 to 8 h post dose when the two drugs were coadministered.

Table 31: Mean (SD) PD parameters following a single oral 240 mg dose of Tolvaptan alone or with Rifampin at steady state (600 mg QD) in normal healthy subjects.

Parameter	Tolvaptan Alone (N = 15)	Tolvaptan + Rifampin (N = 15)
24-Hour urine volume (mL)		
0-24 hours	12335 (2233)	8790 (8900)
24-48 hours	5133 (2571)	2958 (2075)
Fluid balance (mL)		
0-24 hours	-1559 (1355)	-1182 (1157)
24-48 hours	-269 (1478)	1157 (518)

Warfarin

Study 156-01-225 examined the effect of steady-state Tolvaptan on warfarin prothrombin time (PT), activated partial thromboplastin time (aPTT) and international normalised ratio (INR). The geometric mean ratios of the AUC_{PT}, AUC_{INF} and AUC_{aPTT} were all approximately 1, following warfarin 25 mg coadministered with multiple doses of Tolvaptan 60 mg QD compared to warfarin 25 mg alone (Tables 31-32). The ratio of geometric means with 90% confidence intervals for R-and S-warfarin range from 1.01 to 1.07.

Table 31: Summary of PD of Warfarin following single oral 25 mg Warfarin doses given with placebo or with multiple doses of Tolvaptan 60 mg QD.

	Warfarin with placebo			Warfarin with tolvaptan		
Statistics	AUCaPTT (sec·h)	AUCPT (sec·h)	AUCINR (INR·h)	AUCaPTT (sec·h)	AUCPT (sec·h)	AUCINR (INR·h)
N	23	23	23	22	22	22
Median	7882.50	3502.11	288.13	8086.47	3583.79	300.89
Mean	7975.06	3548.71	298.67	8116.99	3654.09	314.65
SD	920.96	308.60	44.34	810.05	299.71	48.02
CV%	11.6	8.7	14.9	10.0	8.2	15.3
Geo. Mean	7927.99	3535.56	295.69	8080.02	3642.85	311.51

Table 32: Ratios of geometric means with 90% CIs for Warfarin PD parameters.

	AUCaPTT	AUCPT	AUCINR
Ratio[a]	1.02	1.02	1.05
90% CI[b]	1.01-1.04	1.01-1.04	1.03-1.07

[a] Ratio of geometric means parameters for warfarin given with tolvaptan (test) to that for warfarin given alone (reference).
[b] 90% confidence interval for the ratio of the geometric means.

P-gp substrates

Study 156-01-234 examined the effects of steady-state digoxin (0.25 mg QD) on urine output following single and repeated doses of 60 mg QD in healthy subjects. Urine output and changes from baseline of urine output following a single oral dose of Tolvaptan coadministered with digoxin (Day 12) were similar to those following Tolvaptan alone (Day 1).

Other diuretics

Study 156-96-205 examined the PD interaction between Tolvaptan and furosemide and Tolvaptan and HCTZ in healthy men. The mean cumulative volume (0 to 24 h) of urine excreted increased by 98.1%, 39.3%, and 106.35% compared to baseline (Day -1) when Tolvaptan alone, furosemide alone, and both drugs were given in combination, respectively. Whereas, the mean cumulative volume of urine excreted increased by 57.3%, 32.3% and 74.7% compared to baseline when Tolvaptan alone, HCTZ alone, and Tolvaptan in combination with HCTZ were given, respectively. Mean plasma osmolality increased by 1.31% and 3.01% compared to baseline 3 h after dosing when Tolvaptan was administered alone and in combination with furosemide, respectively, whereas, when furosemide was administered alone, mean plasma osmolality increased by 0.67% compared to baseline. Mean plasma osmolality increased by 3.43% and 1.60% compared to baseline at 3 h after dosing when Tolvaptan was administered alone and in combination with HCTZ, respectively, whereas when HCTZ was administered alone mean plasma osmolality decreased by 0.67% compared to baseline. Mean urine osmolality decreased by 73.44%, 60.76% and 42.62% compared to baseline at 5 h after dosing when Tolvaptan was administered alone and in combination with furosemide, and when furosemide was administered alone, respectively. Mean urine osmolality decreased by 67.75%, 54.30%, and 8.96% compared to baseline at 5 h after dosing following administration of Tolvaptan alone and in combination with HCTZ, and when HCTZ was administered alone, respectively. Mean plasma sodium concentration increased by 2.37% and 2.96% compared to baseline 6 h after dosing following administration of Tolvaptan alone and in combination with furosemide, respectively: when furosemide was administered alone, mean plasma sodium concentration decreased by 0.94% compared to baseline 6 h after dosing. Mean plasma sodium concentration increased by 3.33%, 2.37%, and 0.36% compared to baseline at 6 h after dosing when Tolvaptan was administered alone and in combination with HCTZ, and when HCTZ was administered alone, respectively. Mean urine sodium concentration decreased by 77.68%, 86.34% and 72.60% compared to baseline at 7 h after dosing when Tolvaptan was administered alone and in combination with furosemide and when furosemide was administered alone, respectively. Mean urine sodium concentration decreased by 81.88% 53.74% and 17.81% compared to baseline at 7 h after dosing following administration of Tolvaptan alone and in combination with HCTZ, and when HCTZ was administered alone, respectively. Mean plasma AVP concentration increased by 212.1%, 419%, and 6.4% compared to baseline at 4 h following administration of Tolvaptan alone and in combination with furosemide, and when furosemide was administered alone, respectively. Whereas, mean plasma AVP concentration increased by 106% and 92.3% compared to baseline 4 h following administration of Tolvaptan and in combination with HCTZ, respectively. Mean plasma AVP concentration decreased by 17.7% compared to baseline at 4 h after dosing when HCTZ was administered alone. The mean renin activity increased by 30.72%, 457.72%, and 238.90% compared to baseline at 24 h after dosing when Tolvaptan was administered alone and in combination with furosemide and when furosemide was administered alone, respectively. Whereas, the mean renin activity increased by 24.56%, 222.19%, and 233.69% compared to baseline at 24 h after dosing when Tolvaptan was administered alone and in combination with HCTZ, and when HCTZ was administered alone, respectively. The finding that Tolvaptan potentiated the increase in renin activity seen with furosemide is of great clinical significance as hypertension and CHF have been associated with increased renin activity.

Genetic differences in pharmacodynamic response

Study 156-03-242 compared the PD effects of 30 mg Tolvaptan in healthy Japanese and Caucasian men under fasted conditions, following a high fat meal and JSM. Following administration of 30 mg Tolvaptan in either the fasted state or immediately following a

HFM or JSM, mean change from baseline for 24 h urine volumes ranged from 4445 to 5445 mL for both Japanese and Caucasian subjects (Table 33). By contrast, mean fluid balance (fluid intake urine output) was more negative for Japanese subjects (range -1167 to -1577 mL) than Caucasian subjects (range -638 to -831 mL). Therefore, suggesting that Japanese subjects did not increase their fluid intake to the same level as Caucasian subjects following Tolvaptan administration.

Table 33: Mean (SD) change from baseline in 24 h urine volume and fluid balance for Japanese and Caucasian subjects.

Parameter	Fasted	High-fat Meal	Japanese Standard Meal
Japanese Subjects (n=24)			
Urine Volume (mL)	4570 ± 1791	5445 ± 2073	5212 ± 2023[a]
Fluid Balance (mL)	-1167 ± 838	-1265 ± 1014	-1577 ± 1301[a]
Caucasian Subjects (n=23)			
Urine Volume (mL)	4445 ± 1774	5283 ± 1752	4936 ± 1938
Fluid Balance (mL)	-831 ± 663	-638 ± 1348	-799 ± 1178

SD = standard deviation

[a] n=22

Although no studies examined the effects of CYP mutations on the PD of Tolvaptan it should be assumed, as Tolvaptan is primarily metabolised by CYP3A4/5, that patients with known mutations in this isoenzyme may require dose adjustment.

Evaluator's overall conclusions on pharmacodynamics

- In general, administration of Tolvaptan induced: statistically significant and dose dependent increases in urine volume, even in the presence of loop diuretics, leading to statistically significant decreases in body weight in subjects with CHF; statistically significant decreases in urine osmolality and variable decreases in urine sodium concentration; and increases in serum sodium concentration, which occurred slowly and which generally did not exceed the upper limit of the normal range. Increases in serum sodium levels were maintained for the duration of treatment in subjects who were hyponatremic at baseline. However, in subjects with normal sodium levels, the increases were transient and sodium concentrations returned to baseline levels over a period of 2 to 4 weeks.
- The average urine volume excreted in the first 12 h following Tolvaptan administration was 7 litres. Although urine volume increased dose dependently, it did not increase linearly with dose and urine excretion rate and free water clearance plateaued at doses of 180 mg Tolvaptan.
- In Study 156-00-221, which examined the effect of Tolvaptan on renal function in subjects with CHF, Tolvaptan significantly increased effective renal plasma flow (9%) and renal blood flow (10%) compared to placebo and furosemide. In addition, glomerular filtration rate increased (1.37 mL/min) and renal vascular resistance decreased (-1.54 mmHg/dL) compared to placebo.
- There were no significant age/gender interactions for the pharmacodynamic parameters AVP, plasma renin activity, and urine osmolality.
- In Study 156-03-239, following a single oral 240 mg dose of Tolvaptan with rifampin at steady state, Tolvaptan C_{max} values were comparable to those for a 15 mg dose and AUC_t values were comparable to a 30 mg dose, whereas, PD responses were similar to those for a 60 mg dose.

- Coadministration of Tolvaptan had no effect on PD of warfarin and coadministration of digoxin with Tolvaptan had no affect on urine output.
- Tolvaptan acted synergistically with furosemide and significantly potentiated the increase in renin activity seen following administration of furosemide alone. This effect may be of clinical significance as hypertension and CHF have been associated with increased renin activity; therefore, dose adjustment may be required if the two diuretics are to be coadministered.
- In Study 156-03-245, 30 or 300 mg Tolvaptan QD for 5 days had no effect on maximum time matched mean change from baseline in individually corrected QTc.
- Although no studies examined the effects of CYP mutations on the PD of Tolvaptan it should be assumed, as Tolvaptan is primarily metabolised by CYP3A4/5, that patients with known mutations in this isoenzyme may require dose adjustment.

Efficacy

Introduction

The efficacy of Tolvaptan in the treatment of hyponatremia was evaluated in three Phase 3 hyponatremia trials (two pivotal trials [156-02-235 and 156-03-238], one open label trial [156-03-244]), and two Phase 2 hyponatremia trials (156-96-203 and 156-97-204). An additional Phase 2 hyponatremia trial [156-96-201] was stopped due to lack of enrolment. There were six heart failure trials having subpopulations of hyponatremic 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 subgroup of hyponatremic patients from the CHF studies were evaluated as supportive data.

All of these trials were of a randomised, double blind, multiple dose, placebo controlled design with the exception of the open label Phase 3 hyponatremia trial and an open label active controlled (fluid restriction with placebo) Phase 2 hyponatremia trial (156-97-204 which was terminated due to poor enrolment). All were multicentre trials conducted exclusively in the US (hyponatremia trials 156-02-235, 156-96-203, 156-97-204 and heart failure trials 156-97-251, 156-97-252, 156-01-232) or multinationally in the US and Argentina (heart failure trials 156-98-213, 156-00-220), in the US, Canada, and Europe (hyponatremia trials 156-03-238, 156-03-244), or in the US, Canada, South America, Europe, and Russia (CHF trial 156-03-236).

All hyponatremia 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). Titrated regimens of Tolvaptan from 15 mg to 30 or 60 mg were used in the three Phase 3 trials (156-02-235, 156-03-238, and 156-03-244), and from 10 mg to 15, 30, 45, or 60 mg in the remaining Phase 2 trial (156-97-204). These trials employed a dose titration scheme to achieve a slow correction of serum sodium concentrations over the first few days of therapy, as well as to provide flexibility of dosing at the investigator's discretion during the remainder of therapy.

Dose-response and main clinical studies failure trials

Dose response studies

The Phase 2, randomised, double blind, placebo controlled, dose ranging sequential Study 156-96-201 was discontinued after completion of the first treatment period (Tolvaptan 5mg) due to declining enrolment. Daily dose of Tolvaptan 5mg (for 4 days) showed no

significant effects on plasma sodium concentration (primary efficacy variable) or the secondary endpoints of urine osmolality, urine volume and body weight.

The Phase 2, randomised, open label, active controlled (fluid restriction to <1200ml/day and placebo), dose titration efficacy and safety Study 156-97-204 in 28 patients with euvolemic/ hypervolemic hyponatremia was also discontinued prematurely due to very slow enrolment of subjects and protocol specified statistical analyses for efficacy were not done. Patients were started with lowest 10 mg dose and dosing continued on subsequent days using incrementally higher doses (15, 30, 45, and 60 mg) as needed.

Patients in the Tolvaptan groups had higher increases from baseline in mean serum sodium levels than the fluid restriction group for up to Day 5 during the titration phase, and also had numerically higher increases in mean serum sodium levels in the remainder of the titration period. At the last visit, the mean increases in serum sodium levels were 5.73 and 1.00 mEq/L for the Tolvaptan and fluid restriction groups, respectively. During the maintenance phase and follow up, mean increases from baseline in serum sodium levels were similar between the Tolvaptan and fluid restriction groups for up to Days 13/14; and the increases were higher for patients in the Tolvaptan group thereafter. The mean increases in serum sodium levels at the last visit were 9.5 and 9.0 mEq/L for the Tolvaptan and fluid restriction groups, respectively. Compared to the patients in the fluid restriction group, greater percentages of patients in the Tolvaptan group had normalised serum sodium levels during titration phase (73.3% versus 30%) and the maintenance/follow up period (91.7% versus 50%). Mean increases from baseline in serum osmolality during the titration period were slightly greater in the Tolvaptan group compared to the fluid restriction group (mean increase at last visit was 9.38 and 3.50 mOsm/kg for the Tolvaptan and the fluid restriction groups, respectively). Patients in the Tolvaptan group had greater mean total fluid intake and fluid loss than patients in the fluid restriction group; at the last visit, the mean total fluid intake and fluid loss for the Tolvaptan treated patients were 1558.87 mL and 1446.53 mL, respectively. In contrast, the mean total fluid intake and fluid loss for patients in the fluid restriction group at the last visit were 604.8 and 478.9 mL, respectively. No statistically significant differences in the mean total fluid balance were seen between the two treatment groups. Mean thirst scale scores were comparable between the two groups during the titration phase.

Comments: Overall, results from this study showed that Tolvaptan (10-60mg) was more effective than fluid restriction therapy in increasing serum sodium levels during the titration phase. The small numbers of patients in the maintenance/ follow up phase for the fluid restriction group (n=2) precluded meaningful interpretation of effects beyond the initial titration phase. Furthermore, details regarding exposure to each dose of Tolvaptan were not provided in the study report. Hence, results from this study did not provide any information regarding dose-response of Tolvaptan.

Study 156-96-203 was a Phase 2, multicentre, randomised, double blind, placebo controlled, dose ranging trial to assess the efficacy, safety, and pharmacokinetic characteristics of daily doses (for 13 days) of up to five dosage levels (5, 10, 15, 30, and 60 mg QD) of Tolvaptan in 45 subjects with hyponatremia secondary to liver disease. The following criteria were to be met on each of the possible 13 days of treatment in order for dose escalation to occur:

1. The rate of correction did not exceed 8 mEq/L for any 4 h period in more than two patients;
2. the overall increase in plasma sodium did not exceed 15 mEq/L within the 23-h period following dosing in more than two patients;
3. at no time after dosing did the absolute value of plasma sodium exceed 145 mEq/L in more than two patients;

4. the absolute value of plasma potassium at any time after dosing did not exceed 6 mEq/L in more than two patients; and
5. the Tolvaptan plasma concentration did not exceed maximum levels observed in previous phase 1 trials.

Tolvaptan, at doses of 5, 10, 15, 30, and 60 mg QD resulted in higher mean increases in plasma sodium compared to placebo. Although the 60 mg dose seemed to produce the greatest increase while the 5 mg dose showed smallest increase in plasma sodium concentration, the significant variability of results precluded any definite interpretation regarding dose response. Tolvaptan at doses of 30 and 60 mg was associated with consistently greater body weight loss compared to placebo, although this was not evident after Day 5; however, at doses of 5, 10, and 15 mg body weight loss was inconsistent. Tolvaptan treated patients generally had lower urine osmolality than placebo treated patients. At all doses, Tolvaptan caused increases from baseline in urine volume. There were no clinically significant differences in fluid intake between the treatment groups. Patients treated with Tolvaptan experienced a net loss in fluid balance over Days 1 to 4, while patients treated with placebo experienced net fluid gains. The magnitude of fluid loss was greatest in patients treated with Tolvaptan 30 mg and 60 mg. No clinically significant changes in plasma potassium were observed.

Comments: Tolvaptan showed some evidence of increasing serum sodium levels in treatment of hyponatremia secondary to liver disease which was supported by its effect on body weight, urine volume, fluid intake and plasma potassium. The effect of Tolvaptan on serum sodium showed no consistent dose related trends, although small number of subjects and considerable variability may have confounded interpretation.

Main (Pivotal) studies

There were two Phase 3 pivotal hyponatremia studies with similar study design and endpoints**:** Studies 156-02-235 and 156-03-238, also called SALT[10] 1 and 2 studies, respectively.

Study design and patient population

Methods: Both Studies 156-02-235 and 156-03-238 were Phase 3, multicentre, randomised, double blind, placebo controlled, pivotal efficacy and safety studies to evaluate the effects of oral Tolvaptan as adjunct to standard therapy in subjects with non acute hyponatremia in euvolemic or hypervolemic states.

Inclusion/exclusion criteria: The main inclusion criteria were age ≥18 years and Hyponatremia in euvolemic[11] or hypervolemic[12] states, defined as serum sodium level <135 mEq/L prior to randomisation. The main exclusion criteria were:

- Hyponatremia in hypovolemic[13] states, acute and transient hyponatremia associated with head trauma or postoperative state;

[10] SALT: **S**odium **A**ssessment With Increasing **L**evels of **T**olvaptan in Hyponatremia.

[11] Euvolemia was defined as absence of clinical and historical evidence of extracellular fluid volume depletion or sequestration, and absence of edema and ascites.

[12] Hypervolemia was defined as excess extracellular fluid volume manifesting as dependent edema or ascites.

[13] Hypovolemic hyponatremia was defined as the presence of clinical and historical evidence of extracellular fluid volume depletion. Examples of clinical hypovolemic hyponatremia states included conditions where restoration of plasma volume resulted in correction and maintenance of normal plasma sodium concentration or those associated with critically low central venous pressure (< 5 cmH_20) or pulmonary capillary wedge pressure (< 5 mmHg); but did not include

- Hyponatremia due to uncontrolled hypothyroidism or uncontrolled adrenal insufficiency; pregnant/breastfeeding women (or women of childbearing age not using adequate contraception);
- Cardiac surgery or history of MI (myocardial infarction) within 30 days of potential study enrolment, excluding percutaneous coronary interventions;
- History of sustained ventricular tachycardia or ventricular fibrillation within 30 days, unless in the presence of an automatic implantable cardioverter defibrillator;
- Severe angina including angina at rest or at slight exertion and/or unstable angina; History of a cerebrovascular accident within the last 30 days;
- Subjects with psychogenic polydipsia (subjects with other psychiatric illness could have been included);
- Systolic arterial blood pressure < 90 mmHg;
- History of hypersensitivity and/or idiosyncratic reaction to benzazepine or benzazepine derivatives (such as benazepril);
- History of drug or medication abuse within the past year, or current alcohol abuse;
- Uncontrolled diabetes mellitus defined as fasting glucose >300 mg/dL;
- Urinary tract obstruction (except benign prostatic hyperplasia if non obstructive);
- Participation in another clinical drug trial within the past 30 days, or any other Tolvaptan clinical trial;
- Terminally ill or moribund condition with little chance of short term survival;
- Serum creatinine >3.5 mg/dL;
- Haemoglobin <9 mg/dL;
- Serum sodium level <120 mEq/L, with associated neurologic impairment, that is, symptoms such as apathy, confusion, seizures;
- Subjects with progressive or episodic neurologic disease such as multiple sclerosis or history of multiple strokes;
- Child-Pugh score >10 (Subjects with higher scores could have been enrolled if they had been stable for 30 days);
- Subjects receiving IV fluids at a rate greater than “keep vein open”;
- Hyponatremia due to laboratory artefacts (for example, high glucose level >300 mg/dL) - Subjects with prior normal and borderline sodium levels should have been confirmed prior to randomisation;
- Subjects who received AVP or its analogues for treatment of any condition;
- Subjects who received other medications for treatment of hyponatremia within 7 days of randomisation, specifically demeclocycline, lithium carbonate, or urea;
- Subjects who were likely to require or receive IV saline for correction of symptomatic or asymptomatic severe hyponatremia during the course of the study;
- Subjects with severe pulmonary artery hypertension (that is, subjects whose condition was expected to deteriorate with sudden shifts in fluid volumes and pressures); and

conditions such as CHF or cirrhosis where there was evidence of fluid overload (for example, ascites or dependent edema) despite an inappropriate homeostatic response to perceived intravascular volume depletion.

- Hyponatremia as the result of any medication that could safely be withdrawn (examples of drugs often not withdrawn include: anticonvulsants [for example, carbamazepine] and antipsychotics [for example, haloperidol]).

Comments: Chronicity of hyponatremia was not a criterion for study entry; subjects with acute, subacute, or chronic hyponatremia were enrolled, although subjects with acute hyponatremia associated with head trauma or post operative states were excluded. There was no lower limit for serum sodium concentration at study entry, except that subjects with serum sodium concentrations <120 mEq/L were excluded if there was evidence of neurological impairment. These criteria tended to select subjects with mild or moderate hyponatremia, who were not symptomatic, or at least not sufficiently symptomatic to require lV saline. Subjects with more severe hyponatremía (sodium <120 mEq/ L) could be enrolled, but had to be relatively symptom free in order to gain study entry.

Treatments: Subjects who met inclusion and exclusion criteria were randomised to either placebo or 15 mg Tolvaptan. Study drug could be titrated, depending on the subject's serum sodium levels. For subjects randomised to receive 15 mg Tolvaptan, dose titration to 30 mg and then 60 mg of study drug occurred if the subject's change in serum sodium level was < 5 mEq/L from the previous day's measurement and was <135 mEq/L. Titration to the next dose did not occur if the subject's serum sodium level was >135 mEq/L or the change in serum sodium level was > 5 mEq/L from the previous day's measurement. Depending on the subjects' clinical condition, the option of initiating fluid restriction (all fluids) for subjects with serum sodium level <130 mEq/L to 1 L/day was available at the investigator's discretion. If possible, fluid restriction was to be withheld for at least the first 24 h in order to determine the rate and magnitude of serum sodium change. Subjects who were randomised during a hospitalisation remained in the hospital or inpatient observational unit after Day 1 until the investigator determined that the subject could be discharged. Once discharged, the subject returned for outpatient visits on a weekly basis until a total of 30 days of treatment was completed. Outpatients could also have been randomised into the trial if they were willing to be admitted for the first dosing day. Subjects were required to stay overnight in an observational unit or hospital for at least 24 h on Day 1.

Study drug was administered orally at approximately 0900 h (dosing was acceptable between 0700 and 1100 h). No requirements for dosing with respect to food were specified. Treatment compliance was ensured by watching the subject take his/her study medication. For nonclinic days, compliance was assessed by the number of tablets remaining when the subject returned the blister card at the next visit. This information was recorded on the appropriate CRF (Case Report Form) and on the Drug Accounting Form. During the study treatment period, subjects continued their current medications, and were offered standard therapies for hyponatremia as clinically indicated. Medications that were prohibited seven days prior to and during the study were Demeclocycline, Lithium carbonate, Urea, and IV saline (only during the study).

Randomisation/blinding: Randomisation was performed in a 1:1 ratio (Tolvaptan 15 mg or placebo) according to a computer generated randomisation schedule, using random permuted block principle and 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 etiology representing more than 50% of the subjects. A centralised randomisation was used to maintain the overall randomisation ratio of 1:1 (irrespective of the centre). Subjects in each treatment group received Tolvaptan or matching placebo in a randomised, double blinded fashion. 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.

Comments: It is not clear how titration was handled in the placebo group, that is, a greater fraction of subjects in the placebo group would have required upward titration of the dose, which could have led to unblinding

Outcomes/endpoints

The primary efficacy variable was serum sodium level and the primary efficacy endpoints were average daily AUC of change from baseline in serum sodium level up to Day 4 and Day 30 within the double blind treatment period. The secondary efficacy endpoints were:

- average daily AUC of change from baseline in serum sodium level up to Day 4 and Day 30 within the double blind treatment period for subjects with severe hyponatremia (serum sodium level < 130 mEq/L at baseline);
- percentage of subjects with normalised serum sodium level at Day 4 and at Day 30;
- time to first normalisation in serum sodium level;
- change from baseline in serum sodium level at Day 4 and at Day 30;
- percentage of subjects requiring fluid restriction at any time during the double blind treatment period;
- urine output at Day 1;
- change from baseline in body weight at Day 1 (hypervolemic subjects only);
- fluid balance (urine output minus fluid [oral or IV] intake) at Day 1(hypervolemic subjects only);
- change from baseline in the SF-12 (health survey) PCS (Physical Component Summary) and MCS (Mental Component Summary) scales at Week 1 and Day 30;
- categorical change in serum sodium level at Day 4 and Day 30 for subjects with baseline serum sodium level < 130 and ≥130 mEq/L;
- percentage of subjects who were designated as treatment failures due to the need for saline infusion, with or without fluid restriction.

In the two pivotal Phase 3 trials 156-02-235 and 156-03-238, neurological examinations[14] were performed as an exploratory efficacy endpoint.

Sample size and statistical methods

It was estimated that a sample size of 100 subjects per treatment group would yield more than 90% power, at a significance level of 0.025 (two sided), to detect a treatment effect of 1.99 at Day 4 using a two sample t test (SD = 2.7) and a treatment effect of 3 for the comparison at Day 30 at a significance level of 0.025 (two sided), with SD = 3.28. The sample size of 50 subjects with severe hyponatremia (baseline serum sodium level < 130 mEq/L) per treatment group would yield more than 90% power, at a significance level of 0.05 (two sided), to detect a treatment effect of 1.99 at Day 4 using a two sample t test (SD = 3.06) and a treatment effect of 3 for the comparison at Day 30 at a significance level of

[14] The neurological examination included assessment of the following: level of consciousness, ophthalmic examination, facial motor, dysarthria, reflexes, muscle strength, muscle tone, ataxia, tremor, and stance, gait, and coordination. (Assessments of stance, gait, and coordination were included as an amendment to protocol 156-02-235; therefore, these data are not available for all subjects.) The examination was performed at Day 1 (predose); Day 4 (predose) (Trial 156-03-238), Discharge Day (postdose) (Trial 156-02-235); postdose at Weeks 1, 2, and 3 (Week 2 only in Trial 156-03-238); Day 30/ET; and at the 7 day follow up visit.

0.05 (two sided), with SD = 3.63. The analysis for this subgroup was secondary, so no adjustments in the nominal significance level of 0.05 were made. The estimates of SDs used in the sample size estimation described above were obtained from a limited amount of data from small Phase 2 studies that utilised local laboratories in the assessment of serum sodium level and may have lacked precision. In order to ensure that the SDs were not severely underestimated, the protocol allowed for a reestimation of SDs based on blinded data at a time when approximately 50% of the subjects recruited completed the study. If these estimates were much larger than the original SDs used in sample size estimation, sample sizes were planned to be reestimated in a blinded fashion. This sample size reestimation was performed on 7 September 2004 using blinded data of the first 100 subjects. It called to increase the sample size from 100 to 110 for the variable of average AUC up to Day 30 of the severe hyponatremia population, to maintain 90% power for a delta of 3 with a SD of 4.85 (compared to the SD of 3.63 used originally), and a two sided alpha 0.05. For the other endpoints (average AUC up to Day 4 and average AUC up to Day 30 for the ITT (intention to treat) population, and average AUC up to Day 4 of the severe hyponatremia population), the originally proposed sample sizes (200 subjects and 100 subjects, respectively) remained adequate to provide 90%. However, based on the efficacy and safety results of the unblinded Study 156-03-238 in which the efficacy results suggested a larger than expected effect size, the sponsor terminated enrolment in the current study on 25 October 2005, when the total randomised sample size reached 205, exceeding the originally planned sample size of 200 subjects. Following reestimate, the sample size of 167 subjects was adequate to provide at least 90% power for the primary efficacy variables (daily average AUC up to Day 4 and daily average AUC up to Day 30 of the ITT population), and 90 severe hyponatremia subjects were adequate to provide 88% power for the variable of daily average AUC up to Day 4 of the severe hyponatremia population and 83% power for the variable of daily average AUC up to Day 30 of the severe hyponatremia population.

The primary efficacy analysis was performed on the restricted ITT data set using an analysis of covariance (ANCOVA) model with factors of treatment, baseline disease severity and origin, and baseline serum sodium level as covariate. In order to control the overall nominal significance level at 0.05 in the test of these two comparisons, the Hochberg procedure was applied.[15] For secondary endpoints of average AUC of change from baseline in serum sodium level up to Day 4 and Day 30 were analysed similarly to the primary analyses, except that the severe hyponatremia subgroup of the restricted ITT data set was used, only disease origin was used as a factor in the ANCOVA, and no correction for multiple comparisons was made, that is, each comparison was tested at the 0.05 level. The Cochran-Mantel-Haenszel test, stratified by baseline disease severity and origin (using last observation carried forward (LOCF) and observed case (OC) data) was used for analysis of percentage of subjects: with normalised serum sodium[16] level at Day 4 and Day 30, requiring fluid restriction and considered treatment failures due to need for IV saline. The log-rank test was used for variable of time to first normalisation in serum sodium level.[17] Changes from baseline of PCS and MCS scales were analysed using an ANCOVA model with treatment, baseline disease severity, and origin as factors and baseline score

[15] In particular, if both p values were smaller than 0.05, significance was declared for both comparisons. If the larger p value was not less than 0.05, but the smaller p value was less than 0.025, significance was declared for the comparison corresponding to the smaller p value.

[16] Normalised serum sodium level was defined as serum sodium level > 135 mEq/L.

[17] Time to first normalisation in serum sodium = date of first normalization - date of randomisation + 1. Subjects without normalisation in serum sodium level during the double blind treatment period were considered censored, with time to censor = date of the last observation on serum sodium while on therapy - date of randomisation + 1.

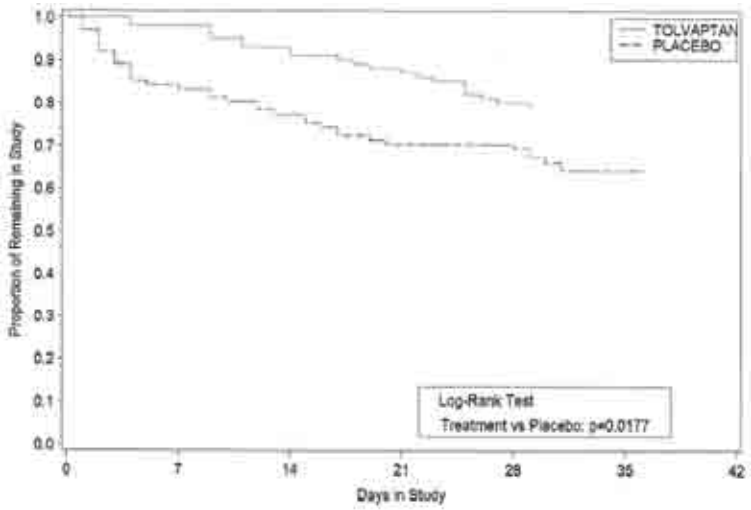
as covariate, at Week 1 and Day 30, respectively (using both LOCF and OC data). The SF-12 PCS and MCS were planned to be analysed as part of a separately reported meta analysis with data from Study 156-03-238.

Results of pivotal Study 156-02-235

This study was conducted from 11/4/2003 to 20/12/2005 at 42 centres in the United States.

Subject disposition: Of the 205 randomised subjects (103 Tolvaptan and 102 placebo), 100 subjects were treated in the Tolvaptan group and 101 subjects were treated in the placebo group. A total of 79/102 (77.5%) subjects in the Tolvaptan group completed the study, as did 65/103 (63.1%) subjects in the placebo group. Approximately 71% (72/102) of Tolvaptan treated subjects and 54% (56/103) of placebo treated subjects completed 28 or more days in the study. The overall incidence of discontinuations was higher in the placebo (38/103, 36.9%) group compared with Tolvaptan (23/102, 22.5%) with AE (adverse event) and withdrawal of consent being the most common reasons for discontinuation in both treatment groups. The rate of discontinuation was not much different in Tolvaptan treated subjects when analysed by baseline severity of hyponatremia, but for placebo treated subjects, it was slightly increased in the 'severe hyponatremia' group; discontinuation rate in the 'mild hyponatremia' subgroup were (placebo versus Tolvaptan) 31.4% versus 20.4%, while those in the 'severe hyponatremia' group were 42.3% versus 24.5%. The difference between the Tolvaptan group and the placebo group for time to discontinuation due to all reasons was statistically significant in favour of Tolvaptan (p= 0.0177) (Figure 5).

Figure 5: Kaplan-Meier curves for time to discontinuation due to all reasons.



Numbers analysed: Overall, 190 subjects (97 in the Tolvaptan group and 93 in the placebo group) qualified for the ITT population, defined as all randomised subjects (excluding subjects from Centres 004 and 006). A total of 184 subjects (95 in the Tolvaptan group and 89 in the placebo group) were analysed for efficacy and qualified for the primary efficacy population (the restricted ITT population).[18]

Protocol deviations and treatment compliance: Clinically significant protocol deviations were reported for 184/205 (89.8%) subjects. For clinically significant protocol deviations, 159/205 (77.6%) subjects had procedural deviations, 88/205 (42.9%) subjects had dosing deviations, 22/205 (10.7%) subjects had entry criterion deviations,

[18] Restricted ITT dataset defined as all subjects who were randomised, treated, and had both a baseline and at least one postbaseline serum sodium assessment within the double blind treatment period (excluding subjects from Centres 004 and 006 due to unreliable data).

and 79/205 (38.5%) subjects had "other" deviations with similar incidence in Tolvaptan and placebo groups.

Overall, 92/100 (92%) of subjects in the Tolvaptan group were ≥ 90% compliant with study medication, compared with 86/101 (85.1%) of subjects in the placebo group. According to drug accountability records, only 4/201 (2.0%) subjects were < 70% compliant with study medication, one in the Tolvaptan group and 3 in the placebo group.

Baseline demographics and disease characteristics:

Overall, 126/243 (51.9%) randomised subjects had mild hyponatremia and 117/243 (48.1%) had severe hyponatremia. A total of 128/205 (62.4%) subjects were euvolemic with SIADH/other in 90/205 (43.9%), 30/205 (14.6%) had CHF and 16/205 (7.8%) had liver cirrhosis (alcohol use=12/16). Overall, 75/205 (36.6%) subjects were hypervolemic with SIADH/other in 8/205 (3.9%), 44/205 (21.5%) had CHF and 30/205 (14.6%) had liver cirrhosis (alcohol use=16/30; hepatitis C=10/30). The incidence of hypervolemic state was slightly higher in the Tolvaptan group compared with placebo (40.2% versus 33%) (Table 34). Additionally, there were more subjects receiving diuretics in the Tolvaptan group (66/97, 68.0%) than in the placebo group (52/93, 55.9%).

Table 34: Hypnotraemia history.

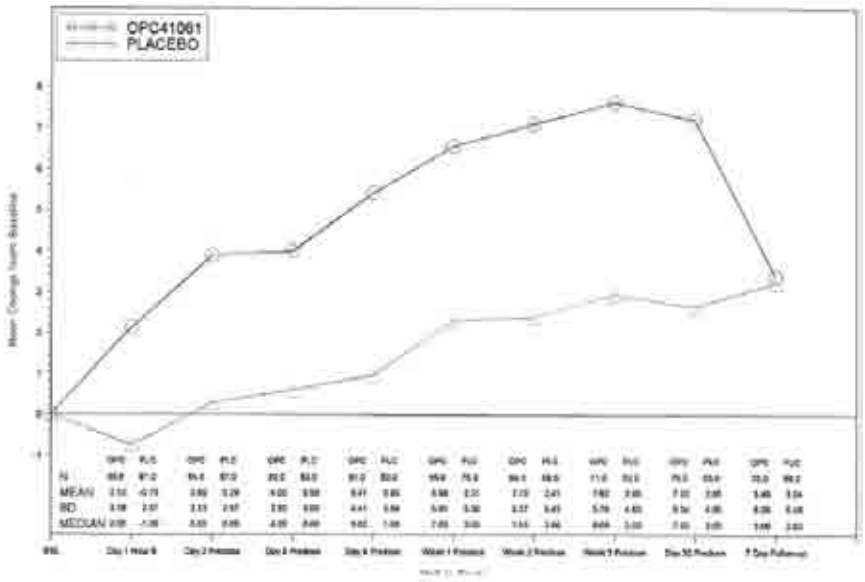
Characteristic	Tolvaptan (N = 102) n (%)	Placebo (N = 103) n (%)	Total (N = 205) n (%)
Child-Pugh Classification			
Normal	46 (45.1)	43 (41.7)	89 (43.4)
Grade A	23 (22.5)	16 (15.5)	39 (19.0)
Grade B	22 (21.6)	28 (27.2)	50 (24.4)
Grade C	8 (7.8)	8 (7.8)	16 (7.8)
Euvolemic	61 (59.8)	67 (65.0)	128 (62.4)
SIADH	22 (21.6)	22 (21.4)	44 (21.5)
CHF	15 (14.7)	15 (14.6)	30 (14.6)
Liver cirrhosis	8 (7.8)	8 (7.8)	16 (7.8)
Other[a]	18 (17.6)	28 (27.2)	46 (22.4)
Hypervolemic	41 (40.2)	34 (33.0)	75 (36.6)
SIADH	5 (4.9)	3 (2.9)	8 (3.9)
CHF	23 (22.5)	21 (20.4)	44 (21.5)
Liver cirrhosis	17 (16.7)	13 (12.6)	30 (14.6)
Other[a]	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic encephalopathy grade			
Grade 0	95 (93.1)	95 (92.2)	190 (92.7)
Grade I	6 (5.9)	5 (4.9)	11 (5.4)
Grade II	1 (1.0)	0 (0.0)	1 (0.5)
Grade III	0 (0.0)	0 (0.0)	0 (0.0)
Grade IV	0 (0.0)	0 (0.0)	0 (0.0)

[a]Other includes subjects who could not be allocated to any of the 3 primary hyponatremia etiology groups (SIADH, CHF, or cirrhosis).

Primary efficacy results: Tolvaptan group showed a statistically significant ($p < 0.0001$) greater increase in the average daily AUC of change from baseline in serum sodium level from the start of treatment to Day 4 (treatment difference: 3.41 mEq/L; 95% CI: 2.75, 4.02) and to Day 30 (4.57 mEq/L; 95% CI: 3.64, 5.5). Changes from baseline in serum sodium level by visit showed that highly statistically significant improvements in serum sodium levels were observed in the Tolvaptan group compared to placebo within 8 h after initiating treatment, and persisted throughout the treatment period. Loss of efficacy on

discontinuation of treatment was seen only in the Tolvaptan group; improvements over placebo in serum sodium levels observed during treatment were no longer seen at the 7 day follow up evaluation (Figure 6).

Figure 6: Mean change from baseline in serum sodium level (mEq/L) by visit – ITT (observed cases).

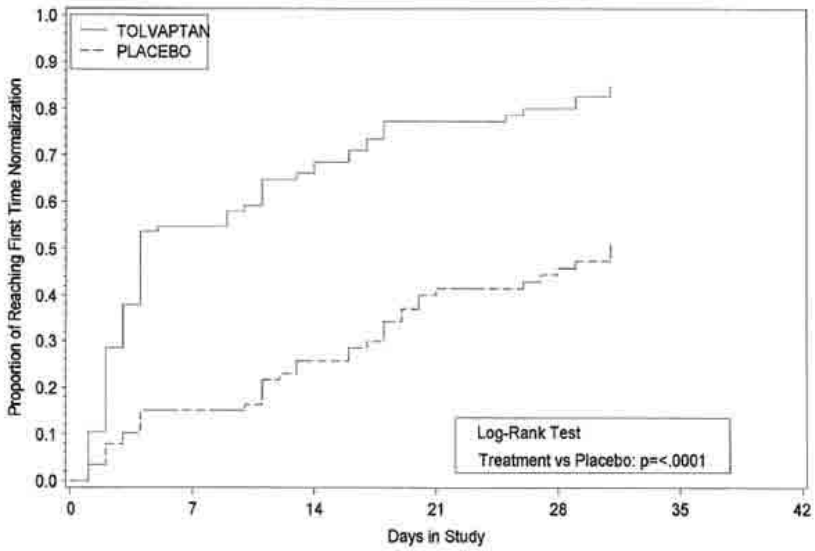


OPC = tolvaptan; PLC = placebo

Secondary efficacy results: In severe hyponatremia subjects, the Tolvaptan group showed a statistically significant ($p < 0.0001$) increase in the average daily AUC of change from baseline in serum sodium level from the start of treatment to Day 4 (diff= 3.88 mEq/L; 95% CI: 2.93, 4.84), and to Day 30 (5.64 mEq/L; 95% CI: 4.23, 7.05). Similar statistically significant ($p < 0.0001$) improvements in the Tolvaptan group compared to the placebo group were observed for the mild hyponatremia subgroup at Day 4 (2.92 mEq/L; 95% CI: 2.02, 3.82) and Day 30 (3.43 mEq/L; 95% CI; 2.28, 4.59).

The percentage of subjects with normalised serum sodium level was statistically significantly ($p <0.0001$) greater in the Tolvaptan group compared with placebo at Day 4 (40.0% versus 13.4%) and at Day 30 (52.6% versus 24.7%). The percentage of subjects with normalised serum sodium level was statistically significantly greater in the Tolvaptan group compared to the placebo group for both the mild and severe hyponatremia subgroups at Day 4 and Day 30. At each visit, the percentage of subjects with normalised serum sodium levels was statistically significantly greater in the Tolvaptan group (ranging from 12.3% to 53.6%) compared to placebo (3.7% to 24.7%) using LOCF analysis and the ITT population. In the severe hyponatremia subgroup, the percentage of subjects with normalised serum sodium levels was statistically significantly greater in the Tolvaptan group (6.2% to 50.9%) compared to placebo (0% to 19.1%) at all visits except for Day 1, Hour 8. Tolvaptan treated subjects were 3.0, 3.3 and 3.4 times more likely than placebo treated subjects to have normalised serum sodium levels at any point in time ($p <0.0001$) for the ITT population, mild and severe hyponatremia subgroups, respectively (Figure 7). The shift to normalised serum sodium levels was rapid and highly statistically significant for Tolvaptan versus placebo; however, it was accompanied by relatively few episodes of too rapid serum sodium correction.

Figure 7: Kaplan-Meier curves for time to first normalisation in serum sodium level (greater than 135 mEq/L) – ITT population.



Statistically significant increases from baseline to Day 4 and Day 30 in serum sodium level were observed in the Tolvaptan group compared to placebo for the ITT population (4.45 and 4.86 mEq/L at day 4 and day 30, respectively), mild hyponatremia (3.61 and 2.92 mEq/L, respectively) and severe hyponatremia subgroups (5.24 and 6.61 mEq/L, respectively).

For 'subjects with fluid restriction added during treatment'[19], fewer Tolvaptan treated subjects required fluid restriction than did placebo treated subjects; although the difference was not statistically significant, a positive trend was observed for the ITT population (p = 0.0764) and the severe hyponatremia subgroup (p = 0.0758). For 'subjects on any fluid restriction during treatment'[20], the percentage of subjects requiring fluid restriction was statistically significantly lower in the Tolvaptan group (19/96, 19.7%) than in the placebo group (29/91, 31.8%) (p = 0.0246), but the differences between treatment groups were not statistically significant for the mild or severe hyponatremia subgroups.

The 'mean urine output at Day 1'[21] was statistically significantly ($p \leq 0.0025$) greater for the Tolvaptan group than the placebo group for all 3 populations tested (ITT: Tolvaptan placebo LS mean diff=1142 mL; mild hyponatremia: 1135 mL; severe hyponatremia: 1148 mL). In hypervolemic patients, mean body weight was changed by -1.03 kg in the Tolvaptan group compared to the placebo group in the ITT population (p = 0.0415); however, no statistically significant changes from baseline to Day 1 in body weight were observed for Tolvaptan compared to placebo in mild hyponatremia group (by -0.81 kg)

[19] A subject on "fluid restriction added during treatment" was defined as one who had no baseline fluid restriction, but had fluid restriction imposed during the double blind treatment period of the study. This definition treated all subjects who had baseline fluid restriction as subjects who did not require fluid restriction during the double blind treatment period.

[20] A subject on "any fluid restriction during treatment" was defined as one who had no baseline fluid restriction, but a fluid restriction imposed during the double blind treatment period, or one who had fluid restriction imposed at baseline and maintained fluid restriction throughout the double-blind treatment period.

[21] There was no baseline 24 h urine collection in this study. At Day 1 all Tolvaptan treated subjects were receiving the 15 mg dose; therefore, the analysis of urine output at Day 1 includes data only for the 15 mg Tolvaptan dose versus placebo.

and severe hyponatremia group (-0.91 kg). Improvements (that is, decreases) in mean fluid balance at Day 1 were statistically significant for Tolvaptan over placebo for hypervolemic subjects in the ITT population (-1516 mL; p = 0.0020) and for hypervolemic subjects in the severe hyponatremia subgroup (-1732 mL; p = 0.0125), and approached statistical significance for Tolvaptan over placebo for hypervolemic subjects in the mild hyponatremia subgroup (-1334 mL; p = 0.0580).

Comments: Interpretation of results regarding urine volume and body weight may have been confounded by greater use of diuretics in the Tolvaptan group (68%) compared to the placebo group (56%).

Although the Tolvaptan group showed slight improvements in PCS in the ITT, mild and severe hyponatremia groups, the difference from placebo was not statistically significant. The MCS score was statistically significantly improved at Day 30 in the Tolvaptan group over placebo in the ITT population [by 5.24 (p = 0.0052) (OC) and 3.89 (p = 0.0210) (LOCF)], and severe hyponatremia subgroup [by 7.07 (p = 0.0056; OC), and by 5.14 (p = 0.0193; LOCF) with no significant improvement in the mild hyponatremia group.

At Day 4, half of the Tolvaptan treated subjects were stable (Tolvaptan versus placebo: 50% versus 50%) and had normalised serum sodium levels (50% versus 26.1%). None of the Tolvaptan subjects were worsened at Day 4, compared to 23.8% of placebo subjects. Similarly, at Day 30, the majority of Tolvaptan treated subjects had normalised serum sodium levels (Tolvaptan versus placebo: 54.5% versus 33.3%), and the majority of placebo subjects were stable (45.4% versus 47.6%). None of the Tolvaptan subjects worsened at Day 30, compared to 19.0% of placebo subjects. The analysis of the percentage of subjects who were treatment failures because they required saline infusion showed no statistically significant differences between treatment groups for the ITT population [Tolvaptan versus placebo: 3/95 (3.16%) versus 4/91 (4.40%)], the mild hyponatremia group [1/44 (2.27%) versus 1/43 (2.33%)] and the severe hyponatremia group [2/51 (3.92%) versus 3/48 (6.25%)].

The following muscle groups affecting gross motor skills, specifically having to do with balance and gait, were statistically significantly improved for Tolvaptan over placebo in Trial 156-02-235: for the ITT Dataset, reflexes in the right Achilles at Week 1 (p = 0.0096) and reflexes in the left Achilles at Week 1 (p = 0.0104). For subjects with severe hyponatremia in Trial 156-02-235, notable statistically significant improvements in the Tolvaptan group were seen in reflexes of the right Achilles at Week 1 (p = 0.0463), and reflexes in the left Achilles at Week 1 (p = 0.0286). A number of other individual examination tests demonstrated improvements over placebo, but were not bilaterally concordant. The notable statistically significant improvements in muscle groups affecting gross motor skills seen in the Tolvaptan group were: for the ITT Dataset, ataxia right finger to nose test at Day 37 (p = 0.0190) and stance with eyes closed at Week 2 (p = 0.0010).

Results of pivotal Study 156-03-238

This study was conducted from 20/11/2003 to 6/7/2005 at 72 centres in the United States, Canada, Germany, Belgium, Czech Republic, Spain, Poland, Hungary, and Italy.

Subject disposition: Of the 243 randomised subjects (123 Tolvaptan and 120 placebo), 92/123 (74.8%) subjects in the Tolvaptan group completed the study, as did 89/120 (74.2%) subjects in the placebo group. Approximately 80% (99/123) of Tolvaptan treated subjects and 75% (91/120) of placebo treated subjects completed 28 or more days in the study. The overall incidence of discontinuations was similar in the placebo group compared with Tolvaptan in the ITT, mild and severe hyponatremia groups with AE and withdrawal of consent were the most common reasons for discontinuation in both treatment groups. There was no statistical significant difference between the Tolvaptan group and the placebo group for time to discontinuation due to all reasons.

Numbers analysed: Of the 243 subjects enrolled, all subjects (123 in the Tolvaptan group and 120 in the placebo group) qualified for the ITT population, defined as all randomised subjects (excluding Centre 237 subjects due to unreliable data). A total of 232 subjects (118 in the Tolvaptan group and 114 in the placebo group) were analysed for efficacy and qualified for the primary efficacy population (the restricted ITT population).

Protocol deviations and treatment compliance: Clinically significant protocol deviations were reported for 195/243 (80.2%) subjects; 172/243 (70.8%) subjects had procedural deviations, 84/243 (34.6%) subjects had dosing deviations, 9/243 (3.7%) subjects had entry criterion deviations, and 50/243 (20.6%) subjects had "other" deviations. Approximately 93% of subjects in each treatment group were ≥ 90% compliant with study medication. According to drug accountability records, only two (0.8%) subjects were <70% compliant with study medication, both in the Tolvaptan group.

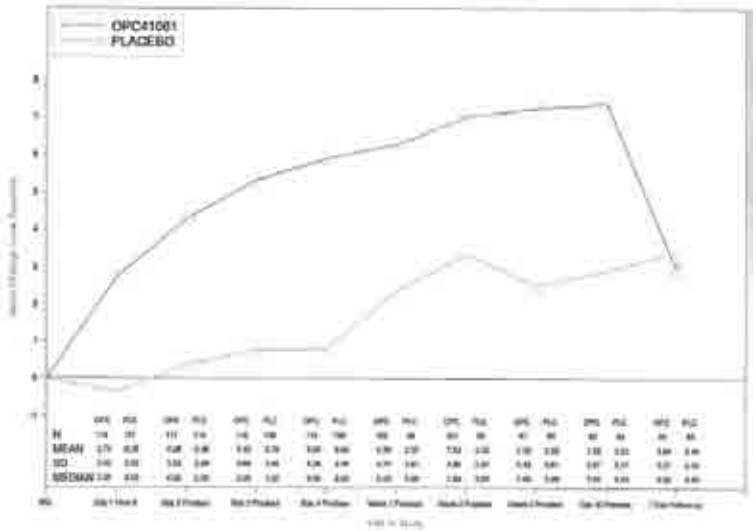
Baseline demographics and disease characteristics: The two treatment groups had similar baseline demographics and disease characteristics. The majority of subjects in this study were male (60.9%), Caucasian (93.4%) and the mean age was 63 years of age (range, 27 years to 100 years). A total of 64/243 (26.3%) were smokers and 86/243 (35.4%) were exsmokers. Overall, 91/243 (37.4%) subjects in the study had NYHA (New York Heart Association) class I-IV heart failure;[22] the majority of these (36/243; 14.8%) were NYHA class III. A total of 123/243 (50.6%) subjects were euvolemic with SIADH/other in 98/243 (40.3%), 19/243 (7.8%) had CHF and 12/243 (4.9%) had liver cirrhosis (alcohol use=5/12 and hepatitis C=5/12). Overall, 118/243 (48.6%) subjects were hypervolemic with liver cirrhosis in 62/243 (25.5%; hepatitis C=17/62), CHF in 55/243 (22.6%), and SIADH/other in 10/243 (4.1%). Diuretics, ACE inhibitors, analgesics, antacids and anti thrombotics were the most commonly used concomitant medications with no significant difference between the Tolvaptan and placebo groups.

Primary efficacy results: For the primary efficacy endpoints, the Tolvaptan group showed a highly statistically significant ($p < 0.0001$) increase in the average daily AUC of change from baseline in serum sodium level from the start of treatment to Day 4 (Tolvaptan – placebo diff = 4.04 mEq/L; 95% CI: 3.36, 4.73) and to Day 30 (4.54 mEq/L; 95% CI: 3.6, 5.47). Changes from baseline in serum sodium level by visit showed that highly statistically significant improvements in serum sodium levels were observed in the Tolvaptan group compared to placebo within 8 h after initiating treatment, and persisted throughout the treatment duration. Loss of efficacy on discontinuation of treatment was seen only in the Tolvaptan group; improvements over placebo in serum sodium levels observed during treatment were no longer seen at the 7 day follow up evaluation (Figure 8).

[22] New York Heart Association (NYHA) functional classes (I-IV) are:

> Class I: no limitation is experienced in any activities; there are no symptoms from ordinary activities.
>
> Class II: slight, mild limitation of activity; the patient is comfortable at rest or with mild exertion.
>
> Class III: marked limitation of any activity; the patient is comfortable only at rest.
>
> Class IV: any physical activity brings on discomfort and symptoms occur at rest.

Figure 8: Mean change from baseline in serum sodium level (mEq/L) by visit – ITT (observed cases).

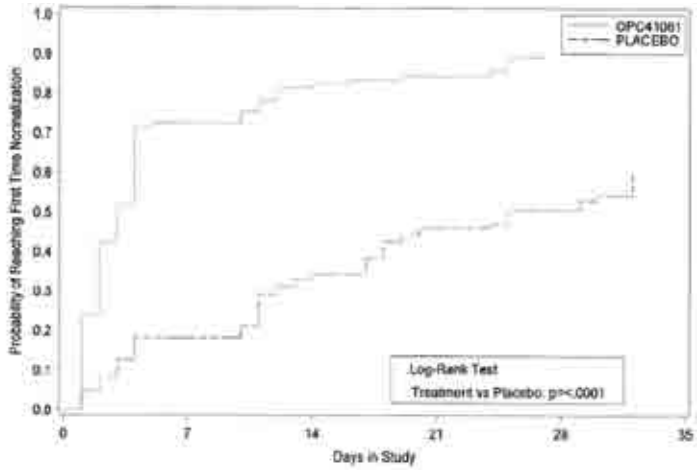


Secondary efficacy results: In severe hyponatremia subjects, the Tolvaptan group showed a statistically significant ($p < 0.0001$) increase in the average daily AUC of change from baseline in serum sodium level from the start of treatment to Day 4 (4.63 mEq/L; 95% CI: 3.5, 5.75) and to Day 30 (5.22 mEq/L; 95% CI: 3.65, 6.75). Similar statistically significant improvements in the Tolvaptan group compared to the placebo group were observed for the mild hyponatremia subgroup at Day 4 (3.40 mEq/L; 95% CI: 2.61, 4.20) and Day 30 (3.75 mEq/L; 95% CI: 2.72, 4.78).

The percentage of subjects with normalised serum sodium level in the ITT population was statistically significantly ($p < 0.0001$) greater in the Tolvaptan group than the placebo group at Day 4 (55% versus 11%) and at Day 30 (58% versus 25%). The percentage of subjects with normalised serum sodium level was statistically significantly greater in the Tolvaptan group compared to the placebo group for both the mild and severe hyponatremia subgroups at Day 4 and Day 30. At each visit, the percentage of subjects with normalised serum sodium levels was statistically significantly greater in the Tolvaptan group (ranging from 26% to 62%) compared to placebo (5% to 25%) using LOCF analysis and the ITT population. In the severe hyponatremia subgroup, the percentage of subjects with normalised serum sodium level was statistically significantly greater in the Tolvaptan group (7% to 51%) compared to placebo (2% to 21%) at all visits except for Day 1, Hour 8.

Tolvaptan-treated subjects were 3.5, 3.9 and 4.2 times more likely than placebo-treated subjects to have normalised serum sodium levels at any point in time ($p < 0.0001$) for the ITT population, mild and severe hyponatremia subgroups, respectively (Figure 9). The shift to normalised serum sodium levels was rapid and highly statistically significant for Tolvaptan versus placebo; however, it was accompanied by relatively few episodes of too rapid serum sodium correction. Statistically significant increases from baseline to Day 4 and Day 30 in serum sodium level were observed in the Tolvaptan group compared to placebo for the ITT population (treatment difference Tolvaptan – placebo = 5.37 and 4.29 mEq/L at Day 4 and Day 30, respectively), mild hyponatremia (4.50 and 4.40 mEq/L, respectively) and severe hyponatremia subgroups (6.21 and 3.85 mEq/L, respectively).

Figure 9: Kaplan-Meier curves for time to first normalisation in serum sodium level (greater than 135 mEq/L) – restricted ITT population.



No statistically significant differences between treatment groups in the percentage of subjects requiring fluid restriction[23] were observed; however, trends approaching statistical significance were observed in the ITT population (Tolvaptan versus placebo: 7% vs 14%, p = 0.0732) and the severe hyponatremia subgroup (10% versus 22%, p=0.0831) with similar incidence in the mild hyponatremia subgroup (3% s 5%, p=0.5671). The 'mean urine output at Day 1'[24] was statistically significantly ($p \leq 0.0119$) greater for the Tolvaptan group than the placebo group for all three populations tested (ITT: Tolvaptan placebo LS mean diff=1289 mL; mild hyponatremia: 1023 mL; severe hyponatremia: 1563 mL). In hypervolemic patients, no significant changes in body weight were observed for Tolvaptan compared to placebo in the ITT population (-0.06kg) or in the severe (-0.18kg) and mild (0.09kg) hyponatremia subgroups. Improvements (that is, decreases) in mean fluid balance at Day 1 were statistically significant for Tolvaptan over placebo for hypervolemic subjects in the ITT population (-1173 mL; p = 0.0012) and for hypervolemic subjects in the severe hyponatremia subgroup (-1864 mL; p = 0.0065), and approached statistical significance for Tolvaptan over placebo for hypervolemic subjects in the mild hyponatremia subgroup (-580 mL; p = 0.0813).

For the ITT population, the PCS score was improved in the Tolvaptan group by 2.48 over placebo at Week 2 (OC) (p = 0.0500). The PCS score was also improved in the Tolvaptan group at Day 30 although the difference between treatment groups was not statistically significant (LOCF and OC). Although the Tolvaptan group showed slight improvements in PCS in the mild and severe hyponatremia groups, the difference from placebo was not statistically significant. The MCS score improved at each time point in the Tolvaptan group over placebo; however, no statistically significant differences between treatment groups were noted at any time point for the ITT population or for the mild or severe hyponatremia subgroups. In the ITT population, the relative shifts in MCS scores at Day 30 were from 44.34 at baseline to 49.07 in the Tolvaptan group, and from 44.93 at baseline to 47.18 in the placebo group (LOCF). For the severe hyponatremia subgroup, the MCS score was improved in the Tolvaptan group by 4.35 over placebo at Day 30 (OC), approaching statistical significance at p = 0.0762. Here, the relative shifts in MCS scores from baseline

[23] Subjects in fluid restriction were defined as those subjects who instituted fluid restriction during the double blind treatment period. Subjects with fluid restrictions imposed before the day of randomisation or after the day of study termination (completion or ET) were not included.

[24] There was no baseline 24 h urine collection in this study. At Day 1, all Tolvaptan treated subjects were receiving the 15 mg dose; therefore, the analysis of urine output at Day 1 includes data only for the 15 mg Tolvaptan dose versus placebo.

to Day 30 were from 43.87 to 50.60 for Tolvaptan and from 42.79 to 45.45 for placebo (OC).

At Day 4, the majority of Tolvaptan treated subjects were normalised (73% for Tolvaptan versus 16% for placebo), whereas the majority of placebo subjects were stable (73% for Tolvaptan versus 27% for placebo). None of the Tolvaptan subjects were worsened at Day 4 compared to 11% of placebo subjects. Similarly at Day 30, the majority of Tolvaptan treated subjects were normalised (71% for Tolvaptan versus 32% for placebo), and the majority of placebo subjects were stable (25% for Tolvaptan versus 50% for placebo). Three percent of Tolvaptan subjects worsened compared to 18% of placebo subjects. The probability factors favoured Tolvaptan at Day 4 (0.7393) and Day 30 (0.6403), and were statistically significant compared to placebo at both visits ($p < 0.0001$) (Table 35). One placebo subject (1/114; 0.88%) was designated as a treatment failure due to the need for saline infusion. None of the Tolvaptan treated subjects required saline infusion. The between group comparison was not statistically significant.

Table 35: Categorical changes in serum sodium level for subjects with baseline serum sodium level less than 130 mEq/L (LOCF).

Visit	Treatment Group	Normalized (> 135) n (%)	Improved (≥ 130, ≤ 135) n (%)	Stable (< 130) n (%)	Probability That Tolvaptan is Better Than Placebo[a]	95% CI	P-value[b]
Day 4	Tolvaptan	22 (37)	25 (42)	12 (20)	0.7816	0.683-0.880	< 0.0001
	Placebo	3 (5)	15 (26)	40 (69)			
Day 30	Tolvaptan	27 (46)	16 (27)	16 (27)	0.6600	0.562-0.758	0.0009
	Placebo	10 (17)	21 (36)	27 (47)			

Note: Serum sodium levels as reported by local laboratories.

[a] A value of > 0.5 favored tolvaptan.[33]

[b] Derived from Cochran-Mantel-Haenszel mean score test with modified ridit score (van Elteren test), using baseline etiology as stratification factor.

For subjects with severe hyponatremia, Tolvaptan showed statistically significant improvements in muscle strength, specifically ataxia right finger to nose test at Day 37 ($p = 0.0143$), ataxia left finger to nose test at Day 37 ($p = 0.0325$), and stance with eyes closed at Week 2 ($p = 0.0170$).

Long term efficacy

Study design: Study 156-03-244 is an ongoing, multicentre, uncontrolled, open label trial being conducted in 33 centres in Europe and North America as an extension to the pivotal randomised, placebo controlled, Phase 3 hyponatremia trials (156-02-235 and 156-03-238) to provide additional long term efficacy/safety information for oral Tolvaptan treatment (up to 214 weeks) in 'real world conditions'. The data presented in the submitted dossier is an interim assessment of safety and efficacy based on data from CRFs as of the clinical cutoff of 1 February 2007. Safety was the primary endpoint of this long term study. However, efficacy was evaluated as the secondary endpoints.[25] Subjects were

[25] (1) Sodium levels obtained at designated intervals were compared to each subject's baseline sodium concentration at the beginning of placebo controlled therapy in their parent trial and from baseline on initiation of therapy in the open-label trial (current trial), (2) Percentage of subjects with varying degrees of hyponatremia (severe < 130 mEq/L, mild 130 to 135 mEq/L, normal > 135 mEq/L) at Baseline and each trial visit, (3) Percentage of subjects requiring prescription of fluid restriction, hypertonic saline or other medications for the express purpose of treating hyponatremia during each period of the trial, assessed descriptively at each visit, (4) Body weight at each visit, (5) Change from baseline in the 12 Item Short form Health Survey (SF-12) physical component summary (PCS) and mental component summary (MCS) scales at Baseline, Day 31, Week 26, Week 34, Week 42, Week 50, Week 58, Week 70, Week 82, Week 94, Week 106, and Week 214/ET, (6) Change from baseline in a hyponatremia specific subject and investigator

not randomised for the extension trial, but Tolvaptan was administered as a titrated oral dose of 15, 30, or 60 mg daily for up to 214 weeks followed by a one week, post treatment, follow up assessment.

Results: Of the 111 patients enrolled in the long term study, majority were Caucasian (94%) with mean age of 64 years and equal number of male and female patients; baseline demographics and sodium levels were similar in the prior placebo and Tolvaptan groups. However, at baseline of the current trial, there were fewer subjects with severe hyponatremia compared with the parent trial baseline, indicating a shift during the parent trial from severe to mild. Subjects could enrol in this open label trial even if they were not currently hyponatremic (in fact, ten subjects had serum sodium concentrations >135 mEq/L at baseline of the current trial).

Statistically significant increases from baseline in serum sodium concentrations were observed in both the 'prior Tolvaptan' group and the 'prior placebo' group at all on treatment visits up to Week 106 (using both LOCF and OC data). The increases in serum sodium concentration in the 'prior placebo' group, which received Tolvaptan for the first time in this open label trial, were similar in magnitude to those observed in the group that had previously received Tolvaptan. In the 'prior Tolvaptan' group, increases in serum sodium concentration were consistent over time, indicating no apparent loss of effect. Within 7 days following Tolvaptan discontinuation (the follow up visit), a decrease in serum sodium concentrations was observed in both the prior placebo and prior Tolvaptan groups. Generally, the increases in serum sodium concentration in the severe hyponatremia subgroup were of greater magnitude than those observed in the mild hyponatremia subgroup although the increases in serum sodium concentration for subjects who had previously received placebo were similar to those subjects who had previously received Tolvaptan. In the total population (OC), statistically significant greater mean changes in serum sodium concentration relative to baseline in the parent trial were observed at all 'on treatment' visits from Day 1 post dose through Week 106 for subjects with CHF or SIADH/other but only from Day 14 through Week 10 in subjects with cirrhosis.

Analysis of sodium categories by selected visits for subjects with a baseline sodium value of <130 mEq/L (severe hyponatremia) and ≥130 mEq/L (mild hyponatremia), respectively (parent trial baseline, OC) showed that for both of these subsets of subjects, 50% or more of the subjects had normal serum sodium concentrations (that is, >135 mEq/L) by Day 31 of the open label trial, regardless of prior treatment group and were sustained through Week 106, with the exception of the prior placebo group for subjects with a baseline sodium value ≥130 mEq/L.

The percentage of subjects who had normalised serum sodium concentrations at each on treatment visit was generally greater than for those who did not have normalised concentrations. This was especially evident for subjects in the severe hyponatremia subgroup, wherein the percentage with normalised concentrations ranged from 57.1% to 100.0% between baseline and Week 106, compared with 0.0% to 42.9% of severe hyponatremic subjects who did not achieve normalised concentrations.

Overall, very few subjects required additional fluid restriction (5 subjects with mild and 7 with sever hyponatremia); however, the percentage of subjects who required fluid restriction was slightly greater in the 'prior placebo' (8/58, 13.8%) group than in the 'prior Tolvaptan' (4/42, 9.5%) group (Table 36).

questionnaire at Baseline, Day 31, Week 10, Week, 18, Week 26, Week 34, Week 42, Week 50, Week 58, Week 70, Week 82, Week 94, Week 106, and Week 214/ET.

Table 36: Summary of time to first fluid restriction by baseline hyponatremia severity (parent trial baseline).

Hyponatremia Severity at Baseline[a]	N[b]	n[c] (%)	Mean Number of Days (SD)
Prior placebo	58	8 (13.8)	114.8 (190.0)
Mild	22	4 (18.2)	13.8 (15.2)
Severe	36	4 (11.1)	215.8 (238.3)
Prior tolvaptan	42	4 (9.5)	103.3 (204.5)
Mild	20	1 (5.0)	1.0
Severe	22	3 (13.6)	137.3 (236.1)
All subjects	100	12 (12.0)	110.9 (185.5)
Mild	42	5 (11.9)	11.2 (14.3)
Severe	58	7 (12.1)	182.1 (220.7)

Note: Fluid restriction imposed during the titration period is not counted.
Note: Parent trial = Trial 156-02-235 or Trial 156-03-238.
[a] Hyponatremia severity at baseline was based on the baseline serum sodium value from the parent trial and was defined as follows: Serum sodium concentration > 135 mEq/L = normal; serum sodium concentration 130 to 135 mEq/L = mild; serum sodium concentration < 130 mEq/L = severe.
[b] Total number of subjects in the current trial.
[c] Subjects who only started fluid restriction in the parent trial are not counted.

Mean changes from baseline in body weight were variable over time; however, reductions in body weight from baseline values reached statistical significance at the Day 14 visit in the total population (-0.7 kg; p = 0.0102) and in the prior Tolvaptan group (-1.3 kg; p = 0.0041), and at Week 106 in the prior placebo group (-4.0 kg; p = 0.0266). No other statistically significant changes in body weight were observed.

The changes from baseline in SF-12 PCS score showed no significant changes; in the current trial, scores were generally decreased compared to baseline (start of OL study) although changes from baseline in the parent trial showed improved scores (that is, increases compared to baseline) at all visits. Similar results were observed in the mild and severe hyponatremia subgroups. Analysis of the SF-12 MCS scores showed similar results to those seen for the PCS scores: the changes from baseline in the current trial were generally decreased. However, changes from baseline in the parent trial showed improved scores (that is, increases compared to baseline) at all visits. Statistical significance was not reached for most time points for any of the analysis sets.

Comments: Statistically significant increases from baseline in serum sodium concentrations were observed at all on treatment visits up to Week 106 in both the prior Tolvaptan group and the prior placebo group for the ITT dataset with similar increases in the prior placebo group, which received Tolvaptan for the first time in this open label trial with similar increase in mild and severe hyponatremia subgroups. In the prior Tolvaptan group, increases were consistent over time, indicating no apparent loss of effect.

Reduction in body weight reached statistical significance at Week 14 and 106; however, analysis of change in body weight in subgroup of patients with hypervolemia would have been more relevant but was not provided in the submitted dossier.

It is important to note that the increase in serum sodium was only maintained till Week 10 in the subgroup of patients with cirrhosis, while the increase in serum sodium was consistently maintained till Week 106 in subgroups of patients with hyponatremia due to CHF or SIADH.

Within seven days following Tolvaptan discontinuation (the follow up visit), a decrease in serum sodium concentrations was observed for all subjects. Very few subjects required the additional therapy of fluid restriction.

The efficacy endpoints reflecting improvement in the serum sodium concentrations were not supported by any benefits in terms of improvement in the 12-Item SF-12 PCS and MCS scales; changes in scores were variable over time. Furthermore, the slight improvements in PCS and MCS seen in the pivotal, placebo controlled studies did not appear to be maintained in the open label study.

Clinical studies in special populations

Pooled data for Studies 156-02-235 and 156-03-238 was used for subgroup analyses to evaluate effect of baseline disease severity (that is, baseline serum sodium level ≥ or <130 mEq/L), aetiology (cirrhosis, CHF, and SIADH/other), age, gender, race, fluid restriction use and diuretic use on the efficacy of Tolvaptan in treatment of hyponatremia.

Effect of baseline disease severity (severe and mild hyponatremia)

Demographics were comparable across the severe hyponatremia and mild hyponatremia subgroups, except that there was a larger non Caucasian representation overall in the subgroup of subjects with mild hyponatremia (40/207, 19.3%) than in subjects with severe hyponatremia (28/217, 12.9%). This was seen to an even greater extent in Study 156-02-235, where the percentage of non Caucasian subjects was 36.7% (33/90) for subjects with mild hyponatremia compared with 19.0% (19/100) for subjects with severe hyponatremia. Baseline hyponatremia characteristics were also similar in the severe and mild hyponatremia subgroups. The majority of subjects in both subgroups had aetiology of SIADH/other (89/217 [41.0%] subjects with severe hyponatremia, and 90/207[43.5%] subjects with mild hyponatremia). In subjects with mild hyponatremia, more subjects had CHF (66/207; 31.9%) than cirrhosis (51/207; 24.6%); whereas, in subjects with severe hyponatremia, slightly more subjects had cirrhosis (66/217; 30.4%) than CHF (62/217; 28.6%).

In the subgroup of patients with severe hyponatremia, the mean changes from baseline in serum sodium concentration at Day 4 and Day 30 were statistically significantly greater for Tolvaptan compared with placebo. Significant increases from baseline in serum sodium concentration were consistently observed in the Tolvaptan group compared to the placebo group at all on treatment visits using both LOCF and OC for the individual trials and the pooled analysis. The percentage of subjects with normalised serum sodium concentrations in the ITT population (OC) was statistically significantly greater in the Tolvaptan group than the placebo group as early as Day 1 (Hour 8) and at all subsequent on treatment visits. In the pooled analysis, the percentage of subjects with normalised serum sodium concentration was (Tolvaptan versus placebo) 34.9% versus 4.2% $p < 0.0001$ at Day 4, and 55.4% versus 18.3%, $p < 0.0001$ at Day 30. In the pooled analysis of subjects with severe hyponatremia, those treated with Tolvaptan were 3.6 times more likely to have normalised serum sodium concentrations at any point during the trial than those treated with placebo ($p<0.0001$). As expected, a greater percentage of subjects with severe hyponatremia required fluid restriction than did subjects with mild hyponatremia. However, even in subjects with severe hyponatremia, for the pooled analysis, the percentage of subjects requiring fluid restriction was statistically significantly lower in the Tolvaptan group (12-19%) compared with the placebo group (24-36%), regardless of the definition used for fluid restriction. Urine output was consistently and statistically significantly greater in the Tolvaptan group than the placebo group, with a difference between groups of 1391 mL in the pooled analysis ($p < 0.0001$). Fluid intake was also greater in the Tolvaptan group compared with placebo; however, the difference from placebo was not as great (332 mL in the pooled analysis) and was not statistically significant in the individual trials or the pooled analysis. The overall fluid balance (IV or oral fluid intake - urine output) was consistently statistically significantly improved (that is, decreased) in the Tolvaptan group compared with the placebo group. In the pooled analysis, the MCS Score improved by 6.3 in the Tolvaptan group compared with 0.4 in the placebo group ($p = 0.0025$) (OC), and in Study 156-02-235 the MCS Score improved by 7.5 in the Tolvaptan group compared with a change of -1.8 in the placebo group ($p = 0.0039$) (OC).

Similar efficacy was shown for most parameters in subgroup of patients with mild hyponatremia (>130mEq/L). In the pooled analysis, the percentage of subjects with normalised serum sodium concentration was more than three fold greater in the

Tolvaptan group (63.0%) compared with the placebo group (18.5%) ($p < 0.0001$) at Day 4, and nearly two fold greater in the Tolvaptan group (64.3%) compared with the placebo group (34.2%) ($p < 0.0001$) at Day 30. In the pooled analysis for subjects with mild hyponatremia, those treated with Tolvaptan were 3.6 times more likely than those treated with placebo to have normalised serum sodium concentrations at any point during the trial. In subjects with mild hyponatremia, the MCS Score improved at Day 30 by a potentially clinically significant score of 6.3 in the Tolvaptan group compared with 3.1 in the placebo group; however, there were no statistically significant differences between treatment groups.

Comments: Efficacy of Tolvaptan was shown in patients with severe hyponatremia (<130mEq/L). The analyses on subjects in the milder hyponatremia subgroup (baseline serum sodium level >130 mEq/L) were not sufficiently powered; therefore, any trend toward significance in the analyses for this subgroup was considered positive.

Aetiology of hyponatremia

Tolvaptan consistently showed statistically significant improvements over placebo for the average daily AUC of mean change from baseline in serum sodium concentration up to Day 4 and Day 30 in the individual trials and pooled analysis, regardless of hyponatremia aetiology. For subjects with SIADH/other and CHF, the magnitude of response was greater at Day 30 than Day 4; whereas, for cirrhosis subjects, the response was greater at Day 4 than Day 30. For the pooled analysis, in all three subgroups (SIADH/others, CHF and cirrhosis), the mean changes in serum sodium concentrations from baseline to Day 4 and Day 30 were statistically significantly greater in Tolvaptan treated patients compared with placebo (with exception of cirrhosis patients at Day 30). Overall for cirrhosis subjects, the average increases in serum sodium concentration at Day 30 were lower than those observed in subjects with SIADH/other or CHF.

Similar results were observed for the percentage of subjects with normalised serum sodium concentrations which was statistically significantly greater in the Tolvaptan group than the placebo group as early as Day 1 (Hour 8), and at all subsequent on treatment visits (except at Week 2 in CHF patients and day 30 in cirrhosis patients). In the pooled analysis, compared with placebo, Tolvaptan treated subjects were 5.4, 2.4 and 2.3 times more likely to have normalised serum sodium concentrations at any point during the trial in subgroups of patients with SIADH/others, CHF and cirrhosis, respectively. In general, use of fluid restriction was greatest in cirrhosis subjects, regardless of treatment group. In subjects with cirrhosis and those with CHF, no statistically significant differences were observed between the Tolvaptan and placebo treatment groups in the percentage of subjects requiring fluid restriction, regardless of the definition used for fluid restriction. For subjects with SIADH/other, the percentage of subjects requiring fluid restriction was statistically significantly lower for Tolvaptan compared with placebo in the pooled analysis and in Study 156-03-238.

Efficacy in euvolemic and hypervolemic patients

Tolvaptan consistently showed statistically significant improvements over placebo for the average daily AUC of mean change from baseline in serum sodium concentration up to Day 4 and Day 30 in the individual trials and the pooled analysis, regardless of volume status. Statistically significant increases from baseline in serum sodium concentration were consistently observed in the Tolvaptan group compared to the placebo group as early as Day 1 (Hour 8) and at all subsequent on treatment visits, regardless of volume status for both LOCF and OC using the ITT Dataset. Overall, the magnitude of change at each visit was greater for euvolemic subjects than for hypervolemic subjects. The percentage of subjects with normalised serum sodium concentrations was statistically significantly greater in the Tolvaptan group than the placebo group as early as Day 1 (Hour 8), and at all subsequent on treatment visits in euvolemic and hypervolemic subgroups (except for

Day 1, Hour 8 in hypervolemic subgroup). In euvolemic subjects, statistically significant fewer patients treated with Tolvaptan required fluid restriction compared with placebo; however, in the hypervolemic subgroup, no statistically significant differences were observed between the Tolvaptan and placebo treatment groups in the percentage of subjects requiring fluid restriction, regardless of the definition used for fluid restriction. Hypervolemic subjects showed no significant difference between Tolvaptan and placebo groups for change in SF-12 MCS, while euvolemic subjects showed statistically significant improvement with Tolvaptan.

Efficacy in other subgroups:

Analysis by gender (male, female), age (<65 years, ≥65 years), race (Caucasian, non Caucasian), fluid restriction use (yes, no) and diuretic medication use (yes, no) did not appear to have any significant effect on the ability of Tolvaptan to increase serum sodium concentrations and all subgroups showed statistically significant improvements with Tolvaptan relative to placebo at both Day 4 and Day 30 ($p < 0.0001$) and these factors.

Analysis performed across trials (pooled analysis and metanalysis)

Pooled efficacy analysis was performed using data from the two pivotal, Phase 3 placebo controlled, randomised, double blind studies in hyponatremic subjects (Studies 156-02-235 and 156-03-238) as both these studies had similar study design and patient population. The population consisted of subjects with chronic or intermittent hyponatremia in a euvolemic or hypervolemic state, approximately 50% with severe (that is, serum sodium concentrations <130 mEq/L) and 50% with mild (that is, serum sodium concentrations ≥130 to ≤135 mEq/L) hyponatremia. Fluid restriction was permitted as necessary, but not required, and as is consistent with typical medical practice, a minority of subjects had fluid restriction imposed. In the pooled analysis, a total of 424 subjects were included in the Randomised Subject Dataset (216 in the Tolvaptan group and 208 in the placebo group); 416 subjects were included in the ITT Dataset and in the Restricted ITT Dataset (213 in the Tolvaptan group and 203 in the placebo group). Overall, the percentage of patients that discontinued was slightly greater in the placebo group (29.3%) compared with Tolvaptan (24.1%). In Study 156-02-235, discontinuations due to AE were greater in placebo subjects (14/93, 15.1%) than in Tolvaptan subjects (8/97. 8.2%); whereas, in Study 156-03-238, discontinuations due to AE were greater in Tolvaptan subjects (18/119, 15.1%) than in placebo subjects (10/115, 8.7%). Baseline hyponatremia characteristics were similar across treatment groups for the individual trials and pooled analysis. In the pooled analysis, the mean (SD) serum sodium concentration at baseline was 129.0 (4.0) mEq/L in the Tolvaptan group (range, 114 to 136 mEq/L) and 128.8 (4.3) mEq/L in the placebo group (range, 115 to 136 mEq/L). In the pooled analysis, majority of the subjects had SIADH/other aetiology (179/424, 42.2%), followed by CHF (128/424, 30.2%), and then by cirrhosis (117/424, 27.6%); the majority of subjects were euvolemic (238/424, 56.1%); and the majority of subjects were receiving diuretic medications at baseline (270/424, 63.7%). Baseline hyponatremia characteristics were similar in the individual trials, except that in Study 156-03-238, there were slightly fewer subjects with SIADH/other (94/234, 40.2%) and more subjects had cirrhosis (73/234, 31.2%) than had CHF (67/234, 28.6%), thus fewer subjects were euvolemic (118/234, 50.4%); whereas, in Trial 156-02-235, slightly more subjects had SIADH/other (85/190, 44.7%) and CHF (61/190, 32.1%) than had cirrhosis (44/190, 23.2%), and more subjects were euvolemic (120/190, 63.2%).

In the pooled analyses using the OC analysis, statistically and clinically significantly greater improvements in serum sodium concentration were observed in the Tolvaptan group over the placebo group as measured by an average daily AUC of mean change from baseline in serum sodium concentration up to Day 4 (4.0 and 0.4 mEq/L for Tolvaptan and placebo, respectively; estimated treatment effect = 3.7 mEq/L, $p < 0.0001$) and up to

Day 30 (6.2 and 1.8mEq/L, respectively; estimated treatment effect=4.6 mEq/L, p <0.0001) (Table 37).

Table 37: Average daily AUC up to Day 4 and Day 30 of change from baseline in serum sodium concentration (mEq/L) in the placebo controlled Phase 3 hyponatremia trials; restrictved ITT dataset.

Visit	Treatment Group	N	Mean (SD)	P-value[a]	Estimated Treatment Effect	95% CI	Significant[b]
156-02-235							
Up to Day 4	Tolvaptan	95	3.62 (2.68)	< 0.0001	3.41	2.75 - 4.07	Yes
	Placebo	89	0.25 (2.08)				
Up to Day 30	Tolvaptan	95	6.22 (4.10)	< 0.0001	4.57	3.64 - 5.50	Yes
	Placebo	89	1.66 (3.59)				
156-03-238							
Up to Day 4	Tolvaptan	118	4.33 (2.87)	< 0.0001	4.04	3.36 - 4.73	Yes
	Placebo	114	0.42 (2.56)				
Up to Day 30	Tolvaptan	118	6.20 (3.92)	< 0.0001	4.54	3.60 - 5.47	Yes
	Placebo	114	1.84 (3.83)				
Pooled							
Up to Day 4	Tolvaptan	213	4.01 (2.80)	< 0.0001	3.73	3.25 - 4.21	Yes
	Placebo	203	0.35 (2.36)				
Up to Day 30	Tolvaptan	213	6.21 (3.99)	< 0.0001	4.57	3.91 - 5.22	Yes
	Placebo	203	1.77 (3.72)				

Restricted ITT Dataset comprises data from all randomized subjects (excluding subjects from Sites 004, 006, and 237) treated with trial medication and having a baseline serum sodium observation and at least one posthaseline serum sodium observation within the trial treatment period or no more than one day after the day of last dose.

[a] P-values were derived from an ANCOVA model with factors of treatment, baseline hyponatremia origin and severity, and baseline serum sodium concentration as covariate. An additional factor of trial was added to the ANCOVA model for the pooled data.

[b] Significance was determined by the Hochberg procedure within the trial.

In the pooled analysis, severity of hyponatremia (< or >130mEq/L) or aetiology (euvolemic/ hypervolemic or cirrhosis/CHF/SIADH) did not affect the efficacy of Tolvaptan with statistically significant improvement observed for the Tolvaptan group relative to placebo in the analyses of average daily AUC of change from baseline in serum sodium concentration up to Day 4 and up to Day 30 for each of the subgroups ($p < 0.0001$ for all).

The onset of statistically significantly improved serum sodium concentrations in the Tolvaptan group compared to the placebo group was observed as early as Hour 8 (Day 1) post dose as measured by change from baseline results with a magnitude of 2.5 mEq/L for Tolvaptan compared with -0.5 for placebo (an estimated treatment effect of 3.1 mEq/L) with similar significant ($p<0.0001$) improvements maintained till Day 30. When treatment is discontinued, serum sodium concentrations in Tolvaptan subjects decrease approximately to the values observed in placebo subjects, despite the reinstatement of standard of care therapy. At 7 days after discontinuation of trial medication, there were no differences between Tolvaptan and placebo groups.

Tolvaptan subjects are > 4 times more likely to achieve normalisation of their serum sodium concentrations (> 135 mEq/L) than placebo subjects by Hour 8 (Day 1), and > 2 times more likely to maintain this advantage over time ($p < 0.0001$). In the pooled analysis, the relative risk was 3.203 ($p < 0.0001$), indicating that Tolvaptan subjects were 3.2 times more likely than placebo subjects to have normalised serum sodium concentrations at any point during the trial. At all on therapy time points, significantly more Tolvaptan subjects than placebo subjects have normalised serum sodium concentrations (Table 38). Similarly significant results are observed for the subgroups of subjects with mild hyponatremia and severe hyponatremia at baseline.

Table 38: Percentage of subjects with normalised serum sodium concentration (>135 mEq/L) at selected time points in the placebo controlled Phase 3 hyponatremia trials; ITT dataset (OC).

Visit	Tolvaptan		Placebo		P-value[a]
	N	n (%)	N	n (%)	
156-02-235					
Day 1, Hour 8	89	11 (12.36)	81	3 (3.70)	0.0148
Day 2	94	25 (26.60)	87	6 (6.90)	<0.0001
Day 4	91	36 (39.56)	80	9 (11.25)	<0.0001
Day 30	75	41 (54.67)	63	15 (23.81)	0.0002
Day 37[b]	75	18 (24.00)	66	16 (24.24)	0.9161
156-03-238					
Day 1, Hour 8	112	29 (25.89)	107	5 (4.67)	<0.0001
Day 2	117	45 (38.46)	113	6 (5.31)	<0.0001
Day 4	115	64 (55.65)	108	12 (11.11)	<0.0001
Day 30	92	59 (64.13)	84	24 (28.57)	<0.0001
Day 37[b]	94	27 (28.72)	85	24 (28.24)	0.9380
Pooled					
Day 1, Hour 8	201	40 (19.90)	188	8 (4.26)	<0.0001
Day 2	211	70 (33.18)	200	12 (6.00)	<0.0001
Day 4	206	100 (48.54)	188	21 (11.17)	<0.0001
Day 30	167	100 (59.88)	147	39 (26.53)	<0.0001
Day 37[b]	169	45 (26.63)	151	40 (26.49)	0.9939

Normalized serum sodium is defined as serum sodium > 135 mEq/l.

ITT Dataset comprises data from all randomized subjects (excluding subjects from Sites 004, 006, and 237) who had a baseline and a postbaseline efficacy evaluation.

[a] P-values were derived from the CMH test, stratified by baseline hyponatremia severity and origin. The CMH test was stratified by trial and baseline hyponatremia severity and origin for the pooled data.

[b] Assessment performed 7 days after discontinuation of trial medication.

Tolvaptan appears to prevent worsening of hyponatremia in subjects with mild hyponatremia at baseline. At Day 4, 15% of placebo subjects progressed from mild to severe hyponatremia, whereas none of Tolvaptan subjects did ($p < 0.0001$). Over the 30 day course of study, the percentage of subjects who progressed from mild hyponatremia at baseline to severe hyponatremia at any on-therapy time point was more than three fold higher in the placebo group (49.0%) than the Tolvaptan group (15.5%) ($p < 0.0001$). Furthermore, the percentage of subjects with severe hyponatremia who had a decrease in serum sodium concentration of at least 3 mEq/L at any post baseline time point, was statistically significantly lower in the Tolvaptan group (11/110, 10.0%) than the placebo group (46/105, 43.8%) ($p < 0.0001$).

Statistically significantly fewer subjects required formal fluid restriction (<1000 mL/day) while on Tolvaptan than subjects on placebo ($p < 0.01$). Furthermore, on Day 1, treatment with Tolvaptan was associated with a significantly greater effective aquaresis and urine output than treatment with placebo; statistically significant mean improvement in fluid balance was observed in Tolvaptan (-1232 mL) compared to placebo subjects (-344 mL), a net difference of -886 mL ($p < 0.0001$).

For the SF-12 Health Survey PCS, baseline scores were low but similar for both treatment groups in the pooled analysis (OC) (33.2 for Tolvaptan and 33.4 for placebo). Minor improvements in PCS scores were observed in the individual trials and in the pooled analysis (LOCF and OC), but none of the changes from baseline were statistically significant compared with placebo. For the SF-12 Health Survey MCS, baseline scores were also low and similar for both treatment groups in the pooled analysis (OC) (43.5 for Tolvaptan and 44.9 for placebo). Improvements in MCS Scores were observed in the individual trials and in the pooled analysis, with changes from baseline to Day 30 being statistically significant in the pooled analysis and in Study 156-02-235. In the pooled analysis, the MCS Score improved at Day 30 by 6.3 in the Tolvaptan group compared with 1.8 in the placebo group ($p = 0.0036$) (OC), and in Study 156-02-235, the MCS Score improved at Day 30 by 8.0 in the Tolvaptan group compared with 0.9 in the placebo group ($p = 0.0046$) (OC). Similar results were observed in Study 156-03-238, but the differences between Tolvaptan and placebo did not reach statistical significance. Post hoc analysis of

the correlations between the AUC of mean change from baseline in serum sodium concentration at Day 30 and the change from baseline in SF-12 Health Survey MCS Scores at Day 30 in the pooled analysis using the ITT Dataset (LOCF) showed that both the correlation coefficient and the partial correlation coefficient demonstrated a close association of improving MCS Score with increasing sodium and were statistically significant (p = 0.0021 and p = 0.0289, respectively). In both of the placebo controlled Phase 3 hyponatremia trials, several of the motor skills were improved in the Tolvaptan group compared with placebo. In one of the two pivotal trials (Study 156-03-238), a pre specified but exploratory Hyponatremia Disease specific Survey[26] also indicated that Tolvaptan subjects receive a quality of life benefit with respect to mental health. Tolvaptan subjects scored significantly higher on the Hyponatremia Disease specific Survey MCS than placebo subjects at Day 30 (a change from baseline for Tolvaptan [-2.2] compared with placebo [-0.7], where a negative change favours Tolvaptan; p = 0.0292) (OC). A correlation analysis between the average daily AUC of mean change from baseline in serum sodium concentration at Day 30 (LOCF) and the change from baseline in Hyponatremia Disease specific Survey MCS Score was also significant (correlation p value = 0.0029; partial correlation p value = 0.0151).

Comments: The analyses of the SF-12 Health Survey PCS and MCS Scores were pre specified as a meta analysis with pooled data from pivotal Studies 156-02-235 and 156-03-238. In the case of the SF-12 health survey instrument, LOCF analyses were performed but might be considered inappropriate. The instrument used has been validated for a four week recall period, thus the data acquired at one or two weeks may be considered exploratory at best and therefore should be censured rather than carried forward. Since the intent was to determine if early effects on physical and mental functioning were occurring, these interim evaluations were made for purposes of OC analyses; however, these and the LOCF analyses should not be relied upon as part of the 'validated' dataset. The improvements in the MCS score may represent a clinically meaningful improvement in MCS Score, as a change of one half SD (that is, 5 points on the SF-12 Health Survey), is most often related to the minimum clinically important difference. However, interpretation of the MCS results was confounded by issues regarding unblinding, lack of correction for multiplicity in statistical analysis and inconsistent results across the pivotal studies.

[26] Questions were formulated to assess cognitive and physical domains reportedly influenced by chronic hyponatremia, and questions pertaining to general health, thirst, and hyponatremia awareness. These questions were generally posed to the subjects, but were accompanied by specific and familial examples of how one's function might be affected by this disorder. Subjects were asked to rate themselves on the following:

- Their general health over the past two days (excellent, very good, good, fair, or poor);
- How their thinking ability had been limited, specifically concentrating, calculating, language, and memory activities (not at all, slightly, moderately, quite a bit, or extremely) (these items constituted the MCS for the Hyponatremia Disease specific Survey);
- How their strength or coordination had been limited, specifically endurance, strength, gross coordination, and fine coordination activities (not at all, slightly, moderately, quite a bit, or extremely) (these items constituted the PCS for the Hyponatremia Disease specific Survey);
- Their self perception, without prompting by knowledge of their laboratory test, of their current sodium concentration (very low, a little low, or normal);
- Their thirst sensation, disregarding the amount of fluid ingested, over the past two days (not thirsty, little thirsty, normal thirst, extra thirst, or very thirsty); and
- Overall assessments of how the subject and how the investigator believed the study treatment affected their activity, symptoms, and emotional well being (much better, somewhat better now, about the same, somewhat worse now, or much worse now).

Supportive studies

Introduction

The Phase 3 CHF Study 156-03-236 contributed supportive efficacy data for the hyponatremia subgroup of subjects (prespecified in the protocol as baseline serum sodium concentrations <134 mEq/L). Effect of Tolvaptan in CHF patients with hyponatremia was also evaluated in five Phase 2 HF studies, four of which were conducted in subjects with stable heart failure (156-97-251, 156-97-252, 156-00-220, and 156-01-232) and one study (156-98-213) were in patients with worsening heart failure. Serum sodium concentrations were evaluated as efficacy endpoints in all CHF trials except Studies 156-97-251, 156-97-252, and 156-01-232. For these latter trials, serum sodium concentration data were available for ISE analysis due to collection as part of the safety clinical laboratory tests.

Fixed doses were used in all HF trials and only the 30 mg dose of Tolvaptan was assessed in each of the trials. Two of the HF Studies 156-97-251 and 156-97-252 were short term (up to 13 and 25 days, respectively). The treatment period in Study 156-98-213 was slightly longer (up to 61 days), and the two remaining Phase 2 CHF trials were long term (156-00-220, up to 169 days; 156-01-232, 54 weeks). In the Phase 3 CHF trial, subjects received 30 mg QD Tolvaptan treatment for a minimum of 60 days for up to 32 months. In the HF trials, subjects were randomised to treatment dose groups in equal proportions except in 156-97-251 sequential cohort, ascending dose HF trial, in which randomisation was 2:1 (Tolvaptan to placebo).

Phase 3 HF Study 156-03-236

One Phase 3 HF trial (156-03-236) contributed supportive efficacy data for the hyponatremia subgroup of subjects (prespecified in the protocol as baseline serum sodium concentrations < 134 mEq/L) with heart failure; however, for consistency in these analyses, all subjects with baseline serum sodium concentrations <135 mEq/L were included. This trial evaluated the long term efficacy and safety of Tolvaptan in subjects hospitalised with worsening heart failure. In this event driven trial, subjects were treated for a minimum of 60 days and up to 32 months, until 1065 deaths occurred, that is, the number required to test superiority. A unique aspect of this trial was its 3 in 1 design, consisting of a Long term Outcome Trial (including an optional substudy) and two distinct Short term Clinical Status Trials. The purpose of the two Short-term Clinical Status Trials was to assess the short term effects of Tolvaptan on signs and symptoms of worsening heart failure. Each centre was assigned to one of the Short term Clinical Status Trials at the end of the trial according to a prespecified algorithm. Analyses on the hyponatremia subgroup based on baseline serum sodium concentration were applied to the clinical efficacy endpoints of both the Long term Outcome Trial and the two Short-term Clinical Status Trials. The primary endpoint of each of these two Short-term Clinical Status Trials was the composite of change in patient assessed global clinical status and change in body weight at Inpatient Day 7 or Discharge if earlier.

A total of 2072 subjects received Tolvaptan 30 mg and 2061 subjects received placebo. The differences between the treatment groups were not statistically significant for the mortality and morbidity endpoints in nearly all subgroups, including those based on age, gender, race, or region. The differences between the treatment groups were statistically significant, favoring Tolvaptan 30 mg, in most subgroups for the change from baseline in body weight at Inpatient Day 1, change from baseline in serum sodium concentration (for subjects with baseline serum sodium concentration less than 134 mEq/L) at Inpatient Day 7 or Discharge if earlier, and patient assessed dyspnea at Inpatient Day 1 (for subjects with physician assessed dyspnea at baseline). For the other efficacy endpoints, the differences between the treatment groups were not statistically significant in the majority of subgroups.

Overall, only 475 (12%) were hyponatremic (< 135 mEq/L) at baseline (243 Tolvaptan subjects and 232 placebo subjects). In both treatment groups, the most common reasons for discontinuation were death (161/475 [33.9%]), subject withdrew consent (65/475 [13.7%]), and AEs (31/475 [6.5%]) with similar incidence in both treatment groups. A total of 92 subjects had severe hyponatremia of which 38 received Tolvaptan and 54 received placebo; 383 subjects had mild hyponatremia of which 205 received Tolvaptan and 178 received placebo. As expected for this subject population, more subjects in the severe hyponatremia subgroup discontinued due to death compared to the mild hyponatremia subgroup (49/92 [53.3%] versus (112/383 [29.2%]). The demographic and baseline characteristics were similar between the mild/severe hyponatremia subgroups and between the Tolvaptan/placebo groups. The majority of subjects were male (388/475, 81.7%), Caucasian (412/475, 86.7%), and with mean age of 64 years (range 18-93 years, 52.6% ≥65years). Of the 243 Tolvaptan subjects, most subjects were exposed to Tolvaptan for less than 58 weeks (187/243, 77.0%). A total of 13/243 (5.3%) subjects were exposed to Tolvaptan for a minimum of 58 weeks, and 3/243 (1.2%) subjects were exposed to Tolvaptan for a minimum of 106 weeks.

For subjects with baseline serum sodium concentration < 135 mEq/L using the ITT Dataset (OC), statistically significantly greater mean changes from baseline in serum sodium concentration were observed in the Tolvaptan group compared to the placebo group at all time points through Outpatient Week 40 and at Outpatient Week 72. The percentage of subjects with normalised serum sodium concentration in the Tolvaptan group was greater than or equal to that in the placebo group at all time points except Outpatient Week 48; the difference between the groups was statistically significant at Inpatient Days 1 and 7 and at Outpatient Weeks 1, 4, 8, 32, and 40. For subjects with severe hyponatremia (<130mEq/L), the percentage of subjects with normalised serum sodium concentration in the Tolvaptan group was greater than or equal to that in the placebo group at all time points with statistically significant difference between the groups at Inpatient Day 7 and at Outpatient Weeks 4, 16, 64, and 80.

The relative risk favoured Tolvaptan over placebo for subjects with baseline serum sodium concentration < 135 mEq/L (relative risk of 2.024, p < 0.0001) and those with baseline serum sodium concentrations < 130 mEq/L (relative risk of 2.388, p = 0.0008), indicating that Tolvaptan subjects were at least two times more likely than placebo subjects to have normalised serum sodium concentrations at any point during the trial. At any time during the trial 45/203 (22.2%) subjects in the Tolvaptan group and 66/176 (37.5%) subjects in the placebo group shifted from mild hyponatremia at baseline (>130 and <135 mEq/L) to severe hyponatremia (< 130 mEq/L). The relative risk was 0.59111 (p = 0.0011), indicating that Tolvaptan subjects were approximately half as likely to shift from mild to severe hyponatremia at any point during the trial. In the overall HF patient population (not just CHF patients with hyponatremia), the incidence of potentially clinically significant increase in sodium concentrations (> 146 mEq/L) was much higher in Tolvaptan treated subjects compared to placebo (48.4% Tolvaptan, 27.1% placebo).

Phase 2 HF studies

In the Phase 2, parallel group Study 156-97-252**,** subjects received Tolvaptan (30, 45, or 60 mg) or placebo QD for 25 days on an outpatient basis. Subjects must have been on a controlled oral dose of furosemide for at least seven days prior to enrolment, and randomization was stratified according to subjects' baseline furosemide dose (40 to 79 mg, 80 to 240 mg). However, only 33 out of 254 randomised subjects had baseline serum sodium concentrations < 135 mEq/L of which 21 received Tolvaptan (6, 4, and 11 subjects, respectively, received 30, 45, and 60 mg Tolvaptan) and 12 received placebo. Majority of subjects were male (22/33, 66.7%), Caucasian (21/33, 63.6%) with median age of 67 years (range 41 to 93 years, 54.5% > 65years) and nearly all (32/33) subjects had mild hyponatremia (serum sodium concentration > 130 mEq/L and < 135 mEq/L) at

baseline. The duration of exposure to trial medication was 22 to 26 days for 28/32 (84.8%) subjects. Greater mean changes from baseline in serum sodium concentration were consistently observed in the Tolvaptan groups compared with the placebo group at all treatment visits except at Day 10 with the greatest changes from baseline were observed in the 60 mg Tolvaptan group. At Day 4, mean changes from baseline were 4.3, 2.8, 5.2 and 1.7mEq/L in the 30, 45, 60 mg Tolvaptan and placebo groups, respectively; at Day 28, the mean changes were 2.7, 2.8, 5.9 and 1.7mEq/L, respectively. At all time points through Day 28, a greater percentage of subjects in the 30 mg (4/6, 66.7%) and 60 mg (7/8, 87.5%) groups had normalised serum sodium concentrations compared with placebo (3/10, 30%); difference between the 60 mg Tolvaptan group and placebo was statistically significant (p = 0.0248).

The Phase 2 Study 156-98-213 was performed in subjects hospitalised for the treatment of worsening heart failure with similar study design to that of the Phase 3 CHF Study 156-03-236. A total of 50 out of 319 randomised subjects had baseline serum sodium levels < 135 mEq/L of which 39 received Tolvaptan (9, 21, and 9 subjects, respectively, received 30, 60, and 90 mg Tolvaptan) and 11 received the placebo. The majority of subjects were male (33/50, 66.0%), Caucasian (23/50, 46.0%; 20/50, 40% were Hispanic) with mild hyponatremia (37/50, 74.0%) and median age was 65 years (range 32-89 years). The majority of subjects (39/50, 78.0%) had a minimum of 15 days of exposure to trial medication: 8/9 subjects in the 30 mg Tolvaptan group, 18/21 subjects in the 60 mg. Greater mean changes from baseline in serum sodium concentration were observed in the 30, 60, and 90 mg Tolvaptan groups compared with the placebo group at Days 2, 4, and 5 and at Weeks 1, 3, and 5. At Day 4, mean changes of 4.6, 6.3, 4.5 and 2.5mEq/L were observed in the 30, 60, 90 mg Tolvaptan and placebo groups, respectively; at Week 7, the mean changes in serum sodium concentrations were 5.0, 7.4, 4.3 and 4.8mEq/L, respectively. At Week 1, 33.3% (2/6), 57.1% (8/14), 100% (3/3) and 12.5% (1/8) of subjects in the 30, 60, 90 mg Tolvaptan and placebo groups, respectively, had normalised serum sodium concentrations.

In the sequential cohort, ascending dose Phase 2 CHF Study 156-97-251 in CHF patients, 17 out of 55 randomised subjects had baseline serum sodium concentrations < 135 mEq/L of which 10 received Tolvaptan (3, 1, 2, 1, and 3 subjects received 10, 30, 60, 90, and 120 mg Tolvaptan, respectively) and 7 received placebo. The majority of subjects were male (11/17, 64.7%), Caucasian (15/17, 88.2%) and only one subject in the 120 mg Tolvaptan group had severe hyponatremia at baseline while the remaining subjects had mild hyponatremia. The duration of exposure to trial medication was 13 days for 15/17 (88.2%) subjects. Subjects in the Tolvaptan groups generally had greater mean changes in serum sodium concentrations than the placebo group throughout the study and almost all patients (67-100%) treated with Tolvaptan doses >30mg had normalised sodium levels by day 14. However, the small number of subjects in each group precluded meaningful analysis.

The Phase 2, placebo controlled, parallel group Study 156-00-220 evaluated the efficacy of Tolvaptan 15, 30, and 60 mg QD in conjunction with conventional therapy over a six month period in subjects with CHF and persistent fluid overload. A total of 21 out of 330 randomised subjects had baseline serum sodium concentrations <135 mEq/L of which 16 received Tolvaptan (5, 3 and 8 subjects received 15, 30, and 60 mg Tolvaptan, respectively) and 5 received placebo. The majority of subjects were male (14/21, 66.7%), Caucasian (18/21, 85.7%), had a median age of 67 years (range 44-84 years, 57.1% > 65 years), had mild hyponatremia (18/21, 85.7%), and 16/21 (76.2%) had 24 to 25 weeks of exposure to trial. At Week 1, mean changes of 1.6, 4.0, 5.8 and 0.50mEq/L were observed in the 15, 30, 60 mg Tolvaptan and placebo groups, respectively; at Week 2, the mean changes in serum sodium concentrations were 4.2, 2.5, 6.3 and 2mEq/L, respectively, and at Day 170, the mean changes were 1.8, 4.5, 8.6 and 4.8mEq/L, respectively. There were no statistically significant differences between Tolvaptan and placebo detected in the

percentage of subjects with normalised serum sodium concentrations at any visit, although interpretation was limited by small number (n=21) of subjects with hyponatremia.

In the Phase 2, long term (54 weeks) placebo controlled, parallel group Study 156-01-232 in patients with CHF and left ventricular systolic dysfunction, 6/240 randomised subjects had baseline serum sodium concentrations <135 mEq/L of which three received Tolvaptan and three received placebo. One placebo subject had severe hyponatremia at baseline, and the remaining five subjects had mild hyponatremia. The 30 mg Tolvaptan group had greater mean changes in serum sodium concentrations than placebo at Weeks 4, 12, 36, and 44 while the placebo group had greater mean changes at Weeks 20, 28, and 54. However, the small number of subjects in each group precluded meaningful analysis.

Evaluator's overall comments on clinical efficacy

- The Samsca (Tolvaptan) clinical programme for hyponatremia consists of six trials: two placebo controlled phase 3 trials (N=216 for Samsca and N=208 for placebo), three placebo controlled Phase 2 trials (N=51 for Samsca and N=26 for placebo), and one open label Phase 3 trial (N=111). The underlying aetiologies in the target population included CHF, cirrhosis, and SIADH. Subjects who truly required treatment for hyponatremia (lV saline) were not enrolled by intention. Chronicity of hyponatremia was not a criterion for study entry; subjects with acute, subacute, or chronic hyponatremia were enrolled, although subjects with acute hyponatremia associated with head trauma or post operative states were excluded. Overall, the inclusion/exclusion criteria tended to select subjects with mild or moderate hyponatremia, who were not symptomatic, or at least not sufficiently symptomatic to require lV saline.
- The results in the two pivotal studies were virtually identical demonstrating consistency of Tolvaptan's effects and tolerability. The primary efficacy endpoints were the averaged daily correction of sodium concentration from baseline through Day 4 and Day 30 as compared to placebo to assess acute and sustained effects. Statistically and clinically significantly greater improvements in serum sodium concentration were observed in the Tolvaptan group over the placebo group as measured by an average daily AUC of mean change from baseline in serum sodium concentration up to Day 4 (4.0 and 0.4 mEq/L for Tolvaptan and placebo, respectively, estimated treatment effect of 3.7 mEq/L, $p < 0.0001$) and up to Day 30 (6.2 and 1.8 mEq/L, respectively; estimated treatment effect of 4.6 mEq/L, $p < 0.0001$).
- The onset of statistically significantly improved serum sodium concentrations in the Samsca (Tolvaptan) group compared to the placebo group is observed as early as Hour 8 (Day 1) post dose as measured by change from baseline results with a magnitude of 2.5 mEq/L for Tolvaptan compared with -0.5 for placebo (an estimated treatment effect of 3.1 mEq/L). The maximal difference from placebo on serum sodium concentrations observed with Tolvaptan titration is achieved by Day 4, after which increases in serum sodium are maintained for the duration of therapy. The mean change from baseline was (Tolvaptan versus placebo) 2.5 versus -0.5 mEq/L at Hour 8 (Day 1), 5.7 versus 0.9 mEq/L at Day 4, 6.4 versus 2.3 mEq/L at Week 1, 7.I versus 3.0 mEq/L at Week 2, 7.4 versus 2.7 mEq/L at Week 3, and 7.3 versus 2.8 mEq/L at Day 30 ($p < 0.0001$ at all time points). At all on therapy time points, significantly more Tolvaptan subjects than placebo subjects have normalised serum sodium concentrations; Hour 8 (Day 1) (Tolvaptan versus placebo: 19.9% versus 4.3%); Day 2 (33.2% versus 6.0%), Day 4 (48.5% versus 11.2%) and Day 30 (59.9% versus 26.5%). When treatment is discontinued, serum sodium concentrations in Tolvaptan subjects decrease approximately to the values observed in placebo subjects, despite the reinstatement of standard of care therapy.

- Tolvaptan appears to prevent worsening of hyponatremia in subjects with mild hyponatremia at baseline. At Day 4, 15% of placebo subjects progressed from mild to severe hyponatremia, whereas none of Tolvaptan subjects did ($p < 0.0001$). Over the 30 day course of study, the percentage of subjects who progressed from mild hyponatremia at baseline to severe hyponatremia at any on therapy time point was more than three fold higher in the placebo group (49.0%) than the Tolvaptan group (15.5%) ($p < 0.0001$). Furthermore, the percentage of subjects with severe hyponatremia who had a decrease in serum sodium concentration of at least 3 mEq/L at any post baseline time point, was statistically significantly lower in the Tolvaptan group (11/110, 10.0%) than the placebo group (46/105, 43.8%) ($p < 0.0001$).
- In addition to the efficacy in increasing serum sodium concentration, 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. 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. Statistically significantly ($p < 0.01$) fewer subjects required formal fluid restriction (< 1000 mL/day) while on Tolvaptan (8-14%) compared with placebo (15-25%).
- Any potential symptomatic benefit due to increase in sodium levels produced by Tolvaptan was examined by effects on quality of life using the 12 item Short form (SF-12) Health Survey. Both studies showed some improvement in SF-12 PCS although difference between Tolvaptan and placebo groups was not significant. Mental status was assessed using the Mental Component Summary of the SF-12 Health Survey, evaluated at Day 30 compared to baseline. Statistically significant improvements in SF-12 MCS were shown in the ITT and severe hyponatremia subgroup in pivotal Study 156-02-235 although significant improvements were not observed in the other pivotal Study 156-03-238. Improvements in SF-12 MCS scores related to and were associated with changes in serum sodium. When the three aetiologies were analysed separately (although these were not individually powered to find a difference), there were statistically significant improvements in MCS on Day 30 for Tolvaptan compared to placebo ($p<0.0129$) for subjects with SIADH/others in the pooled analysis. Furthermore, there was a significant beneficial effect of Tolvaptan versus placebo on the MCS Score of the combined group ($p = 0.0036$), especially in severe hyponatremic patients ($p = 0.0025$). The MCS finding was supported by improvements in memory, concentration and calculating ability and general wellbeing in a pre specified but not validated Hyponatremia disease specific questionnaire in only one of the pivotal Phase 3 studies (156-03-238). However, the MCS analysis was confounded by a multiplicity issue (MCS was not specified in the statistical analysis plan as a key secondary end point but was one of several), potential unblinding (as Tolvaptan treatment was associated with greater thirst and urine output and that more placebo subjects would have required up titration of dose) and the fact that SF-12 does not address symptoms typical of hyponatremia and has not been validated in a clinical setting. Due to the above limitations, it cannot formally be concluded that a statistically significant effect has been demonstrated on the MCS endpoint.
- There was no systematic evaluation of the objective effects of Tolvaptan on nervous system. Both pivotal hyponatremia studies showed improvements in Tolvaptan treated patients in muscle strength (especially in patients with severe hyponatremia) although these did not demonstrate symmetrical concordance and are therefore of doubtful importance. Of potential importance were changes in measures associated with proprioception and coordination; ataxia right and left finger to nose test and stance with eyes closed. These data are of some interest given the previous reports of untoward effects of hyponatremia on gait and balance. However, additional study with

large numbers of subjects would be necessary to assess the clinical relevance of these effects.

- In the open label Study 156-03-244, 111 patients (94 of them hyponatremic with serum sodium <135mEq/L) previously on Tolvaptan or placebo treatment were given Tolvaptan as a titrated regimen (15 to 60 mg daily) after having returned to standard care for at least seven days (during which serum sodium levels had fallen to between their original baseline and post placebo level. The proportions of patients with the three 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: l8% Cirrhosis. 30% CHF and 52% SIADH). This is an ongoing extension trial and is yet to be completed (data cutoff of 1 February 2007). Overall, 33 CHF, 20 Cirrhosis and 58 SIADH patients have been followed up for 106 weeks. Of these, 13, 5 and 35 respective aetiologies are continuing in the trial while 19, l5 and l6 respectively discontinued for variable reasons. Overall, the numbers of cirrhosis and CHF patients followed long term are small. Upon initiation of therapy, average serum sodium levels increased to approximately same levels as observed for those previously treated with Tolvaptan and were sustained for at least a year. It is important to note that the increase in serum sodium was only maintained till Week 10 in the subgroup of patients with cirrhosis, while the increase in serum sodium was consistently maintained till week 106 in subgroups of patients with hyponatremia due to CHF or SIADH. The efficacy endpoints reflecting improvement in the serum sodium concentrations were not supported by any benefits in terms of improvement in the 12 Item SF-12 PCS and MCS scales; changes in scores were variable over time. Furthermore, the slight improvements in PCS and MCS seen in the pivotal, placebo controlled studies did not appear to be maintained in the open label study.
- Efficacy in subgroups: Similar results with similar magnitudes of improvement were observed for the Tolvaptan group relative to placebo in the analyses of average daily AUC of change from baseline in serum sodium concentration up to Day 4 and up to Day 30 for each of the following subgroups: severe/mild hyponatremia (<130mEq/L or >130mEq/L; euvolemia or hypervolemia; aetiology of CHF, cirrhosis or SIADH/others) ($p < 0.0001$ for all). However, the biggest difference compared to placebo was 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, respectively and Cirrhosis 3.15 and 2.83, respectively) and the percentage of subjects with normalised sodium levels was not significantly different from placebo in cirrhosis patients at Day 30. Analysis by demographic subgroup: gender (male, female); age (< 65 years, > 65 years); race (Caucasian, non Caucasian); fluid restriction use (yes, no); and diuretic medication use (yes, no) also showed statistically significant improvements with Tolvaptan relative to placebo at both Day 4 and Day 30 ($p < 0.0001$).
- Supportive evidence of efficacy of Tolvaptan in hyponatremia in CHF patients was provided by a prespecified analysis evaluating changes from baseline in serum sodium concentration in a subgroup of 475 subjects with hyponatremia enrolled in a Phase 3 CHF Study 156-03-236 that demonstrated early and persistent improvements in serum sodium concentrations for Tolvaptan over placebo lasting up to at least 40 weeks. The magnitude of change in serum sodium concentration in the Tolvaptan group was 4.6, 4.9, 5.6, 6.7 and 6.5mEq/L at Day 1, Day 7, Week 4, Week 24, and Week 40, respectively. Additional supportive data are available in 127 subjects with hyponatremia enrolled in five Phase 2 CHF Studies 156-97-251, 156-97-252, 156-98-213, 156-00-220, and 156-01-232. Subjects treated with Tolvaptan, particularly at doses of ≥30 mg/day, generally had greater mean increases in serum sodium concentrations than subjects treated with placebo throughout each of the trials.

- In summary, Samsca (Tolvaptan) is an effective agent for the treatment of non acute dilutional (hypervolemic and euvolemic) hyponatremia (including patients with heart failure, cirrhosis, SIADH), although evidence is not as convincing for cirrhosis. The data clearly demonstrate that correction of hyponatremia occurs progressively over the first four days of treatment, thereby minimising the negative impact of overly rapid increases in serum sodium. The improvements were sustained over long term treatment and importantly, when treatment is interrupted, sodium concentrations decrease to those seen with placebo patients. These data suggest that Samsca (Tolvaptan) should be used in the chronically affected patients as long as needed, to maintain normal sodium concentrations. However, it has not been established that raising serum sodium with Tolvaptan provides a symptomatic benefit to patients.

Safety

Introduction

A total of 4,414 subjects have been exposed to Tolvaptan in 57 trials conducted in North America, South America, Europe and Asia. Medical terms were coded using MedDRA version 9.0. In developing the standard structure of analyses, guidance available from ICH, FDA, and other sources directed the selection of data and type of analysis in order to provide a comprehensive data summary in a format that did not obscure safety signals. The safety analysis was done on three pooled patient populations:

1. 'All heart failure subjects and all hyponatremia subjects' consisting of patients with a baseline diagnosis of heart failure or hyponatremia treated in any of the placebo controlled completed Phase 2/3 multiple dose trials with Tolvaptan;
2. 'All heart failure subjects' from multiple dose, controlled trials in the heart failure and hyponatremia program as well as clinical pharmacology/other indication supportive Studies 156-01-231 and 156-03-001; and
3. 'All hyponatremia subjects' from placebo controlled, multiple dose Tolvaptan trials in hyponatremia and hyponatremic subset of subjects from heart failure trials.

Comments: The third group of patients is the most relevant for this submission seeking approval for treatment of hyponatremia (the sponsor is not seeking approval for CHF) and will be discussed in more detail compared to safety results in the other two pooled populations.

The hyponatremia population consisted of three etiological subgroups, heart failure, liver cirrhosis and SIADH all characterised by baseline sodium levels below 135 mmol/L. The heart failure population included patients in NYHA Classes I-IV[22] with signs of extracellular volume expansion with or without hyponatremia. All subjects enrolled in Phase 2/3 Tolvaptan trials were scheduled to undergo a thorough medical evaluation[27] generally within 14 days prior to the initiation of trial therapy (within 48 h for Study 156-03-236). After the initiation of trial therapy, the schedules for the completion of safety assessments varied across protocols. Subjects were usually evaluated at weekly intervals during the initial 4 to 6 weeks of trial therapy (in trials with in hospital periods, for example, in Studies 156-03-236 and 156-98-213 subjects were evaluated during the hospital period and at regular intervals during the outpatient period). AEs, review of concomitant medications, vital signs, and body weight were collected at each trial visit.

[27] These safety assessments included a review of relevant medical history and concomitant medications, physical examination (including vital signs, body weight, 12 lead ECGs), and clinical laboratory tests.

Laboratory assessments and 12 lead ECGs were completed at least once during the initial treatment period and approximately every two to four weeks thereafter (in some trials, ECGs were collected more frequently). Additional laboratory assessments and ECGs were performed if clinically indicated during the course of a clinical trial. All safety assessments were additionally performed at the end of a clinical trial (or early withdrawal for any reason) and at the end of a trial phase within a clinical trial.

Due to the large number of AEs and the high incidence of many events associated with the underlying disease state in populations studied in trials with Tolvaptan, a more systematic approach for identification of potential drug effects was undertaken to ensure consistent assessment of both high and low incidence events and to identify specific adverse events that may be related to use of Tolvaptan. The screening process evaluated individual adverse events occurring in both Tolvaptan and placebo treated patients from the perspective of frequency, dose association, time to onset, and consistency across studies. Statistical screening tests were used to evaluate differences between drug and placebo event rates (Fisher's Exact Test), differences between drug and placebo event rates as a function of dose (Jonckheere-Terpstra Test), differences between drug and placebo event rates as a function of time to onset (Log Rank Test), and the consistency in differences between drug and placebo event rates across clinical trials (Breslow-Day Test).

Patient exposure

Exposure for the hyponatremia population was driven by both the Phase 3 placebo controlled hyponatremia Studies 156-02-235 and 156-03-238 (Tolvaptan 15-60 mg), the long term open label hyponatremia Study 156-03-244 (Tolvaptan 15-60 mg), and the Phase 3 heart failure Study 156-03-236 (Tolvaptan 30 mg), where many of the subjects had hyponatremia. Overall, 607 patients were treated with Tolvaptan and 518 with placebo in this hyponatremia safety dataset. The extent of exposure to study medication over time was comparable between the Tolvaptan and placebo group. Approximately half of the subjects (n=296) received at least 30 days of treatment, and approximately a third of subjects (n=199) received at least three months of treatment. Fewer than 15% (n=69) of subjects received more than one year of treatment. The rate of discontinuation was slightly higher in the placebo (44.0%) compared to the Tolvaptan group (41.7%), which was mostly due to the higher rate of 'withdrawal of consent' in the placebo group. In both treatment groups, the most common reasons for premature discontinuation were death (Tolvaptan versus placebo: 14.2% versus 14.5%), adverse experience (12.7% versus 10.0%), and withdrawal of consent (7.6% versus 11.0%). The demographic characteristics for the subjects with hyponatremia were comparable between the Tolvaptan group (All Tolvaptan) and placebo group with majority of patients being Caucasian (82%), male (70%), median age of 63 years (46% were $\geq$65 years), had mild hyponatremia (about 67% had a baseline serum sodium value of <135 and ≥130 mEq/L) with an aetiology of CHF (66%, 16% and 16% had CHF, cirrhosis and SIADH/other, respectively) and were hypervolemic (75-78%). Overall, the treatment groups were comparable with respect to baseline hyponatremia characteristics.

Adverse events (AEs)

The overall incidence of AE was similar in Tolvaptan and placebo groups (86%). The percentage of patients with potentially drug related TEAE was higher in the Tolvaptan group than in the placebo group (45.3% versus 32.0%), mainly due to expected pharmacological action of Tolvaptan (thirst, dry mouth, and pollakiuria[28]). No other relevant differences were observed between the Tolvaptan and placebo groups.

[28] Pollakiuria is abnormally frequent urination.

The most frequent TEAE in both treatment groups were cardiac failure, nausea, and cardiac failure congestive, all of which occurred in between 10% to 20% of subjects. The frequency of these and most other TEAE was comparable between the treatment groups. The only TEAE with a notably higher frequency in the Tolvaptan group compared to the placebo group were thirst (Tolvaptan versus placebo: 14.0% versus 3.9%), dry mouth (8.9% versus 3.3%), pollakiuria (5.4% versus 1.5%), nausea and polyuria (Table 39).

Table 39: Frequency of TEAEs that occurred in ≥2% of Tolvaptan or placebo subjects by preferred term – all hyponatremia subjects from multiple dose placebo controlled trials.

Preferred Term (MedDRA)	Number (%) of Subjects	
	All Tolvaptan (N=607)	Placebo (N=518)
Cardiac failure	100 (16.5)	85 (16.4)
Nausea	87 (14.3)	61 (11.8)
Thirst	85 (14.0)	20 (3.9)
Cardiac failure congestive	69 (11.4)	61 (11.8)
Dizziness	59 (9.7)	43 (8.3)
Hypotension	56 (9.2)	61 (11.8)
Constipation	55 (9.1)	45 (8.7)
Dry mouth	54 (8.9)	17 (3.3)
Diarrhoea	51 (8.4)	37 (7.1)
Headache	49 (8.1)	43 (8.3)
Hyperkalaemia	43 (7.1)	30 (5.8)
Urinary tract infection	43 (7.1)	41 (7.9)
Hypokalaemia	39 (6.4)	31 (6.0)
Insomnia	39 (6.4)	36 (6.9)
Abdominal pain	38 (6.3)	26 (5.0)
Oedema peripheral	38 (6.3)	35 (6.8)
Chest pain	37 (6.1)	29 (5.6)
Vomiting	37 (6.1)	38 (7.3)
Fatigue	36 (5.9)	32 (6.2)
Pollakiuria	33 (5.4)	8 (1.5)
Anaemia	31 (5.1)	39 (7.5)
Asthenia	34 (5.6)	19 (3.7)
Cough	29 (4.8)	28 (5.4)
Renal failure acute	25 (4.1)	23 (4.4)
Anxiety	25 (4.1)	19 (3.7)
Pruritus	25 (4.1)	16 (3.1)
Renal failure	25 (4.1)	22 (4.2)
Ecchymosis	26 (4.3)	13 (2.5)
Hyperglycaemia	23 (3.8)	16 (3.1)
Hyponatraemia	23 (3.8)	28 (5.4)

Table 39 (continued): Frequency of TEAEs that occurred in ≥2% of Tolvaptan or placebo subjects by preferred term – all hyponatremia subjects from multiple dose placebo controlled trials.

Preferred Term (MedDRA)	Number (%) of Subjects	
	All Tolvaptan (N=607)	Placebo (N=518)
Pyrexia	23 (3.8)	10 (1.9)
Ventricular tachycardia	24 (4.0)	20 (3.9)
Back pain	23 (3.8)	21 (4.1)
Hypoglycaemia	22 (3.6)	14 (2.7)
Ascites	25 (4.1)	22 (4.2)
Atrial fibrillation	21 (3.5)	22 (4.2)
Muscle spasms	23 (3.8)	27 (5.2)
Pain in extremity	20 (3.3)	18 (3.5)
Dehydration	20 (3.3)	8 (1.5)
Hyperuricaemia	18 (3.0)	21 (4.1)
Pneumonia	18 (3.0)	17 (3.3)
Rash	19 (3.1)	18 (3.5)
Abdominal distension	17 (2.8)	15 (2.9)
Blood creatinine increased	20 (3.3)	12 (2.3)
Confusional state	17 (2.8)	19 (3.7)
Dyspnoea	20 (3.3)	24 (4.6)
Anorexia	17 (2.8)	3 (0.6)
Oedema	20 (3.3)	12 (2.3)
Depression	14 (2.3)	17 (3.3)
Epistaxis	16 (2.6)	13 (2.5)
Cardiac arrest	14 (2.3)	6 (1.2)
Dyspepsia	16 (2.6)	8 (1.5)
Upper respiratory tract infection	14 (2.3)	13 (2.5)
Abdominal pain upper	13 (2.1)	13 (2.5)
Blood urea increased	13 (2.1)	9 (1.7)
Blood uric acid increased	12 (2.0)	6 (1.2)
Diabetes mellitus	12 (2.0)	4 (0.8)
Dyspnoea exacerbated	13 (2.1)	14 (2.7)
Arthralgia	12 (2.0)	8 (1.5)
Fall	12 (2.0)	9 (1.7)
Polyuria	14 (2.3)	2 (0.4)
Sepsis	12 (2.0)	6 (1.2)
Gout	9 (1.5)	14 (2.7)
Pain	9 (1.5)	12 (2.3)
Pleural effusion	10 (1.6)	12 (2.3)
Skin ulcer	9 (1.5)	11 (2.1)
Hypomagnesaemia	7 (1.2)	12 (2.3)
Dysuria	7 (1.2)	13 (2.5)
Haematoma	7 (1.2)	13 (2.5)
Hypertension	4 (0.7)	17 (3.3)
Agitation	3 (0.5)	11 (2.1)
Total [a]	524 (86.3)	441 (85.1)

Dose response data in hyponatremia were limited because of the dose titration regimen used in most the trials. From the pooled hyponatremia subject data, higher incidences of TEAE at increasingly higher Tolvaptan doses were observed for congestive cardiac failure, ventricular tachycardia, and headache. The rates of these TEAE were lower in the combined Tolvaptan 15 to 60 mg dose group (the proposed commercial dose range) than in the placebo group (80.3% versus 85.1%). A number of TEAE showing higher incidence rates with increasing Tolvaptan dose were observed in too few subjects (<4% incidence in overall Tolvaptan group) for meaningful conclusions. These TEAE (and their incidence rates in the overall Tolvaptan group versus placebo group) were increased blood

creatinine (3.3% versus 2.3%), dehydration (3.3% versus 1.5%), rash (3.1% versus 3.5%), decreased appetite (1.8% versus 0.8%), and chills (1.0% versus 0.4%).

Comments: Generally, the incidences of cardiovascular TEAE in hyponatremia subjects cannot be easily compared between the titrated dose group (Tolvaptan 15-60 mg) and individual fixed dose groups because of the population differences (that is, heart failure subjects represented 100% of the population at the fixed doses compared to approximately one third of the population at the titrated doses) and exposure differences (that is, exposure up to and beyond one year in the longest duration heart failure fixed dose trials compared to 30 day observation period in the titrated regimen hyponatremia trials).

There were no relevant differences between both treatment groups in the incidence of any individual TEAE associated with electrolyte disturbances, the only exception being nausea occurring at a slightly higher rate with Tolvaptan than with placebo (Tolvaptan versus placebo: 14.3% versus 11.8%); other electrolyte disturbances were hypokalaemia (6.4% versus 6.0%), fatigue (5.9 % versus 6.2%) and hyperkalaemia (7.1% versus 5.8%). Hyponatremia was reported in 3.8% of subjects with Tolvaptan and in 5.4% of subjects with placebo.

The overall incidence of cardiac AEs (Tolvaptan versus placebo: 15.0% versus 14.5%) and ischemic events (14.2% versus 13.1%) was similar in the Tolvaptan and placebo groups. The most common cardiac disorders of interest were chest pain (6.1% versus 5.6%) and ventricular tachycardia (4.0% versus 3.9%). Except for cardiac arrest (2.3% versus 1.2%), all other events occurred with a frequency of <2% in both treatment groups with no relevant differences between both treatment groups (Table 40).

Table 40: Frequency of TEAEs associated with cardiac disorders of interest in >1% of subjects in either treatment group – all hyponatremia subjects from multiple dose placebo controlled trials.

Medical concept	Number (%) of Subjects	
Preferred Term (MedDRA)	All Tolvaptan (N=607)	Placebo (N=518)
Cardiac arrest	**91 (15.0)**	**75 (14.5)**
Ventricular tachycardia	24 (4.0)	20 (3.9)
Cardiac arrest	14 (2.3)	6 (1.2)
Cardiogenic shock	10 (1.6)	8 (1.5)
Sudden death	10 (1.6)	8 (1.5)
Sudden cardiac death	8 (1.3)	5 (1.0)
Syncope	8 (1.3)	8 (1.5)
Ventricular fibrillation	8 (1.3)	3 (0.6)
Bradycardia	6 (1.0)	9 (1.7)
Ventricular arrhythmia	6 (1.0)	2 (0.4)
Ventricular extrasystoles	5 (0.8)	6 (1.2)
Ischemic events	**86 (14.2)**	**68 (13.1)**
Chest pain	37 (6.1)	29 (5.6)
Cardiac arrest	14 (2.3)	6 (1.2)
Sudden death	10 (1.6)	8 (1.5)
Sudden cardiac death	8 (1.3)	5 (1.0)
Angina pectoris	7 (1.2)	5 (1.0)
Angina unstable	1 (0.2)	5 (1.0)

TEAEs were defined as AEs that started after start of trial medication treatment, or if the event was continuous from baseline and was serious, trial medication-related, or resulted in death, discontinuation, interruption or reduction of trial therapy. Events are ordered by descending frequency in the "All Tolvaptan" column.

Subgroup analysis for TEAE:

Subgroup analyses of TEAE by age group (<65 years versus ≥65 years), gender, and race category (Caucasian versus non Caucasian), and by baseline hyponatremia characteristics were conducted in all subjects with hyponatremia from multiple dose placebo controlled trials.

Age and gender: Overall, the findings of the subgroup analyses by age and gender were consistent with those in the overall population of hyponatremia subjects with the following exceptions: slightly higher incidences were reported with Tolvaptan compared with placebo for cardiac failure (Tolvaptan vs placebo: 16.7% versus 13.6% placebo), diarrhoea (9.1% versus 6.2%), and asthenia (7.3% versus 5.0%) in elderly subjects and for cardiac failure congestive (9.3% versus 5.8%), hyperkalaemia (7.8% versus 5.1%), and abdominal pain (7.5% versus 5.1%) in non elderly subjects. Compared to those <65 years old, Tolvaptan treated patients >65 years reported a slightly higher incidence of CHF (<65yrs versus >65yrs: 9.3% versus 13.8%), hypotension (8.1% versus 10.5%), dizziness (8.4% versus 11.3%), constipation (7.5% versus 10.9%) and urinary tract infection (4.2% versus 10.5%).

Slightly higher incidences were reported with Tolvaptan compared with placebo for cardiac failure (Tolvaptan versus placebo: 21.8% versus 18.5%) in men and for nausea (16.8% versus 12.9%), oedema peripheral (9.7% versus 5.8%), fatigue (9.2% versus 5.8%), and asthenia (7.6% versus 5.8%) in women. Compared to females, Tolvaptan treated males reported a higher incidence of cardiac failure (male versus female: 21.8% vs 4.1%), CHF (13% versus 7.6%) and hypotension (10.4% versus 6.5%) although these results should be interpreted with caution as majority of patients were males (422 males versus 185 females in the Tolvaptan group).

Volume status: In the subgroup analysis of TEAE by volume status (euvolemic or hypervolemic), the majority of hyponatremia subjects were hypervolemic (476/607 Tolvaptan; 389/518 placebo); only 131/607 subjects in the Tolvaptan group and 129/518 subjects in the placebo group were euvolemic. In general, fewer subjects with at least one TEAE were seen in the euvolemic versus hypervolemic groups (73.3% versus 89.9% for Tolvaptan and 70.5% versus 90.9% for placebo) which is most likely a reflection of the complexity of the underlying disease (mostly CHF and cirrhosis). In the euvolemic subgroup, TEAEs occurring at an incidence of >10% in the Tolvaptan group were dry mouth (Tolvaptan versus placebo: 12.2% versus 3.9%), headache (11.5% versus 6.2%) and thirst (10.7% versus 5.4%). In the hypervolemic subgroup, TEAE occurring at an incidence of > 10% in the Tolvaptan group were thirst (14.9% versus 3.3%), dizziness (10.3% versus 9.0%); TEAE occurring at an incidence of > 10% in hypervolemic subjects regardless of treatment were cardiac failure (20.6% versus 21.6%), nausea (15.5% versus 13.4%), congestive cardiac failure (13.7% versus 14.9%) and hypotension (10.1% versus 13.9%). Compared with hypervolemic subjects, those with euvolemic hyponatremia treated with Tolvaptan were more likely to have asthenia (hypervolemia versus euvolemia: 7.6% versus 5.0%) whereas the incidence was somewhat less in those treated with placebo (2.3% versus 4.1%). The incidence of fatigue was also higher in euvolemic than hypervolemic subjects but similar proportions were seen between the treatment groups (7.6% versus 5.5% in the Tolvaptan group, and 7.8% versus 5.7% in the placebo group). Nausea was less common in euvolemic versus hypervolemic subjects regardless of treatment (9.9% versus 15.5% in the Tolvaptan group and 7.0% versus 13.4% in the placebo group). Subjects with euvolemic hyponatremia treated with Tolvaptan had a lower incidence of vomiting compared to those treated with placebo whereas the incidence of vomiting in hypervolemic subjects was similar between the treatment groups (euvolemic versus hypervolemic: 2.3% versus 7.1%), in the Tolvaptan group; 9.3% versus 6.7%, euvolemic versus hypervolemic in the placebo group). Hyperglycaemia also had a lower frequency among euvolemic versus hypervolemic subjects in both treatment groups (2.3% versus 4.2% in the Tolvaptan group and 0.8% versus 3.9% and in the placebo group); euvolemic subjects treated with Tolvaptan had a higher incidence than those treated with placebo (2.3% versus 0.8%) whereas the incidence rates of hyperglycemia in hypervolemic subjects were similar regardless of treatment (4.2% versus 3.9%). Hypokalaemia was also seen to a greater degree in the hypervolemic versus euvolemic subjects treated with Tolvaptan (7.1% versus 3.8% in the Tolvaptan group); the difference

between the subgroups was less in subjects treated with placebo (6.4% hypervolemic versus 4.7% euvolemic in the placebo group). In the Tolvaptan group, headache was more frequently seen in the euvolemic versus hypervolemic subjects (11.5% versus 7.1%), opposite that seen in the respective placebo groups (6.2% versus 9.0%). The reasons for this are unclear. Overall, volume status had little relation to the incidences of AE, other than that which might be expected due to the underlying disease and treatments associated with that population. Importantly, symptoms such as hypotension were of equivalent incidence and proportion among these populations (euvolemic versus hypervolemic: 6.1% versus 10.1% in the Tolvaptan group; 5.4% versus 13.9%, in the placebo group).

Hyponatremia aetiology: Majority of subjects had CHF (410/607 in the Tolvaptan group and 336/518 in the placebo group); for the any Tolvaptan dose and placebo groups, respectively, 100/607 and 83/518 subjects had cirrhosis and 97/607 and 99/518 has SIADH/other. Overall, the incidence rates of TEAE were similar for CHF and cirrhosis subjects in the Tolvaptan group (367/410, 89.5% and 90/100, 90.0%, respectively) and more than that observed in SIADH/other subjects (67/97, 69.1%). In the placebo group, the incidences of TEAE for subjects with CHF, cirrhosis, and SIADH/other were 303/336 (90.2%), 69/83 (83.1%), and 69/99 (69.7%), respectively.

In the CHF subgroup, most common TEAE were thirst (Tolvaptan versus placebo: 13.2% versus 3.0%), dizziness (12.0% versus 9.5%), cardiac failure (24.1% in both treatment groups), nausea (16.8% versus 14.0%), congestive cardiac failure (16.3% versus 17.6%) and hypotension (11.5% versus 15.5%). In the cirrhosis subgroup, the most frequent TEAE which were slightly more common in Tolvaptan treated subjects were thirst (Tolvaptan versus placebo: 20.0% versus 4.8%), nausea (13.0% versus 10.8%), peripheral oedema (11.0% versus 7.2%), dry mouth (11.0% versus 1.2%), oedema (10.0% versus 8.4%), hyperkalaemia (10.0% versus 7.2%), while those more common in placebo treated subjects were: fatigue (8% versus 12.0%), diarrhoea (7% versus 12.0%) and headache (8% versus 10.8%). The only TEAE occurring at an incidence of >10% in cirrhosis subjects regardless of treatment was ascites (Tolvaptan versus placebo: 19.0% versus 20.5%). Furthermore, in patients with cirrhosis treated with Samsca in hyponatremia trials, gastrointestinal bleeding was reported in 6/63 (10%) Samsca treated patients and 1/57 (2%) placebo treated patients. In the SIADH/other subgroup, common TEAEs were dry mouth (Tolvaptan versus placebo: 15.5% versus 4.0%), thirst (11.3% versus 6.1%) and headache (12.4% versus 7.1%).

As expected, events such as cardiac failure and congestive cardiac failure were seen exclusively among those with heart failure as the aetiology of hyponatremia, while ascites was almost universally seen in those with cirrhosis. The event of hypotension, distributed overall at 9.2% for Tolvaptan and 11.8% for placebo, was also seen with the highest frequency in the CHF group (11.5% Tolvaptan; 15.5% placebo), although was present in a significant fraction of cirrhosis and SIADH/other subjects in both treatment groups (4.0% Tolvaptan and 7.2% placebo in cirrhosis subjects; 5.2% Tolvaptan and 3.0% placebo in SIADH/other).

Dry mouth and pollakiuria were seen with increasing frequency among those with CHF, cirrhosis, and SIADH/other for Tolvaptan subjects (for dry mouth: 6.8%, 11.0%, 15.5%, respectively; for pollakiuria: 4.4%, 6.0%, 9.3%, respectively), and was differentially distributed among these subgroups in placebo subjects (for dry mouth: 3.6%, 1.2%, 4.0%, respectively; for pollakiuria: 1.2%, 1.2%, 3.0%, respectively), however, the number of subjects were quite small. However, thirst was observed in roughly the same percentage of Tolvaptan subjects (11.3% to 20.0%) across aetiologies as it did in placebo (3.0% to 6.1%).

For asthenia, trends favouring placebo over Tolvaptan were observed for CHF and SIADH/other subgroup (5.9% Tolvaptan; 3.6% placebo in CHF subjects; 5.2% versus 1.0%

in SIADH/other subjects), while the incidence rates in cirrhosis subjects were fairly similar but actually favoured Tolvaptan (5.0% versus 7.2%). This is of particular interest since the incidence of fatigue was identical in the CHF subjects (5.1% both treatment groups) and fairly similar but favoured placebo in SIADH/other subjects (7.2% Tolvaptan versus 5.1% placebo), but clearly favoured Tolvaptan for the cirrhosis subjects (8.0% versus 12.0%). The differential presentation of these closely related AE in these treatment groups may occur as a result of the pathophysiology of the underlying diseases.

Hyponatremia severity: The majority of subjects had mild hyponatremia at baseline (serum sodium concentrations >130 mEq/L) (418/607 in the any Tolvaptan dose group and 340/518 in the placebo group); 189/607 and 178/518 subjects in the any Tolvaptan dose and placebo groups, respectively, had severe hyponatremia (< 130 mEq/L). Overall, the TEAE incidence rates were similar across treatments for both mild (Tolvaptan versus placebo: 84.9% versus 84.4%) and severe (89.4% versus 86.5%) hyponatremia subjects. In the mild hyponatremia subgroup, thirst (14.1% vs 2.6%), dizziness (10.0% vs 7.9%), hypotension (9.3% vs 12.1%), cardiac failure (18.9% versus 19.1%), nausea (15.1% versus 11.2%) and congestive cardiac failure (12.7% versus 12.1%) were the most frequent TEAE. In the severe hyponatremia subgroup, the most frequent TEAE were thirst (13.8% versus 6.2%), diarrhoea (12.7% versus 8.4), dry mouth (12.7% versus 4.5%), congestive cardiac failure (8.5% versus 11.2%), nausea (12.7% versus 12.9%) and cardiac failure (11.1% versus 11.2%).

Overall, the incidence of dry mouth was more frequently observed in Tolvaptan (8.9%) versus placebo subjects (3.3%), and more frequently observed in subjects with severe hyponatremia compared with those with mild hyponatremia (12.7% Tolvaptan and 4.5% placebo in the severe hyponatremia subgroup; 7.2% Tolvaptan and 2.6% placebo in the mild hyponatremia subgroup). Thirst, though observed more frequently in subjects treated with Tolvaptan versus placebo (14.0% versus 3.9% overall), had a similar incidence in both the mild and severe subgroups in subjects treated with Tolvaptan (14.1% mild and 13.8% severe in the any Tolvaptan dose group; 2.6% mild and 6.2% severe in the placebo group). Pollakiuria was seen more frequently in the Tolvaptan subjects with mild hyponatremia than in those with severe hyponatremia (6.2% versus 3.7%) but had a similar incidence among mild and severe hyponatremia subjects treated with placebo (1.5% versus 1.7%). Hyperglycaemia was more frequent in the mild versus severe hyponatremia subgroup only in subjects treated with Tolvaptan (3.1% versus 5.3% in the any Tolvaptan dose group, 4.1% versus 1.1% in the placebo group). The incidence of peripheral oedema was nearly equal between treatment groups overall (6.3% Tolvaptan, 6.8% placebo), but was seen more frequently in Tolvaptan subjects with severe hyponatremia than in those with mild hyponatremia (9.5% versus 4.8%) and less frequently in placebo subjects with severe hyponatremia than in those with mild hyponatremia (6.2% versus 7.1%). The overall incidence of hyponatremia was less in subjects treated with Tolvaptan versus those who received placebo (9.2% versus 11.8%) and was greater in the mild hyponatremia subgroup compared with the severe hyponatremia subgroup for both treatments (9.3% versus 9.0% in the any Tolvaptan dose group; 12.9% versus 9.6% in the placebo group). Fatigue was less frequently reported in the mild versus severe hyponatremia subgroups for both treatment groups (4.3% versus 9.5% in the any Tolvaptan dose group; 5.0% versus 8.4% in the placebo group).

Serious adverse events (SAEs), deaths and discontinuations due to AE

The most frequent SAEs were cardiac failure and cardiac failure congestive, accounting for approximately 25% of SAEs in both treatment groups. All other individual SAEs occurred with a frequency of <3% in both treatment groups. There were no relevant differences between the treatment groups in the frequencies of any individual SAE. Most of the SAE of special interest occurred with a difference of ≤1% between the Tolvaptan and the placebo

groups with the exception of cardiac arrest (Tolvaptan: 2.3%; placebo: 1.0%) and hypotension (Tolvaptan: 1.2%; placebo: 2.3%) (Table 41).

Table 41: Frequency of SAEs that occurred in ≥1% of subjects by preferred term – all hyponatremia subjects from multiple dose placebo controlled trials.

Preferred Term (MedDRA)	Number (%) of Subjects	
	All Tolvaptan (N=607)	Placebo (N=518)
Cardiac failure	85 (14.0)	79 (15.3)
Cardiac failure congestive	58 (9.6)	52 (10.0)
Renal failure acute	16 (2.6)	16 (3.1)
Cardiac arrest	14 (2.3)	5 (1.0)
Dehydration	11 (1.8)	4 (0.8)
Cardiogenic shock	10 (1.6)	8 (1.5)
Pneumonia	10 (1.6)	11 (2.1)
Renal failure	10 (1.6)	8 (1.5)
Sepsis	10 (1.6)	5 (1.0)
Sudden death	10 (1.6)	8 (1.5)
Ventricular fibrillation	8 (1.3)	2 (0.4)
Respiratory failure	8 (1.3)	4 (0.8)
Sudden cardiac death	8 (1.3)	5 (1.0)
Ascites	7 (1.2)	2 (0.4)
Hyponatraemia	7 (1.2)	8 (1.5)
Hypotension	7 (1.2)	12 (2.3)
Cardiac failure chronic	6 (1.0)	3 (0.6)
Ventricular tachycardia	6 (1.0)	9 (1.7)
Chest pain	5 (0.8)	7 (1.4)
Gastrointestinal haemorrhage	5 (0.8)	6 (1.2)
Hepatic encephalopathy	3 (0.5)	7 (1.4)
Anaemia	2 (0.3)	6 (1.2)
Urinary tract infection	2 (0.3)	5 (1.0)
Angina unstable	1 (0.2)	5 (1.0)
Multi-organ failure	1 (0.2)	6 (1.2)
Cellulitis	1 (0.2)	6 (1.2)
Total *	281 (46.3)	273 (52.7)

TEAEs were defined as AEs that started after start of trial medication treatment; or if the event was continuous from baseline and was serious, trial medication-related, or resulted in death, discontinuation, interruption or reduction of trial therapy. Subjects were counted once, per term, for the most severe of multiple occurrences of a specific MedDRA preferred term.
Events are ordered by descending frequency in the 'All Tolvaptan' column.
* Subjects with TEAEs in multiple system organ classes were counted only once towards the total.

A total of 21.6% of Tolvaptan subjects and 20.8% of placebo hyponatremia subjects died during the studies. Nearly all of the deaths occurred in the large placebo controlled, Phase 3 heart failure Study 156-03-236 conducted in subjects hospitalised for worsening CHF. The majority of deaths were associated with TEAE in the cardiac disorders system organ class (14.3% Tolvaptan versus 11.8% placebo). The incidence of deaths in the other system organ classes was <1%, with the exception of general disorders and administration site conditions (3.5% Tolvaptan versus 4.2% placebo). The most frequent TEAE leading to death in both treatment groups were cardiac failure and cardiac failure congestive, and the combined incidence of these TEAE accounted for approximately 10% of deaths in the Tolvaptan and 8% of deaths in the placebo group. There were no relevant differences between the treatment groups in the incidence of deaths due to any individual TEAE (Table 42).

Table 42: Summary of all deaths in >1 subject in either treatment group, by preferred term – all hyponatremia subjects from multiple dose placebo controlled trials.

Preferred term (MedDRA)	Number (%) of patients	
	All Tolvaptan (N=607)	Placebo (N=518)
Cardiac failure	35 (5.8)	26 (5.0)
Cardiac failure congestive	25 (4.1)	16 (3.1)
Cardiac arrest	11 (1.8)	4 (0.8)
Sudden death	11 (1.8)	9 (1.7)
Sudden cardiac death	8 (1.3)	5 (1.0)
Cardiogenic shock	6 (1.0)	5 (1.0)
Cardio-respiratory arrest	6 (1.0)	3 (0.6)
Cardiac failure chronic	5 (0.8)	3 (0.6)
Death	2 (0.3)	4 (0.8)
Respiratory failure	2 (0.3)	0 (0.0)
Sepsis	2 (0.3)	2 (0.4)
Ventricular fibrillation	2 (0.3)	1 (0.2)
Multi-organ failure	1 (0.2)	5 (1.0)
Cardiomyopathy	1 (0.2)	3 (0.6)
Pneumonia	1 (0.2)	2 (0.4)
Gastrointestinal haemorrhage	1 (0.2)	2 (0.4)
Hepatic failure	1 (0.2)	2 (0.4)
Hypotension	0 (0.0)	2 (0.4)
Total [a]	144 (23.7)	116 (22.8)

Table includes all reported deaths (no 7 day post-treatment cut-off for 156-03-208 study). A TEAE is defined as an AE that started after start of study drug treatment or if the event was continuous from baseline and was serious, study drug related, resulted in death, discontinuation, interruption or reduction of study therapy.
Subjects are counted once, per term, for the most severe of multiple occurrences of a specific MedDRA preferred term.
Events are ordered by descending frequency in the "All Tolvaptan" column.
[a] Subjects with adverse events in multiple system organ classes were counted only once towards the total.

The incidence of TEAE leading to discontinuation of trial medication was comparable between treatment groups with respect to overall frequency as well as the distribution by system organ classes and preferred terms. The system organ class with the highest frequency of TEAE leading to discontinuation was cardiac disorders (3.6% of Tolvaptan subjects and 2.1% of placebo subjects). The only TEAE leading to discontinuation of trial medication in >1% of subjects in either treatment group were cardiac failure, cardiac failure congestive, and renal failure acute.

Laboratory findings

Serum chemistry: For all hyponatremia subjects from multiple-dose trials, the mean change from baseline to end of treatment period showed a greater increase in the all-Tolvaptan dose group than in the placebo group for the following parameters: mean serum sodium concentrations (Tolvaptan versus placebo: 5.02 versus 2.08 mEq/L), serum osmolality (7.49 versus 2.77 mOsm/kg), and chloride (4.32 versus 1.57 mEq/L). There were minor differences between Tolvaptan and placebo groups for the mean change from baseline at the end of the treatment period in the following parameters (all Tolvaptan versus placebo): creatinine: 1.25 versus 1.29mg/dL, urea nitrogen: 0.28 versus 0.14 mg/dL, uric acid: 0.27 versus -0.37 mg/dL, magnesium 0.09 versus 0.02 mg/dL, potassium: 0.08 versus 0.05 mEq/L, aspartate transaminase (AST): -1.04 versus -2.27 IU/L; however, differences between treatment groups did not appear to be clinically relevant and did not suggest any adverse renal, electrolyte, or hepatic effects. There were no other notable mean differences between Tolvaptan and placebo in other serum chemistry parameters. The incidences of shifts in serum chemistry tests (from normal baseline to abnormally high or low during the treatment period) showed a ≥10% difference between Tolvaptan and placebo for the following parameters: Shifts to

abnormally below the lower normal limit: sodium (Tolvaptan versus placebo: 37.5% versus 53.3%), chloride (26.7% versus 47.6%), total cholesterol (28.6% versus 42.4%), and serum osmolality (23.6% versus 33.5%). The Tolvaptan group showed a higher incidence of 'shifts to abnormally above the upper normal limit' for the following: serum osmolality (72.7% versus 60.8%), uric acid (42.6% versus 26.9%) and glucose levels (66% versus 57%) (Table 43). The only potentially clinically significant laboratory abnormalities with a ≥ 5% difference in incidence between treatment groups was decreased sodium, which had a lower incidence in the all Tolvaptan dose group (116 of 588 subjects [19.7%]) than in the placebo group (179 of 504 [35.5%]) (Table 44). None of the TEAE related to serum chemistry abnormalities occurred at a higher or lower incidence in the Tolvaptan group than the placebo group (that is, the incidences for Tolvaptan and placebo differed by <1%), with the exception of hyperkalaemia (Tolvaptan versus placebo: 7.1% versus 5.8%), hyponatremia (3.8% versus 5.4%) and hyperuricaemia (3% versus 4.1%) (Table 45).

Table 43: Serum chemistry: shifts from normal at baseline to abnormally high or low during treatment period in >10% of subjects in either treatment group – all hyponatremia subjects from multiple dose placebo controlled trials.

Test	Number of Subjects (n/N [%])			
	Normal to Below Normal		Normal to Above Normal	
	All Tolvaptan	Placebo/ Other	All Tolvaptan	Placebo/ Other
Albumin	93 / 366 (25.4)	83 / 320 (25.9)	24 / 366 (6.6)	22 / 320 (6.9)
Alkaline phosphatase	0 / 381 (0.0)	1 / 339 (0.3)	101 / 381 (26.5)	84 / 339 (24.8)
ALT (SGPT)	12 / 460 (2.6)	10 / 373 (2.7)	113 / 460 (24.6)	89 / 373 (23.9)
AST (SGOT)	6 / 382 (1.6)	7 / 317 (2.2)	110 / 382 (28.8)	99 / 317 (31.2)
Bilirubin, total	18 / 362 (5.0)	14 / 313 (4.5)	55 / 362 (15.2)	58 / 313 (18.5)
Calcium	68 / 506 (13.4)	48 / 430 (11.2)	52 / 506 (10.3)	39 / 430 (9.1)
Chloride	93 / 348 (26.7)	130 / 273 (47.6)	17 / 348 (4.9)	5 / 273 (1.8)
Cholesterol, total	57 / 199 (28.6)	61 / 144 (42.4)	34 / 199 (17.1)	20 / 144 (13.9)
Creatinine	3 / 369 (0.8)	5 / 306 (1.6)	119 / 369 (32.2)	93 / 306 (30.4)
Glucose	45 / 276 (16.3)	28 / 207 (13.5)	182 / 276 (65.9)	118 / 207 (57.0)
Glutamyl transferase	4 /182 (2.2)	3 / 169 (1.8)	54 /182 (29.7)	43 / 169 (25.4)
Lactic dehydrogenase	0 / 288 (0.0)	0 / 269 (0.0)	100 / 288 (34.7)	90 / 269 (33.5)
Osmolality, serum	39 / 165 (23.6)	53 / 158 (33.5)	120 / 165 (72.7)	96 / 158 (60.8)
Potassium	47 / 489 (9.6)	44 / 437 (10.1)	118 / 489 (24.1)	87 / 437 (19.9)
Protein, total serum	76 / 467 (16.3)	68 / 394 (17.3)	122 / 467 (26.1)	90 / 394 (22.8)
Sodium	33 / 88 (37.5)	32 / 60 (53.3)	4 / 88 (4.5)	2 / 60 (3.3)
Triglycerides	74 / 489 (15.1)	68 / 411 (16.5)	68 / 489 (13.9)	52 / 411 (12.7)
Urea nitrogen	12 / 327 (3.7)	0 / 260 (0.0)	133 / 327 (40.7)	99 / 260 (38.1)
Uric acid	4 / 310 (1.3)	13 / 249 (5.2)	132 / 310 (42.6)	67 / 249 (26.9)

A subject is counted once if he/she crossed the lower (higher) limit of the reference range of a laboratory test. The subject may return to normal or remain abnormally low (high) after the cross. A subject who crossed a lower (higher) limit and then crossed a higher (lower) limit is counted once for each limit.
Includes all laboratory tests where upper and/or lower limits of normal were defined.
n = number of subjects with shifts from normal baseline value to an abnormally high or low value during treatment; N = number of subjects with normal baseline values (denominator).

Table 44: Serum chemistry: potentially clinically significant abnormalities – all hyponatremia subjects from multiple dose placebo controlled trials.

Test	Abnormality [a]	Number of Subjects (n/N [%])	
		All Tolvaptan	Placebo
Glucose	Increased	180 / 571 (31.5)	145 / 483 (30.0)
Uric acid	Increased	167 / 577 (28.9)	124 / 495 (25.1)
Urea nitrogen	Increased	167 / 581 (28.7)	132 / 495 (26.7)
Sodium	Decreased	116 / 588 (19.7)	179 / 504 (35.5)
Glutamyl transferase	Increased	88 / 449 (19.6)	81 / 434 (18.7)
Albumin	Decreased	100 / 572 (17.5)	77 / 485 (15.9)
Potassium	Increased	94 / 542 (17.3)	73 / 467 (15.6)
Creatinine	Increased	99 / 582 (17.0)	88 / 497 (17.7)
Bilirubin, total	Increased	75 / 564 (13.3)	72 / 476 (15.1)
Protein, total serum	Decreased	45 / 580 (7.8)	48 / 496 (9.7)
Calcium	Decreased	43 / 581 (7.4)	30 / 497 (6.0)
AST (SGOT)	Increased	39 / 561 (7.0)	21 / 462 (4.5)
ALT (SGPT)	Increased	29 / 566 (5.1)	28 / 477 (5.9)
Alkaline phosphatase	Increased	23 / 578 (4.0)	15 / 491 (3.1)
Glucose	Decreased	20 / 571 (3.5)	18 / 483 (3.7)
Calcium	Increased	15 / 581 (2.6)	11 / 497 (2.2)
Potassium	Decreased	15 / 572 (2.6)	13 / 482 (2.7)
Cholesterol, total	Increased	12 / 577 (2.1)	13 / 495 (2.6)
Magnesium, serum	Increased	8 / 449 (1.8)	7 / 437 (1.6)
Sodium	Increased	10 / 588 (1.7)	4 / 504 (0.8)
Triglycerides	Increased	10 / 580 (1.7)	7 / 495 (1.4)
Magnesium, serum	Decreased	5 / 449 (1.1)	6 / 437 (1.4)

n = number of subjects meeting the criteria for potential clinical significance.
N = total number of subjects with baseline and at least one post-baseline result for the test (denominator).
ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase).

Table 45: Abnormal serum chemistry values reported as TEAEs in >2% of Tolvaptan subjects – all hyponatremia subjects from multiple dose placebo controlled trials.

Preferred Term	Number (%) of Subjects	
	All Tolvaptan (N=607)	Placebo (N=518)
Hyperkalaemia	43 (7.1)	30 (5.8)
Hypokalaemia	39 (6.4)	31 (6.0)
Hyponatraemia	23 (3.8)	28 (5.4)
Hyperglycaemia	23 (3.8)	16 (3.1)
Hypoglycaemia	22 (3.6)	14 (2.7)
Blood creatinine increased	20 (3.3)	12 (2.3)
Hyperuricaemia	18 (3.0)	21 (4.1)
Blood urea increased	13 (2.1)	9 (1.7)
Blood uric acid increased	12 (2.0)	6 (1.2)

TEAEs were defined as AEs that started after start of trial medication treatment; or if the event was continuous from baseline and was serious, trial medication-related, or resulted in death, discontinuation, interruption or reduction of trial therapy.
Subjects were counted once, per term, for the most severe of multiple occurrences of a specific MedDRA preferred term.
System organ classes are ordered by descending frequency in the "Tolvaptan 30 mg" group.

Haematology: There were no notable mean changes from baseline at the end of the treatment period for any haematology parameter, especially haematocrit (mean change from baseline was 0% for Tolvaptan and -0.56% for placebo), suggesting no adverse implication for red blood cell indices. Shifts to abnormally below the lower normal limit included: absolute eosinophils (Tolvaptan versus placebo: 4.7% versus 16.7%), haematocrit (32.2% versus 42.6%), and absolute lymphocytes (34.8% versus 7.7%) while

shifts to abnormally above the upper normal limit included: haemoglobin (38.7% versus 3.1%) (Table 46).

Table 46: Haematology: shifts from normal at baseline to abnormally high or low during treatment period in >10% of subjects in either treatment group – all hyponatremia subjects from multiple dose placebo controlled trials.

Test	Number of Subjects (n/N [%])			
	Normal to Below Normal		Normal to Above Normal	
	All Tolvaptan	Placebo/ Other	All Tolvaptan	Placebo/ Other
aPTT	124 / 353 (35.1)	86 / 301 (28.6)	91 / 353 (25.8)	96 / 301 (31.9)
Basophils	0 / 506 (0.0)	0 / 442 (0.0)	57 / 506 (11.3)	34 / 442 (7.7)
Eosinophils	0 / 493 (0.0)	0 / 436 (0.0)	63 / 493 (12.8)	61 / 436 (14.0)
Eosinophils, absolute	2 / 42 (4.7)	4 /24 (16.7)	2 /42 (4.7)	2 /24 (8.3)
Hematocrit	104 / 323 (32.2)	118 / 277 (42.6)	38 / 323 (11.8)	20 / 277 (7.2)
Hemoglobin	110 / 284 (38.7)	122 / 261 (46.7)	17 / 284 (38.7)	8 / 261 (3.1)
Lymphocytes, absolute	8 / 23 (34.8)	1 / 13 (7.7)	1 / 23 (4.3)	1 / 13 (7.7)
Mean corpuscular hemoglobin concentrate	97 / 376 (25.8)	77 / 364 (21.2)	0 / 376 (0.0)	0 / 364 (0.0)
Mean corpuscular volume	19 / 246 (5.5)	30 / 327 (9.2)	76 / 246 (22.0)	52 / 327 (15.9)
Monocytes	61 / 456 (13.4)	45 / 388 (11.6)	79 / 456 (17.3)	71 / 388 (18.3)
Monocytes, absolute	10 / 41 (24.4)	4 / 21 (19.0)	2 / 41 (4.9)	0 / 21 (0.0)
Neutrophil, segs	5 / 68 (7.4)	1 / 40 (2.5)	22 / 68 (32.4)	9 / 40 (22.5)
Neutrophils	19 / 256 (7.4)	8 / 230 (3.5)	95 / 256 (37.1)	97 / 230 (42.2)
Neutrophils, absolute	1 / 33 (3.0)	1 / 18 (5.6)	7 / 33 (21.2)	4 / 18 (22.2)
Platelet count	67 / 412 (16.3)	53 / 352 (15.1)	47 / 412 (11.4)	50 / 352 (14.2)
Prothrombin time	12 / 286 (4.2)	12 / 265 (4.5)	79 / 286 (27.9)	74 / 265 (27.9)
Prothrombin time INR	0 / 0 (0.0)	0 / 8 (0.0)	0 / 0 (0.0)	2 / 8 (25.0)
Red blood cell count	1 / 3 (33.3)	2 / 7 (28.6)	0 / 3 (0.0)	0 / 7 (0.0)
White blood count	0 / 7 (0.0)	1 / 13 (7.7)	1 / 7 (14.3)	3 / 13 (23.1)

A subject is counted once if he/she crossed the lower (higher) limit of the reference range of a laboratory test. The subject may return to normal or remain abnormally low (high) after the cross. A subject who crossed a lower (higher) limit and then crossed a higher (lower) limit is counted once for each limit.
Includes all laboratory tests where upper and/or lower limits of normal were defined.
n = number of subjects with shifts from normal baseline value to an abnormally high or low value during treatment; N = number of subjects with normal baseline values (denominator).
aPTT = activated partial thromboplastin time; INR = International Normalized Ratio

The only potentially clinically significant abnormality with a >5% difference in incidence between treatment groups were decreased haemoglobin and decreased absolute neutrophil that were both reported more frequently in Tolvaptan subjects than in placebo subjects (Table 47). The most frequent haematology abnormality reported as a TEAE (≥2% in the any oral dose Tolvaptan group), for Tolvaptan subjects compared with placebo subjects was anaemia that occurred at a slightly higher frequency with placebo (7.5%) than with Tolvaptan (5.1%). Most other laboratory TEAE related to haematology abnormalities occurred in <1% of subjects in both treatment groups.

Table 47: Haematology: potentially clinically significant abnormalities – all hyponatremia subjects from multiple dose placebo controlled trials.

Test	Abnormality [a]	Number of Subjects (n/N [%])	
		All Tolvaptan	Placebo
Prothrombin time INR	Increased	18 / 90 (20.0)	6 / 43 (14.0)
Lymphocytes, absolute	Decreased	9 / 46 (19.6)	4 / 24 (16.7)
Hemoglobin	Decreased	87 / 539 (16.1)	82 / 464 (17.7)
Neutrophils, absolute	Decreased	4 / 41 (9.8)	0 / 21 (0.0)
aPTT	Increased	37 / 500 (7.4)	28 / 430 (6.5)
White blood count	Increased	26 / 538 (4.8)	30 / 464 (6.5)
Platelet count	Decreased	21 / 523 (4.0)	448 / 18 (4.0)
White blood count	Decreased	7 / 538 (1.3)	10 / 464 (2.2)
Hemoglobin	Increased	2 / 539 (0.4)	1 / 464 (0.2)

n = number of subjects meeting the criteria for potential clinical significance
N = total number of subjects with baseline and at least one post-baseline result for the test (denominator)
aPTT = activated partial thromboplastin time; INR = International Normalized Ratio

Comments: The effects on haematocrit and haemoglobin values may be a consequence of aquaresis. Interpretation of changes in differential blood counts were confounded by wide variability and the fact that Tolvaptan did not affect total white blood counts.

No TEAE related to urinalysis abnormalities were reported in ≥2% of subjects in either treatment group, and there were no relevant differences between the treatment groups.

Vital signs and ECG: There were no clinically meaningful differences between the Tolvaptan group and the placebo group in mean change from baseline in vital signs measurements at the end of the treatment period. The most commonly reported AEs associated with abnormal vital signs were dizziness and hypotension. The distribution of potentially clinically significant vital sign abnormalities was comparable between the treatment groups**.**

No notable differences between the Tolvaptan and placebo groups were observed in mean changes for ECG parameters. None of the potentially clinically significant individual ECG abnormalities was reported at a higher incidence in the Tolvaptan group compared with the placebo group, with the exception of outliers in ventricular rate (16.5% Tolvaptan versus 11.9% placebo). The only ECG abnormality reported as a TEAE in ≥2% of subjects in either the all Tolvaptan or placebo groups was ventricular tachycardia (4.0% Tolvaptan and 3.9% placebo). The treatment groups were comparable with respect to the incidence of TEAE related to ECG abnormalities.

Safety in special populations

Safety in all heart failure patients

The heart failure population included patients in NYHA classes I-IV with signs of extracellular volume expansion with or without hyponatremia. The Tolvaptan clinical program for heart failure consisted of seven multiple dose trials: one Phase 3 trial and one Phase 2 trial conducted in subjects hospitalised with worsening heart failure and five Phase 2 trials conducted in subjects with stable CHF. The Tolvaptan doses investigated in subjects hospitalised with worsening heart failure were 30, 60, and 90 mg QD, although the vast majority of subjects (2527/3147, 80.3%) received 30 mg QD. The Tolvaptan doses investigated in subjects with stable heart failure were 10, 15, 30, 45, 60, 90, and 120 mg QD. In all trials, Tolvaptan was provided as an adjunct to subjects' existing conventional therapy for heart failure. The primary safety data in the Tolvaptan heart failure program was from a multinational, double blind, placebo controlled Phase 3 Study 156-03-236 in which 4133 subjects were randomised within 48 h of an acute hospitalization for worsening heart failure to Tolvaptan 30 mg QD (N=2072) or placebo QD (N=2061) for a

minimum treatment duration of 60 days. All 3147 subjects were exposed to Tolvaptan for ≤30 days, 1372 subjects were exposed to a Tolvaptan for ≥180 days, with 817 subjects exposure for at least 360 days. The extent of exposure to study medication over time was comparable between the two treatment groups. In both groups, approximately half of the subjects received study medication for between 180 and 360 days, while approximately one third of subjects received study medication for between 361 and 720 days. About two thirds of subjects in both treatment groups completed the study according to protocol. The most common reasons for premature discontinuation were death (Tolvaptan versus placebo: 11.9% versus 15.0%), adverse experience (9.2% versus 6.7%), and withdrawal of consent (8.3% versus 9.4%) with no significant difference between treatment groups. Majority of the subjects were Caucasian (77.7% versus 83.0%), male (71.6% versus 75.1%) with mean age of 65 years (about 56% of subjects in both treatment groups were 65 years or older).

No relevant differences were seen between treatment groups regarding the frequency of TEAE, serious TEAE, and trial discontinuations due to TEAE or death. The most frequent TEAE in both treatment groups were cardiac failure, cardiac failure congestive, and nausea, all of which occurred in between 10% and 20% of subjects. The frequency of these and most other TEAE was comparable between the two treatment groups (notably hypotension, hypertension, and renal failure). The only TEAE with a higher frequency in the Tolvaptan than in the placebo group were thirst (Tolvaptan versus placebo: 18.1% versus 2.5%), dry mouth (9.2% versus 2.4%), pollakiuria (6.0% versus 1.2%), and polyuria (3.3% versus 0.6%), all of which are consistent with the pharmacological effects of Tolvaptan. Nausea, diarrhoea, ventricular tachycardia, and hypernatremia showed higher incidence at increasingly higher Tolvaptan doses; rate was comparable between the Tolvaptan and placebo groups for nausea, diarrhoea and ventricular tachycardia, but the incidence rates for hypernatremia were higher in the Tolvaptan than the placebo group but generally low overall (Tolvaptan:1.8%; placebo: 0.4%). Additionally, dry mouth showed a potential dose response trend, that is, incidences on Tolvaptan of 4.2% at 15 mg, 8.9% at 30 mg, 8.0% at 15-60 mg, 13.2% at 45 mg, 14.5% at 60 mg, 11.0% at 90 mg, and 0% at 120 mg compared to 2.4% on placebo. The proportion of subjects with potentially drug related TEAE was higher in the Tolvaptan group (48.8%) than in the placebo group (30.8%); however, the majority of this difference was accounted for by TEAE expected with the pharmacological action of Tolvaptan such as thirst (Tolvaptan versus placebo: 17.0% versus 2.3%), dry mouth (8.4% versus 2.0%), pollakiuria (5.2% versus 0.9%), and polyuria (3.1% versus 0.5%).

TEAE associated with arrhythmias occurred with comparable frequencies in both treatment groups (Tolvaptan versus placebo: all atrial arrhythmias 6.6% versus 6.7%; all ventricular arrhythmias: 13.5% versus 13.8%). The most common individual TEAE associated with arrhythmias were ventricular tachycardia (5.5% versus 5.1%), atrial fibrillation (4.6% versus 5.2%) and syncope (2.3% in each group). The incidence of AE related to cardiac arrest or ischemic events was also similar in Tolvaptan and placebo groups.

A total of 17.8% of Tolvaptan subjects and 20.9% of placebo subjects died during the CHF studies. The TEAE leading to death in >1% of subjects in either treatment group were cardiac failure, cardiac failure congestive, sudden death, sudden cardiac death, and cardiac arrest, with the combined incidence of these TEAE accounting for about 10% of deaths in both treatment groups. There were no relevant differences between the treatment groups in the incidence of deaths due to any individual TEAE. Overall, there was no excess of mortality events in the Tolvaptan compared with placebo groups, a finding that is consistent with the results in the larger pool of subjects with heart failure or hyponatremia. The most frequent serious TEAE were cardiac failure and cardiac failure congestive, accounting for about 30% of serious TEAE in both treatment groups. All other individual serious TEAE occurred with a frequency of <3% in both treatment groups.

There were no relevant differences between the treatment groups in the frequencies of any individual serious TEAE. Of note, the serious TEAE of special interest (including ventricular tachycardia, cardiac arrest, hyperkalaemia, cerebrovascular accident, renal failure, and hypotension) all occurred with differences of <1% between the Tolvaptan and placebo groups (Table 48). The incidence of TEAE leading to discontinuation of trial medication was comparable between treatment groups with respect to overall frequency as well as the distribution by system organ classes and preferred terms. The only TEAE leading to discontinuation of trial medication in >0.5% of subjects in both treatment groups were cardiac failure, cardiac failure congestive, and renal failure acute.

Table 48: Frequency of SAEs that occurred in ≥1% of subjects by preferred term – all heart failure subjects from multiple dose trials.

Preferred Term (MedDRA)	Number (%) of Subjects	
	All Tolvaptan mg (N=3147)	Placebo (N=2571)
Cardiac failure	491 (15.6)	453 (17.6)
Cardiac failure congestive	383 (12.2)	328 (12.8)
Pneumonia	86 (2.7)	70 (2.7)
Ventricular tachycardia	71 (2.3)	49 (1.9)
Renal failure acute	64 (2.0)	72 (2.8)
Chest pain	56 (1.8)	36 (1.4)
Renal failure	54 (1.7)	59 (2.3)
Sudden death	51 (1.6)	50 (1.9)
Cardiac arrest	49 (1.6)	26 (1.0)
Sudden cardiac death	46 (1.5)	44 (1.7)
Atrial fibrillation	41 (1.3)	40 (1.6)
Angina unstable	37 (1.2)	38 (1.5)
Cerebrovascular accident	37 (1.2)	34 (1.3)
Hypotension	37 (1.2)	30 (1.2)
Syncope	37 (1.2)	27 (1.1)
Dehydration	37 (1.2)	26 (1.0)
Cardiogenic shock	35 (1.1)	25 (1.0)
Anaemia	32 (1.0)	30 (1.2)
Ventricular fibrillation	26 (0.8)	25 (1.0)
Acute myocardial infarction	25 (0.8)	31 (1.2)
Cardio-respiratory arrest	17 (0.5)	26 (1.0)
Chronic obstructive pulmonary disease	25 (0.8)	25 (1.0)
Total [a]	**1506 (47.9)**	**1353 (52.6)**

TEAEs were defined as AEs that started after start of trial medication treatment; or if the event was continuous from baseline and was serious, trial medication-related, or resulted in death, discontinuation, interruption or reduction of trial therapy.
Subjects were counted once, per term, for the most severe of multiple occurrences of a specific MedDRA preferred term.
Preferred terms are ordered by descending frequency in the "All tolvaptan" column.
[a] Subjects with TEAEs in multiple system organ classes were counted only once towards the total.

For all heart failure subjects from multiple dose trials, there was a greater mean increase (from baseline to end of treatment period) in Tolvaptan subjects for the following: serum sodium concentrations (Tolvaptan versus placebo: 1.66 versus -0.22 mEq/L), serum osmolality (4.08 versus 1.64 mOsm/kg) and chloride (1.69 versus 0.13 mEq/L). There were no other notable mean differences between Tolvaptan and placebo in other serum chemistry parameters and there were no clinically relevant shifts from baseline. The only potentially clinically significant serum chemistry abnormality with a >4% difference in incidence between treatment groups was increased urea nitrogen, sodium, uric acid, and glucose (all with a greater incidence with Tolvaptan) and decreased sodium (greater incidence with placebo) (Table 49). The incidence of TEAE related to serum chemistry abnormalities were similar in the Tolvaptan and placebo group (Table 50). The change

from baseline in haematology parameters and the incidence of potentially clinically significant haematological abnormalities did not show any clinically relevant difference between Tolvaptan and placebo groups. There were no clinically meaningful differences between Tolvaptan and placebo in mean change from baseline in vital sign measurements at the end of the treatment period. The most frequent vital sign abnormalities that were reported as TEAE (>2% in the Tolvaptan group) were hypotension (Tolvaptan versus placebo: 9.1% versus 9.6%), dizziness (9.1 % versus 8.2%), pyrexia (3.3 versus 3.2%), syncope (2.2 % versus 2.2%), hypertension (2.0 % versus 2.6%), and weight increased (1.9 % versus 1.6%). No notable differences between Tolvaptan and placebo groups were observed in mean changes for ECG parameters for all heart failure subjects from the multiple dose trials and none of the potentially clinically significant individual ECG abnormalities was reported at a higher incidence for Tolvaptan compared with placebo. The most frequent ECG abnormalities that were reported as TEAE (≥2% in the Tolvaptan group) were ventricular tachycardia (Tolvaptan versus placebo: 5.4% versus 5.1%) and atrial fibrillation (4.6% versus 5.2%).

Table 49: Serum chemistry: potentially clinically significant laboratory abnormalities – all heart failure subjects from multiple dose trials.

Test	Abnormality [a]	Number of Subjects (n/N [%])	
		All Tolvaptan	Placebo
Glucose	Increased	1171 / 2942 (39.8)	848 / 2425 (35.0)
Uric acid	Increased	1128 / 2988 (37.8)	834 / 2464 (33.8)
Urea nitrogen	Increased	1044 / 2989 (34.9)	1046 / 2468 (42.4)
Glutamyl transferase	Increased	465 / 2313 (20.1)	448 / 2211 (20.3)
Potassium	Increased	588 / 2953 (19.9)	479 / 2427 (19.7)
Creatinine	Increased	565 / 2987 (18.9)	431 / 2469 (17.5)
Sodium	Increased	331 / 2986 (11.1)	148 / 2464 (6.0)
Bilirubin, total	Increased	272 / 2955 (9.2)	251 / 2433 (10.3)
Albumin	Decreased	255 / 2917 (8.7)	210 / 2435 (8.6)
Sodium	Decreased	165 / 2986 (5.5)	251 / 2464 (10.2)
ALT(SGPT)	Increased	151 / 2937 (5.1)	133 / 2415 (5.5)
Phosphorus inorganic	Decreased	2 / 40 (5.0)	0 / 0 (0.0)
Calcium	Increased	138 / 2990 (4.6)	98 / 2469 (4.0)
AST (SGOT)	Increased	130 / 2898 (4.5)	109 / 2356 (4.6)
Cholesterol, total	Increased	127 / 2989 (4.2)	96 / 2466 (3.9)
Calcium	Decreased	120 / 2990 (4.0)	118 / 2469 (4.8)
Triglycerides	Increased	93 / 2988 (3.1)	75 / 2466 (3.0)
Protein, total serum	Decreased	80 / 2990 (2.7)	81 / 2468 (3.3)
Glucose	Decreased	76 / 2942 (2.6)	70 / 2425 (2.9)
Alkaline phosphatase	Increased	63 / 2980 (2.1)	54 / 2454 (2.2)
Magnesium, serum	Increased	41 / 2162 (1.9)	28 /2162 (1.3)
Potassium	Decreased	51 / 2953 (1.7)	52 / 2427 (2.1)
Magnesium, serum	Decreased	11 / 2162 (0.5)	11 / 2162 (0.5)

n = number of subjects meeting the criteria for potential clinical significance.
N = total number of subjects with baseline and at least one post-baseline result for the test (denominator).

Table 50: Abnormal serum chemistry values reports as TEAEs in >2% of subjects in the all Tolvaptan dose group – all heart failure subjects from multiple dose trials.

Preferred Term	Number (%) of Subjects	
	All Tolvaptan (N=3147)	Placebo/Other (N=2571)
Hyperkalaemia	206 (6.5)	154 (6.0)
Hypokalaemia	198 (6.3)	210 (8.2)
Hyperuricaemia	148 (4.7)	119 (4.6)
Hypoglycaemia	117 (3.7)	81 (3.2)
Blood creatinine increased	113 (3.6)	77 (3.0)
Hyperglycaemia	99 (3.1)	82 (3.2)
Blood uric acid increased	95 (3.0)	57 (2.2)
Blood urea increased	84 (2.7)	71 (2.8)
Hyponatraemia	70 (2.2)	72 (2.8)

TEAEs were defined as AEs that started after start of trial medication treatment; or if the event was continuous from baseline and was serious, trial medication-related, or resulted in death, discontinuation, interruption or reduction of trial therapy. Subjects were counted once, per term, for the most severe of multiple occurrences of a specific MedDRA preferred term. System organ classes are ordered by descending frequency in the "All Tolvaptan" group.

Safety in all HF and hyponatremia patients

In the pooled analysis of subjects with heart failure or hyponatremia, a total of 3294 subjects have been exposed to any Tolvaptan dose for ≤30 days, 1372 subjects were exposed to any Tolvaptan dose for >180 days, with 817 subjects exposed for at least 360 days. The extent of exposure over time was comparable between the Tolvaptan and placebo groups, although a trend was seen for higher exposure in the placebo treatment group: the proportion of subject with an exposure time of more than 180 days was higher in the placebo group (51.1%) than in the Tolvaptan group (41.7%). Approximately 65% of subjects in both treatment groups completed the study according to protocol. The most common reasons for premature discontinuation were death (Tolvaptan versus placebo: 11.4% versus 14.1%), withdrawal of consent (8.2% versus 9.4%), and adverse experience (9.5% versus 7.2%). The majority of subjects were Caucasian (Tolvaptan versus placebo: 78.4% versus 83.1%), male (70.7% versus 74.2%) with mean age of 65 years (about 55% of subjects in both treatment groups were ≥ 65 years).

No relevant differences were seen between treatment groups regarding the frequency of TEAE, serious TEAE, and trial discontinuations due to TEAE or death. The most frequent TEAE in both treatment groups were cardiac failure, cardiac failure congestive, and nausea, all of which occurred in between 10% and 20% of subjects. The frequency of these and most other TEAE was comparable between the two treatment groups. The proportion of subjects with potentially drug related TEAE was higher in the Tolvaptan group (48.8%) than in the placebo group (30.7%), with the majority of this difference being accounted for by thirst (Tolvaptan versus placebo: 17.1% versus 2.4%), dry mouth (8.5% versus 2.1%), pollakiuria (5.4% versus 0.9%), and polyuria (3.1% versus 0.5%), all of which are consistent with the pharmacological effects of Tolvaptan.

Among the 'all heart failure and hyponatremia subjects', 17.2% in the Tolvaptan group and 20.0% in the placebo subjects died during the on treatment period, that is, during treatment and up to 7 days after the last dose of study drug. The TEAE leading to death in >1% of subjects in either treatment group were cardiac failure, cardiac failure congestive, sudden death, sudden cardiac death, and cardiac arrest, with a combined incidence of approximately 10% in both treatment groups. The overall frequency of serious TEAE was slightly higher in the placebo group (51.1%) than in the Tolvaptan group (47.2%). The most frequent serious TEAE (that is, occurring in >10% of subjects) were cardiac failure and cardiac failure congestive in both treatment groups. All other individual serious TEAE occurred with a frequency of <3% in both treatment groups with no relevant differences between the treatment groups in the frequencies of any individual serious TEAE. Of note, the serious TEAE of special interest (including ventricular tachycardia, cardiac arrest,

hyperkalemia, cerebrovascular accident, renal failure, and hypotension) all occurred with differences of <1% between the Tolvaptan and the placebo groups. A total of 9.4% of subjects in the Tolvaptan group and 7.1% of subjects in the placebo group experienced TEAE that led to discontinuation of trial medication. The most frequent TEAE leading to discontinuation were cardiac failure, cardiac failure congestive and renal failure acute with no relevant differences between the treatment groups.

Specific AE of interest in the 'combined HF and hyponatremia patient population'

Aquaresis: The most common TEAE associated with aquaresis were thirst, dry mouth, pollakiuria, polyuria, blood creatinine increased, dehydration, hypotension, renal failure, and renal failure acute. Most TEAE occurred with comparable frequencies in both treatment groups. TEAE that occurred more frequently in the Tolvaptan group than in the placebo group were thirst (18.1% versus 2.7%), dry mouth (9.5% versus 2.4%), pollakiuria (6.2% versus 1.3%) and polyuria (3.3% versus 0.6%), which is consistent with the aquaretic effect of Tolvaptan.

Electrolyte disturbances: TEAE associated with electrolyte disturbances were grouped by the following electrolytes: sodium, potassium, magnesium, and calcium. The most common TEAE associated with electrolyte disturbances were nausea (Tolvaptan versus placebo: 10.4% versus 11.0%), hypokalaemia (6.3% versus 7.9%), fatigue (6.2% versus 4.3%), and hyperkalaemia (6.6% versus 5.8%). There were no relevant differences between both treatment groups in the incidence of any individual TEAE associated with electrolyte disturbances, notably hyponatremia (2.2% versus 2.8%).

Vasopression: TEAE associated with vasopression were grouped according to the following medical concepts: blood pressure, thrombosis/hypercoagulable state, and coagulation/haemostatic disorders/increased bleeding. TEAE associated with vasopression occurred with comparable frequencies in both treatment groups (Tolvaptan versus placebo) for all three medical concepts (blood pressure: 17.7% versus 19.1%; thrombosis/hypercoagulable state: 6.6% versus 6.8%; coagulation/hemostatic disorders/increased bleeding: 11.4% versus 12.0%). The most common TEAE associated with vasopression were hypotension (9.1% versus 9.6%) and headache (6.7% versus 6.6%). Most other TEAE occurred with a frequency of <1% in both treatment groups with no relevant differences between both treatment groups in the incidence of any individual TEAE associated with vasopression.

Renal function: TEAE associated with renal function occurred with comparable frequencies in both treatment groups (Tolvaptan versus placebo: 24.9% versus 24.3%). The most common TEAE were hyperkalaemia (6.6% versus 5.8%), renal failure (5.0% versus 5.6%), renal failure acute (3.2% versus 4.1%), and blood creatinine increased (3.5% versus 2.9%). TEAE of blood urea increased, blood uric acid increased, and haematuria occurred with a frequency of between 2% and 3% in both treatment groups. The incidence of most other TEAE was <1% in both treatment groups with no relevant differences between both treatment groups in the incidence of any individual TEAE associated with renal function.

Arrhythmias: TEAE associated with arrhythmias were grouped according to the following medical concepts: atrial arrhythmias and ventricular arrhythmias. These TEAE occurred with comparable frequencies in both treatment groups (atrial arrhythmias: 6.3% in both groups; ventricular arrhythmias: 12.8% Tolvaptan versus 13.0% placebo). The most common TEAE associated with arrhythmias were ventricular tachycardia (5.2% versus 4.8%) and atrial fibrillation (4.4% versus 4.9%). All other TEAE occurred in <2% of subjects with the exception of syncope (reported for 2.2% of subjects in both groups). There were no relevant differences between both treatment groups in the incidence of any individual TEAE associated with arrhythmias, especially the differences between Tolvaptan and placebo in the individual atrial arrhythmia events (arrhythmia

supraventricular, atrial fibrillation, atrial flutter, atrial tachycardia, long QT syndrome, supraventricular extrasystoles, and supraventricular tachycardia) were all <1%.

Other cardiac AE: These were grouped according to the following medical concepts: cardiac arrest and ischemic events (for example, recurrent myocardial infarction, acute myocardial infarction). These TEAE occurred with comparable frequencies in both treatment groups (Tolvaptan versus placebo: 17.1% versus 18.6%; ischemic events: 16.5% versus 17.1%). The most common cardiac disorders of this category were chest pain (6.9% versus 6.5%) and ventricular tachycardia (5.2% versus 4.8).

Hepatic disorders: Only few TEAE associated with hepatic disorders were reported in the multiple dose placebo controlled trials with Tolvaptan, and these occurred with comparable frequencies in both treatment groups (Tolvaptan versus placebo: 7.9% versus 8.5%). The only hepatic disorders reported for >1% of subjects in either treatment group were gamma-glytamyl-transferase increased (1.6% versus 1.7%) and liver function test abnormal (1.1% versus and 1.2%). There were no relevant differences between both treatment groups in the incidence of any individual TEAE associated with hepatic disorders (all differences between Tolvaptan and placebo <1%).

Metabolic/nutritional disorders: These were grouped according to the following medical concepts: effects on glucose and hyperuricemia/gout and occurred with comparable frequencies in both treatment groups (Tolvaptan versus placebo) for both medical concepts (effects on glucose: 12.8% versus 11.9%; hyperuricaemia/gout: 14.8% versus 13.8%). The most common TEAE associated with metabolic/nutritional disorders were hyperuricaemia, pain in extremity, gout, hyperglycaemia, hypoglycaemia, and blood uric acid increased, all of which occurred in 3% to 5% of subjects in both treatment groups. With the exception of diabetes mellitus and blood glucose increased, all other TEAE occurred in <1% of subjects in both treatment groups.

General system: Dizziness and vertigo were the only TEAE associated with general system disorders that were reported for >1% of subjects in either treatment group. Of these, dizziness (an expected consequence of some side effects related to the use of Tolvaptan, such as dehydration and hypotension) was the more frequent event, occurring in 9.1% of Tolvaptan subjects and 8.2% of placebo subjects (vertigo: 1.2% versus 1.5%).

Neurologic disorders: There were only five TEAE associated with neurologic function, seizures, and cognitive function that were reported for >1% of subjects in either treatment group (headache, depression, confusional state, syncope, and fall). The most frequent of these events was headache (Tolvaptan versus placebo: 6.7% versus 6.6%). The frequency of all TEAE was comparable between both treatment groups. Of note, the incidence of seizures and other extreme symptoms sometimes associated with hyponatremia or its treatment were low. There were no reports of central pontine or peripheral myelinolysis.

Stroke: Overall, the incidence of TEAE associated with stroke was low and comparable between the treatment groups (Tolvaptan versus placebo) for any stroke (2.0% versus 1.9%), haemorrhagic stroke (0.2% in both groups), ischemic stroke (0.5% versus 0.3%), unspecified stroke (1.2% versus 1.4%). The only TEAE reported for >1% of subjects was cerebrovascular accident (1.2% versus 1.3%).

Rare AE: TEAE included in this category were neutropenia related events (agranulocytosis, febrile neutropenia, neutropenia, pancytopenia, neutrophil count increased, neutrophilia), thrombocytopenia related events (pancytopenia, platelet count decreased, platelet count increased, thrombocytopenia, thrombocythaemia), and anaphylactic reactions (sudden death, blood pressure increased, blood pressure systolic increased, diastolic hypertension, and hypertension). The incidence rate (Tolvaptan versus placebo) for these rare AE were: neutropenia related events: 0.4% (14/3294) versus 0.3% (9/2738); for thrombocytopenia related events : 1.6% (53/3294) versus 1.6% (44/2738); and anaphylactic reactions: 4.3% (140/3294) versus 4.9% (135/2738).

Hypertension, which was categorised as an anaphylactic reaction, was the TEAE with the highest incidence rate and was reported at a slightly lower rate for Tolvaptan subjects compared with placebo subjects for the All Subjects population (2.0% versus 2.6%,), for All Heart Failure Subjects (2.0% versus 2.5%), and for All Hyponatremia Subjects (0.7% versus 3.3%). The following additional rare AE were reported in Tolvaptan subjects:

- Colitis ischaemia (2 subjects): both events were not related to Tolvaptan treatment, and both events were serious.
- Coma (9 subjects): all 9 events were assessed as not related to Tolvaptan treatment, and 7/9 events were serious. Of the 9 subjects experiencing coma during treatment, 44% were male, 78% were Caucasian with age ranging from 53-82 years. The event onset day ranged from Day 6 to Day 177. The time to recovery for these subjects ranged from 0 days (resolving the same day the event occurred) to 12 days.
- Glaucoma (7 subjects): all 7 events were assessed as not related to Tolvaptan treatment, and none of the events were serious.
- Myoglobin blood increased (1 subject): the event was assessed as possibly related to Tolvaptan treatment, and the event was not serious.
- Pancytopenia (8 subjects): all 8 events were assessed as not related to Tolvaptan treatment, and 2/8 events were serious.
- Rhabdomyolysis (2 subjects): both events were assessed as not related to Tolvaptan treatment and 1/2 events were serious.

The combined CHF and hyponatremia patient population was analysed for all TEAE associated with the medical concept of thrombosis/hypercoagulation. The grouped TEAE included in this category were MedDRA terms associated with clotting, coagulation, thrombosis, and artery occlusion. No single TEAE in this category was reported at greater than 2% of subjects in any of the three analysis groups. The aggregated frequency (6.8%) was identical for Tolvaptan and placebo. There was no indication of V_{1a} receptor activation associated hypercoagulation states or thrombosis.

Use in pregnancy/lactation

No pregnancy experience in Tolvaptan subjects has been reported in clinical trials to date. A study of embryofetal development in rabbits showed increased postimplantation death and fetal malformations and a study of pre and postnatal development in rats showed increased perinatal death and body weight suppression in the offspring, with oral administration of Tolvaptan at 1000 mg/kg/day. Ongoing clinical trials mandate contraceptive measures for women of childbearing potential and exclude pregnant or lactating women. If pregnancy is confirmed for any person receiving Tolvaptan, that person should be discontinued from Tolvaptan therapy and monitored.

Immunological events, overdose, abuse potential

Single doses up to 480 mg (8 times the maximum recommended dose and 16 times the 30 mg tablet) and multiple doses up to 300 mg per day for five days have been well tolerated in clinical trials in healthy volunteers. The oral LD56 (low dose continuous chemotherapy) of Tolvaptan in rats and dogs is >2 g/kg. No mortality was observed in rats or dogs following single oral doses of 2000 mg/kg (maximum feasible dose). In mice oral doses of 2000 mg/kg lead to decreased locomotor activity, staggering gait, tremor, hypothermia and lethal outcome.

No case of overdose has been reported in clinical trials. With single daily dosing and two strengths at 15 mg and 30 mg, the potential for accidental overdose is minor.

Safety related to drug-drug interactions and other interactions

The most commonly used concomitant medication of interest by subjects who reported AE in the all heart failure and hyponatremia database were ACE inhibitors (Tolvaptan versus placebo: 83.7% versus 85.9%), followed by beta blockers (70.0% versus 75.6%), potassium sparing diuretics (60.1% versus 66.2%), ARBs (58.8% versus 64.5%), digoxin (54.4% versus 52.4%), diabetic agents (37.4% versus 35.3%), warfarin (27.1% versus 27.1%), and CYP3A4 inhibitors/inducers (22.2% versus 22.0%). The most commonly observed AE for all concomitant medication groups of interest were similar to those assessed as related to the pharmacological action of Tolvaptan, that is, increased free water clearance. Thirst, dry mouth and fatigue were reported more often for all concomitant medications of interest. In general, differences in AE incidences were similar for each group of concomitant medications of interest. Differences in AE incidences between the any Tolvaptan oral dose group and the placebo group were minor, and in some case were related to known side effects of the concomitant medication drug class. In addition, the incidences of TEAE by concomitant medication group were similar when compared to the overall incidences of TEAE for all heart failure and hyponatremia subjects from multiple dose, placebo controlled trials. In summary, there were no clinically meaningful differences observed in AE incidence by concomitant medications of interest for the any Tolvaptan oral dose group compared to placebo.

No analyses of potential drug-drug or food interactions with Tolvaptan were conducted in the efficacy/safety trials. The results of the nine clinical pharmacology studies designed to investigate potential drug-drug interactions showed that the concomitant administration of furosemide/hydrochlorothiazide, ketoconazole, lovastatin, warfarin, amiodarone, digoxin, rifampin, and grapefruit juice with Tolvaptan was well tolerated with no unusual or unexpected safety findings. However, because the coadministration of Tolvaptan with a CYP3A4 inhibitor (that is, grapefruit juice) and CYP3A4 inducer (that is, rifampin) led to an increase and decrease, respectively, in the bioavailability of Tolvaptan, caution should be exercised when coadministering these compounds with Tolvaptan. The immediate consequences of increased Tolvaptan concentrations are elevated urine output and thirst, while, for lowered concentrations, an increased Tolvaptan dosage may be considered based on clinical outcomes. Additionally, the coadministration of Tolvaptan with digoxin resulted in increased digoxin concentrations, while Tolvaptan concentrations remained unchanged. Hence, the subject's clinical status should be monitored when these agents are co-administered.

Post marketing experience

Since the launch of Tolvaptan in the US and Europe, the identified risks are: volume depletion and dehydration; electrolyte shifts: hypernatremia; hyperkalaemia; metabolic effects: hyperuricaemia, gout; hyperglycaemia, hypoglycaemia and risks in special populations such as pregnant breast feeding women (based on toxicological data) and the hepatic impaired subjects.

The incidence of serious AE in these categories was minimal during the clinical trial programme, most likely as a result of careful application of inclusion/exclusion criteria.

There are no changes to the safety profile and no actions including change of SmPC (summary of product characteristics) and CCSI (Company Core Safety Information) are planned at this time.

Evaluator's overall comments on clinical safety

- Overall, 3294 subjects with CHF and/or hyponatremía received Tolvaptan in multiple dose, placebo controlled trials. Of these subjects, only 607 subjects included the proposed target population of patients with hyponatremia, defined as a serum sodium

<135 mEq/L. Thus, the vast majority of the safety experience was obtained in subjects with CHF, but without hyponatremia. Moreover, these subjects were largely enrolled in a single Study 156-03-236 and received 30 mg of Tolvaptan.

- **Safety in proposed hyponatremia patients:** The overall incidence of AE was similar in Tolvaptan and placebo groups (86%). The percentage of patients with potentially drug related TEAE was higher in the Tolvaptan group than in the placebo group (45.3% versus 32.0%), mainly due to expected pharmacological action of Tolvaptan (thirst, dry mouth, and pollikuria). The most frequent TEAE in both treatment groups were cardiac failure, nausea, and cardiac failure congestive, all of which occurred in between 10% to 20% of subjects. The most frequent possibly related treatment emergent adverse events were: thirst, -18% in Tolvaptan group -2.5% in SC group, dry mouth (8.5% versus 2%), pollakiuria (frequent day time urination: 5.4% versus 0.9%), fatigue (2.3% versus 0.6%), polyuria (3.3% versus 0.6% SC) and ventricular tachycardia (0.9% versus 0.3% SC).
- The most frequent serious TEAE were cardiac failure and cardiac failure congestive, accounting for approximately 25% of serious TEAE in both Tolvaptan and placebo groups and most of the serious TEAE of special interest (including ventricular tachycardia [VT], cardiac arrest, hyperkalemia, cerebrovascular accident, renal failure, and hypotension) occurred with differences of <1% between the Tolvaptan and the placebo groups with the exception of cardiac arrest (Tolvaptan versus placebo: 2.3% versus 1.0%) and hypotension (1.2% versus 2.3%). The incidence of TEAE leading to discontinuation of trial medication was comparable between treatment (cardiac disorders most common in 3.6% of Tolvaptan and 2.1% of placebo subjects). The only TEAE leading to discontinuation of trial medication in >1% of subjects in either treatment group were cardiac failure, cardiac failure congestive, and renal failure acute. The incidence of deaths was similar in the Tolvaptan and placebo groups (21.6% versus 20.8%) and nearly all of the deaths occurred in the large placebo controlled, Phase 3 CHF trial (Study 156-03-236) conducted in subjects hospitalised for worsening CHF. The majority of deaths were associated with cardiac disorders (14.3% Tolvaptan versus 11.8% placebo) and there were no relevant differences between the treatment groups in the incidence of deaths due to any individual TEAE.
- The incidence of shifts to abnormally below the lower normal limit was higher in placebo group compared to Tolvaptan for sodium (Tolvaptan versus placebo: 37.5% versus 53.3%), chloride (26.7% versus 47.6%), total cholesterol (28.6% versus 42.4%), and serum osmolality (23.6% versus 33.5%); however, the Tolvaptan group showed a higher incidence of 'shifts to abnormally above the upper normal limit' for the following: serum osmolality (72.7% versus 60.8%), uric acid (42.6% versus 26.9%) and glucose levels (66% versus 57%). The only potentially clinically significant laboratory abnormalities with a ≥ 5% difference in incidence between treatment groups was decreased sodium, which had a lower incidence in the all Tolvaptan dose group (116 of 588 subjects [19.7%]) than in the placebo group (179 of 504 [35.5%]). There were no clinically relevant changes in hematology or vital signs/ECG parameters.
- **Safety in all HF and hyponatremia patients:** In the pooled analysis of subjects with heart failure or hyponatremia, a total of 3294 subjects have been exposed to any Tolvaptan dose for ≤30 days, 1372 subjects were exposed to any Tolvaptan dose for >180 days, with 817 subjects exposed for at least 360 days. No relevant differences were seen between treatment groups (Tolvaptan versus placebo) regarding the frequency of TEAE (88.6% versus 84.6%), serious TEAE (47.2% versus 51.1%), trial discontinuations due to TEAE (9.4% versus 7.1%) or deaths (17.2% versus 20%). The most frequent TEAE in both treatment groups were cardiac failure, cardiac failure congestive, and nausea with comparable incidence in both treatment groups. The

proportion of subjects with potentially drug related TEAE was higher in the Tolvaptan group (48.8%) than in the placebo group (30.7%), with the majority of this difference being accounted for by thirst (Tolvaptan versus placebo: 17.1% versus 2.4%), dry mouth (8.5% versus 2.1%), pollakiuria (5.4% versus 0.9%), and polyuria (3.1% versus 0.5%), all of which are consistent with the pharmacological effects of Tolvaptan.

List of questions

Pharmacokinetics

Are there any studies available which examine the effects of mutations in the CYP isoenzymes on the PK of Tolvaptan?

Please provide a full copy of Study 156-05-001 so that the diurnal changes mentioned in the report can be examined.

As the major Tolvaptan metabolite identified in plasma is DM-4103, which has a $t_{1/2}$ of 183 h and its AUC_{24} following 9 days of repeated dosing was 8-10 times that of a single dose (Study 156-05-001), can the applicant please demonstrate or provide information on the activity of this metabolite?

Pharmacodynamics

Are there any studies available which examine the effects of mutations in the CYP isoenzymes on the PD of Tolvaptan?

Efficacy

None.

Safety

None.

Clinical summary and conclusions

Clinical aspects

Pharmacokinetics

Initial studies indicated that the lowest dose that reliably elicited measurable differences in PD responses (decreases in body weight, increases in serum sodium concentration and urine output) was 30 mg. Further studies indicated that a dose of at least 60 mg Tolvaptan was required to maintain the diuretic action of Tolvaptan until 24 h post dose and at doses of greater or equal to 180 mg the PD effects of Tolvaptan plateaued. As Tolvaptan exposure is approximately two fold higher in patients with mild and moderate CHF than in normal subjects the doses in the current application would appear appropriate for the proposed indication.

The median T_{max}, $t_{1/2}$, C_{max} and AUC_{inf} of Tolvaptan following oral administration of a 30 mg tablet were 2 h, 6.7 h, 231 ng/mL and 1731 ng.h/mL, respectively. The mean absolute bioavailability (F) of Tolvaptan tablet was 56%.

Although the overall exposure to Tolvaptan was not affected, the rate of Tolvaptan absorption increased with food.

Following a 60 mg dose of ^{14}C-OPC-41061 radioactive, the CL/F and V/F were 6.0 ml/min/kg and 4.33 l/kg, respectively. A total of 98.9% of the administered radioactivity was recovered with 40.2% in urine and the remaining 58.7% recovered in the faeces. About 80% of the cumulative urine ^{14}C excretion occurred during the first 36 h and approximately 65% of radioactivity was recovered in the faeces within the first 72 h. However, radioactivity could be detected in the faeces for up to 960 h post dose.

Tolvaptan and seven metabolites (DM-4103, DM-4104, DM-4105, DM-4107, DM-4110, DM-4111 and DM-4119) were identified in the subject's plasma. Tolvaptan and its metabolites accounted for 60.4% of the total plasma radioactivity. DM-4103 alone accounted for 52.5% of the plasma radioactivity, whereas unchanged Tolvaptan accounted for 2.8% and the other metabolites combined accounted for 5.1%. *In vivo* studies indicate that the formation and elimination of Tolvaptan and most of its metabolites occurs via CYP3A4/5. Therefore, although no studies specifically examined the effects of CYP mutations on the PK of Tolvaptan it should be assumed that patients with known mutations in this isoenzyme may require dose adjustment.

No studies examined the PK of Tolvaptan in children or in subjects with impaired renal function.

Age and gender had no affect on Tolvaptan PK, whereas, lower weight (kg) was associated with higher C_{max} and CL/F.

Hyponatremia/Liver Disease had a similar affect on the PK of Tolvaptan to mild and moderate CHF, that is, it increased C_{max} and AUC compared to healthy subjects.

The CYP3A4 inhibitor, ketoconazole significantly increased Tolvaptan C_{max} by 3.48 fold and AUC by 5.4 fold. Similarly, grapefruit juice also significantly increased Tolvaptan C_{max} (188%) and AUC_{inf} (173%). By contrast, 600 mg rifampicin QD (a potent inducer of CYP3A4) significantly decreased Tolvaptan C_{max} by 83% and AUC_t by 87%; therefore, an increase in Tolvaptan dose may be required if the two drugs are to be coadministered.

Lovastatin coadministration increased both Tolvaptan C_{max} (113% for the 60 mg dose and 166% for the 90 mg dose, respectively), and AUC_{inf} (126% and 90% for the 60 mg and 90 mg dose of Tolvaptan, respectively).

Steady state digoxin C_{max} and AUC_t were elevated 1.3 and 1.2 fold, respectively, following coadministration of Tolvaptan 60 mg daily. Digoxin renal clearance was also significantly lowered by coadministration with Tolvaptan (decrease of 59%). By contrast, coadministration of digoxin did not affect Tolvaptan PK. Due to the changes in digoxin PK, patients receiving digoxin should therefore be evaluated for excessive digoxin effects when treated with Tolvaptan.

Coadministration of HCTZ had no effect on Tolvaptan PK, whereas, furosemide increased the Tolvaptan C_{max} (8%) and AUC (10%) only slightly.

Tolvaptan had no effect on the PK of amiodarone (in subjects with cardiac arrhythmias), warfarin, lovastatin (or its β-hydroxy acid metabolite), HCTZ or furosemide.

PK population modelling indicated the PK of Tolvaptan in both hyponatremia and heart failure was best described by a one compartment model with first order absorption, random effects on CL/F, V/F, and KA, and exponential residual error. Tolvaptan oral clearance mildly increased with weight while apparent volume was proportional to weight. Child-Pugh Class was identified as a predictor of oral clearance (19 and 24% increase for Class B and C, respectively) and volume (50% increase for Class C) in the core hyponatremia dataset. The expanded hyponatremia dataset showed a mild increase in oral clearance for Class B and C and a 50% increase in volume for Class C. Renal impairment (as estimated by the normalised creatinine clearance calculated from the Cockroft-Gault equation) had no effect on Tolvaptan clearance in the hyponatremia analysis. Coadministration of CYP3A4 inducers resulted in a 45% (7%, 84 % [95% CI]) increase in

Tolvaptan oral clearance, based on data from only five patients in the core hyponatremia analysis and a 75% (44%, 124% [95% CI]) increase from eleven patients in the expanded hyponatremia analysis (hyponatremia trials and patients with hyponatremia enrolled in heart failure trials).

Pharmacodynamics

In general, administration of Tolvaptan induced statistically significant and dose dependent increases in urine volume, decreases urine osmolality and variable decreases in urine sodium concentration even in the presence of loop diuretics leading to statistically significant decreases in body weight in subjects with CHF. Tolvaptan also increased serum sodium concentration, which occurred slowly and generally did not exceed the upper limit of the normal range. Increases in serum sodium levels were maintained for the duration of treatment in subjects who were hyponatremic at baseline. By contrast in healthy subjects, increases in serum Na+ concentrations following both single and repeated administration of 90 and 120 mg Tolvaptan decreased by 24 h post dose; however, Na+ concentrations were still higher than the pretreatment values.

The average urine volume excreted in the first 12 h following Tolvaptan administration was approximately 7 litres.

Although urine volume increased dose dependently, it did not increase linearly with dose and urine excretion rate and free water clearance plateaued at doses of 180 mg Tolvaptan.

In Study 156-00-221, which examined the effect of Tolvaptan on renal function in subjects with CHF, Tolvaptan significantly increased effective renal plasma flow (9%) and renal blood flow (10%) compared to placebo and furosemide. In addition, glomerular filtration rate increased (1.37 mL/min) and renal vascular resistance decreased (-1.54 mmHg/dL) compared to placebo.

There were no significant age/gender interactions for the pharmacodynamic parameters AVP, plasma renin activity, and urine osmolality.

In Study 156-03-239, following a single oral 240 mg dose of Tolvaptan with rifampin at steady state, Tolvaptan C_{max} values were comparable to those for a 15 mg dose and AUC_t values were comparable to a 30 mg dose, whereas PD responses were similar to those for a 60 mg dose.

Coadministration of Tolvaptan had no effect on PD of warfarin and coadministration of digoxin with Tolvaptan had no affect on urine output.

Tolvaptan acted synergistically with furosemide and significantly potentiated the increase in renin activity seen following administration of furosemide alone. This effect may be of clinical significance as hypertension and CHF have been associated with increased renin activity; therefore, dose adjustment may be required if the two diuretics are to be coadministered.

In Study 156-03-245, 30 or 300 mg Tolvaptan QD for five days had no effect on maximum time matched mean change from baseline in individually corrected QT_c.

Although no studies examined the effects of CYP mutations on the PD of Tolvaptan, it should be assumed – as Tolvaptan is primarily metabolised by CYP3A4/5 – that patients with known mutations in this isoenzyme may require dose adjustment.

Efficacy

Tolvaptan's effect in improving serum sodium concentrations in inpatients and outpatients with non acute dilutional (euvolemic or hypervolemic) hyponatremia with serum sodium concentration <135 mEq/L were evaluated in six trials: two pivotal placebo controlled Phase 3 trials, Studies 156-02-235 and 156-03-238 (N=216 for Tolvaptan and N=208 for placebo), three placebo controlled Phase 2 trials (N=51 for Tolvaptan and N=26

for placebo), and one open label Phase 3 trial (N=111). The underlying aetiologies in the target population included CHF, cirrhosis, and SIADH. Subjects who truly required treatment for hyponatremia (lV saline) were not enrolled by intention. The inclusion/exclusion criteria tended to select subjects with mild or moderate hyponatremia, who were not symptomatic, or at least not sufficiently symptomatic to require IV saline.

The results in the two pivotal studies were virtually identical demonstrating consistency of Tolvaptan's effects and tolerability. The primary efficacy endpoints were the averaged daily correction of sodium concentration from baseline through Day 4 and Day 30 as compared to placebo to assess acute and sustained effects. Statistically and clinically significantly greater improvements in serum sodium concentration were observed in the Tolvaptan group over the placebo group up as measured by an average daily AUC of mean change from baseline in serum sodium concentration up to Day 4 (4.0 and 0.4 mEq/L for Tolvaptan and placebo, respectively, estimated treatment effect of 3.7 mEq/L, $p < 0.0001$) and up to Day 30 (6.2 and 1.8 mEq/L, respectively; estimated treatment effect of 4.6 mEq/L, $p < 0.0001$).

The onset of statistically significantly improved serum sodium concentrations in the Tolvaptan group compared to the placebo group was observed as early as Hour 8 (Day 1) post dose, maximal difference from placebo on serum sodium concentrations was achieved by Day 4, after which increases in serum sodium were maintained for the duration of therapy. The mean change from baseline was (Tolvaptan versus placebo) 2.5 versus -0.5 mEq/L at Hour 8 (Day 1), 5.7 versus 0.9 mEq/L at Day 4, 6.4 versus 2.3 mEq/L at Week 1, 7.I versus 3.0 mEq/L at Week 2, 7.4 versus 2.7 mEq/L at Week 3, and 7.3 versus 2.8 mEq/L at Day 30 ($p < 0.0001$ at all time points). This showed that increase in serum sodium was gradual and not overly rapid.

At all on therapy time points, significantly more Tolvaptan subjects than placebo subjects have normalised serum sodium concentrations; Hour 8 (Day 1) (Tolvaptan versus placebo: 19.9% versus 4.3%); Day 2 (33.2% versus 6.0%), Day 4 (48.5% versus 11.2%) and Day 30 (59.9% versus 26.5%). Tolvaptan subjects were >4 times more likely to achieve normalisation of their serum sodium concentrations (> 135 mEq/L) than placebo subjects by Hour 8 (Day 1), and >2 times more likely to maintain this advantage over time ($p < 0.0001$).

Tolvaptan also appears to prevent worsening of hyponatremia in subjects with mild hyponatremia at baseline (Tolvaptan versus placebo: 0% versus 15% at Day 4 and 15% versus 49% at Day 30, $p < 0.0001$ for Day 4 and Day 30). Furthermore, the percentage of subjects with severe hyponatremia who had a decrease in serum sodium concentration of at least 3 mEq/L at any post baseline time point, was also statistically significantly ($p < 0.0001$) lower in the Tolvaptan group (11/110, 10.0%) than the placebo group (46/105, 43.8%).

In addition to the efficacy in increasing serum sodium concentration, 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. 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. Statistically significantly ($p < 0.01$) fewer subjects require formal fluid restriction (< 1000 mL/day) while on Tolvaptan (8-14%) compared with placebo (15-25%).

Any potential symptomatic benefit due to increase in sodium levels produced by Tolvaptan was examined by effects on quality of life using the SF-12 Health Survey. Both studies showed some improvement in SF-12 PCS although difference between Tolvaptan

and placebo groups was not significant. Mental status was assessed using the MCS of the SF-12 Health Survey, evaluated at Day 30 compared to baseline. Statistically significant improvements in SF-12 MCS were shown in the ITT and severe hyponatremia subgroup in pivotal Study 156-02-235 although significant improvements were not observed in the other pivotal Study 156-03-238. Improvements in SF-12 MCS scores related to and were associated with changes in serum sodium. 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/others in the pooled analysis. Furthermore, there was a significant beneficial effect of Tolvaptan versus placebo on the MCS Score of the combined group ($p = 0.0036$), especially in severe hyponatremic patients ($p = 0.0025$). The MCS finding was supported by improvements in memory, concentration and calculating ability and general wellbeing in a pre specified but not validated hyponatremia disease specific questionnaire in only one of the pivotal Phase 3 studies (Study 156-03-238). However, the MCS analysis was confounded by a multiplicity issue (MCS was not specified in the statistical analysis plan as a key secondary end point but was one of several), potential unblinding (as Tolvaptan treatment was associated with greater thirst and urine output and that more placebo subjects would have required up-titration of dose) and the fact that SF-12 does not address symptoms typical of hyponatremia and has not been validated in a clinical setting. Due to the above limitations, it cannot formally be concluded that a statistically significant effect has been demonstrated on the MCS endpoint.

There was no systematic evaluation of the objective effects of Tolvaptan on nervous system. Both pivotal hyponatremia studies showed improvements in Tolvaptan treated patients in muscle strength (especially in patients with severe hyponatremia) although these did not demonstrate symmetrical concordance and are therefore of doubtful importance. Of potential importance were changes in measures associated with proprioception and coordination; ataxia right and left finger to nose test and stance with eyes closed. These data are of some interest given the previous reports of untoward effects of hyponatremia on gait and balance. However, additional study with large numbers of subjects would be necessary to assess the clinical relevance of these effects.

The benefits of Tolvaptan treatment achieved in the SALT trials were maintained for durations exceeding one year in an open label long term follow up trial (SALTWATER or Study 156-03-244). In this open label study**,** 111 patients (94 of them hyponatremic with serum sodium<135mEq/L) previously on Tolvaptan or placebo treatment (in a Phase 3 of Phase 2 hyponatremia trial) were given Tolvaptan as a titrated regimen (15-60 mg daily) after having returned to standard care for at least seven days (during which serum sodium levels had fallen to between their original baseline and post placebo level. Upon initiation of therapy, average serum sodium levels increased to approximately same levels as observed for those previously treated with Tolvaptan and were sustained for at least a year. It is important to note that the increase in serum sodium was only maintained till Week 10 in the subgroup of patients with cirrhosis, while the increase in serum sodium was consistently maintained till Week 106 in subgroups of patients with hyponatremia due to CHF or SIADH. The efficacy endpoints reflecting improvement in the serum sodium concentrations were not supported by any benefits in terms of improvement in the SF-12 PCS and MCS scales as the slight improvements in PCS and MCS seen in the pivotal, placebo controlled studies did not appear to be maintained in the open label study.

Similar results with similar magnitudes of improvement were observed for the Tolvaptan group relative to placebo in the analyses of average daily AUC of change from baseline in serum sodium concentration up to Day 4 and up to Day 30 for each of the following subgroups: severe/mild hyponatremia (<130mEq/L or >130mEq/L; euvolemia or hypervolemia; aetiology of CHF, cirrhosis or SIADH/others) ($p < 0.0001$ for all). However, the biggest difference compared to placebo was 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, respectively and Cirrhosis 3.15 and 2.83, respectively). Furthermore, the percentage of subjects with normalised sodium levels was not significantly different from placebo in cirrhosis patients at Day 30. Analysis by demographic subgroup: gender (male, female); age (<65 years, >65 years); race (Caucasian, non Caucasian); fluid restriction use (yes, no); and diuretic medication use (yes, no) also showed statistically significant improvements with Tolvaptan relative to placebo at both Day 4 and Day 30 ($p < 0.0001$).

Supportive evidence of efficacy of Tolvaptan in hyponatremia in CHF patients was provided by a pre specified analysis evaluating changes from baseline in serum sodium concentration in a subgroup of 475 subjects with hyponatremia enrolled in a Phase 3 heart failure trial (Study 156-03-236) which demonstrated early and persistent improvements in serum sodium concentrations for Tolvaptan over placebo lasting up to at least 40 weeks. The magnitude of change in serum sodium concentration in the Tolvaptan group was 4.6, 4.9, 5.6, 6.7 and 6.5mEq/L at Day 1, Day 7, Week 4, Week 24, and Week 40, respectively. Additional supportive data were available in 127 subjects with hyponatremia enrolled in five Phase 2 heart failure trials (Studies 156-97-251, 156-97-252, 156-98-213, 156- 00-220 and 156-01-232). Subjects treated with Tolvaptan, particularly at doses of ≥30 mg/day, generally had greater mean increases in serum sodium concentrations than subjects treated with placebo throughout each of the trials.

In summary, Samsca (Tolvaptan) is an effective agent for the treatment of non acute, hypervolemic and euvolemic hyponatremia (including patients with heart failure, cirrhosis, SIADH), although evidence is not as convincing for cirrhosis. The data clearly demonstrate that correction of hyponatremia occurs progressively over the first four days of treatment, thereby minimising the negative impact of overly rapid increases in serum sodium. The improvements were sustained over long term treatment and importantly, when treatment is interrupted, sodium concentrations decrease to those seen with placebo patients. These data suggest that Samsca (Tolvaptan) should be used in the chronically affected patients as long as needed, to maintain normal sodium concentrations. However, it has not been established that raising serum sodium with Tolvaptan provides a symptomatic benefit to patients.

Safety

Overall, 3294 subjects with CHF and/or hyponatremía received Tolvaptan in multiple dose, placebo controlled trials. Of these subjects, only 607 subjects had hyponatremia, defined as a serum sodium <135 mEq/L. Thus, the vast majority of the safety experience was obtained in subjects with CHF, but without hyponatremia. Moreover, these subjects were largely enrolled in a single trial (Study 156-03-236) and received 30 mg of Tolvaptan.

In the target patient population of 'all hyponatremia patients', the overall incidence of AE was similar in Tolvaptan and placebo groups (86%). The percentage of patients with potentially drug related TEAE was higher in the Tolvaptan group than in the placebo group (45.3% versus 32.0%), mainly due to expected pharmacological action of Tolvaptan (thirst, dry mouth, and pollikuria). The most frequent TEAE in both treatment groups were cardiac failure, nausea, and CHF, all of which occurred in between 10% to 20% of subjects. The most frequent possibly related TEAEs were: thirst, -18% in Tolvaptan group -2.5% in SC group, dry mouth (8.5% versus 2%), pollakiuria (frequent day time urination: 5.4% versus 0.9%), fatigue (2.3% versus 0.6%), polyuria (3.3% versus 0.6% SC) and ventricular tachycardia (0.9 % versus 0.3% SC).

The most frequent serious TEAE were cardiac failure and CHF accounting for approximately 25% of serious TEAE in both Tolvaptan and placebo groups and most of the serious TEAE of special interest (including ventricular tachycardia [VT], cardiac arrest, hyperkalemia, cerebrovascular accident, renal failure, and hypotension) occurred with

differences of <1% between the Tolvaptan and the placebo groups with the exception of cardiac arrest (Tolvaptan versus placebo: 2.3% versus 1.0%) and hypotension (1.2% versus 2.3%). The incidence of TEAE leading to discontinuation of trial medication was comparable between treatment (cardiac disorders most common in 3.6% of Tolvaptan and 2.1% of placebo subjects). The only TEAE leading to discontinuation of trial medication in >1% of subjects in either treatment group were cardiac failure, cardiac failure congestive, and renal failure acute. The incidence of deaths was similar in the Tolvaptan and placebo groups (21.6% versus 20.8%) and nearly all of the deaths occurred in the large placebo controlled, Phase 3 CHF Study 156-03-236 conducted in subjects hospitalised for worsening CHF. The majority of deaths were associated with cardiac disorders (14.3% Tolvaptan versus 11.8% placebo) and there were no relevant differences between the treatment groups in the incidence of deaths due to any individual TEAE.

The incidence of TEAE was similar in the Tolvaptan and placebo groups for the CHF (Tolvaptan = 367/410, 89.5% versus placebo = 303/336, 90.2%) and SIADH/others (69/97, 69.1% versus 69/99, 69.7%); however, in the cirrhosis subgroup of hyponatremic patients, the incidence of TEAE was higher in the Tolvaptan group compared to placebo (90/100, 90% versus 69/83, 83.1%). Furthermore, in patients with cirrhosis treated with Tolvaptan in hyponatremia trials, gastrointestinal bleeding was reported in 6/63 (10%) Tolvaptan treated patients and 1/57 (2%) placebo treated patients.

The incidence of shifts to abnormally below the lower normal limit was higher in placebo group compared to Tolvaptan for sodium (Tolvaptan versus placebo: 37.5% versus 53.3%), chloride (26.7% versus 47.6%), total cholesterol (28.6% versus 42.4%), and serum osmolality (23.6% versus 33.5%); however, the Tolvaptan group showed a higher incidence of 'shifts to abnormally above the upper normal limit' for the following: serum osmolality (72.7% versus 60.8%), uric acid (42.6% versus 26.9%) and glucose levels (66% versus 57%). The only potentially clinically significant laboratory abnormalities with a ≥5% difference in incidence between treatment groups was decreased sodium, which had a lower incidence in the all Tolvaptan dose group (116/588 subjects [19.7%]) than in the placebo group (179/504 [35.5%]). There were no clinically relevant changes in hematology or vital signs/ECG parameters.

Safety of Tolvaptan was well documented with the most common AE being the ones expected with the pharmacological actions of Tolvaptan (thirst, dry mouth, pollakiuria). Other AE also appeared to be related to the underlying disease such as CHF and cirrhosis and there were no major safety concerns associated with use of Tolvaptan, especially no adverse effects on renal function or AE associated with overly rapid correction of serum sodium.

No cases of demyelinisation 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.

Benefit risk assessment

Benefits

1. The main evidence for efficacy was provided by the two pivotal Phase 3 studies involving 424 patients with hyponatremia (serum sodium <135mEq/L). The superior efficacy of Tolvaptan over placebo was shown in a few efficacy endpoints, including AUC of change from baseline in serum sodium at Day 4 and Day 30, mean serum sodium concentrations at each visit, time to serum sodium normalisation, percentage of subjects with serum sodium normalisation at Days 4 and 30, and categorical change in serum sodium at Days 4 and 30. Tolvaptan subjects are >4 times more likely to

achieve normalisation of their serum sodium concentrations (>135 mEq/L) than placebo subjects by Hour 8 (Day 1), and >2 times more likely to maintain this advantage over time (p <0.0001).

2. The onset of statistically significantly improved serum sodium concentrations in the Tolvaptan group compared to the placebo group was observed as early as Hour 8 (Day 1) post dose, maximal difference from placebo on serum sodium concentrations was achieved by Day 4, after which increases in serum sodium were maintained for the duration of therapy. This showed that Tolvaptan produced a gradual increase in serum sodium over the first 4 days of treatment, thereby minimising the negative impact of overly rapid increases in serum sodium.
3. Tolvaptan prevents worsening of hyponatremia; the incidence of subjects with mild hyponatremia at baseline developing severe hyponatremia during treatment was (Tolvaptan versus placebo) 0% vs 15% at Day 4 and 15% versus 49% at Day 30. Furthermore, the percentage of subjects with severe hyponatremia who had a decrease in serum sodium concentration of at least 3 mEq/L at any post baseline time point, was also significantly lower in the Tolvaptan group (11/110, 10.0%) than the placebo group (46/105, 43.8%).
4. Tolvaptan treatment also led to increase in urine output without any AEs on electrolytes or renal function. 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. Statistically significantly ($p < 0.01$) fewer subjects require formal fluid restriction (<1000 mL/day) while on Tolvaptan (8-14%) than subjects on placebo (15-25%), simplifying treatment for both the patient and the physician.
5. The results were similar in subjects with mild and severe hyponatremia, 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, respectively; Cirrhosis 3.15 and 2.83, respectively). This improvement was independent of the volume status (hypervolemic or euvolemic), age, gender, race, fluid restriction or diuretic use. However, evidence for efficacy in cirrhosis was not conclusive.
6. When treatment is discontinued, serum sodium concentrations in Tolvaptan subjects decrease approximately to the values observed in placebo subjects, despite the reinstatement of standard of care therapy. Furthermore, efficacy was maintained up to 106 weeks in patients with hyponatremia due to SIADH and CHF as suggested by the interim results of the open label Study 156-03-244.
7. Any potential symptomatic benefit due to increase in sodium levels produced by Tolvaptan was examined by effects on quality of life using the SF-12 Health Survey in both pivotal Phase 3 studies and a Hyponatremia disease specific questionnaire in one of the pivotal Phase 3 studies (Study 156-03-238). However, interpretation of these results was confounded by several limitations and failed to provide any conclusive evidence.
8. The supportive studies including those in CHF population where few subjects had hyponatremia provide some evidence of the effect of Tolvaptan on enhanced urine output, selective aquaresis, and correction of hyponatremia. 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.
9. Safety of Tolvaptan was well documented with the most common AE being the ones expected with the pharmacological actions of Tolvaptan (thirst, dry mouth,

pollakiuria). Other AE also appeared to be related to the underlying disease such as CHF and cirrhosis and there were no major safety concerns associated with use of Tolvaptan, especially no AEs on renal function or AE associated with overly rapid correction of serum sodium.

Risks

Evidence for efficacy/safety of Tolvaptan in hyponatremia due to cirrhosis was not conclusive due to the following reasons:

1. Increase in serum sodium was only 2.83 to 3.15mEq/L in cirrhosis patients compared to 2.98 to 4.05 in CHF and 4.70 to 6.15mEq/L in SIADH patients.
2. In cirrhosis patients, the percentage of patients with normalised serum sodium was not significantly greater than placebo at Day 30, while it was so for patients in the CHF and SIADH/others aetiology subgroups.
3. Very few patients with cirrhosis were evaluated for efficacy/safety as only 20/111 hyponatremic patients in the long term open label study had cirrhosis (of whom only 13 were evaluated at 26 weeks and only 1 patient was evaluated at Week 106).
4. In the open label, long term study, Tolvaptan induced increase in serum sodium was only maintained till Week 10 in the subgroup of patients with cirrhosis, while the increase in serum sodium was consistently maintained till Week 106 in subgroups of patients with hyponatremia due to CHF or SIADH.
5. In the 'All hyponatremia' safety dataset, majority of the patients had CHF (410/607 Tolvaptan; 336/518 placebo). It is important to note that the incidence of TEAE was similar in the Tolvaptan and placebo groups for the CHF (Tolvaptan = 367/410, 89.5% versus placebo = 303/336, 90.2%) and SIADH/ others (69/97, 69.1% versus 69/99, 69.7%); however, in the cirrhosis subgroup of hyponatremic patients, the incidence of TEAE was higher in the Tolvaptan group compared to placebo (90/100, 90% versus 69/83, 83.1%). Furthermore, in patients with cirrhosis treated with Tolvaptan in hyponatremia trials, gastrointestinal bleeding was reported in 6/63 (10%) Tolvaptan treated patients and 1/57 (2%) placebo treated patients.

Any potential symptomatic benefit due to increase in sodium levels produced by Tolvaptan was examined by effects on quality of life using the SF-12 Health Survey in both pivotal Phase 3 studies and a Hyponatremia disease specific questionnaire in one of the pivotal Phase 3 studies (Study 156-03-238). Statistically significant improvements in SF-12 MCS were shown in the ITT and severe hyponatremia subgroup in pivotal Study 156-02-235 although significant improvements were not observed in the other pivotal study 156-03-238. The MCS finding was supported by improvements in memory, concentration and calculating ability and general wellbeing in a pre specified but not validated Hyponatremia disease specific questionnaire in only one of the pivotal Phase 3 studies (Study 156-03-238). However, the improvements in these quality of life measures failed to provide conclusive evidence to suggest symptomatic benefit due to the following limitations:

1. The SF-12 does not address symptoms typical of hyponatremia, and the content validity of SF-12 has not been established in a clinical study setting.
2. The MCS analysis was confounded by a multiplicity issue: MCS by (SF-12) 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.
3. It is likely that substantial unblinding occurred that would have served to bias the results of the studies. Potential sources of unblinding include unblinding of subjects and caregivers, given that Tolvaptan treatment was associated with greater thirst and

urine output (approximately 1.2 litre/day in the two studies), and also given that virtually all subjects in the placebo group would have required up titration of their placebo dose.

4. The sponsor states that improvements in SF-12 MCS scores related to and were associated with changes in serum sodium. However, lack of content validity of SF-12 bias due to unblinding and multiplicity issues limits the use of SF-12 MCS as a key secondary end point that shows benefit as a direct correlate or consequence of increase in serum sodium values.
5. The slight improvements in PCS and MCS SF-12 scores observed in the pivotal placebo controlled studies did not appear to be maintained in the open label, long term Study 156-03-244.
6. There was no systematic evaluation of the objective effects of Tolvaptan on nervous system. Both pivotal hyponatremia studies showed improvements in Tolvaptan treated patients in muscle strength (especially in patients with severe hyponatremia) although these did not demonstrate symmetrical concordance and are therefore of doubtful importance. Of potential importance were changes in measures associated with proprioception and coordination; ataxia right and left finger to nose test and stance with eyes closed. These data are of some interest given the previous reports of untoward effects of hyponatremia on gait and balance. However, additional study with large numbers of subjects would be necessary to assess the clinical relevance of these effects.

ln light of the fact that positive results for only one of two endpoints (only MCS and not PCS) at one of two timepoints in one of two trials, lack of content validity, missing data, and potential unblinding, the PRO endpoint is unpersuasive, fails to meet regulatory standards for demonstration of efficacy, and is unusable for labelling. Hence, the proposed PI should clearly state that raising serum sodium with Samsca does not provide a symptomatic benefit to patients.

Safety specifications

The company will need to develop a risk management strategy to ensure that patients are appropriately monitored when treatment is initiated. Presumably, this means that initiation would be restricted to the inpatient setting, and mechanisms would be in place to assure this. Specifically, patients should be advised that:

1. they should not be initiating treatment at home (they should have been started in a hospital).
2. they should not use Tolvaptan if they dont have free access to water;
3. they should not use Tolvaptan if they are incapable of sensing thirst; and
4. if they discontinue Tolvaptan on their own, they should not restart treatment.

A paediatric study will be needed, and the details will need to be worked out. The inclusion/exclusion criteria will need to be congruent with the indicated adult patient population.

Balance

Hyponatremia is a disease characterised by a subnormal concentration of sodium in the blood (serum sodium <135 mEq/L) and is manifest by a range of CNS impairments such as headache, nausea, inability to concentrate, confusion, impaired coordination, and memory deficiencies. Further decreases in sodium can even lead to more serious conditions such as seizure, coma, respiratory arrest, or death. The presence of hyponatremia, even of relatively mild severity is associated with adverse survival. This includes patients with heart and/or hepatic failure and/or acute myocardial infarction.

There is no well established, standardised therapy available for treatment of hyponatremia and current therapeutic approaches all have important limitations, including the two most widely used treatments, hypertonic saline and fluid restriction. Hypertonic saline is mainly used in cases of serious hyponatremia and can be life saving, but overly rapid correction of serum sodium levels can cause severe detrimental effects, for example, quadriplegia. In chronic hyponatremia, fluid restriction is the mainstay of treatment, but the time required for sodium correction is long, patients find it almost impossible to resist the feelings of thirst, and treating physicians find it difficult to obtain patient compliance.

Tolvaptan is an orally administered selective vasopressin V_2 receptor antagonist developed for the treatment of euvolemic and hypervolemic hyponatremia. Tolvaptan is a member of a relatively new chemical and pharmacologic class of drugs known as 'vaptans' or aquaretics. These drugs block the vasopressin V_2 receptor located on the basolateral aspect of collecting duct cells of the renal tubule, lowering urine osmolality, inducing a water diuresis (aquaresis), and raising serum osmolality and sodium concentrations.

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. For the hyponatremic patient, treatment with Samsca (Tolvaptan) leads to a prompt and reliable increase in serum sodium and a prevention of the worsening of hyponatremia. This has been consistently demonstrated for Samsca (Tolvaptan) in clinical trials (SALT-1 and SALT-2, placebo controlled, Phase 3 trials) in hyponatremic patients of different severities from various underlying disease aetiologies (for example, SIADH, heart failure, and liver cirrhosis). Patients treated with Samsca (Tolvaptan) also were found to have a reduced need for fluid restriction (12-19% for Tolvaptan versus 24-36% for placebo patients in pooled two Phase 3 hyponatremia studies), simplifying treatment for both the patient and the physician. 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 comorbidity play a significant role in the clinical picture of hyponatremia. The evidence to support use of Tolvaptan in patient with cirrhosis is not as convincing.

The extensive Samsca (Tolvaptan) clinical safety database (more than 4000 patients treated with Tolvaptan in open label or placebo controlled trials) provides reassurance that supports the safe use of Samsca (Tolvaptan) in patients with a range of underlying diseases and severities of hyponatremia. The most common AEs with Samsca (Tolvaptan) were clearly related to the pharmacological effect of the drug (for example, thirst, pollakiuria). There was no evidence found for any adverse effects on kidney function even for extended treatment durations. There is no evidence to suggest that the drug acts in an unpredictable way.

Overall, there is an unmet medical need for a reliable and safe therapy to satisfactorily treat hyponatremia. There are no pharmacotherapies currently approved in Australia for the treatment of hyponatremia and worldwide also there are only two authorised products in this class of medicines, Vaprisol (conivaptan) and Physuline (mozavaptan). There is limited clinical use of these products as Vaprisol was approved in the US in 2005 for IV use in hospitalised patients only and Physuline, approved in Japan in 2006, has the limited indication of treatment for hyponatremia in SIADH due to an ectopic ADH (Antidiuretic Hormone) producing tumour. Relative to conivaptan, however, Tolvaptan presents important new risks, because conivaptan is an intravenous drug that is approved only for use for four days in hospitalised patients. Thus, whereas monitoring is presumably intense for an IV drug such as conivaptair, there is the strong potential for Tolvaptan to be used casually in an outpatient setting, with only limited monitoring.

The key safety concerns with Tolvaptan treatment are overly rapid rise in serum sodium concentration, and use in appropriate patient populations. Specifically, intensive

monitoring of electrolytes is important when therapy ís initiated (hence treatment should be initiated in an inpatient setting), and particular groups of patients should not be treated. These groups include:

- Patients in whom urgent correction of serum sodium is needed (when there are neurological signs or symptoms, or when they seem impending). Such patients were not studied in the development program, and Tolvaptan's efficacy and safety in such patients is unproven.
- Patients who lack access to free water; who are unable to sense thirst; with hypovolemic hyponatremia;
- Patients with hyponatremia due to cirrhosis, a 'fragile' population where safety data are limíted, and there appears to be excess bleeding, consistent with pre clinical data suggesting that the drug could both deplete vitamin K dependant clotting factors and inhibit platelet aggregation.

Hence, use of Tolvaptan in cirrhotic patients would only be justified if the potential benefit outweighs this risk in an individual patient.

The main concern with this submission is that the whole argument to support approval is based solely on a change in a laboratory parameter. For some diseases, the main laboratory parameter does not begin to represent the overall scope of the disease (for example, glucose in diabetes), whereas in other disease states, the parameter defines the disease as well as its severity (for example, hypokalemia, anaemia). Hyponatremia seems to fit better with the latter group than the former.

For this application, the key question related to quantifying benefit and risk when there is no tangible symptom relief for an individual patient. Thus, approval of Tolvaptan for hyponatremia requires acceptance of an increase in serum sodium concentration as a benefit in itself, independent of any improvement in symptoms. The development program was geared to show an increase in serum sodium, and the application provided little evidence that Tolvaptan improves clinical benefit in a meaningful and tangible way. On retrospect, there was no way for the development program to show symptom relíef, given that symptomatic subjects were largely excluded from participation in the studies.

The applicant argues that the improvements in SF-12 MCS scores related to and were associated with changes in serum sodium in the pooled analysis. However, the MCS analysis had several limitations already outlined. ln light of the fact that positive results for only one of two endpoints (only MCS and not PCS) at one of two timepoints in one of two pivotal trials, lack of content validity, missing data, and potential unblinding, the PRO endpoint is unpersuasive, fails to meet regulatory standards for demonstration of efficacy, and is unusable for labelling. Additionally, the CNS effects were not assessed objectively.

Based on the data submitted, Samsca (Tolvaptan) has a favourable benefit/risk ratio in patients with non acute, euvolemic and hypovolemic hyponatremia including adult patients with heart failure and SIADH. However, the evidence to support efficacy/safety in hyponatremia due to cirrhosis is not convincing. Furthermore, it has not been established that raising serum sodium with Samsca (Tolvaptan) provides a symptomatic benefit to patients.

Conclusions

It is recommended that Samsca (Tolvaptan) be approved for the following indication:

> "Samsca is indicated for the treatment of clinically significant non acute, hypervolemic or euvolemic hyponatremia in adult patients with SIADH and heart failure. It has not been established that raising serum sodium with Samsca provides a symptomatic benefit to patients"

The approval is subject to satisfactory response to queries already outlined.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan that was reviewed by the TGA's Office of Product Review (OPR).

Safety Specification

Subject to the evaluation of the nonclinical aspects of the Safety Specification (SS) by the Toxicology area of the OSE (Office of Scientific Evaluation) and the clinical aspects of the SS by the OMA (Office of Medicines Authorisation), the summary of the Ongoing Safety Concerns as specified by the sponsor is in Table 51.

Table 51: Important identified, potential risks and missing information for Tolvaptan.

Important identified risks	• Volume depletion and dehydration • Electrolyte shifts: hypernatraemia, hyperkalaemia • Hyper- / hypoglycaemia • Hyperuricaemia, gout • Interaction with CYP3A4 Inhibitors • Interaction with CYP3A4 Inducers • Interaction tolvaptan and serum potassium concentration-increasing substances • Interaction tolvaptan and combined administration of warfarin and antiplatelet agents
Important potential risks	• Renal toxicity • Acute urinary retention (patients with urinary outflow obstruction) • Cardiac arrhythmias secondary to electrolyte shifts • Too rapid rise of serum sodium and neurologic sequelae (encephalopathy, osmotic demyelination) • Gastrointestinal bleeding in cirrhotics • Hypercoagulability (stroke, myocardial infarction) • Post-treatment myocardial ischaemia • Dyspnoea • Teratogenicity
Important missing information	• Paediatric data • Pregnancy outcome data • Breast-feeding data

Proposed pharmacovigilance activities

The sponsor proposes routine pharmacovigilance activities, consistent with the European guidelines[29] outlined in *3.1.2 Routine pharmacovigilance practices, Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03),* to monitor all the specified ongoing safety concerns. A description of this pharmacovigilance system, identified as Version 01, dated August 2010, has been provided.

In addition, the sponsor proposes to further monitor all the important identified and potential risks and to capture off label use in general, and specifically in children, by conducting a multicentre, multinational, non interventional, observational Post Authorisation Safety Study (PASS). The primary objective of the Drug Utilisation Survey (DUS) is to monitor and document the drug utilisation patterns of Tolvaptan in routine

[29] European Medicines Agency, "ICH Topic E 2 E Pharmacovigilance Planning (Pvp): Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03)", June 2005, Web, accessed 16 July 2012 <http://www.tga.gov.au/pdf/euguide/ich571603en.pdf>.

medical practice, while the objective of the PASS is to collect information on the safety of Samsca when used in a real life setting.

Approximately 50 hospitals in the UK, Germany, and Nordic countries including sites from other EU countries will be considered when Tolvaptan is launched in the respective countries. Hospital pharmacists will record prescription data (DUS) if available from Tolvaptan requests to the pharmacy. In hospitals where pharmacy requests do not include individual level prescription data, pharmacists will inform the study coordinator who will follow up with the respective prescriber. The actual safety study (PASS) will be conducted by the hospital physicians who will enrol patients and record safety and clinical data. Community based physicians will continue documentation of safety outcomes for patients who stay on Tolvaptan after discharge from hospital. Patients will be followed up for the time of treatment. Chronically treated patients will be followed up for a minimum of 12 months after initiation of treatment. A population of at least 200 SIADH patients treated with Tolvaptan will be enrolled into the PASS over a recruitment period of approximately two years.

Data analysis will first be performed by descriptive statistics including subgroup analyses. Second, an analysis of demographics and indications of all patients included in the PASS will be performed to assess the feasibility of an historical control group. If feasible, AE frequencies collected for PASS patients will be compared to spontaneous incidence rates of such events reported for these patients in relevant epidemiological and literature databases. Third, patient exposure time normalised AE frequencies recorded for PASS patients will be compared to and discussed in the context of the corresponding numbers observed during the clinical development of Tolvaptan.

The drug utilisation analysis will describe the number of prescriptions, their distribution between different medical specialties, indication for use as compared to the SmPC, age and gender distributions on a prescription level.

Sodium levels at baseline and rate of sodium correction under therapy will be analysed and safety findings will be described. The number of all non serious and serious adverse reactions and the relative frequencies will be analysed in consideration of the risk categories defined in the RMP (Risk Management Plan):

- Renal safety
- Aquaresis related adverse effects (urinary retention, volume depletion)
- Electrolyte shifts related risks (cardiac arrhythmias, osmotic demyelination)
- Metabolic effects (gout, hyperglycaemia)
- Potential effects on blood coagulation (stroke, GI bleeding, post treatment MI)
- Dyspnoea
- CYP3A4 interactions
- Interactions with serum potassium concentration increasing substances
- Interactions with warfarin and antiplatelet agents
- Teratogenic potential
- AEs in paediatric patients

Subgroup analyses will be performed for all safety findings by indication subgroups (SIADH and other indications), subgroups according to SIADH underlying diseases, age groups, hepatically impaired patients and renally impaired patients.

It is stated that the planned date for submission of interim data is 6-9 months after the study start, then annually. The planned date for submission of final data is 6 months after the study end.

The sponsor has now advised that the corresponding study protocol (Study 156-09-101, Version 3, dated 26 June 2010) was accepted by the EMA/CHMP (European Medicines Agency/Committee for Medicinal Products for Human Use) on 23 September 2010 and the first site has been initiated. The sponsor has now provided a copy of the final study protocol.

OPR reviewer's summary in regard to the pharmacovigilance plan (PP) and appropriateness of milestones

In principle, there is no objection to the sponsor implementing additional pharmacovigilance activities to further monitor the specified ongoing safety concerns. However, the nonclinical and clinical aspects of the SS remain subject to the evaluation by the Toxicology area of the OSE and by the OMA, respectively.

Furthermore, the extent to which Study 156-09-101 can be generalised to the Australian context will be limited by the degree to which the EU and the Australian approved indications are aligned, and in regard to drug utilisation data the differences between how this medicine is made accessible in these different markets. Nevertheless, this initiated study is not considered to be part of the planned clinical studies in the pharmacovigilance plan. The related study protocol has thereby not been reviewed, but an update on the progress/results/analysis of this study, as outlined in the RMP, will be expected in future PSURs.

Risk minimisation activities

In this section of the RMP, the sponsor appears to have some difficulty differentiating between pharmacovigilance and risk minimisation activities. Nonetheless, the sponsor states that the post marketing safety information is in concord with clinical trial safety data. Consequently, the sponsor concludes that routine risk minimisation activities as described in the product information (PI, CMI and packaging) are sufficient.

OPR reviewer comment

The sponsor's conclusion of the need for risk minimisation activities appears to be contrary to the US FDA decision that a Medication Guide for patients and a Communication Plan for HCPs (health care providers), including a Dear Healthcare Provider Letter and a Prescriber Brochure, was required to achieve the following:

- Educating HCPs on the risk of overly rapid correction of serum sodium associated with Tolvaptan and the need for initiating Tolvaptan in a hospital to ensure proper titration and monitoring.
- Informing patients of the serious risk associated with the use of Tolvaptan, particularly the risk of osmotic demyelination syndrome.

The sponsor should provide a justification as to why similar additional risk minimisation activities should not be implemented in Australia, while a REMS (Risk Evaluation and Mitigation Strategy) is required in the US. In addition, the nonclinical and clinical aspects of the SS remain subject to the evaluation by the Toxicology area of the OSE and by the OMA respectively.

Potential for medication errors

The sponsor has advised that none are anticipated.

OPR reviewer comment:

Given the post marketing exposure of Tolvaptan in the US and EU, the sponsor should provide information on the occurrence and frequency of medication errors from related PSURs. In addition, the need for visual (or physical) differentiation between strengths should be discussed. This part of the RMP should be amended accordingly.

Risk minimisation plan

Routine risk minimisation activities will include contraindications and warnings or notification of undesirable effects in the Australian PI for all the specified ongoing safety concerns, except for the important identified risks:

- 'hyperuricaemia and gout'
- 'interaction Tolvaptan with combined administration of warfarin and antiplatelet agents';

and the important potential risks:

- 'cardiac arrhythmias'
- 'hypercoagulability and stroke'
- 'post treatment myocardial ischaemia'
- 'dyspnoea'

and the important missing information:

- 'off label use'.

The sponsor claims that routine risk minimisation is not required for these ongoing safety concerns as the potential risks resulting from electrolyte shift associated cardiac arrhythmias, hypercoagulability (stroke; myocardial infarction), post treatment myocardial ischaemia, and dyspnoea are at this stage considered to be potential risks, with no evidence of a significant risk to public health.

In hyponatremia patients, the sponsor states that Tolvaptan treatment was not associated with increased reporting rates for hyperuricaemia and gout, although increases in blood uric acid were seen in slightly higher incidences with the Tolvaptan group.

Clinical trial data indicated that concomitant warfarin slightly increased the risk of stroke compared to the placebo arm, while concomitant antiplatelet agents reduced risk compared to the placebo arm. The sponsor states that based on the available data the imbalance in stroke reporting is considered a chance finding and interaction with the combined administration of warfarin and antiplatelet agents is a potential risk that is not yet confirmed.

OPR reviewer comment:

The sponsor's proposed routine risk minimisation activities would appear to be reasonable, except in regard to the important potential risk: 'Acute urinary retention (patients with urinary outflow obstruction)'. The related warning statements proposed in the RMP:

> *"Urinary output must be secured. Patients with partial obstruction of urinary outflow, for example patients with prostatic hypertrophy or impairment of micturition, have an increased risk of developing acute retention"*

have been replaced in the proposed Australian PI by the statement:

> *"Patients with urinary outflow obstructions must be monitored to ensure urinary output is achieved".*

The sponsor should revert to the former warning statements to enhance patient safety and to be aligned with the currently approved SmPC.

The sponsor should also clarify why 'interaction Tolvaptan with combined administration of warfarin and antiplatelet agents' has been classified as an important identified risk while the SS of the RMP states that it is a potential risk which has not yet been confirmed.

In addition, the 'Summary of Planned Actions' and 'Summary of the Risk Management Plan' sections appear to indicate that the important potential risk 'Gastrointestinal bleeding in patients with liver cirrhosis' does not require routine risk minimisation. There is a subsection in the 'Precautions' section of the proposed Australian PI that relates to 'Use in patients with cirrhosis' stating Tolvaptan should only be used in cirrhotic patients when the need to treat outweighs the risk of gastrointestinal bleeding. These parts of the RMP should be amended accordingly.

For the important identified risk 'Interaction Tolvaptan and serum potassium concentration increasing substances', the RMP section 'Summary of Planned Actions' (no routine risk minimisation is required) appears to be inconsistent with the RMP itself: 'Summary of the Risk Management Plan'. This apparent internal inconsistency should be corrected.

For the important missing information, the section 'Use in the hepatic impaired' appears to be inconsistent with the RMP itself. This apparent internal inconsistency should be corrected.

It was previously noted that the CHMP recommended approval for Tolvaptan in only the treatment of adult patients with hyponatremia secondary to SIADH. It would also appear that numerous routine risk minimisation activities in the form of contraindications, notification of adverse effects and the warning statement:

> *"Fluid and electrolyte status should be monitored in all patients and particularly in those with renal and hepatic impairment"*

which were identified in the currently approved SmPC have not been included in the proposed Australian PI. The sponsor has provided no explicit explanation or justification for these differences. Consequently, in regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft product information document be revised as follows to be aligned with the currently approved SmPC to enhance patient safety:

- For the important identified risk: 'Volume depletion and dehydration' and the important potential risks 'Renal toxicity' and 'Rapid rise of serum sodium and neurologic sequelae', subjects with volume depletion should be contraindicated.
- For the important identified risk 'Electrolyte shifts', subjects with hypernatraemia should be contraindicated.
- For the important missing information 'Teratogenicity, Lack of pregnancy data', the currently approved SmPC states:

  > *"There are no adequate data from the use of Tolvaptan in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Women of childbearing potential should use adequate contraceptive measures during Tolvaptan use. Samsca must not be used during pregnancy."*

Consequently, 'Pregnancy' should be a contraindication.

- For the important missing information 'Lack of breastfeeding experience', breastfeeding should be a contraindication.

- For the important potential risk 'Renal toxicity', a warning that increases in blood creatinine is a common undesirable effect should be included.
- For the important identified risk 'Volume depletion and dehydration', a warning that dehydration is a common undesirable effect should be included.
- For the important identified risk 'Electrolyte shifts', a warning that hypernatraemia and hyperkalaemia are common undesirable effects should be included.
- For the important identified risk 'Hyperuricaemia and gout', a warning that hyperuricaemia is a common undesirable effect should be included.
- For the important potential risk 'Rapid rise of serum sodium and neurologic sequelae' and the important missing information 'Use in the hepatic impaired', the warning statement:

  "Fluid and electrolyte status should be monitored in all patients and particularly in those with renal and hepatic impairment"

should be included.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and the submitted RMP is applicable without modification in Australia unless so qualified:

- The nonclinical and clinical aspects of the SS remain subject to the evaluation by the Toxicology area of the OSE and by the OMA, respectively.
- The summary of the Ongoing Safety Concerns appears to be inconsistent with the following and these apparent internal inconsistencies should be corrected:
  - RMP section 'Summary of Safety Concern and Planned PV Actions of the RMP' – important missing information: 'Off label use' not included.
  - RMP section 'Detailed Action Plan for Specific Safety Concerns' – important missing information: 'Use in the hepatic impaired' not included.
  - RMP section 'Summary of Planned Actions' – important missing information: 'Off label use' & 'Use in the hepatic-impaired' not included.
  - RMP section 'Summary of the Risk Management Plan' – important missing information: 'Off label use' & 'Use in the hepatic impaired' not included.
- In principle, there is no objection to the sponsor implementing additional pharmacovigilance activities to further monitor the specified ongoing safety concerns.
- The extent to which Study 156-09-101 can be generalised to the Australian context will be limited by the degree to which the EU and the Australian approved indications are aligned, and in regard to drug utilisation data the differences between how this medicine is made accessible in these different markets. Nevertheless, this initiated study is not considered to be part of the planned clinical studies in the pharmacovigilance plan; the related study protocol has not been reviewed. An update on the progress/results/analysis of this study, as outlined in the RMP, will be expected in future PSURs.
- The sponsor's conclusion of the need for risk minimisation activities appears to be contrary to the US FDA decision that a REMS was required. The sponsor should provide a justification as to why similar additional risk minimisation activities should not be implemented in Australia.

- Given the post marketing exposure of Tolvaptan in the US and EU, the sponsor should provide information on the occurrence and frequency of medication errors from related PSURs. In addition, the need for visual (or physical) differentiation between strengths should be discussed. The 'Potential for Medication Errors' section of the RMP should be amended accordingly.
- The sponsor's proposed routine risk minimisation activities would appear to be reasonable except in regard to the important potential risk: 'Acute urinary retention (patients with urinary outflow obstruction)'. The related warning statements proposed in the RMP: *"Urinary output must be secured. Patients with partial obstruction of urinary outflow, for example patients with prostatic hypertrophy or impairment of micturition, have an increased risk of developing acute retention"* have been replaced in the proposed Australian PI by the statement: *"Patients with urinary outflow obstructions must be monitored to ensure urinary output is achieved".* The sponsor should revert to the former warning statements to enhance patient safety and to be aligned with the currently approved SmPC.
- The sponsor should clarify why 'Interaction Tolvaptan with combined administration of warfarin and antiplatelet agents' has been classified as an important identified risk while the SS of the RMP states that it is a potential risk which has not yet been confirmed.
- The RMP sections 'Summary of Planned Actions' and 'Summary of the Risk Management Plan' appear to indicate that the important potential risk 'Gastrointestinal bleeding in patients with liver cirrhosis' does not require routine risk minimisation. However, there is a subsection in the 'Precautions' section of the proposed Australian PI that relates to 'Use in patients with cirrhosis' stating Tolvaptan should only be used in cirrhotic patients when the need to treat outweighs the risk of gastrointestinal bleeding. These parts of the RMP should be amended accordingly.
- For the important identified risk 'Interaction Tolvaptan and serum potassium concentration increasing substances', the RMP section 'Summary of Planned Actions' (no routine risk minimisation is required) appears to be inconsistent with the RMP section 'Summary of the Risk Management Plan'. This apparent internal inconsistency should be corrected.
- For the important missing information 'Use in the hepatic impaired', the RMP section 'Summary of Planned Actions' appears to be inconsistent with the RMP section 'Summary of the Risk Management Plan'. This apparent internal inconsistency should be corrected.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

All chemistry and quality control issues have been resolved. The tablets are blue, unscored and uncoated. They are differentiated by embossing and tablet shape.Tolvaptan is present as a racemate.

The mean absolute bioavailability (Study 156-05-254) was 56% (range 42-80%) compared with IV Tolvaptan.

Bioequivalence of different strengths, 15 mg, 30 mg and 60 mg was assessed in Study 156-01-233 where they were shown to be bioequivalent. A high fat meal increased C_{max} (1.40; 1.17-1.67), not AUC.

Study 156-05-305 examined the PK of the enantiomers. S (-) Tolvaptan concentration was markedly higer than the R (+) enantiomer.

This application was considered at the 139th PSC (Pharmaceutical Sub Committee) meeting. There was no objection to registration.

The evaluator recommends approval from a chemistry point of view.

Nonclinical

The evaluator mentions that adequate studies on PK, pharmacodynamics and safety have been performed according to relevant guidelines.

Tolvaptan was shown to act as a vasopressin V_2 receptor antagonist with nanomolar potency. The human metabolites (DM-4103 and DM-4107) did not have significant V_2 receptor affinity. Tolvaptan is a racemate with S and R enantiomers having equivalent affinity for the target receptor (that is, antagonism). Oral administration of Tolvaptan increased urine volume, decreased urine osmolality and increased serum sodium concentration in laboratory animal species.

In terms of secondary pharmacodynamic studies, there was no significant activity at other receptors or ion channels. The evaluator mentions that significant effects were observed only with IV administration. There were no ECG abnormalities observed in dogs. The hERG K+ channel was not inhibited by Tolvaptan, and only weakly by DM-4103.

Tolvaptan was rapidly absorbed (mice, rats, rabbits, dogs and humans). Oral bioavailability was lower in rats and dogs (approximately 15%) compared with humans (56%). There were dose proportional kinetics and wide tissue distribution. Plasma protein binding was high in humans (≥98%) and in animals. It is extensively metabolised; CYP3A4 being mainly responsible. It is mainly excreted faecally (humans, rabbits and dog).

The evaluator mentions that Tolvaptan displayed low order of acute oral toxicity in laboratory animals.

Repeat dose toxicity with oral Tolvaptan in rats (26 weeks) and dogs (52 weeks) showed exaggerated pharmacology effects. Highest dose without adverse event was 100 mg/kg/day in dogs and female rats, 1000 mg/kg/day in male rats.

Tolvaptan was not genotoxic or carcinogenic.

The evaluator mentions that “findings of embryofetal lethality and teratogenicity in rabbits at low or relatively low exposure margins (1.7–4.9), albeit in conjunction with maternotoxicity, warrant placement of Tolvaptan in Pregnancy Category D (rather than C as the sponsor has proposed) and strengthening of the warning against use in pregnancy in the Product Information document”.

Overall, the evaluator recommends approval.

Clinical

Pharmacokinetics

The evaluator mentions 25 pharmacokinetic studies.

Three single dose Studies 156-00-001, 156-98-210 and 156-01-229 were discussed. The first study examined 15-120 mg in 56 subjects where there was dose linearity observed in

relation to C_{max} and AUC. Median T_{max} ranged from 2.3-4 h. The two other studies used doses above the range (60 mg to 240 mg) and conclusions on dose linearity are of limited relevance to this submission where the maximum dose proposed is 60 mg.

Multiple dose Studies 156-00-003 and 156-05-001 examined doses of 30 mg to 120 mg/day for 7 days. There was no accumulation seen with Tolvaptan. However, the second study showed an eight to nine fold increase in AUC in relation to DM-4103, a metabolite of Tolvaptan.

The median T_{max}, $t_{1/2}$, C_{max} and $AUC_{0\text{-}inf}$ of Tolvaptan following oral administration of a 30 mg tablet were 2 h, 6.7 h, 231 ng/mL and 1731 ng.h/mL respectively.

The bioavailability study was conducted on 14 healthy subjects. 1 mg IV Tolvaptan (1mg/10mL) was compared to the 30 mg tablet. The mean absolute bioavailability was 56% (range 42% to 80%).

There were two bioequivalence studies. Of note, Study 156-01-233, showed bioequivalence in terms of C_{max} and AUC with the 15 mg, 30 mg and 60 mg tablet.

Two additional Studies 156-00-002 and 156-05-256 examined the effect of food, in healthy subjects. Whilst the AUC was within the prespecified range for bioequivalence, C_{max} exceeded this criterion in both studies. Thus, the rate of absorption of Tolvaptan increased with food intake.

A radiolabelled single dose (60 mg Tolvaptan) single centre open label study is discussed. This was conducted in 12 healthy male subjects. The mean total recovery of the radioactivity administered is about 99% with about 40% excreted in urine and about 59% in the faeces. The main route of total radioactivity is non renal (59%). The absorption of the parent drug and or metabolites is ≥ 40%. The parent compound is excreted mainly by non renal pathways. In plasma, urine and faeces, 7, 5 and 4 metabolites are identified, respectively. About 60% of the total radioactivity circulating in plasma is definitely identified. DM-4103 is the most abundant in plasma. Similarly, the most abundant metabolite in urine is DM-4107. The parent drug present in faeces accounts for 14% radioactivity. DM-4107 was the most abundant in faeces.

Metabolites

The pharmacokinetic results of the metabolites varied widely, with DM-4103 showing greater AUC and $t_{1/2}$. The different combinations of 60 mg (4 x 15 mg, 2 x 30 mg and 1 x 60 mg) showed similar PK in relation to DM-4103. Coadministration of lovastatin 80 mg (Study 156-01-233) resulted in halving of T_{max} (24 to 12 h) and an increase in C_{max} and AUC in relation to DM-4103.

No studies examined the PK of Tolvaptan in children. In Study 156-98-202 using 60 mg dose, the effect on age and sex were examined. No clinically significant effect was seen. No studies were conducted on patients with renal impairment.

CYP inhibitors

Tolvaptan plasma concentrations are increased after the administration of CYP3A4 inhibitors (for example, ketoconazole, macrolide antibiotics, diltiazem). Coadministration with grape juice also resulted in increased exposure.

CYP3A4 inducers

Coadministration (rifampicin, barbiturate) decreased the plasma concentration of tolavptan.

CYP substrates had no significant effect.

There was no clinically significant effect with loop and thiazide diuretics, warfarin or hypertonic saline. There was an increase in warfarin C_{max} and AUC when coadministered with Tolvaptan.

The evaluator states that, "hyponatremia severity, concomitant administration of diuretics, CYP3A4 inhibitors, heart failure concomitant medications, and P-gp inhibitors did not have a meaningful influence on Tolvaptan PK for the patient populations investigated".

Pharmacodynamics

A total of 19 studies are reported that involved 869 subjects.

The evaluator mentions that following the administration of a single dose of 30 mg Tolvaptan (Study 156-05-254), the plasma concentrations (24-44 ng/mL) were sufficient to suppress urine osmolality for the entire sampling period of 0-24 h.

Ascending dose studies

Study 156-00-001 examined single doses of 15 mg to 120 mg. There was a significant increase in urine excretion rate within 2 h of dosing. The increase in urine volume was dose dependent. Urine excretion rates returned to baseline after 24 h.

Study 156-98-210 examined doses ranging from 60 mg to 240 mg in healthy volunteers where volumetric fluid replacement (Period 1) was given and Period 2 were no fluid replacement was given. No changes in serum or urinary electrolytes were observed in Period 1. Mean urinary volume excretion increased dose dependently in Period 2.

Study 156-01-229 examined single doses ranging from 180 mg to 480 mg in healthy adults. There was no increase in urine excretion rate and free water clearance with increasing dose.

Multiple dose studies

Study 156-00-003 reported 30 and 60 mg doses that were used as single dose followed by 7 day multiple dosing (after a 2 day washout period) in 6 healthy subjects. The evaluator reports that the plasma AVP concentration and serum osmolality increased "markedly". However, the magnitude was greater after the single dose regimen. This was also the case for serum electrolytes (Na^+, K^+, Cl^-, Mg^+). The evaluator states that "there were no significant changes in the quantity of Na^+ excreted in 24 h cumulative urine following administration of Tolvaptan, and the quantities in the Tolvaptan treated subjects and the placebo group remained similar throughout the treatment period ... Cumulative urine volume, urine excretion rate, and cumulative fluid intake increased markedly in the Tolvaptan treated subjects compared to placebo and the degree of increase was similar following both single and repeated administration. "

Study 156-05-01 examined 90 mg, 120 mg or placebo in healthy males (n=6). 24 h cumulative urine volume increased with dose.

Study 156-95-305 employed a once daily administration of 30 mg, 60 mg Tolvaptan versus placebo for 28 days. Urine output and osmolality increased in a dose dependent manner. There was no accumulation of drug in serum after 28 days.

In patients with CHF

The evaluator states that in Study 156-00-221, which examined the effect of Tolvaptan on renal function in subjects with CHF, Tolvaptan significantly increased effective renal plasma flow (9%) and renal blood flow (10%) compared to placebo and furosemide. In addition, glomerular filtration rate increased (1.37 mL/min) and renal vascular resistance decreased (-1.54 mmHg/dL) compared to placebo. There were no significant age/gender

interactions for the pharmacodynamic parameters AVP, plasma renin activity, and urine osmolality". The effect of Tolvaptan on other medications used in CHF is not known.

There was no effect seen on maximum time matched mean change form baseline in individually corrected QT_c in Study 156-03-245 which examined 30mg or 300 mg Tolvaptan QD for five days.

The evaluator also mentions that no studies are submitted that examined the effects on CYP mutations on the pharmacodynamics of Tolvaptan since Tolvaptan is primarily metabolised by CYP3A4/5, patients with known mutations would require dose adjustments.

Efficacy

Dose finding studies

Three Studies 156-96-203, 156-96-201 and 156-97-204 were submitted. The latter two were discontinued because of a declining enrolment and will not be discussed further. Study 156-96-203 was a double blind randomised placebo controlled Phase II study examining five dose levels (5, 10, 15, 20, 30 and 60 mg once daily) for 13 days in 45 subjects with hyponatremia secondary to liver disease. Several restrictions were in place to ensure that the plasma Na^+ levels did not increase rapidly. Plasma Na^+ increased dose dependently, though wide variation was seen with the doses. This was supported by effect on body weight, urine volume, fluid intake and plasma potassium levels. The effect was not consistent and the small numbers also confounded the interpretation.

Pivotal efficacy studies

Two Studies 156-02-235 and 156-03-258 were submitted. These were Phase 3 double blind randomised placebo controlled studies in subjects with non acute hyponatremia in euvolemic or hypervolemic states. The main inclusion criterion was ≥18 years and hyponatremia in euvolemic or hypervolemic states defined as serum sodium level <135 mEq/L prior to randomisation. Those with hyponatremia due to hypovolaemic states were excluded. The evaluator mentions that, "the criteria included tended to select subjects with mild or moderate hyponatremia who were not symptomatic or at least not sufficiently symptomatic to require IV saline". The subjects were stratified according to the serum sodium level (130-134 mEq/L or <130mEq/L). There was no lower limit for serum sodium for inclusion; however, this subgroup had to be symptom free at entry.

The treatment duration was 30 days. Both studies included dose titration commencing at 15 mg/day. The evaluator mentions that dose titration in the placebo group is not specified.

The co-primary efficacy endpoints were average daily AUC of change from baseline in serum sodium level up to Day 4 and Day 30 within the double blind treatment period.

Secondary endpoints included parameters that assessed efficacy in subgroups with <130 mEq/ L and ≥130 mEq/L Na+. Other endpoints also related to changes in fluid balance, body weight, need for fluid restriction, treatment failure and changes in SF-12 Health Survey.

The evaluator mentions that the "primary efficacy analysis was performed on the restricted ITT data set using an ANCOVA model with factors of treatment, baseline disease severity and origin, and baseline serum sodium level as covariate".

The relevant demographics are given in Table 52.

Table 52: Demographics of Studies 156-02-235 and 156-03-238.

	Trial 156-02-235		Trial 156-03-238	
	Tolvaptan n=102	Placebo n=103	Tolvaptan n=123	Placebo n=120
Mean age (range)	60 (18-86)	60 (35-90)	62 (27-92)	63 (28-100)
Male	50.9%	60.2%	61.0%	60.8%
Baseline serum sodium <130 mEq/L	52.0%	50.5%	48%	48.3%
Diseases:				
SIADH	26.5%	24.3%	20.3%	27.5%
HF	37.3%	35.0%	30.1%	30.8%
Liver cirrhosis	24.5%	20.4%	30.9%	30.0%
Other	17.6%	27.2%	21.1%	20.0%
Hypervolemic hyponatraemia	40.2%	33%	47.2%	50%
Fluid restriction at baseline	17.5%	18.3%	6.7%	12.2%

In these studies, 24.1% in the Tolvaptan group and 29.3% in the placebo group withdrew. Approximately 12% of those randomised withdrew in each group due to AEs.

The coprimary endpoints showed a statistically significant difference favouring Tolvaptan over placebo (Table 53).

Table 53: Coprimary endpoints from Studies 156-02-235 and 156-03-238.

156-02-235						
Visits up to:	Treatment	N	LS Mean	p value	Estimated treatment effect	95% CI
Day 4	Tolvaptan	95	3.64	<0.0001	3.40	2.74, 4.07
	Placebo	89	0.23			
Day 30	Tolvaptan	95	6.23	<0.0001	4.59	3.66, 5.53
	Placebo	89	1.64			
156-02-238						
Visits up to:	Treatment	N	LS Mean	p value	Estimated treatment effect	95% CI
Day 4	Tolvaptan	118	4.37	<0.0001	4.00	3.32, 4.68
	Placebo	114	0.37			
Day 30	Tolvaptan	118	6.29	<0.0001	4.54	3.62, 5.47
	Placebo	114	1.75			

Several secondary endpoints addressed changes in serum sodium. These results supported the findings in coprimary efficacy endpoints. Changes in urine output, fluid balance, weight were numerically greater in the Tolvaptan group. There were some changes seen in Study 156-02-235 in relation to the mental component in SF-12. However, this was of minimum relevance as no method for adjusting for multiple comparisons in the analysis of secondary endpoints was prespecified.

There was a secondary endpoint relating to fluid restriction. The majority of subjects were not fluid restricted during the study.

SF-12 addressed symptomatic benefit associated with correcting hyponatremia. Mental status was assessed using the MCS of the SF-12 survey (from baseline to day 30). MCS was statistically significant in Study 156-02-235, not in Study 156-03-238. This finding is of limited significance as this was not statistically preplanned; there was also no adjustment for multiplicity.

Subgroup analysis to assess the effect of baseline disease severity, aetiology, age, sex, fluid restriction and diuretic use of the efficacy of Tolvaptan is discussed. Efficacy was preserved in these subgroups. **The efficacy results in those with baseline serum sodium level of less than 120 mEq/L is not found in the report. The sponsor should**

submit this in the pre ACPM (Advisory Committee on Prescription Medicines) response.

The evaluator mentions five supportive studies on heart failure; four studies were Phase 2 studies. Serum sodium concentration was determined as efficacy (secondary endpoint without addressing multiplicity issues) or safety endpoints. There was a reduction in serum sodium observed in Tolvaptan groups compared with placebo these studies.

Long term efficacy

This was an extension of the pivotal studies and was open and uncontrolled for up to 214 weeks. Results at 106 weeks are presented. Safety was the primary endpoint. Efficacy measures were secondary. A total of 111 subjects were included. The evaluator mentions that there was statistically significant increase in serum sodium from baseline; there appeared to be no loss of effect.

The effects were maintained till Week 106 in subjects with SIADH and CHF. However, in those with underlying cirrhosis of the liver, the effect was maintained only till Week 10. The SF-12 and MCS scales did not show a significant improvement.

Safety

The evaluator discusses the safety results: "all hyponatremia subjects" is discussed ahead of those with other aetiologies that were included in this submission.

The evaluator mentions that 697 patients were treated with Tolvaptan and 518 subjects with placebo in this data set. Approximately 50% (n=296) were treated for one month; a third (n=190) for three months, and less than 15% received Tolvaptan for over 12 months.

Baseline demographics (serum Na level, age, disease origin) were included.

Overall incidence of AEs was similar between groups (86%). The evaluator mentions that "The only TEAE with a notably higher frequency in the Tolvaptan group compared to the placebo group were thirst (Tolvaptan versus placebo: 14.0% vs. 3.9%), dry mouth (8.9% versus 3.3%), pollakiuria (5.4% versus 1.5%), nausea and polyuria.

The most frequent serious TEAEs were CCF, cardiac failure (approximately 25% in both groups). The incidence of death (approximately 20%) was similar between groups and the majority (14.3% versus 11.8%) were due to cardiac disorders.

In relation to laboratory investigations, "potentially clinically significant laboratory abnormalities with a ≥ 5% difference in incidence between treatment groups was decreased sodium, which had a lower incidence in the Tolvaptan treatment group (19.7% versus 35.5%). There were no other clinically significant changes seen with other parameters. There were no clinically significant changes in blood pressure or ECG.

In the heart failure studies the safety results in relation to TEAEs were similar between groups. The most common events were CCF, CF and nausea in both groups. There was a difference in potentially drug related TEAEs which were higher in Tolvaptan (48.8% versus 30.7%), thirst (17.1% versus 2.4%), dry mouth (8.5% versus 2.1%), pollakiuria (5.4 versus 0.9%) and polyuria (3.1% versus 0.5%).

There were no events that suggest osmotic demyelination or cerebral oedema arising from a rapid change in serum sodium levels.

Overall conclusion and recommendation of clinical evaluator

The evaluator mentions that the efficacy results were similar in those with mild and severe hyponatremia, the biggest difference being observed in the SIADH population. Tolvaptan at doses of 15-60 mg/day showed a statistical significant change in serum Na^+

AUC (change from baseline) at Day 4 and Day 30. The change was observed at 8 h and was maximum at Day 4. This change was maintained during treatment. There was an increase in urine output without adversely effecting renal function or electrolytes. The results were similar in mild and severe hyponatremia. The effect was sustained up to 106 weeks (in an open label uncontrolled study). This was evident in the subgroups with CHF and SIADH but not cirrhosis.

The potential symptomatic benefit assessed through questionnaires was inconclusive.

The safety results did not reveal any undue trends and were related to the pharmacological action of Tolvaptan. There were no effects that suggested osmotic demyelination that is associated with rapid correction of the Na.

The evaluator also mentions that efficacy/safety was inconclusive in relation to cirrhosis as:

- The rise in serum sodium was small (2.83 to 3.15 m Eq/ L)
- There was no significant difference in active versus placebo at 30 days.
- Long term data were scarce (13 at 26 weeks and 1 and 106 weeks).
- There was also an increase in TEAEs compared with other subgroups.

The evaluator recommends approval for "the treatment of clinically significant non acute, hypervolemic or euvolemic hyponatremia in adult patients with SIADH and heart failure. It has not been established that raising serum sodium with Tolvaptan provides a symptomatic benefit to patients".

Risk management plan

Overall, the evaluator is supportive of the submitted RMP; it is recommended that some internal inconsistencies be corrected.

Risk-benefit analysis

Delegate Considerations

The pivotal studies demonstrate the efficacy of Tolvaptan in increasing serum sodium in those with levels of 135 mEq/L or lower. This was seen in relation to the coprimary efficacy endpoints. However, there was no robust evidence of symptomatic relief (the MCS of the SF-12 did not provide consistent results in the two pivotal studies; also this was one of fifteen secondary endpoints which was not prespecified for statistical purposes, nor was multiplicity factored in).

Thus, efficacy of Tolvaptan is only demonstrated in increasing levels of serum sodium but **not** in producing a clinical benefit, that is, symptomatic relief.

It appears from the US summary review that subjects were stratified as having "mild" hyponatremia (serum sodium 130-134 mEq/L) or "severe" hyponatremia (serum sodium <130 mEq/L). The data on those with levels less than 120mEq/L are not provided. Those with hyponatremia (less than 120 mEq/L) or those requiring IV saline should be contraindicated as these groups have not been adequately studied. *The sponsor should provide an efficacy analysis on those with serum sodium 125 mEq/L or less that is the cutoff, in the US approved indication, in the pre ACPM response.*

The proposed indication, "treatment of clinically significant dilutional hyponatremia" has not been defined in the context of the submitted clinical studies. The data support the efficacy of Tolvaptan "in hyponatremia in euvolemic or hypervolemic states defined as

serum sodium level < 135 mEq/L in patients with heart failure and SIADH". The efficacy in cirrhosis has not been shown for the reasons discussed above.

Current data only provide efficacy information for 30 days treatment. Long term use is not recommended based on the submitted data.

I propose to register Tolvaptan for the treatment of hyponatremia in euvolemic or hypervolemic states defined as serum sodium level less than 135 mEq/L in patients with heart failure and SIADH.

The committee's advice is sought.

Response from sponsor

This is in response to your letter dated 16 December 2011, enclosing the Delegate's proposed action and request for ACPM advice.

We agree with the Delegate's proposal to register Tolvaptan for the treatment of hyponatremia in euvolemic or hypervolemic states defined as serum sodium level less than 135 mEq/L in patients with heart failure and SIADH. Please find below specific comments in relation to the TGA evaluation reports received:

Delegate overview

The TGA Delegate has requested the following specific information be included in the pre ACPM response:

> *"The indication for use in heart failure was withdrawn, both in the USA and EU. The reasons for this should be specified in the pre ACPM response."*

The reason is the same as that specified in the EMA assessment report. 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 hypothesised 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. The FDA also had almost the same opinion; therefore, Otsuka withdrew the indication.

> *"The efficacy results in those with baseline serum sodium level of less than 120 mEq/L is not found in the report. The sponsor should submit this in the pre ACPM response."*

We have enclosed some data for the efficacy in those with baseline serum sodium of less than 125mEq/L or 120mEq/L. As for the results in those with baseline serum sodium less than 120mEq/L, please note that the number of subjects was very small because subjects with serum sodium <120 mEq/L were associated with neurologic impairment, that is, symptoms such as apathy, confusion, seizures and were therefore excluded according to exclusion criteria.

> *"The sponsor should provide an efficacy analysis on those with serum sodium 125 mEq/L or less that is the cutoff, in the US approved indication, in the pre-ACPM response."*

It has not been possible in the timeframe available to complete the requested efficacy analysis.

Advisory committee considerations

The ACPM, taking into account the submitted evidence of pharmaceutical efficacy, safety and quality considered this product to have a positive benefit-risk profile for the indication;

> *Treatment of clinically significant hypervolaemic or euvolaemic hyponatremia (serum sodium less than 125 mM/L) or less marked hyponatremia that has resisted correction with fluid restriction in patients with SIADH. (SIADH should include cardiac and renal causes.)*
>
> *(Causes of hyponatremia including psychogenic, thiazide diuretics and hypothyroidism must be excluded).*

The ACPM supported the amendments proposed by the delegate to the PI and CMI and advised of the addition of including;

- a statement in the *Precautions* section to highlight the need to ensure frequent monitoring of changes in the patients serum sodium due to the risk of demyelination.
- a statement in the *Precautions* section to screen patients for hypothyroidism and hypoadrenalism before treatment with this product.
- a statement in the appropriate sections of the PI to ensure prescriber awareness that the product has no evidence to support its safe and effective use in cardiac failure.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Samsca (Tolvaptan) 15 and 30 mg tablets (oral administration). The approved indication reads as follows:

> *Samsca is indicated for the treatment of clinically significant hypervolemic or euvolemic hyponatremia (serum sodium less than 125 mmol/L, or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction) including patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).*

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au
Reference/Publication #

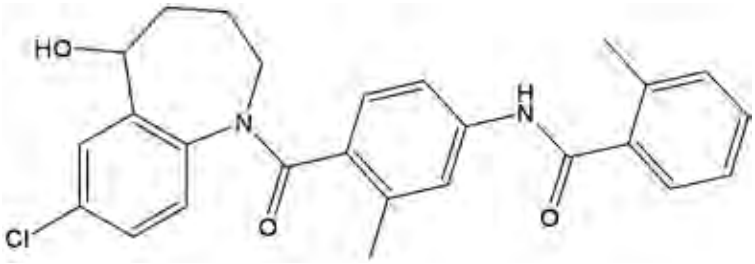
PRODUCT INFORMATION

SAMSCA®

Tolvaptan 15 mg and 30 mg tablets

NAME OF THE MEDICINE

Tolvaptan



DESCRIPTION

Tolvaptan is (±)-4'-[(7-chloro-2,3,4,5-tetrahydro-5-hydroxy-1*H*-1-benzazepin-1-yl) carbonyl]-*o*-tolu-*m*-toluidide. The empirical formula is $C_{26}H_{25}ClN_2O_3$. Molecular weight is 448.94. The CAS Registry Number for tolvaptan is 150683-30-0.

Tolvaptan is practically insoluble in water and the aqueous solubility of the drug substance is poor (~ 0.1 mg/250mL) across all pH ranges. It is slightly soluble in ethyl acetate, sparingly soluble in ethanol, soluble in methanol and freely soluble in benzyl alcohol. The octanol:water partition coefficient was reported to be greater than 5000 at 25°C.

SAMSCA tablets for oral use contain 15 mg or 30 mg of tolvaptan. Inactive ingredients include maize starch, hydroxypropylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose and indigo carmine (CI73015) aluminium lake as colorant.

The 15 mg tablet is blue, triangular, shallow-convex, debossed with “OTSUKA” and “15” on one side. The 30 mg tablet is blue, round, shallow-convex, debossed with “OTSUKA” and “30” on one side.

Tolvaptan is a Vasopressin antagonist: ATC code C03XA01.

PHARMACOLOGY

Pharmacodynamic properties

Tolvaptan is a selective vasopressin V_2-receptor antagonist with an affinity for the V_2-receptor greater than that of native arginine vasopressin. When taken orally, 15 to 60 mg doses of SAMSCA tablets cause an increase in urine excretion resulting in increased

aquaresis, decreased urine osmolality and increased serum sodium concentrations. Urine excretion of sodium and potassium are not significantly affected.

Tolvaptan metabolites do not appear to have relevant pharmacological activity at clinical concentrations in humans.

Oral administration of 15 to 120 mg doses of SAMSCA produced a significant increase in urine excretion rate within 2 hours of dosing. The increase in 24-hour urine volume was dose dependent. Following single oral doses of 15 to 60 mg, urine excretion rates returned to baseline levels after 24 hours. A mean of about 7 litres was excreted during 0 to 12 hours, independent of dose. Markedly higher doses of tolvaptan produce more sustained responses without affecting the magnitude of excretion, as active concentrations of tolvaptan are present for longer periods of time.

Pharmacokinetic properties

Absorption and distribution

After oral administration, tolvaptan is rapidly absorbed with peak plasma concentrations occurring about 2 hours after dosing. The absolute bioavailability of tolvaptan is about 56%. Co-administration with food has no effect on plasma concentrations. Following single oral doses of ≥ 300 mg, peak plasma concentrations appear to plateau, possibly due to saturation of absorption. Tolvaptan binds reversibly (98%) to plasma proteins and is distributed into an apparent volume of distribution of about 3 L/kg.

Biotransformation and elimination

Tolvaptan is extensively metabolised by the liver. Less than 1% of intact active substance is excreted unchanged in the urine. Radio-labelled tolvaptan experiments showed that 40% of the radioactivity was recovered in the urine and 59% was recovered in the faeces where unchanged tolvaptan accounted for 32% of radioactivity. Tolvaptan is only a minor component in plasma (3%). The terminal elimination half-life is about 8 hours and steady-state concentrations of tolvaptan are obtained after the first dose. After oral dosing, clearance is about 4 mL/min/kg.

Linearity

Tolvaptan has linear pharmacokinetics for doses of 15 to 60 mg.

CLINICAL TRIALS

In two double-blind, placebo-controlled, multi-center studies (SALT-1 and SALT-2), a total of 424 patients with euvolaemic or hypervolaemic hyponatraemia (serum sodium < 135 mmol/L) resulting from a variety of underlying causes (heart failure, liver cirrhosis, syndrome of inappropriate antidiuretic hormone [SIADH] and others) were treated for 30 days with SAMSCA or placebo, and were followed for an additional 7 days after withdrawal.

The mean serum sodium concentration at study entry was 129 mmol/L. Fluid restriction was to be avoided if possible during the first 24 hours of therapy to avoid overly rapid correction

of serum sodium. During the first 24 hours of therapy 87% of patients had no fluid restriction. Thereafter, patients could resume or initiate fluid restriction (defined as fluid intake of ≤ 1.0 liter/day) as clinically indicated.

The dose of SAMSCA could be increased at 24 hour intervals to 30 mg once daily, then to 60 mg once daily, until either the maximum dose of 60 mg or normonatreamia (serum sodium > 135 mmol/L) was reached. Serum sodium concentrations were determined at 8 hours after study drug initiation and daily up to 72 hours, within which time titration was typically completed. Treatment was maintained for 30 days with additional serum sodium assessments on Days 11, 18, 25 and 30. On the day of study discontinuation, all patients resumed previous therapies for hyponatraemia and were reevaluated 7 days later.

The primary endpoint for the studies was the average daily AUC for change in serum sodium from baseline to Day 4 and baseline to Day 30 in patients with a serum sodium less than 135 mmol/L. Compared to placebo, SAMSCA caused a statistically significant greater increase in serum sodium ($p < 0.0001$) during both periods in both studies (see Table 1). In addition, for patients with a serum sodium of < 130 mmol/L or < 125 mmol/L, the effects at Day 4 and Day 30 was also significant (see Table 1 below). This effect was also seen across all disease etiology subsets (e.g., CHF, cirrhosis, SIADH/other).

Table 1- Effects of Treatment with SAMSCA tablets 15 mg/day to 60 mg/day – pooled data from SALT-1 and SALT-2

	SAMSCA 15 mg/day-60 mg/day	Placebo	Estimated Effect (95% CI)
Subjects with Serum Sodium < 135 mmol/L (ITT population)			
Change in average daily serum [Na+] AUC baseline to Day 4 (mmol/L) Mean (SD) N[#]	4.0 (2.8) 213	0.4 (2.4) 203	3.7 (3.3-4.2) $p < 0.0001$
Change in average daily serum [Na+] AUC baseline to Day 30 (mmol/L) Mean (SD) N[#]	6.2 (4.0) 213	1.8 (3.7) 203	4.6 (3.9-5.2) $p < 0.0001$
Percent of Patients Needing Fluid Restriction*	14% 30/215	25% 51/206	$p < 0.0017$
Subgroup with Serum Sodium < 130 mmol/L			
Change in average daily serum [Na+] AUC baseline to Day 4 (mmol/L) Mean (SD) N	4.8 (3.0) 110	0.7 (2.5) 105	4.2 (3.5-5.0) $p < 0.0001$
Change in average daily serum [Na+] AUC baseline to Day 30 (mmol/L) Mean (SD) N	7.9 (4.1) 110	2.6 (4.2) 105	5.5 (4.4-6.5) $p < 0.0001$
Percent of Patients Needing Fluid Restriction*	19% 21/110	36% 38/106	$p < 0.01$
Subgroup with Serum Sodium < 125 mmol/L			
Change in average daily serum [Na+] AUC baseline to Day 4 (mmol/L) Mean (SD) N	5.7 (3.8) 26	1.0 (1.8) 30	5.3 (3.8-6.9) $p < 0.0001$

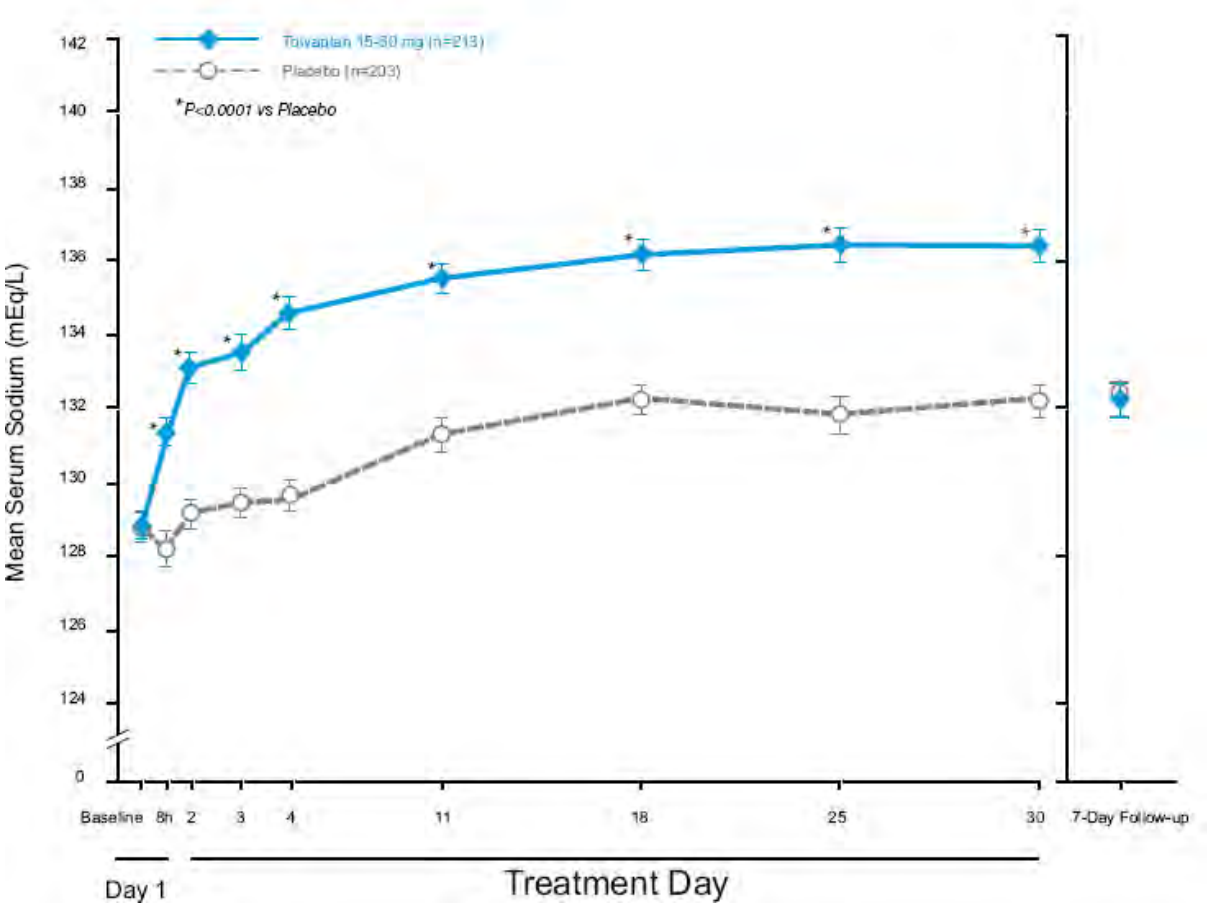
	SAMSCA 15 mg/day-60 mg/day	**Placebo**	**Estimated Effect (95% CI)**
Change in average daily serum [Na+] AUC baseline to Day 30 (mmol/L) Mean (SD) N	10.0 (4.8) 26	4.1 (4.5) 30	5.7 (3.1-8.3) $p < 0.0001$
Percent of Patients Needing Fluid Restriction*	35% 9/26	50% 15/30	$p = 0.14$

* Fluid Restriction defined as < 1L/day at any time during treatment period.
#ITT Dataset

In patients with hyponatraemia (defined as < 135 mmol/L), serum sodium concentration increased to a significantly greater degree in SAMSCA-treated patients compared to placebo-treated patients as early as 8 hours after the first dose, and the change was maintained for 30 days. The percentage of patients requiring fluid restriction (defined as ≤ 1 L/day at any time during the treatment period) was also significantly less ($p < 0.0017$) in the SAMSCA-treated group (30/215, 14%) as compared with the placebo-treated group (51/206, 25%).

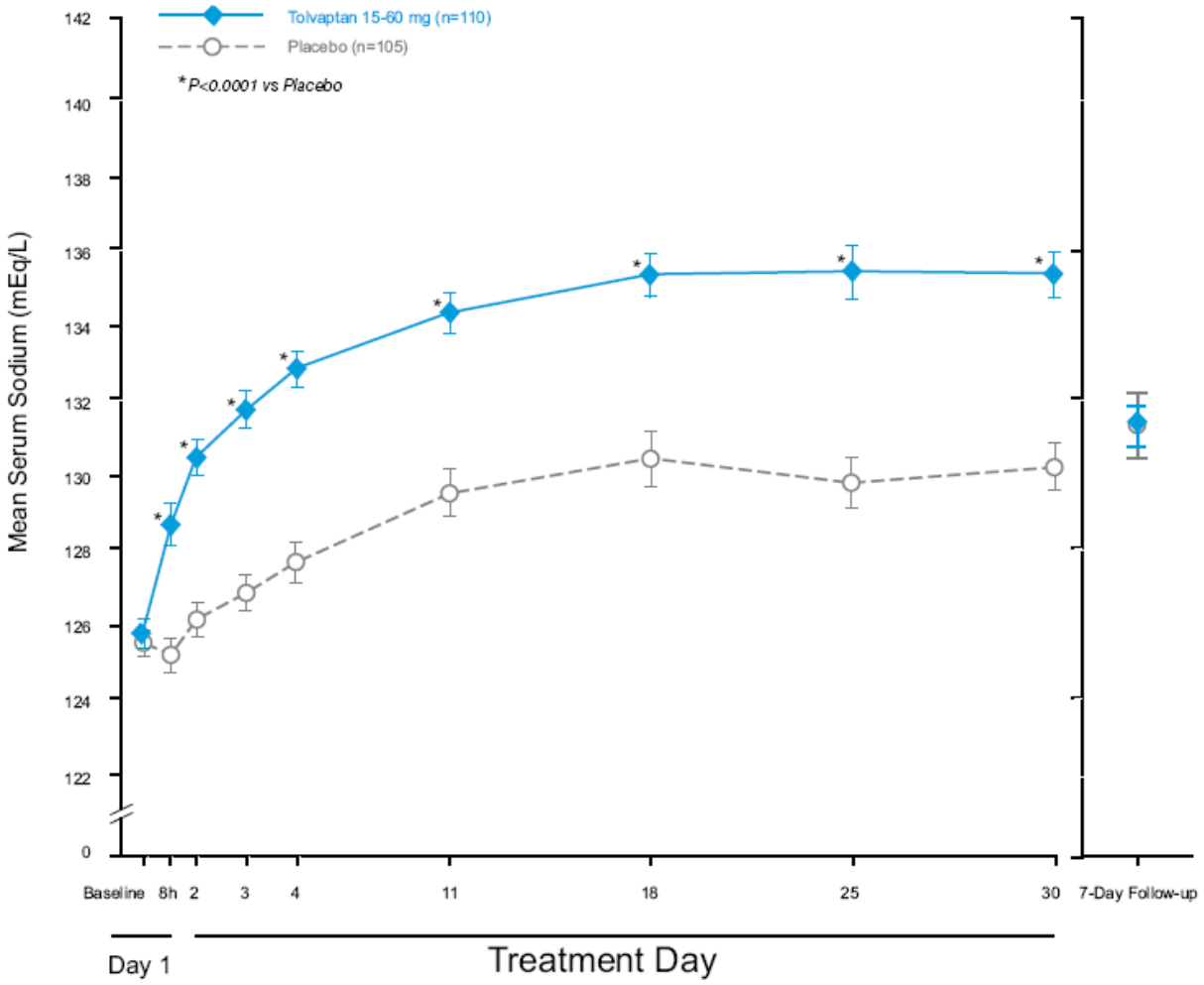
Figure 1 shows the change from baseline in serum sodium by visit in patients with serum sodium < 135 mmol/L. Within 7 days of SAMSCA discontinuation, serum sodium concentrations in SAMSCA-treated patients declined to levels similar to those of placebo-treated patients.

Figure 1: Pooled SALT Studies: Analysis of Mean Serum Sodium (± SE, mmol/L) by Visit - Patients with Baseline Serum Sodium < 135 mmol/L



*p-value < 0.0001 for all visits during tolvaptan treatment compared to placebo

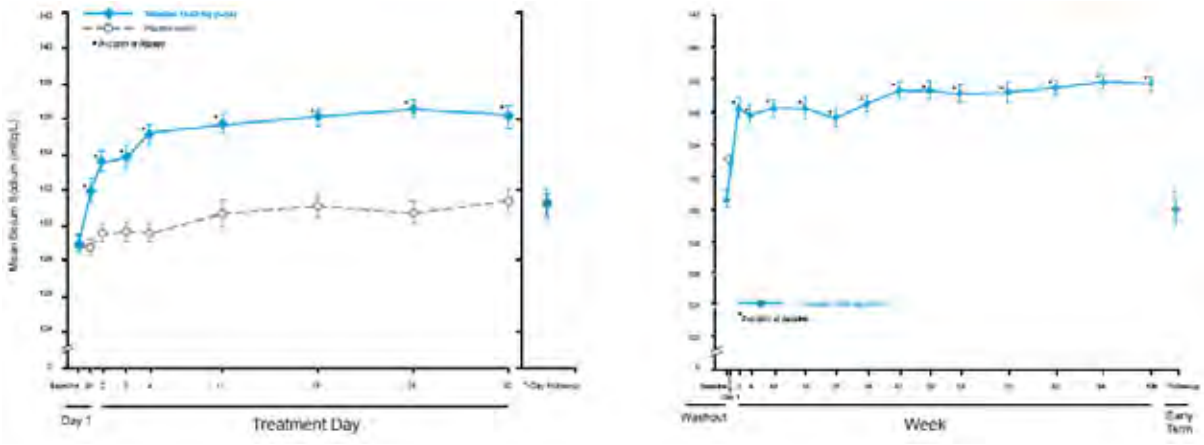
Figure 2: Pooled SALT Studies: Analysis of Mean Serum Sodium (± SE, mmol/L) by Visit - Patients with Baseline Serum Sodium < 130 mmol/L



*p-value < 0.0001 for all visits during tolvaptan treatment compared to placebo

In the open-label study SALTWATER, 111 patients, 94 of them hyponatraemic (serum sodium < 135 mmol/L), previously on SAMSCA or placebo therapy were given SAMSCA as a titrated regimen (15 to 60 mg once daily) after having returned to standard care for at least 7 days. By this time, their baseline mean serum sodium concentration had fallen to between their original baseline and post-placebo therapy level. Upon initiation of therapy, average serum sodium concentrations increased to approximately the same levels as observed for those previously treated with SAMSCA, and were sustained for at least a year. Figure 3 shows results from 111 patients enrolled in the SALTWATER Study.

Figure 3: SALTWATER: Analysis of Mean Serum Sodium (± SE, mmol/L) by Visit



*p-value < 0.0001 for all visits during tolvaptan treatment compared to baseline

INDICATIONS

SAMSCA is indicated for the treatment of clinically significant hypervolemic or euvolemic hyponatremia (serum sodium less than 125 mmol/L, or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction) including patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).

CONTRAINDICATIONS

SAMSCA is contraindicated in;

- Patients hypersensitive to the active substance, benzazepine derivatives or any of the excipients.
- Patients who are unable to sense or appropriately respond to thirst.
- Patients suffering from hypovolaemic hyponatraemia.
- Patients with anuria.

PRECAUTIONS

Heart Failure

Efficacy of SAMSCA for the treatment of heart failure has not been established.

Hypothyroidism and hypoadrenalism

Patients should be screened and treated for hypothyroidism and hypoadrenalism before treatment with SAMSCA.

Urgent need to raise serum sodium acutely

SAMSCA has not been studied in a setting of urgent need to raise serum sodium acutely. For such patients, alternative treatment should be considered.

Too rapid increases in serum sodium

Patients should be monitored frequently during initiation and after each titration for serum sodium and volume status to avoid any adverse outcomes that may result from rapid increases (e.g., >12 mmol/L/24hr) in serum sodium. Too rapid correction of hyponatraemia can cause osmotic demyelination which may result in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma and death. Slower titration should be applied particularly in patients suffering from severe malnutrition, alcoholism, SIADH or advanced liver disease.

Dehydration and Hypovolaemia

Patients receiving SAMSCA should have access to water and should continue ingestion of fluid in response to thirst.

SAMSCA therapy induces copious aquaresis, which is normally partially offset by fluid intake. Dehydration and hypovolaemia can occur, especially in potentially volume-depleted patients receiving diuretics or those who are fluid restricted.

In patients treated with SAMSCA who develop medically significant signs or symptoms of hypovolaemia, treatment with SAMSCA should be discontinued or interrupted. In such patients the fluid balance, electrolyte levels and vital signs should be carefully managed. Fluid restriction during therapy with SAMSCA may increase the risk of dehydration and hypovolaemia.

Hyperkalaemia or Drugs that Increase Serum Potassium

Treatment with SAMSCA is associated with an acute reduction of the extracellular fluid volume which could result in increased serum potassium. Serum potassium levels should be monitored after initiation of SAMSCA treatment in patients with a serum potassium > 5 mmol/L as well as those who are receiving drugs known to increase serum potassium levels.

Urinary outflow obstruction

Urinary output must be secured. Patients with partial obstruction of urinary outflow have an increased risk of developing acute retention. Patients with urinary outflow obstructions must be monitored to ensure urinary output is achieved.

Lactose and galactose intolerance

SAMSCA contains lactose as an excipient. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Use in Patients with Renal Impairment

Exposure and response to SAMSCA are similar in patients with a creatinine clearance 10-79 mL/min and in patients without renal impairment. No dose adjustment is necessary. Exposure and response to SAMSCA in patients with a creatinine clearance < 10 mL/min or in patients on chronic dialysis have not been studied. SAMSCA is contraindicated in anuric patients. No benefit can be expected in patients who are anuric.

Use in Patients with Hepatic Impairment

Moderate and severe hepatic impairment do not affect exposure to SAMSCA to a clinically relevant extent. No dose adjustment of SAMSCA is necessary.

Use in Patients with Cirrhosis

In patients with cirrhosis treated with SAMSCA in hyponatraemia trials, gastrointestinal bleeding was reported in 6 out of 63 (10%) SAMSCA-treated patients and 1 out of 57 (2%) placebo-treated patients. SAMSCA should be used in cirrhotic patients only when the need to treat outweighs this risk. The safety and efficacy in subjects with cirrhosis who have hyponatraemia has not been established.

Effects on fertility

Fertility was unaffected in male and female rats given tolvaptan at oral doses up to 1000 mg/kg/day (yielding 1.3-times in males and 3.4-times in females the AUC in patients at the maximum recommended human dose [MRHD] of 60 mg per day). However, oestrus cycles were altered in rats at oral doses ≥300 mg/kg/day (2.5-times the clinical AUC at the MRHD).

Use in pregnancy (Category D)

There are no adequate and well controlled studies of SAMSCA use in pregnant women. SAMSCA should not be used during pregnancy unless the potential benefit clearly justifies the potential risk to the fetus.

Tolvaptan and/or its metabolites were shown to cross the placenta in rats and rabbits. In rats treated with tolvaptan during organogenesis, reduced fetal weights and delayed fetal ossification occurred at an oral dose of 1000 mg/kg/day (yielding 12-times the clinical AUC at the MHRD. In rabbits, there were abortions at oral doses ≥300 mg/kg/day (≥0.8-times the clinical AUC at the MRHD). At 1000 mg/kg/day (about 5-times the clinical AUC at the MRHD), there were increased rates of embryo-fetal death, fetal microphthalmia, open eyelids, cleft palate, brachymelia and skeletal malformations. These adverse effects on embryofetal development were observed in conjunction with maternal toxicity (reduced maternal body weight gain and food consumption) although a direct effect of the drug can not be excluded.

The effect of SAMSCA on labour and delivery in humans is unknown.

Use in lactation

It is not known whether tolvaptan is excreted into human milk. Studies in rats have shown excretion of tolvaptan and/or its metabolites in breast milk at high levels. Breast feeding should be discontinued when receiving tolvaptan.

Paediatric use

Safety and effectiveness of SAMSCA in pediatric patients have not been established.

Use in Elderly

Of the total number of hyponatraemic subjects treated with SAMSCA in clinical studies, 42% were 65 and over, while 19% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Increasing age has no effect on tolvaptan plasma concentrations.

Carcinogenicity

Up to two years of oral administration of tolvaptan to male and female rats at doses up to 1000 mg/kg/day (yielding 1.3- and 3.4-times respectively, the AUC for tolvaptan in patients at the maximum recommended human dose [MRHD]), to male mice at doses up to 60 mg/kg/day (relative exposure, 0.3) and to female mice at doses up to 100 mg/kg/day (relative exposure, 0.4) did not increase the incidence of tumours. The predictive value of these studies is limited by the inability to obtain high multiples of the clinical exposure to tolvaptan. However, negative findings in genotoxicity assays and the absence of pre-neoplastic lesions observed in these and other studies lend support to tolvaptan being unlikely to pose a particular carcinogenic risk in patients.

Genotoxicity

Tolvaptan tested negative for genotoxicity in *in vitro* (bacterial reverse mutation assay, mammalian forward mutation assay and chromosomal aberration test in Chinese hamster lung fibroblast cells) and *in vivo* (rat micronucleus assay) test systems.

Effect on ability to drive and use machines

When driving vehicles or using machines it should be taken into account that occasionally dizziness, asthenia or syncope may occur.

INTERACTIONS WITH OTHER MEDICINES

Ketoconazole and Other Strong CYP 3A Inhibitors

SAMSCA is metabolized primarily by CYP 3A. Ketoconazole is a strong inhibitor of CYP 3A and also an inhibitor of P-glycoprotein. Co-administration of SAMSCA and ketoconazole 200 mg daily results in a 5-fold increase in exposure to SAMSCA.

Co-administration of SAMSCA with 400 mg ketoconazole daily or with other strong CYP 3A inhibitors (e.g., clarithromycin, itraconazole, telithromycin, saquinavir, nelfinavir, ritonavir and nefazodone) at the highest labeled dose would be expected to cause an even greater increase in SAMSCA exposure. Thus, SAMSCA and strong CYP 3A inhibitors should not be co-administered.

Moderate CYP 3A Inhibitors

The impact of moderate CYP 3A inhibitors (e.g., erythromycin, fluconazole, aprepitant, diltiazem and verapamil) on the exposure to co-administered SAMSCA has not been assessed. A substantial increase in the exposure to SAMSCA would be expected when SAMSCA is co-administered with moderate CYP 3A inhibitors. Co-administration of SAMSCA with moderate CYP3A inhibitors should therefore generally be avoided.

Rifampin and Other CYP 3A Inducers

Rifampin is an inducer of CYP 3A and P-glycoprotein. Co-administration of rifampin and SAMSCA reduces exposure to tolvaptan by 85%. Therefore, the expected clinical effects of SAMSCA in the presence of rifampin and other inducers (e.g., rifabutin, rifapentin, barbiturates, phenytoin, carbamazepine and St. John's Wort) may not be observed at the usual dose levels of SAMSCA. The dose of SAMSCA may have to be increased.

P-glycoprotein (P-gp) Inhibitors

Tolvaptan is a substrate for P-glycoprotein. Reduction in the dose of SAMSCA may be required in patients concomitantly treated with P-gp inhibitors, such as e.g., cyclosporine, based on clinical response.

Lovastatin, Warfarin, Amiodarone, Frusemide, and Hydrochlorothiazide

Co-administration of SAMSCA does not appear to alter the pharmacokinetics of lovastatin, warfarin, frusemide, hydrochlorothiazide, or amiodarone (or its active metabolite, desethylamiodarone) to a clinically significant degree.

Digoxin

Steady state digoxin concentrations have been increased (1.3-fold increase in maximum observed plasma concentration [C_{max}] and 1.2-fold increase in area under the plasma concentration-time curve over the dosing interval [AUCτ]) when co administered with

multiple once daily 60 mg doses of SAMSCA. Patients receiving digoxin should therefore be evaluated for excessive digoxin effects when treated with SAMSCA.

Co-administration with Hypertonic saline

There is no experience with concomitant use of SAMSCA and hypertonic saline. Concomitant use with hypertonic saline is not recommended.

ADVERSE EFFECTS

In multiple-dose, placebo-controlled trials, 607 hyponatraemic patients (serum sodium < 135 mmol/L) were treated with SAMSCA. The mean age of these patients was 62 years; 70% of patients were male and 82% were Caucasian. One hundred eighty nine (189) SAMSCA -treated patients had a serum sodium < 130 mmol/L, and 52 patients had a serum sodium < 125 mmol/L. Hyponatraemia was attributed to cirrhosis in 17% of patients, heart failure in 68% and SIADH/other in 16%. Of these patients, 223 were treated with the recommended dose titration (15 mg titrated to 60 mg as needed to raise serum sodium).

Overall, over 4,000 patients have been treated with oral doses of SAMSCA in open-label or placebo-controlled clinical trials. Approximately 650 of these patients had hyponatraemia; approximately 219 of these hyponatraemic patients were treated with SAMSCA for 6 months or more.

The most common adverse reactions (incidence≥ 5% more than placebo) seen in two 30 -day, double-blind, placebo-controlled hyponatraemia trials in which SAMSCA was administered in titrated doses (15 mg to 60 mg once daily) were thirst, dry mouth, asthenia, constipation, pollakiuria or polyuria and hyperglycemia. In these trials, 10% (23/223) of SAMSCA -treated patients discontinued treatment because of an adverse event, compared to 12% (26/220) of placebo-treated patients; no adverse reaction resulting in discontinuation of trial medication occurred at an incidence of > 1% in tolvaptan-treated patients.

Table 2 lists the adverse reactions reported in t SAMSCA -treated patients with hyponatraemia (serum sodium < 135 mmol/L) and at a rate at least 2% greater than placebo-treated patients in two 30-day, double-blind, placebo-controlled trials. In these studies, 223 patients were exposed to tolvaptan (starting dose 15 mg, titrated to 30 and 60 mg as needed to raise serum sodium). Adverse events resulting in death in these trials were 6% in SAMSCA -treated-patients and 6% in placebo-treated patients.

Table 2. Adverse Reactions (> 2% more than placebo) in SAMSCA -Treated Patients in Double-Blind, Placebo-Controlled Hyponatraemia Trials

System Organ Class MedDRA Preferred Term	SAMSCA 15 mg/day-60 mg/day (N = 223) n (%)	Placebo (N = 220) n (%)
Gastrointestinal Disorders		
Dry mouth	28 (13)	9 (4)
Constipation	16 (7)	4 (2)
General Disorders and Administration Site Conditions		
Thirst[a]	35 (16)	11 (5)
Asthenia	19 (9)	9 (4)
Pyrexia	9 (4)	2 (1)
Metabolism and Nutrition Disorders		
Hyperglycaemia[b]	14 (6)	2 (1)
Anorexia[c]	8 (4)	2 (1)
Renal and Urinary Disorders		
Pollakiuria or polyuria[d]	25 (11)	7 (3)

The following terms are subsumed under the referenced ADR in Table 2:
[a] polydipsia; [b] diabetes mellitus; [c] decreased appetite; [d] urine output increased, micturition urgency, nocturia

In a subgroup of patients with hyponatraemia (N = 475, serum sodium < 135 mmol/L) enrolled in a double-blind, placebo-controlled trial (mean duration of treatment was 9 months) of patients with worsening heart failure, the following adverse reactions occurred in tolvaptan-treated patients at a rate at least 2% greater than placebo: mortality (42% tolvaptan, 38% placebo), nausea (21% tolvaptan, 16% placebo), thirst (12% tolvaptan, 2% placebo), dry mouth (7% tolvaptan, 2% placebo) and polyuria or pollakiuria (4% tolvaptan, 1% placebo).

The following adverse reactions occurred in < 2% of hyponatraemic patients treated with SAMSCA and at a rate greater than placebo in double-blind placebo-controlled trials

(N = 607 tolvaptan; N = 518 placebo) or in < 2% of patients in an uncontrolled trial of patients with hyponatraemia (N = 111) and are not mentioned elsewhere in the label.

- *Blood and Lymphatic System Disorders:* Disseminated intravascular coagulation
- *Cardiac Disorders:* Intracardiac thrombus, ventricular fibrillation
- *Investigations:* Prothrombin time prolonged
- *Gastrointestinal Disorders:* Ischemic colitis
- *Metabolism and Nutrition Disorders:* Diabetic ketoacidosis

- *Musculoskeletal and Connective Tissue Disorders:* Rhabdomyolysis
- *Nervous System:* Cerebrovascular accident
- *Renal and Urinary Disorders:* Urethral hemorrhage
- *Reproductive System and Breast Disorders (female):* Vaginal hemorrhage
- *Respiratory, Thoracic, and Mediastinal Disorders:* Pulmonary embolism, respiratory failure
- *Vascular disorder:* Deep vein thrombosis

DOSAGE AND ADMINISTRATION

Due to the need for a dose titration phase with close monitoring of serum sodium and volume status, **treatment with SAMSCA should be initiated and re-initiated in hospital**.

Treatment with SAMSCA should be initiated at a dose of 15 mg, orally, 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. Increase from the starting dose should be done incrementally (first to 30 mg and then to 60 mg if required) at intervals $\geq$ 24 hours. During titration, patients should be monitored for serum sodium and volume status.

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 SAMSCA treatment. SAMSCA treatment is expected to last until the underlying disease is adequately treated or until such time that hyponatraemia is no longer a clinical issue.

SAMSCA tablets should be taken orally, preferably in the morning, without regard to meals. Tablets should be swallowed without chewing with a glass of water.

SAMSCA tablets should not be taken with grapefruit juice.

Patient Monitoring

1. In patients receiving SAMSCA who develop too rapid a rise in serum sodium, treatment with SAMSCA should be discontinued or interrupted and administration of hypotonic fluids should be considered. Fluid restriction during the first 24 hours of therapy with SAMSCA may increase the likelihood of overly-rapid correction of serum sodium, and should generally be avoided.
2. **Hyperkalaemia or Drugs that Increase Serum Potassium:** Serum potassium levels should be monitored after initiation of SAMSCA treatment in patients with a serum potassium > 5 mmol/L as well as those who are receiving drugs known to increase serum potassium levels.
3. **Drug withdrawal:** Following discontinuation of SAMSCA, patients should be advised to resume fluid restriction and should be monitored for changes in serum sodium and volume status.

OVERDOSAGE

Single oral doses up to 480 mg and multiple doses up to 300 mg of SAMSCA, taken once daily for 5 days have been well tolerated in studies in healthy subjects.

There is no specific antidote for SAMSCA overdose. The signs and symptoms of an acute overdose can be anticipated to be those of excessive pharmacologic effect: a rise in serum sodium concentration, polyuria, thirst, and dehydration/hypovolaemia.

The oral LD_{50} of tolvaptan in rats and dogs is > 2000 mg/kg. No mortality was observed in rats or dogs following single oral doses of 2000 mg/kg (maximum feasible dose). A single oral dose of 2000 mg/kg was lethal in mice, and symptoms of toxicity in affected mice included decreased locomotor activity, staggering gait, tremor and hypothermia.

If overdose occurs, estimation of the severity of poisoning is an important first step. A thorough history and details of overdose should be obtained, and a physical examination should be performed. The possibility of multiple drug involvement should be considered.

Treatment should involve symptomatic and supportive care, with respiratory, ECG and blood pressure monitoring and water/electrolyte supplements as needed. A profuse and prolonged aquaresis should be anticipated, which, if not matched by oral fluid ingestion, should be replaced with intravenous hypotonic fluids, while closely monitoring electrolytes and fluid balance.

ECG monitoring should begin immediately and continue until ECG parameters are within normal ranges. Dialysis may not be effective in removing tolvaptan because of its high binding affinity for human plasma protein (> 99%). Close medical supervision and monitoring should continue until the patient recovers.

PRESENTATION AND STORAGE CONDITIONS

SAMSCA is supplied as 15 mg and 30 mg tolvaptan tablets in PVC/aluminium perforated unit dose blister packs of 10 or 30* tablets each.

*Not available in Australia.

Storage Condition

Store below 25°C. Protect from light and moisture.

NAME AND ADDRESS OF THE SPONSOR

Orphan Australia Pty Ltd
(a member of the Aspen Australia group of companies)
34-36 Chandos Street
St Leonards NSW 2065
Australia

POISON SCHEDULE OF THE MEDICINE

S4

SAMSCA® is a registered trademark of Otsuka Pharmaceutical Co., Ltd.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

5th April 2012