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Tolvaptan (OPC-41061)

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Glossary of Abbreviations and Definitions

Abbreviation	Definition
ACE	Angiotensin-converting enzyme
ADME	Absorption, distribution, metabolism, and excretion
ADPKD	Autosomal dominant polycystic kidney disease
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ARB	Angiotensin II receptor blocker
ARPKD	Autosomal recessive polycystic kidney disease
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$A_{e,0-24}$	Amount of drug excreted in the urine from time zero to 24 hours
AUC_{∞}	Area under the concentration-time curve from time zero to infinity
$AUC_{\infty,u}$	Area under the concentration-time curve from time zero to infinity of unbound drug
AUC_t	Area under the concentration-time curve calculated to the last observable concentration at time t
AUC_{τ}	Area under the concentration-time curve during a dosing interval (τ) at steady-state
AUC_{0-8h}	Area under the concentration-time curve from time zero to 8 hours
AUC_{0-24h}	Area under the concentration-time curve from time zero to 24 hours
AUC_{0-28h}	Area under the concentration-time curve from time zero to 28 hours
AVP	Arginine vasopressin
BA	Bioavailability
BCRP	Breast cancer resistance protein
BE	Bioequivalence
BID	Twice daily
BMI	Body mass index
BP	Blood pressure
BSEP	Bile salt export pump
BT	Total bilirubin
C	China
cAMP	Cyclic adenosine monophosphate
CHF	Congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	Apparent clearance of drug from plasma after extravascular administration
C_{max}	Maximum plasma (or serum) concentration

CNS	Central nervous system
cont	Continued
CrCL	Creatinine clearance
$C_{ss,max}$	Maximum steady-state drug concentration in the plasma during a dosage interval
$C_{ss,min}$	Minimum steady-state drug concentration in the plasma during a dosage interval
CV	Cardiovascular
CYP	Cytochrome P450
DDAVP	1-deamino-8-D-arginine vasopressin
DMNA	Dimethylnitrosamine
ECG	Electrocardiogram
$eCrCL_{CG}$	Estimated creatinine clearance determined using the Cockcroft-Gault formula
eGFR	Estimated glomerular filtration rate
$eGFR_{CKD-EPI}$	Estimated glomerular filtration rate determined using the Chronic Kidney Disease Epidemiology Collaboration formula
$eGFR_{MDRD}$	Estimated glomerular filtration rate determined using the modification of diet in renal disease formula
EMA	European Medicines Agency
EU	European Union
F	Female
FDA	Food and Drug Administration
GFR	Glomerular filtration rate
GMR	Geometric mean ratio
hANP	Human atrial natriuretic peptide
HCTZ	Hydrochlorothiazide
HeLa	Human endocervical carcinoma cell line
hERG	Human ether-a-go-go related gene
HF	Heart failure
HPC	Hydroxypropyl cellulose
HPLC	High-performance liquid chromatography
HR	Hazard ratio
IC_{50}	Concentration that produces 50% inhibition of the maximal response
ID	Intraduodenal
IMP	Investigational Medicinal Product
IR	Immediate-release
ITT	Intent-to-treat
IV	Intravenous
J	Japan
JM	Jet-milled
K	Korea
K_a	Absorption rate constant
KDQOL	Kidney Disease Quality of Life Short Form
K_i	Inhibition constant

LC-ESI-MS/MS	Liquid chromatography with electrospray ionization and tandem mass spectrometry
LOCF	Last observation carried forward
M	Male
MATE	Multidrug and toxin extrusion
MDR1	Multidrug resistance 1 (gene)
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Japanese Ministry of Health, Labour, and Welfare
MMRM	Mixed-model repeated measures
MN	Multinational
MR	Modified-release
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
N	Netherlands
NA	Not applicable
NOAEL	No observed adverse effect level
NYHA	New York Heart Association
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
ODS	Osmotic demyelination syndrome
OPC	Tolvaptan (OPC-41061)
P	Powder
PCK	Polycystic kidney
PCWP	Pulmonary capillary wedge pressure
PD	Pharmacodynamic
P-gp	P-glycoprotein
PIF	Photo-irritation factor
PK	Pharmacokinetic
PKD	Polycystic kidney disease
PO	Oral
PT	Prothrombin time
QD	Daily
QOL	Quality of life
QTc	Corrected QT interval
QTcI	Individually corrected QT interval
RBF	Renal blood flow
RCHN	Rapid correction of hyponatremia
RPF	Renal plasma flow
SAE	Serious adverse event
S-D	Spray-dried
SD	Standard deviation
SDT	Slow-disintegration tablet
SIAD	Syndrome of inappropriate antidiuresis
SIADH	Syndrome of inappropriate secretion of antidiuretic hormone

SRBC	Sheep red blood cells
T	Taiwan
TEAE	Treatment-emergent adverse event
TKV	Total kidney volume
TLV	Tolvaptan
t_{lag}	Lag time
t_{max}	Time to reach maximum plasma (or serum) concentration
$t_{1/2,z}$	Terminal-phase elimination half-life
UK	United Kingdom
ULN	Upper limit of normal
URL	Uniform Resource Locator
US	United States
V/F	Apparent volume of distribution
V_c/F	Apparent volume of distribution for central compartments
vs	Versus
V_z/F	Volume of distribution

1 Summary

Tolvaptan (OPC-41061) is a benzazepine derivative synthesized by Otsuka Pharmaceutical Company, Ltd. Tolvaptan was approved by the United States (US) Food and Drug Administration (FDA) on 19 May 2009, by the European Medicines Agency (EMA) on 03 Aug 2009, and subsequently in 10 other countries for the treatment of specific forms of hyponatremia. Tolvaptan was approved by the Japanese Ministry of Health, Labour, and Welfare (MHLW) on 27 Oct 2010 for the adjunct treatment of volume overload in heart failure when adequate response is not obtained with other diuretics; in Sep 2013 for body fluid retention in hepatic cirrhosis when adequate response is not obtained with other diuretics; and in Mar 2014 for suppression of progression of autosomal dominant polycystic kidney disease (ADPKD) with increased kidney volume and a rapid rate of increase. In Feb 2015, Health Canada approved JINARC™ (tolvaptan) to slow the progression of kidney enlargement (indicative of renal cyst burden) in patients with ADPKD. Also in Feb 2015, the EMA Committee for Medicinal Products for Human Use (CHMP) recommended approval of JINARC in the European Union (EU) for patients with ADPKD. Phase 3 development for hepatic edema has completed in China. Tolvaptan is also being developed for the treatment of ADPKD in the US and multinationally; for the adjunct treatment of chronic renal failure treated with peritoneal dialysis and hematodialysis or hemodiafiltration; for carcinomatous edema in Japan; and for cardiac edema in China and Taiwan.

Tolvaptan is a vasopressin antagonist that specifically blocks the binding of arginine vasopressin (AVP) at the V_2 receptors of the distal portions of the nephron, thereby inducing water diuresis (aquaresis) without depletion of electrolytes. Tolvaptan inhibited the binding of [^{3}H]AVP in human V_2 receptor-expressing human endocervical carcinoma cell line (HeLa) cells and also inhibited the AVP (1 nM)-induced production of cyclic adenosine monophosphate (cAMP), an intracellular second messenger; however, the compound itself caused no increase in cAMP levels.

In in vivo animal experiments, the compound antagonized the antidiuretic action of exogenous vasopressin in hyponatremia models and inhibited the development of polycystic kidney disease (PKD) in the polycystic kidney (PCK) rat model of autosomal recessive polycystic kidney disease (ARPKD). Tolvaptan also decreased renal cAMP concentrations, and a positive correlation was observed between tissue cAMP levels and the severity of PKD. Several other models of PKD, including a mouse model of human ADPKD, have been tested with tolvaptan and all have shown beneficial effects.

In humans, single oral tolvaptan doses ranging from 5 to 480 mg/day and multiple oral doses ranging from 7.5 to 60 mg/day caused aquaresis. Single doses of tolvaptan ≥ 180 mg/day resulted in maximal urinary excretion on Day 1 and an increased urinary excretion rate from 48 to 72 hours postdose; higher doses produced a more sustained, but not greater, response, as active concentrations of tolvaptan were present for longer periods of time. In phase 1 trials in the United States (US), United Kingdom (UK), Argentina, Japan, China, and Republic of Korea (hereafter referred to as Korea), the most commonly reported (incidence > 10% and greater than placebo) treatment-emergent adverse events (TEAEs) in healthy subjects treated with tolvaptan (N = 1071) were thirst, pollakiuria, and headache.

Information on the use of tolvaptan in patients with hyponatremia in the US and the EU can be found in the EU Summary of Product Characteristics for Samsca (Appendix 4) and for ADPKD in the Canadian Product Monograph for JINARC (Table 5.5-1). Information on the use of tolvaptan in Japan in patients with cardiac edema, hepatic edema, and ADPKD can be found in the Japanese label for tolvaptan. Product labels for each region with approved marketing status can be accessed online via the Uniform Resource Locators (URLs) listed for each region in Table 5.5-1.

In subjects with congestive heart failure (CHF), when administered concomitantly with furosemide, tolvaptan significantly increased urine volume, free water clearance, and serum sodium concentrations and decreased urine osmolality compared with furosemide alone. Tolvaptan, with or without furosemide, elevated plasma AVP levels without clinically significantly influencing the renin-angiotensin-aldosterone system. In contrast, furosemide increased plasma renin activity and norepinephrine levels, and it reduced atrial natriuretic peptide levels. In a beagle dog model of CHF, tolvaptan produced a significant decrease in cardiac preload without affecting cardiac afterload or renal functions. Consequently, tolvaptan can be expected to be useful for the treatment of the volume overload state of heart failure without having any undesirable effects on renal function, systemic hemodynamics, or circulating neurohormones.

In a large phase 3 trial in subjects hospitalized with worsening heart failure and symptoms of fluid overload, tolvaptan in addition to continued conventional therapy including diuretics, had the following effects: increased weight reduction, improved patient-assessed dyspnea and pedal edema in the first 7 days, normalized serum sodium concentrations in subjects with hyponatremia (maintained for more than 6 months), and maintained renal function in comparison to placebo.

In subjects with hepatic edema that had not resolved despite routine diuretic therapy, a phase 2 trial (Trial 156-06-005) was conducted and the 7.5 mg dose was selected for phase 3 trials based on the results obtained. Three phase 3 trials in Japan and one phase 2 and one phase 3 trial in China have been completed.

In subjects with ADPKD, tolvaptan has been studied using surrogates of vasopressin action (eg, urine osmolality) and ADPKD disease progression (eg, total kidney volume [TKV] and estimated glomerular filtration rate [eGFR]). Tolvaptan can suppress AVP action over 24 hours in most subjects when given in a twice-daily regimen using the immediate-release (IR) formulation, or with single-daily oral doses of modified-release (MR) formulations. When administered chronically, the TKV is initially reduced (as early as 1 week and for up to 2 months) after which the rate of TKV growth appears to be slowed when compared with historical controls (over 3 years). In these subjects, eGFR declines initially (weeks) and transiently, then stabilizes with a rate of decline which again is less than that observed for historic controls (over 3 years). In a large phase 3 trial in subjects with ADPKD, tolvaptan treatment slowed the rate of TKV growth and renal function decline, and reduced the risk of medically significant renal pain and dysfunction.

Tolvaptan oral bioavailability following a 30 mg dose was determined to be 56%. The terminal-phase elimination phase half-life ($t_{1/2,z}$) is about 3 hours, consequently no accumulation of tolvaptan concentrations is observed following once-daily dosing. Maximal plasma concentrations (C_{max}) are obtained at 2 hours post dose as absorption occurs primarily in the upper small intestine. Low levels of continuing absorption from the lower gastrointestinal tract results in longer apparent $t_{1/2,z}$ values. A high-fat meal increases the early absorption of tolvaptan for doses above 30 mg, with an approximately 2-fold increase in C_{max} and no change in the area under the concentration-time curve (AUC) observed for a 90-mg dose. There is no clinically meaningful effect on aquaresis as tolvaptan plasma concentrations at this dose are already higher than needed to saturate the V_2 receptor.

Tolvaptan is a sensitive cytochrome P450 (CYP)3A4 substrate with no inhibitory activity at CYP3A4 or CYP2C9. Tolvaptan is a P-glycoprotein (P-gp) substrate. Elimination is primarily via metabolism and fecal excretion; less than 1% of the dose is excreted unchanged in the urine. Tolvaptan pharmacokinetics are not affected by race, age, or gender. In subjects with severe hepatic impairment (Child-Pugh Class C) compared to subjects with mild or moderate impairment, tolvaptan concentrations are about 1.3-fold

higher. In subjects with severe renal impairment (creatinine clearance [CrCL] < 30 mL/min) compared to subjects with CrCL > 60 mL/min, tolvaptan concentrations are 1.9-fold higher. Neither hepatic nor renal impairment changes tolvaptan plasma protein binding, which is greater than 98%. In subjects with heart failure compared to healthy subjects, tolvaptan concentrations are 1.2- to 1.6-fold higher with no change in elimination half-life. In subjects with ADPKD and well-preserved renal function, tolvaptan concentrations are similar to healthy subjects. Values for median time to reach maximum plasma concentration (t_{max}), steady-state exposure to tolvaptan, and daily urine volume at steady state following administration of MR 60 mg daily (QD) to subjects with ADPKD and eGFR of > 60 mL/min/1.73 m^2, were similar to values for healthy subjects.

As of 31 Mar 2015, pooled safety data from 91 trials across all development programs indicate that the most commonly reported (incidence > 10%, and greater than placebo) TEAEs for tolvaptan-treated subjects (N = 7343) were thirst and dry mouth, followed closely by pollakiuria, which was reported in 9.7% of tolvaptan subjects.

2 Introduction

Arginine vasopressin (also known as “antidiuretic hormone”) is a neuropeptide hormone synthesized in the nuclei of the hypothalamic neuronal cell bodies whose axons extend to the posterior pituitary where it is ultimately released into the bloodstream. Secretion of this hormone from hypothalamic neurons is regulated by baroreceptors and osmoreceptors and is affected by such factors as drugs, central nervous system (CNS) disorders, infections, cardiopulmonary diseases, and endocrinopathies. A decrease in blood pressure, or an increase in plasma osmolality, leads to an increase in blood AVP concentrations. Arginine vasopressin causes vasoconstriction via V_{1a} receptors and promotes water reabsorption in the kidneys via V_2 receptors, both of which are G-protein-coupled transmembrane receptors and the latter of which is primarily responsible for AVP's antidiuretic effects.

Patients with various disorders, including heart failure, liver cirrhosis, and syndrome of inappropriate secretion of antidiuretic hormone (SIADH), which more comprehensively is coming to be known as syndrome of inappropriate antidiuresis (SIAD),[1] are at risk of experiencing excess water retention or inadequate water disposal due to increased vasopressin secretion. Electrolyte imbalances with unclear etiologies, in particular hyponatremia, often occur in such patients. Unfortunately, the use of conventional diuretics to treat these patients promotes an inappropriate loss of electrolytes and thus exacerbates hyponatremia and other electrolyte imbalances, resulting in neurologic and cardiac complications.[2,3] For example, diuretic-induced hyponatremia may induce stupor, coma, and death, and diuretic-induced hypokalemia may induce fatal cardiac arrhythmia. Therefore, a selective vasopressin V_2 receptor antagonist, which could promote free-water loss without disturbing electrolytic balance, would be clinically useful for the treatment of disease states associated with hyponatremia or fluid excess. Agents with these properties have been called "aquaretics" and are being studied in subjects with hyponatremia and in diseases associated with hypo- or normo-natremic fluid overload.

Otsuka Pharmaceutical Company discovered tolvaptan, (±)-4’-[(7-chloro-2,3,4,5-tetrahydro-5-hydroxy-1*H*-1-benzazepin-1-yl) carbonyl]-*o*-tolu-*m*-toluidide, an orally effective nonpeptide AVP V_2 receptor antagonist. Tolvaptan is being developed as an oral aquaretic agent for the treatment of fluid volume-overload conditions. While sharing many of the characteristics of traditional diuretics, tolvaptan has substantial benefits to make it a useful complement to the currently available agents for the treatment of volume overload associated with decompensated heart failure, cardiac edema, hepatic edema, and

carcinomatous edema. Tolvaptan is also being investigated for the indication of ADPKD, a condition in which AVP concentrations are normal or elevated, with resultant activation of the kidneys' AVP V_2 receptors, leading to cyst development. Tolvaptan treatment is also being investigated in chronic renal failure.

2.1 References

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2 Rivera-Santos A, Star R. Sodium: volume depletion and hyponatremia. In: Seldin D, Giebisch G, editors. Diuretic agents - clinical physiology and pharmacology. San Diego, CA: Academic Press Inc; 1997. p. 559-69.

3 Palmer BF. Potassium disturbances associated with the use of diuretics. In: Seldin D, Giebisch G, editors. Diuretic agents – clinical physiology and pharmacology. San Diego, CA: Academic Press Inc; 1997. p. 571-83.

3 Physical, Chemical, and Pharmaceutical Properties and Formulation

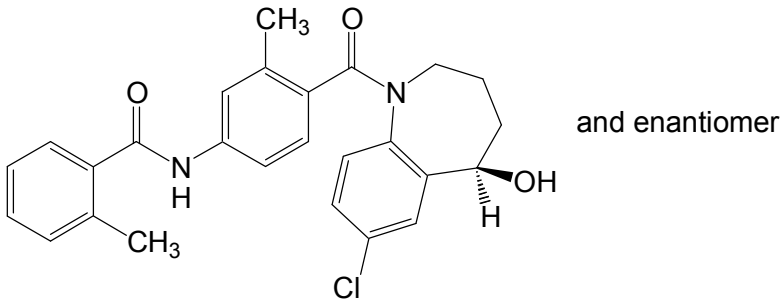
3.1 Drug Substance

3.1.1 Description and Characterization

Chemical name: (±)-4'-[(7-chloro-2,3,4,5-tetrahydro-5-hydroxy-1*H*-1-benzazepin-1-yl) carbonyl]-*o*-tolu-*m*-toluidide

Code name: OPC-41061

Chemical structure:



INN, USAN: Tolvaptan

Molecular formula: $C_{26}H_{25}ClN_2O_3$

Molecular weight: 448.94

Appearance: OPC-41061 is a white crystalline powder.

Melting point: 227.5°C

Optical rotation: $[\alpha]^{20}_{D} = 0°$; racemate

Solubility at 25°C: 0.0005 mg/mL in water, 22.0 mg/mL in 95% ethanol, and 3.7 mg/mL in n-octanol

pH-solubility profile in buffer:

Table 3.1.1-1 pH-Solubility Profile of OPC-41061 in Britton-Robinson Buffer at 25°C

pH	Solubility (mg/mL)
2.0	0.0004
4.0	0.0004
7.0	0.0004

Note: Britton-Robinson buffer is prepared by mixing the appropriate amount of Solution A and Solution B. Solution A is composed of 4.61 g of 85% phosphoric acid, 2.40 g of acetic acid, and 2.47 g of boric acid per liter. Solution B is 0.2 M sodium hydroxide solution (8.00 g of sodium hydroxide per litre).

3.1.2 Structural Similarities to Other Known Compounds

There are three other drugs in this class that has a similar chemical structure to that of tolvaptan (conivaptan, lixivaptan, and mozavaptan). Conivaptan was approved in United States in 2005.

3.2 Drug Product – Tablets

3.2.1 List of Components for Tablet Formulations

Each tablet contains 3.75-mg, 7.5-mg, 15-mg, 30-mg, or 60-mg of tolvaptan drug substance. A list of all components in the 3.75-mg, 7.5-mg, 15-mg, 30-mg, and 60-mg tablets is presented in Table 3.2.1-1.

Table 3.2.1-1 Components of Tolvaptan 3.75-mg, 7.5-mg, 15-mg, 30-mg, and 60-mg Tablets

Component	Function
Tolvaptan	Active ingredient
Lactose monohydrate	Diluent
Corn starch	Diluent
Microcrystalline cellulose	Diluent
Hydroxypropyl cellulose (HPC-SL)	Solubilizer
Hydroxypropyl cellulose (HPC-L)	Binder
Low-substituted hydroxypropyl cellulose	Disintegrant
Magnesium stearate	Lubricant

3.2.2 Storage and Handling for Tablet Formulations

Study drugs should be stored under conditions specified in the investigational product label.

Study drugs must be stored in a securely locked cabinet or enclosure. Access should be strictly limited to the investigators and designees. Neither the investigators nor any designees may provide study drug to any subject not participating in an approved tolvaptan study.

3.3 Drug Product – Modified Release (MR) Capsules

3.3.1 List of Components for MR Capsule Formulations

Each capsule contains 20-mg, 50-mg, or 80-mg of tolvaptan drug substance. A list of all components for the MR capsules is presented in Table 3.3.1-1.

Table 3.3.1-1 Components of Tolvaptan 20-mg, 50-mg, and 80-mg MR Capsules	
Component	**Function**
Tolvaptan	Active ingredient
Maltose	Diluent
D-mannitol[a]	Diluent
Microcrystalline cellulose	Diluent
Hydroxypropyl cellulose (HPC-SL)	Solubilizer
Hydroxypropyl cellulose (HPC-L)	Binder
Methacrylic acid copolymer, Type B	Binder
Silicon dioxide	Glidant
Magnesium stearate[a]	Lubricant
Capsule[b]	---

[a] used for only 20- and 50-mg MR capsules

[b] The component mainly consists of hypromellose.

3.3.2 Storage and Handling for MR Capsule Formulations

Study drug should be stored under conditions specified in the investigational product label.

Study drugs must be stored in a securely locked cabinet or enclosure. Access should be strictly limited to the investigators and designees. Neither the investigators nor any designees may provide study drugs to any subject not participating in an approved tolvaptan study.

3.4 Drug Product – Suspension Syrup

3.4.1 List of Components for Suspension Syrup Formulations

Suspension syrup contains 0.1% of tolvaptan drug substance. A list of all components for the suspension syrup is presented in Table 3.4.1-1.

Table 3.4.1-1 Components of Tolvaptan 0.1% Suspension Syrup	
Component	**Function**
Tolvaptan	Active ingredient
Sorbitol	Sweetener
Sucralose	Sweetener
Xanthan Gum	Suspending agent
Hypromellose 2910	Suspending agent, Solubilizer
Sodium Benzoate	Preservative
Edetate Disodium	Stabilizer
Citric Acid Monohydrate	pH adjuster
Sodium hydroxide	pH adjuster
Cherry flavor	Flavor
Purified water	Vehicle

3.4.2 Storage and Handling for Suspension Syrup Formulations

The study drug should be stored under conditions specified in the investigational product label.

The study drug must be stored in a securely locked cabinet or enclosure. Access should be strictly limited to the investigators and designees. Neither the investigators nor any designees may provide the study drug to any subject not participating in an approved tolvaptan study.

4 Nonclinical Studies

4.1 Nonclinical Pharmacology

4.1.1 Efficacy Pharmacology

Tolvaptan (OPC-41061) inhibited AVP-induced water reabsorption at the renal collecting ducts by competitively blocking the binding of AVP to V_2 receptors, resulting in an increase in water excretion without any change in electrolyte excretion, ie, aquaresis.

4.1.1.1 AVP Antagonism (In Vitro Studies)

AVP antagonism by tolvaptan

In a binding study using human AVP receptors expressed in HeLa cells, tolvaptan blocked the binding of [^{3}H]AVP to cloned human V_2 and V_{1a} receptors with an inhibition constant (K_i) of 0.43 ± 0.06 and 12.3 ± 0.8 nM, respectively.[1,2] Tolvaptan did not inhibit the binding of [^{3}H]AVP to human V_{1b} receptors.[3] Tolvaptan was 29 times more selective for V_2 receptors than for V_{1a} receptors.

Similar findings were seen in receptor binding studies using rat liver (V_{1a} receptors) and kidney (V_2 receptors) membrane preparations,[4] and canine platelet (V_{1a} receptors) and kidney (V_2 receptors) membrane preparations.[5]

Tolvaptan inhibited not only the binding of [^{3}H]AVP but also the AVP (1 nM)-induced production of cAMP, an intracellular second messenger, in V_2 receptor-expressing HeLa cells.[1]

AVP antagonism by optical isomers

There were no differences in antagonism to human V_2 and V_{1a} receptors between the two isomers [(R)-(+)-tolvaptan (DM-4101) and (S)-(–)-tolvaptan (DM-4102)] and tolvaptan (racemic form).[1,6] Neither isomer showed any antagonism for human V_{1b} receptors.[7] Reflecting this similar potency in the inhibition of AVP binding to V_2 receptors, no

differences were seen between the racemate and the two optical isomers in inhibition of AVP-induced cAMP production.[1]

AVP antagonism by tolvaptan metabolites

The metabolites of tolvaptan (See Section 4.2.3) showed weaker antagonistic activity for human, rat and canine AVP V_2 and V_{1a} receptors than did tolvaptan.[1,4,6,8,9,10,11,12,13] Neither tolvaptan nor any of the metabolites showed any antagonistic activity for human V_{1b} receptors.[7,14]

4.1.1.2 Intrinsic V_2 Receptor Stimulating Action

Tolvaptan did not stimulate cAMP production in V_2 receptor-expressing HeLa cells,[15] and did not show any antidiuretic effect in water-loaded, alcohol-anesthetized rats with suppressed endogenous AVP secretion,[16] These results demonstrated that tolvaptan possesses no intrinsic V_2 receptor agonistic activity. Furthermore, the optical isomers and metabolites of tolvaptan also showed no agonistic activity against AVP V_2 receptors.[15]

4.1.1.3 Aquaretic Action of Tolvaptan in Normal Animals

Single-dose studies

The diuretic effects of tolvaptan were examined by oral administration to conscious mice,[17] rats,[18,19] rabbits,[20] and dogs.[21] Tolvaptan increased urine excretion and decreased urine osmolality at the same dose range of 0.3 to 10 mg/kg in mice, rats, rabbits, and dogs. Tolvaptan elevated free water clearance to a positive value at 10 mg/kg in rats and mice, and at 3 mg/kg in rabbits and at 1 mg/kg and higher in dogs.

Tolvaptan slightly increased urinary sodium excretion in mice,[17] rats[18,19] and rabbits,[20] but not in dogs.[21] However, the increase in sodium excretion induced by tolvaptan was considerably smaller than that induced by furosemide.[19] Serum sodium concentration was elevated in mice,[17] rats,[18,19] rabbits,[20] and dogs[21] administered tolvaptan, while furosemide tended to decrease serum sodium concentration in rats[19] and dogs.[21]

Serum AVP concentration was increased following tolvaptan administration in rats[19] and dogs,[21] since tolvaptan increased serum osmolality after aquaresis. However, tolvaptan did not enhance serum renin activity or elevate aldosterone concentration in either rats[19] or dogs.[21] Furthermore, tolvaptan did not affect norepinephrine and epinephrine concentrations in dogs.[21] In contrast, furosemide enhanced serum renin activity and elevated aldosterone and epinephrine concentrations.[19,21]

Repeated-dose study

The aquaretic effects of tolvaptan were examined by oral administration at 1 and 10 mg/kg/day once daily for 4 weeks to rats.[22] Urine volume increased, and urine osmolality decreased. These changes remained constant throughout the study at both doses. There were no changes in pituitary AVP content or in the number and affinity of AVP receptors in the kidney throughout the study period. These results confirmed that 4 weeks of repeated orally administered tolvaptan produced potent aquaresis without affecting the target organ's function.

Interaction with furosemide

When tolvaptan was administered concomitantly with furosemide in rats[19] and dogs,[21] it increased urine volume and free water clearance and decreased urine osmolality compared with furosemide alone. Serum sodium concentration tended to decrease when furosemide was administered alone but increased dose-dependently when tolvaptan was administered concomitantly with furosemide. These results showed that tolvaptan retained its aquaretic potency even in the presence of furosemide.

Interaction with human atrial natriuretic peptide

The aquaretic and cardiovascular effects of tolvaptan in combination with human atrial natriuretic peptide (hANP) were evaluated in anesthetized dogs.[23] Tolvaptan was intravenously administered in bolus injection at a dose of at 0.3 mg/kg and hANP was intravenously administered for 90-minute infusion at 0.3 and 1 μg/kg/min. Tolvaptan and hANP alone respectively showed aquaretic and natriuretic effects, and tolvaptan retained its aquaretic potency even in the presence of hANP. Tolvaptan alone tended to decrease pulmonary capillary wedge pressure, an index of cardiac preload. When tolvaptan was administered concomitantly with hANP, cardiac preload was further decreased compared to hANP alone. These results indicate that the combination of tolvaptan and hANP

produces an additive diuretic effect and further reduction of cardiac preload without affecting other cardiac and renal hemodynamic parameters.

4.1.1.4 Effects of Tolvaptan in a Dog Model of Congestive Heart Failure

The aquaretic potency of tolvaptan was evaluated following single oral administration to conscious dogs with pacing-induced heart failure.[24] Tolvaptan at 0.3 to 10 mg/kg exhibited free water diuresis in CHF dogs, as it did in normal dogs. Furthermore, tolvaptan did not stimulate either the sympathetic or renin-angiotensin-aldosterone system in spite of its potent aquaretic effect. The administration of a combination of 3 mg/kg of tolvaptan and 1 mg/kg of furosemide further increased urine volume in comparison with furosemide alone, and urine osmolality was lower than plasma osmolality, demonstrating that tolvaptan retained its aquaretic potency even in the presence of furosemide.[25] Effects on hemodynamics and renal function were evaluated in sedated conscious dogs with pacing-induced heart failure. Oral tolvaptan at 10 mg/kg showed clear aquaresis, resulting in a significant increase in serum sodium and a decrease in cardiac preload without affecting cardiac afterload or renal function.[26] Consequently, tolvaptan can be expected to be useful for the treatment of the volume-overload state of CHF without having any undesirable effects on renal function, systemic hemodynamics, or circulating neurohormones.

4.1.1.5 Effects of Tolvaptan in Animal Models of Edema

The effects of tolvaptan on edema were evaluated in two edema models, a rat model of histamine-induced increased vascular permeability[27] and a rat model of carrageenin-induced paw edema.[28] In both models, single oral administration of tolvaptan (1 to 10 mg/kg) demonstrated dose-dependent improvement of edema as observed with furosemide, a natriuretic agent. These results suggest that tolvaptan has a potential clinical benefit in the treatment of edema.

4.1.1.6 Effects of Tolvaptan in Rat Models of Hyponatremia

The effects of tolvaptan on hyponatremia were evaluated in rat acute and chronic models of hyponatremia. In the rat model of acutely progressive hyponatremia, combined treatment of subcutaneous infusion (10 ng/hr subcutaneous [SC]) of [deamino-Cys^1, D-Arg^8]-vasopressin (DDAVP), a peptide V_2 agonist and water loading progressively decreased plasma sodium concentration, resulting in severe hyponatremia associated with

high mortality. Oral doses of tolvaptan at 1, 3, and 10 mg/kg showed dose-dependent aquaresis resulting in an increase in plasma sodium concentration and a decrease in mortality rate.[29] In the rat model of chronic hyponatremia induced by DDAVP infusion (1 ng/hr SC) and liquid diet, plasma sodium concentration was reduced to about 110 mEq/L and maintained at that level without any deaths. Oral dose titration of tolvaptan from 0.25 to 8 mg/kg gradually increased plasma sodium concentration to the normal levels, and improved the wet weight of kidney and water content in the brain and heart, which were increased by sustained hyponatremia.[30] Thus, tolvaptan is considered to present therapeutic implications in the management of patients with hyponatremia.

4.1.1.7 Effects of Tolvaptan in Animal Models of Polycystic Kidney Disease (PKD)

In several recent studies,[31,32] vasopressin V_2 receptor antagonists have demonstrated efficacy in animal models of PKD by decreasing levels of intracellular cAMP, which plays a major role in cyst formation by promoting transepithelial fluid secretion and stimulating cyst-derived cell proliferation. The effects of tolvaptan on PKD were evaluated in three different animal models of PKD.[33,34,35,36,37,38,39] Tolvaptan was administered via the diet. In *pcy* mice,[37] an animal model of human nephronophthisis, tolvaptan at 0.01% to 0.3% in diet showed a dose-dependent inhibition of the progression of PKD, as reflected by decreases in kidney weight, kidney cyst volume, kidney fibrosis volume, and mitotic index. Tolvaptan also showed a dose-dependent aquaretic action at the same dose range. The maximum renoprotective and aquaretic effects were observed at a dose of 0.1%. Kidney cAMP content which was elevated in the pcy mice also showed a dose-dependent decrease by tolvaptan. In PCK rats,[33] an animal model of human ARPKD, tolvaptan at 0.01% to 0.1% in diet decreased kidney weight and cyst and fibrosis volume, indicating inhibiting effects on the development of PKD.[33] Furthermore, the Ras/mitogen-activated protein kinase pathway that was suggested to mediate the proliferative response to cAMP in vitro was activated in PCK rats and was inhibited by tolvaptan.[40] In *Pkd2*$^{WS25/-}$ mice,[35] an animal model of human ADPKD, tolvaptan at 0.01% to 0.1% in diet also inhibited the progression of PKD. In human cultured cells derived from the cyst walls of patients with ADPKD,[41] tolvaptan inhibited AVP-induced cell proliferation in a dose-dependent manner, and this inhibition of cell proliferation was mediated by a decrease in intracellular cAMP level. These findings indicate the importance of cAMP in the pathogenesis of PKD and suggest that tolvaptan can also become a useful drug for treating patients with PKD.

4.1.1.8 Effects of Tolvaptan in a Rat Model of Liver Cirrhosis

The effects of tolvaptan on cirrhotic ascites were evaluated in a rat model of liver cirrhosis.[42] Cirrhotic ascites and hypoalbuminemia secondary to hepatic disease were induced in rats by repeated intraperitoneal injection of dimethylnitrosamine (DMNA). Body weight and abdominal circumference were used as indexes of ascites volume. Single oral administration of tolvaptan at 1 and 3 mg/kg showed a dose-dependent diuretic effect, resulting in improvement of cirrhotic ascites as reflected by decreases in body weight and abdominal circumference. Tolvaptan significantly increased daily excretion of urinary sodium and improved hypoalbuminemia although this was not statistically significant. These results suggest that tolvaptan has therapeutic implications for patients with ascites due to cirrhosis of the liver.

4.1.1.9 Effects of Tolvaptan on Platelet Aggregation

It is well known that AVP induces platelet aggregation through V_{1a} receptors in vitro.[43] Therefore, the effects of tolvaptan on platelet aggregation using human platelet-rich plasma were examined.[44]

Tolvaptan inhibited AVP (80 nM)-induced platelet aggregation with an IC_{50} (concentration that produces 50% inhibition of the maximal response) of 1.28 ± 0.20 μM, but the compound at 1 and 10 μM did not inhibit adenosine diphosphate (4 μM)-induced platelet aggregation. Tolvaptan itself did not induce platelet aggregation, showing no V_{1a} receptor agonistic activity.

4.1.1.10 Effects of Tolvaptan on Various Other Receptors and Ion Channels

Oxytocin is a neurohypophysial hormone that is synthesized in the hypothalamus and released from the pituitary in the same way as AVP, and is similar to AVP in structure. Tolvaptan had a low affinity for human oxytocin receptors, with a K_i value of 431 ± 63 nM, and its main metabolite DM-4103 showed little affinity.[45] For various other receptors and ion channels, ie, acetylcholine, adenosine, adrenoceptors, angiotensin II, bradykinin, calcitonin gene-related peptide, dopamine, endothelin, epidermal growth factor, histamine, opioid, serotonin, somatostatin, and vasoactive intestinal peptide receptors, calcium, potassium, and sodium channels, neither tolvaptan, DM-4103, nor DM-4107 showed any notable affinity at a concentration of 10 μM.[46]

4.1.2 Safety Pharmacology / General Pharmacology

Safety pharmacology and general pharmacology studies of tolvaptan were conducted to evaluate its effects on general symptoms and behavior, the central nervous system (CNS), somatic nervous system, autonomic nervous system, smooth muscle, and respiratory, cardiovascular, and digestive systems. In addition to these studies, safety pharmacology studies of the major metabolites of tolvaptan (DM-4103 and DM-4107) were conducted to evaluate their effects on general symptoms and behavior, and respiratory and cardiovascular systems.

The experiment on general symptoms and behavior of mice showed an increase in urine output at 100 mg/kg oral (PO) and higher. No other specific changes or findings were observed.[47]

CNS experiments in mice revealed that tolvaptan showed no effect on spontaneous motor activity,[48] hexobarbital-induced hypnosis,[49] body temperature,[50] or motor coordination;[51] had no anesthetic,[49] convulsion-inducing,[52] or analgesic action;[53,54] and caused no augmentation of minimal electronic-, strychnine-, or pentetrazol-induced convulsions[52] at doses up to 1000 mg/kg PO.

In somatic nervous system experiments, tolvaptan exhibited no muscle-relaxing action in mice at doses up to 1000 mg/kg PO.[51]

In autonomic nervous system and smooth muscle experiments, tolvaptan showed no effect on the isolated guinea-pig ileum at 3×10^{-6} M, but caused a slight increase in spontaneous movement of the ileum and a transient, slight increase followed by a slight decrease in the resting tension at 10^{-5} M and higher concentrations. Tolvaptan antagonized the actions of acetylcholine and histamine at 10^{-5} M or higher and the action of barium chloride at 3×10^{-5} M.[55]

In respiratory and cardiovascular system experiments in anesthetized dogs, tolvaptan decreased the T wave amplitude in electrocardiogram (ECG) at 3 mg/kg intravenous (IV) or higher, and caused increases in respiration rate and heart rate and decreases in blood pressure and femoral arterial blood flow at 10 mg/kg IV.[56] In conscious dogs,[57] although shortening of the PR interval at 100 and 1000 mg/kg PO and a decrease in the T-wave amplitude at 1000 mg/kg PO were noted, no other influences on the cardiovascular

system were observed. No influences on the respiratory system were observed at up to 1000 mg/kg PO. The mean maximum serum concentrations of the unchanged compound in the 100- and 1000-mg/kg groups were 0.46 and 2.83 μg/mL, respectively. Tolvaptan did not affect the action potential parameters in guinea-pig ventricular papillary muscle[58] at the tested concentrations of up to 3×10^{-5} M, which was about 36 times higher than the maximum serum levels in humans (374 ng/mL, refer to Section 5.2.1.6) orally administered 60 mg of a spray-dried formulation of tolvaptan. Tolvaptan did not affect human ether-a-go-go related gene (hERG) channel current at concentrations up to 2×10^{-6} M, the solubility limit.[59] The changes in T wave amplitude and PR interval observed in conscious dogs occurred under a water-restricted condition. The aquaresis induced by tolvaptan resulted in significant increases in urine volume and plasma Na^+ and Cl^- concentrations. In the dog 4- and 52-week repeated oral dose toxicity studies in which the animals received tolvaptan at up to 1000 mg/kg/day with free access to water, the concentrations of plasma electrolytes were unchanged and no ECG parameters were affected. It was therefore concluded that the changes in T-wave amplitude and PR interval were not due to any direct action of tolvaptan on the heart but occurred under a severe condition suggestive of hemoconcentration induced by the aquaretic action of tolvaptan.

In digestive system experiments, tolvaptan was devoid of any action on mouse intestinal propulsion at doses up to 1000 mg/kg PO[60] and on rat gastric motility at up to 3 mg/kg IV. However, at 10 mg/kg IV, the amplitude of rat gastric motility decreased 5 minutes after dosing and the tonus of the gastric muscle also decreased 1 and 5 minutes after dosing.[61] Gastric secretion in rats was not affected at 100 mg/kg intraduodenal (ID), but the volume and acidity of the gastric juice and the amount of acid secretion tended to decrease at 300 mg/kg ID, and at 1000 mg/kg ID, these values decreased markedly with an increase in the pH of the gastric juice.[62]

The serum concentration of tolvaptan was determined following single oral administration of tolvaptan to ICR mice.[63] C_{max} and area under the concentration-time curve from time zero to 8 hours ($AUC_{0\text{-}8h}$) following administration of jet-milled tolvaptan at 1000 mg/kg were 3.973 μg/mL and 5.692 μg·h/mL, respectively.

Safety pharmacology studies of DM-4103 and DM-4107, the major metabolites of tolvaptan, were conducted. Treatment with DM-4103 had no effect on general symptoms

and behavior in mice[64] or on the respiratory and cardiovascular systems in conscious dogs.[65] hERG channel current was decreased by DM-4103 at 3×10^{-5} M and higher,[66] but the decrease was slight and no effect on corrected QT interval (QTc) was seen in the conscious dogs. DM-4107 had no effect on general symptoms and behavior in mice[67] or on hERG channel current.[68] In conscious dogs, ST segment was significantly elevated at 1 or 15 minutes after IV administration of DM-4107 at 1 and 10 mg/kg.[69] ST segment was not affected in the conscious dogs following oral administration of tolvaptan at up to 1000 mg/kg, at which dose the maximum plasma concentration of DM-4107 was 0.71 µg/mL.

It was concluded that the effects of tolvaptan on the nervous, muscular (smooth muscle), respiratory, cardiovascular, and gastrointestinal systems and the effects of DM-4103 and DM-4107, the major metabolites of tolvaptan, on the nervous, respiratory, and cardiovascular systems did not suggest the necessity of any special attention in clinical use.

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4.2 Nonclinical Pharmacokinetics and Product Metabolism

Pharmacokinetic studies of tolvaptan were carried out using non-radiolabeled and ^{14}C-labeled tolvaptan ([^{14}C]tolvaptan)[1,2,3,4] in Sprague-Dawley rats, New Zealand White rabbits, and beagle dogs. The serum and urinary concentrations of tolvaptan and its metabolites and the serum concentrations of enantiomers of tolvaptan were determined using high-performance liquid chromatography[5,6,7,8,9,10,11,12,13,14] and high-performance liquid chromatographic-electrospray ionization tandem mass spectrometry.[15]

4.2.1 Absorption

Oral

Spray-dried tolvaptan

Pharmacokinetic studies of a fine-granule formulation of spray-dried tolvaptan were carried out in rats and dogs.[16,17,18,19] In male and female rats, C_{max} and AUC_t increased dose-dependently, and serum concentration of tolvaptan was higher in females than in males. In male dogs, C_{max} and AUC_t increased dose-dependently. The results obtained are summarized below in Table 4.2.1-1.

Table 4.2.1-1 Pharmacokinetic Parameters of Tolvaptan in Fasted Rats and Dogs After a Single Oral Administration of Spray-dried Tolvaptan

Male/female rats					Male beagle dogs				
Dose (mg/kg)	**t_{max} (h)**	**C_{max} (µg/mL)**	**$AUC_{(0-t)}$ (µg·h·mL^{-1})**	**$t_{1/2}$ (h)**	**Dose (mg/kg)**	**t_{max} (h)**	**C_{max} (µg/mL)**	**$AUC_{(0-t)}$ (µg·h·mL^{-1})**	**$t_{1/2}$ (h)**
1	0.25/0.5	0.011/0.095	0.009/0.228	1.07/1.39	**0.67**	1.0	0.022	0.072	1.98
3	0.5/1.0	0.042/0.270	0.093/0.780	1.34/1.74	**2**	1.3	0.050	0.214	2.18
10	0.5/2.0	0.113/1.230	0.332/4.304	1.44/1.34	**6.7**	1.4	0.151	0.604	2.52
30	0.5/2.0	0.358/3.384	1.152/12.755	1.74/1.50	**20**	1.3	0.326	1.517	2.49

Jet-milled tolvaptan

The time courses of the serum concentration of the unchanged compound were determined after a single oral dose of jet-milled tolvaptan at 1 to 1000 mg/kg to male and female rats,[20,21] male New Zealand White rabbits,[22] and male and female dogs.[23,24] The compound was rapidly absorbed, with a t_{max} of 4 hours or less. The serum concentration of the unchanged compound was highest in female rats, similar among male and female dogs and male rabbits, and lowest in male rats.

The effect of food on the absorption of tolvaptan was investigated by oral administration of tolvaptan to male rats[25] and male dogs.[23] The serum tolvaptan concentration in this study[25] was lower than that in a previous study using fasted male rats.[20] In dogs, the AUC value was higher in non-fasted dogs than in fasted dogs.[23]

Following 14-day repeated oral doses of tolvaptan at 30 mg/kg/day to male beagle dogs,[26] the daily time-course of the serum concentration of the unchanged compound showed similar patterns throughout the dosing period, indicating no changes in the serum pharmacokinetics of tolvaptan after repeated oral doses.

^{14}C-labeled tolvaptan

The serum concentrations of radioactivity and of the unchanged compound were determined after a single oral dose of [^{14}C]tolvaptan at 30 mg/kg to male and female Sprague-Dawley rats[27,28] and male beagle dogs.[29] The serum concentration of radioactivity peaked at 2 to 4 hours after dosing with C_{max} values of 4.441 and 7.739 μg·eq./mL, respectively, in male and female rats and 6.193 μg·eq./mL in male dogs, and decreased with a half-life of 4.4 and 6.4 hours, respectively, in male and female rats and 4.8 hours in male dogs. The ratio of serum concentration of unchanged compound to that of the radioactivity was highest in female rats, followed in descending order by male dogs and male rats.

Following 14-day repeated oral doses of [^{14}C]tolvaptan at 30 mg/kg/day to male rats,[30] the blood concentration of radioactivity gradually increased, reaching a plateau on the 12th dosing day. The concentration decreased gradually after the final dosing.

Intravenous

Following a single intravenous dose of tolvaptan at 1 to 30 mg/kg to male rats, the volume of distribution ranged from 3400 to 5002 mL/kg, elimination half-life was 0.50 to 0.81 hour, total body clearance was 4163 to 6369 mL/kg/h, and AUC_t was 0.202 to 7.185 μg·h/mL.[31] The absolute bioavailability of tolvaptan was determined to be 0.63% and 16% in male rats after single oral administration of jet-milled and spray-dried tolvaptan, respectively. To male dogs, a single intravenous dose of 3 mg/kg of tolvaptan was administered. The volume of distribution was 3526 mL/kg, elimination half-life was 1.84 hours, total body clearance was 1317 mL/kg/h, and AUC_t was 2.199 μg·h/mL.[32] The absolute bioavailability of tolvaptan was determined to be 2.0% and 14.6% in male dogs after single oral administration of jet-milled and spray-dried tolvaptan, respectively.

4.2.2 Distribution

Jet-milled tolvaptan

The concentration of the unchanged compound in the kidneys was about 4 times as high as that in the serum after a single oral dose of tolvaptan at 10 or 100 mg/kg to female rats.[33]

^{14}C-labeled tolvaptan

Following a single oral dose of [^{14}C]tolvaptan at 30 mg/kg to male[34] and female rats,[35] the concentration of radioactivity was high in the liver, stomach, small intestine, adrenals, large intestine, and kidneys in both male and female rats, and was also high in the pituitary gland, Harder's gland, mandibular gland, heart, lung, and pancreas in female rats. The concentrations of radioactivity in the melanin-containing tissues (eyeballs and pigmented skin) were lower than those in the serum in the pigmented rats.[36] In pregnant female rats, the concentration of radioactivity was low in the fetus and amniotic fluid on Day 18 of gestation.[37,38] In lactating rats, radioactivity in milk was generally higher than that in maternal blood with a with a the highest radioactivity being 15.8 times that in blood after a single oral dose of [^{14}C]tolvaptan at 30 mg/kg on Day 14 post partum.[38]

Following 14-day repeated oral doses of [^{14}C]tolvaptan at 30 mg/kg/day to male rats,[39] although the concentration of radioactivity showed distribution patterns similar to those

in the previous single-dose study in rats,[34] the elimination of radioactivity from the tissues was slower in this study than in the previous single-dose study.

Transfer rate of radioactivity to the blood cells was 32.3% or lower after a single oral dose of [^{14}C]tolvaptan at 30 mg/kg to male and female rats,[27,28] and male dogs.[29]

The in vitro plasma protein binding of [^{14}C]tolvaptan was investigated by adding [^{14}C]tolvaptan at 0.1 to 10 µg/mL to rat,[40] dog,[41] mouse[42] and rabbit[42] plasma. The plasma protein binding of [^{14}C]tolvaptan was 97.2% or higher. [^{14}C]tolvaptan was administered to male and female rats[40] and male dogs[41] orally at 30 mg/kg and plasma protein binding was investigated in vivo. The binding of [^{14}C]tolvaptan was 93.0% or higher.

4.2.3 Metabolism

Structural characterization of the metabolites of tolvaptan formed by incubation of tolvaptan with the 9000 × g supernatant fraction of rat liver revealed one hydroxide of the benzazepine ring (DM-4110) and its isomers (DM-4111 and DM-4119), one oxide of the hydroxy group at the 5’ position (MOP-21826), and six metabolites with the benzazepine ring cleaved (DM-4103, DM-4104, DM-4105, DM-4107, DM-4113, and DM-4116).[43]

Spray-dried tolvaptan

Following a single oral dose of tolvaptan (30 mg/kg) to rats, the metabolites DM-4103, DM-4104, DM-4105, DM-4107, DM-4110, DM-4111, DM-4119, DM-4121, and MOP-21826 were found in the serum using HPLC[44] and LC-ESI-MS/MS.[45] In male rats, the serum concentrations of metabolites DM-4103 and DM-4107 were higher than that of the unchanged compound, but in female rats, the serum concentration of the unchanged compound was higher than that of any metabolite, indicating a sex difference in the pharmacokinetics of the compound in rat serum.[44] Metabolites seen in the serum of dogs[46] and rabbits[47] after a single oral dose of tolvaptan were similar to those found in rats.

In a study involving 7-day oral dosing of tolvaptan (10, 100, or 300 mg/kg/day) to female rats, significant increases in cytochrome b5 content and aminopyrine N-demethylase activity were seen at 300 mg/kg/day, suggesting that tolvaptan has potential in the

induction of hepatic drug-metabolizing enzymes.[48]

Following single oral doses of tolvaptan to male and female rats[49] and to male rabbits,[50] the serum concentration of (R)-(+)-tolvaptan was higher than that of (S)-(–)-tolvaptan. In rats, transformation of (S)-(−)-tolvaptan into (R)-(+)-tolvaptan was observed, but transformation of (R)-isomer into (S)-isomer was not observed.[51] In dogs, however, the serum concentration of (S)-(–)-tolvaptan was higher than that of (R)-(+)-tolvaptan,[52] and the transformation of (R)-(+)-tolvaptan into (S)-(–)-tolvaptan was observed to a slight degree, but transformation of (S)-isomer into (R)-isomer was not observed.[53]

^{14}C-labeled tolvaptan

Following a single oral dose of [^{14}C]tolvaptan at 30 mg/kg in male mice, rats, dogs, and rabbits, serum concentrations of tolvaptan and its metabolites were determined in the following order: DM-4110 > DM-4111 > DM-4103 > DM-4139 > DM-4121, and followed by 7 metabolites in mice;[54] DM-4103 > tolvaptan > DM-4121 > DM-4119 > DM-4139, and followed by 16 metabolites in rats;[55] tolvaptan > DM-4104 > DM-4111 > DM-4103 > DM-4119, and followed by 9 metabolites in dogs;[56] and DM-4103 > DM-4107 > DM-4119 > unknown-4 > DM-4139 > tolvaptan, and followed by 12 metabolites in rabbits.[57]

4.2.4 Excretion

Jet-milled tolvaptan

Following a single oral dose of tolvaptan at 10 to 100 mg/kg to male dogs and male rats, the unchanged compound in the urine accounted for less than 0.1% of the administered dose at all doses tested.[23,58]

^{14}C-labeled tolvaptan

Following a single oral dose of [^{14}C]tolvaptan at 30 mg/kg to male and female rats[59] and male dogs,[60] 91.7% to 96.6% of the administered dose was excreted in the feces, 3.9% to 8.1% was excreted in the urine, and 98.9% to 100.4% was excreted in total in both rats and dogs. In rats, only 0.1% of the administered dose was detected in the expired air and 51.4% to 58.1% was excreted via the bile. Of the radioactivity excreted via the bile,

39.5% underwent enterohepatic circulation.[59] After 14-day repeated oral administration of [^{14}C]tolvaptan at 30 mg/kg/day to male rats, 90.9% of the administered dose was excreted in the feces and 6.5% in the urine.[61]

4.2.5 References

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4.3 Toxicology

The toxic potential of tolvaptan was investigated in single and repeated oral dose studies in rats and dogs, genotoxicity studies *in vitro and in vivo* (in rats), carcinogenicity studies in mice and rats, reproductive and developmental toxicity studies in rats and rabbits, juvenile animal toxicity studies in rats, mechanistic studies in rats and dogs, an antigenicity study in guinea pigs, an immunotoxicity study in rats, and phototoxicity studies in vitro and in vivo (in guinea pigs, and rabbits). Single-dose toxicity studies, genotoxicity studies, and phototoxicity studies of the major metabolites of tolvaptan were also conducted.

4.3.1 Single-dose Studies

The single oral dose toxicity of tolvaptan was evaluated at doses of up to 2000 mg/kg in rats[1] and beagle dogs.[2] No deaths or toxic signs in general condition were observed in either rats or dogs. In rats, a transient decrease in food consumption and a transient suppression of body weight gain were noted at 2000 mg/kg. The approximate lethal dose was considered to be higher than 2000 mg/kg in both rats and dogs.

4.3.2 Repeated-dose Studies

The toxicity of tolvaptan was evaluated by 4-week[3] and 26-week[4] repeated oral dose studies in rats and by 4-week[5] and 52-week[6] repeated oral dose studies in dogs. In the rat 26-week study at doses of 30, 100, and 1000 mg/kg/day[4] the results showed neither overt toxicity nor target organ toxicity even at 1000 mg/kg/day, except that 3 females at 1000 mg/kg/day were sacrificed in a moribund state of dehydration attributable to an excessive pharmacological action. Therefore, the NOAEL in this study was estimated to be 1000 mg/kg/day in the males and 100 mg/kg/day in the females (serum drug concentration at 4th week of administration: C_{max} of 1.37 and 3.42 μg/mL and $AUC_{0\text{-}24h}$ of 12.72 and 20.76 μg·h/mL in males and females, respectively).

In the dog 52-week administration study at doses of 30, 100, and 1000 mg/kg/day,[6] the results showed no notable target organ toxicity even at 1000 mg/kg/day. However, one male and two females at 1000 mg/kg/day were sacrificed in a moribund state due to decreases in body weight and food consumption. Therefore, the no observed adverse effect level (NOAEL) of tolvaptan in this study was estimated to be 100 mg/kg/day in both sexes (serum drug concentration at 52nd week of administration: C_{max} of 5.46 and 6.05 μg/mL and $AUC_{0\text{-}24h}$ of 31.45 and 42.35 μg·h/mL in males and females, respectively).

4.3.3 Genotoxicity

The genotoxic potential of tolvaptan was evaluated by conducting a bacterial reverse-mutation test[7] a mouse lymphoma assay[8] a chromosomal aberration test using Chinese hamster lung cells[9] and an in vivo micronucleus test using bone marrow cells from male and female rats.[10] Tolvaptan tested negative for genotoxic effects in all of the assay systems used.

4.3.4 Carcinogenicity

Two 104-week carcinogenicity studies, one in mice[11] and one in rats[12] were conducted to evaluate the carcinogenicity of tolvaptan. In the mouse study, the dose levels were set at 0, 10, 30 and 60 mg/kg/day in males and 0, 10, 30 and 100 mg/kg/day in females. There was no increase in either mortality or tumors in the treated groups as compared with the control group. In the rat study, the dose levels were set at 0, 100, 300 and 1000 mg/kg/day in males and 0, 30, 100, 300 and 1000 mg/kg/day in females. There was no increase in either mortality or tumors in the treated groups as compared with the control group. These results indicated that tolvaptan does not have carcinogenic potential.

4.3.5 Reproductive and Developmental Toxicity

To evaluate the effects of tolvaptan on reproductive performance and embryo-fetal development, the compound was administered orally to male and female rats in a fertility study at doses of 100, 300 and 1000 mg/kg/day.[13] Suppressed body weight gain and decreased food consumption were noted in both sexes at 100 mg/kg/day and higher, and changes in estrous cycle were noted in the females at 300 mg/kg/day and higher. Tolvaptan had no effect on copulation rate or fertility rate in rats. No changes were observed in the fetuses. Thus, the NOAEL was considered to be lower than 100 mg/kg/day in both males and females for general toxicological effects, 1000 mg/kg/day in males and 100 mg/kg/day in females for effects on reproduction, and 1000 mg/kg/day for embryo-fetal development.

The effects of tolvaptan on embryo-fetal development were evaluated in pregnant rats and rabbits. In rats, an embryo-fetal development study was conducted at doses of 10, 100, and 1000 mg/kg/day. Suppressed body weight gain and decreased food consumption were noted in the dams at 100 mg/kg/day and higher, and decreased body weight and delayed ossification were noted in the fetuses at 1000 mg/kg/day. The NOAEL in this study was considered to be 10 mg/kg/day for general toxicological effects, 1000 mg/kg/day for effects on reproduction in dams, and 100 mg/kg/day for

embryo-fetal development.[14] The $AUC_{0\text{-}24h}$ on day 17 of gestation for tolvaptan at 100 and 1000 mg/kg/day was respectively 28.67 and 113.78 μg·h/mL, 8.4 and 33.2 times higher than the area under the concentration-time curve from time zero to infinity (AUC_{∞}) observed in healthy humans after a single oral dose of 60 mg (3.421 μg·h/mL).[15]

In pregnant rabbits, tolvaptan was administered orally at doses of 10, 30 and 100 mg/kg/day. Although suppressed body weight gain and decreased food consumption were noted in the dams at 30 mg/kg/day and higher, no changes were observed in the fetuses.[16] An additional embryo-fetal development study was conducted at doses of 100, 300, and 1000 mg/kg/day. Five dams at 1000 mg/kg/day and one dam at 300 mg/kg/day aborted. The animals at all doses showed suppressed body weight gain and decreased food consumption. The fetuses at 1000 mg/kg/day showed an increase in embryo-fetal death and occurrences of malformations at low incidences in one or two litters: microphthalmia, open eyelids, cleft palate, brachymelia (zygopodium malformations), and fused phalanx. The NOAEL in this study was considered to be lower than 100 mg/kg/day for general toxicological effects, 100 mg/kg/day for effects on reproduction in dams, and 300 mg/kg/day for embryo-fetal development.[17] The $AUC_{0\text{-}24h}$ on day 18 of gestation for tolvaptan at 300, and 1000 mg/kg/day was respectively 8.12 and 16.92 μg·h/mL, 2.4 and 4.9 times higher[18] than the AUC_{∞} observed in healthy humans after a single oral dose of 60 mg (3.421 μg·h/mL).

Subsequent embryo-fetal development studies revealed that the sensitive period for fetal malformations was days 6-11 of gestation and the period of maximum risk was days 9-11 of gestation[19] and that a dose of 300 mg/kg/day administered during days 9-11 of gestation was not teratogenic.[20] The $AUC_{0\text{-}24h}$ on day 11 of gestation when tolvaptan was administered on days 9-11 of gestation at 300 and 1000 mg/kg/day was respectively 17.02 and 48.34 μg·h/mL, 5.0 and 14.1 times higher[21] than the AUC_{∞} in healthy humans after a single oral dose of 60 mg. The concentrations of tolvaptan and its major metabolites were lower in the embryos when compared with the serum concentrations in the dams when tolvaptan was orally administered at 1000 mg/kg/day on days 9 - 11 of gestation.[22]

Several studies were further conducted to explore the mechanism of teratogenicity. In rabbits, due to its aquaretic action, tolvaptan increased plasma osmolality, the plasma concentrations of electrolytes (sodium and chloride) and plasma AVP level with increased urine volume, decreased urine osmolality, and increased water consumption.[23,24] The relationship between excessive pharmacological effect on dams

and fetal malformations was investigated by restricting water supply to explore these changes in plasma. However, the relationship was not clear.[25,26] Because similar malformations have been reported to be caused by biotin deficiency in mice and hamsters[27,28] biotin concentrations in rabbit embryos were determined although the biotin deficiency-induced malformations have not been reported in rabbits. Tolvaptan decreased biotin concentration in rabbit embryos.[29]

To evaluate the effects of tolvaptan on pre- and postnatal development, including maternal function, tolvaptan was administered to pregnant rats at 10, 100 and 1000 mg/kg/day. In dams, decreased food consumption at 10 mg/kg/day and higher and suppressed body weight gain at 100 mg/kg/day and higher were noted, and one dam died at 1000 mg/kg/day. Increased perinatal death and suppressed body weight gain were noted in the offspring at 1000 mg/kg/day. The NOAEL was considered to be less than 10 mg/kg/day for general toxicological effects in dams, 1000 mg/kg/day for effects on reproduction in dams, and 100 mg/kg/day for effects on pre- and postnatal development.[30]

4.3.6 Juvenile Animal Toxicity Studies

The toxic potential of tolvaptan in juvenile rats was investigated in 2 studies.

In one study, male and female rats at 25 days of age (4 days after weaning) were orally administered tolvaptan for 6 weeks at doses of 30, 100, and 1000 mg/kg/day.[31] Treatment-related changes were generally qualitatively comparable to those observed in adult rat toxicity studies of tolvaptan. Pharmacologically-mediated increases in urine volume and water consumption and related changes in urine electrolytes were noted at all doses. No animals died, but toxicities were noted at 1000 mg/kg/day, including suppressed body weight gain and food consumption in males and females, prolonged prothrombin time (PT) and activated partial thromboplastin time in males, delayed balanopreputial separation in males, and delayed vaginal opening in females. Changes seen at 1000 mg/kg/day showed reversibility after a 4-week recovery period. The NOAEL in both male and female juvenile rats was considered to be 100 mg/kg/day (serum drug concentrations on Day 42 of administration: C_{max} of 1.14 and 5.51 μg/mL and $AUC_{0\text{-}24h}$ of 5.92 and 39.13 μg·h/mL in males and females, respectively).[31]

In the second study, male and female pups at 4 days of age were orally administered tolvaptan for 9 weeks at doses of 10, 30, and 100 mg/kg/day.[32] Similar to the above study, pharmacologically mediated changes were noted in urine volume, water consumption, and urine electrolytes at all doses. Dilated renal pelvis considered to be

attributable to increased urine volume during very early infancy was noted in males at 30 mg/kg/day and higher and females at 100 mg/kg/day. Toxicities were noted at 100 mg/kg/day, including death in one male, suppressed body weight gain and food consumption in males and females, and delayed balanopreputial separation and prolonged PT in males. Except for prolonged PT, all changes noted during the administration period showed reversibility after a 4-week recovery period. The NOAEL in both males and females was considered to be 30 mg/kg/day (serum drug concentrations on Day 63 of administration: C_{max} of 0.54 and 2.68 μg/mL and AUC_{0-24h} of 2.52 and 12.60 μg·h/mL in males and females, respectively).[32]

4.3.7 Special Studies

4.3.7.1 Antigenicity Study

Tolvaptan was administered subcutaneously and intramuscularly at doses of 1 and 10 mg/kg to guinea pigs together with Freund's complete adjuvant to attempt sensitization, and the antigenic potential of tolvaptan was assessed by evaluating active systemic anaphylaxis and passive cutaneous anaphylaxis at a challenge dose of 10 mg/kg.[33] Tolvaptan exhibited no antigenicity under the conditions of the study.

4.3.7.2 Immunotoxicity Study

The effects of tolvaptan on immune response were examined in terms of the production of antibody to T cell-dependent antigen.[34] Male and female rats were orally administered tolvaptan at 0, 30, 100, or 1000 mg/kg/day for 4 weeks and immunized with sheep red blood cells (SRBC), and a plaque-forming cell assay was performed. No effect on the SRBC-specific antibody response was observed.

4.3.7.3 Phototoxicity Studies

The in vitro phototoxicity of tolvaptan was examined in BALB/3T3 cells.[35] Cell survival was reduced at precipitating concentrations of 0.13 mg/mL and higher. The IC_{50} was 0.31 mg/mL under a non-irradiated condition and 0.14 mg/mL under an irradiated condition, for a ratio (photo-irritation factor [PIF]) of 2.2, classified as "probably phototoxic". However, the cytotoxicity of tolvaptan was considered to be weak, because this phototoxic effect was not reproducible, the PIF in the dose-range finding assay was 0.61, and cytotoxicity was noted at concentrations at which precipitation of the compound occurred. Additionally, the IC_{50} under irradiation was 370 times higher than the tolvaptan plasma C_{max} (0.374 μg/mL) achieved in humans administered tolvaptan at 60 mg (refer to Section 5.2.1.6).

In vivo phototoxicity studies were conducted in Hartley guinea pigs at doses up to 2000 mg/kg/day[36] and in New Zealand White rabbits at doses up to 1000 mg/kg/day.[37] In both studies, the irradiation of UVA to the ear and dorsum did not affect skin reactions or the thickness of the ear at any dose tested. At the highest doses, serum levels of tolvaptan at the start of irradiation in guinea pigs and rabbits were respectively 2.5 times and 7.0 times the C_{max} in humans at 60 mg.

4.3.7.4 Toxicity Studies of Major Metabolites of Tolvaptan

4.3.7.4.1 Single Dose Toxicity Studies

The toxicity of DM-4103 and DM-4107, the major metabolites of tolvaptan in humans, was investigated by single subcutaneous administration of each metabolite dissolved in dimethyl sulfoxide to male rats at doses of 100 and 500 mg/kg, Neither metabolite showed any notable toxicity at either dose and at up to exposure levels as follows: DM-4103 C_{max} of 54 µg/mL and AUC_{0-24h} of 743 µg·h/mL and DM-4107 C_{max} of 310 µg/mL and AUC_{0-24h} of 3906 µg·h/mL.[38,39]

4.3.7.4.2 Genotoxicity

The genotoxic potential of DM-4103 and DM-4107 was evaluated by conducting a bacterial reverse-mutation test[40,41] and a mouse lymphoma assay.[42,43] DM-4103 and DM-4107 tested negative for genotoxic effects in both the assay systems used.

4.3.7.4.3 Phototoxicity Studies

The in vitro phototoxicity of DM-4103 and DM-4107 was examined in BALB/3T3 cells. For DM-4103, cell survival was reduced at precipitating concentrations of 0.50 and 1.0 mg/mL under a non-irradiated condition. The IC_{50} was 0.99 mg/mL under a non-irradiated condition and 0.0061 mg/mL under an irradiated condition, for a PIF of 162, indicating that DM-4103 showed phototoxicity in vitro.[44] For DM-4107, cell survival was reduced only at the highest concentration of 1.0 mg/mL: 77.9% and 51.1% of the control under non-irradiated and irradiated conditions, respectively. The PIF of DM-4107 could therefore not be calculated and the compound was categorized as "phototoxicity indeterminable." However, as the cytotoxic effects were almost the same under both conditions, it was considered that DM-4107 is unlikely to be phototoxic.[45] As described in Section 4.3.7.4, in vivo phototoxicity studies of tolvaptan were conducted in guinea pigs and rabbits, and no phototoxicity was noted at any of the doses tested. At the highest doses, the serum level of DM-4103 in guinea pigs and rabbits at the start of exposure was respectively 0.5 times and 22 times the C_{max} (2.2 µg·h/mL) in humans at

60 mg. These results suggest that the phototoxicity observed in vitro was not relevant to in vivo phototoxicity.

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5 Effects in Humans

5.1 Clinical Overview

Tolvaptan was approved by the US FDA, by the EMA, and in 10 other countries for the treatment of specific forms of hyponatremia. Tolvaptan was also approved by the Japanese MHLW for the adjunct treatment of volume overload in heart failure when adequate response is not obtained with other diuretics; for body fluid retention in hepatic cirrhosis when adequate response is not obtained with other diuretics; and for suppression of progression of ADPKD in patients with increased kidney volume and a rapid rate of increase (Table 5.5-1). In Feb 2015, Health Canada approved JINARC™ (tolvaptan) to slow the progression of kidney enlargement in patients with ADPKD.

Phase 3 development in China for hepatic edema has been completed. Tolvaptan is also being developed in the US and multinationally for the indication of ADPKD; for the adjunct treatment of chronic renal failure treated with peritoneal dialysis and hematodialysis or hemodiafiltration, for carcinomatous edema in Japan; and for cardiac edema in China and Taiwan. As of 31 Mar 2015, the tolvaptan clinical development program consists of a total of 105 trials: 97 trials have been completed worldwide, 4 trials were terminated, 3 in the US (2 due to slow enrollment and 1 based on futility analysis results) and 1 in Korea (due to changes in indication based on safety information), and 8 trials are ongoing; 4 open-label or observational, and 4 blinded.

These 105 trials are listed according to subject population (healthy subjects and by disease state) in Table 5.1-1 and Table 5.1-2, respectively. Key details of each tolvaptan trial, including trial design, treatments, enrollment status, demographics, and primary endpoints, are summarized in Appendix 1. The order of presentation of the trials in Appendix 1 follows the order shown in Table 5.1-1 and Table 5.1-2 by reading the columns from top to bottom and from left to right.

There are 93 trials included in the pooled exposure database (Table 5.4.1.1-1). Of these 93 trials, a total of 11,719 subjects were enrolled in studies using an oral tolvaptan formulation, of which 7373 subjects were exposed to at least one oral dose of tolvaptan. Of these, data from 30 subjects are not included in the pooled adverse event data (Table 5.4.2-1); however, they are included in the pooled exposure data. These 30 subjects were exposed in early phase 1 trials conducted in Japan (Trials 156-94-001 and 156-94-002) using the jet-milled formulation. In addition, exposure and adverse event data for 4 additional completed open-label, long-term trials (Trial 156-03-244 in subjects with hyponatremia and Trials 156-04-250, 156-05-002, and 156-09-003 in subjects with

ADPKD) are presented separately by indication and are not included in the pooled all trial data.

The available phase 2/3/4 clinical pharmacokinetic (PK), efficacy, and safety information is reflected in the current version of the SmPC for Samsca (Appendix 4).

Healthy Subjects

Forty-seven phase 1 clinical pharmacology trials of tolvaptan have been completed and analyzed in healthy subjects: 12 trials were conducted in Japan, 7 in the UK, 3 in China, 1 in Korea, 23 in the US, and 1 multinational (US and Argentina) in otherwise healthy subjects with a history of arrhythmia on oral maintenance amiodarone therapy. A special population trial to study the effect of varying degrees of renal impairment was also conducted in the US (156-09-282).

Hyponatremia Program

In the hyponatremia program, four phase 2 and five phase 3 trials have been conducted in the US, China, and multinationally, and 1 phase 4 trial has been conducted in Korea (Table 5.1-2). In addition, subpopulations of subjects with hyponatremia from 3 trials in the heart failure program (Trials 156-97-252, 156-98-213, and 156-03-236) are also relevant to the hyponatremia program. The population for these hyponatremia trials was subjects with nonhypovolemic, nonacute hyponatremia arising from a variety of etiologies including heart failure, cirrhosis, SIADH, and others. Two of the phase 2 trials conducted in the US (Trials 156-96-201 and 156-97-204) were terminated because of insufficient enrollment; one phase 3b trial conducted in the US (Trial 156-08-275) was terminated based on futility analysis results; and one phase 4 trial conducted in Korea (156-KOB-1101i) was terminated due to a change in indication based on safety information. Three hyponatremia trials are ongoing: an observational, phase 4, multinational safety trial (Trial 156-09-101), a phase 4 placebo-controlled safety and efficacy trial in Korea (Trial 156-KOB-1201i) in subjects with hyponatremia who are hospitalized with worsening heart failure), and a phase 1b, double-blind, multinational PK/pharmacodynamic (PD) trial (Trial 156-12-203) in subjects with euvolemic hyponatremia secondary to SIADH. Data for the 2 ongoing, double-blind trials will not be presented in this Investigator's Brochure (IB) update. Pediatric trials are planned for subjects with hypervolemic, chronic hyponatremia secondary to heart failure, liver failure or SIADH/other ranging from 4 weeks old to 17 years old at time of enrollment.

Cardiac Edema Program

In the cardiac edema program, one phase 2 trial (Trial 156-03-001), three phase 3 trials (Trials 156-06-002, 156-06-004, and 156-06-006), and one phase 4 trial (156-10-005) have been completed in Japan for the indication of cardiac edema in subjects with extracellular volume expansion secondary to CHF. Additionally, one phase 3 trial (Trial 156-12-809-01) in China in subjects with CHF with body fluid retention after current diuretic treatment, and 1 phase 3 placebo-controlled efficacy and safety trial in Taiwan (156-TWA-1101i) in subjects with stabilized heart failure after an acute exacerbation episode, have been completed. Three previously conducted US trials (Trials 156-97-251, 156-97-252, and 156-00-222) from the heart failure program (described below) are also relevant to the cardiac edema program.

Heart Failure Program

In the heart failure program, nine phase 2 trials and one phase 3 trial have been completed. Four placebo-controlled phase 2 trials were conducted in subjects with CHF (Trials 156-97-251, 156-97-252, 156-98-213, and 156-00-220). An additional placebo-controlled phase 2 trial (Trial 156-00-222) was conducted to compare the effects of tolvaptan with furosemide and the combination of tolvaptan and furosemide in subjects with CHF. Four other phase 2 trials in subjects with heart failure were completed: one (Trial 156-00-221) evaluating the effects of tolvaptan and furosemide on renal function and renal hemodynamics in CHF subjects, a second (Trial 156-01-231) comparing the effects of tolvaptan 30 mg QD versus 15 mg twice daily (BID), a third (Trial 156-01-232) assessing the effects of tolvaptan 30 mg QD on left ventricular dilatation and function in subjects with heart failure, and a fourth (Trial 156-04-247) evaluating the effects of tolvaptan on hemodynamic parameters. One phase 3 multinational trial with embedded 3-in-1 trials (Trial 156-03-236) evaluating the acute symptomatic improvement and long-term efficacy and safety of tolvaptan in subjects hospitalized with worsening CHF was completed.

Hepatic Cirrhosis Program

In the hepatic cirrhosis program, one phase 1 trial in subjects with hepatic impairment in China, three phase 2 trials in subjects with hepatic edema (two in Japan and one in China), and four phase 3 trials (three in Japan and one in China) have been completed. The phase 1 trial (Trial 156-09-806-01) in China assessed the pharmacokinetics, pharmacodynamics, and safety of tolvaptan in Chinese subjects with Child-Pugh Class B hepatic impairment. For the two completed phase 2 trials in Japan: Trial 156-03-002 was an open-label trial that evaluated subjects with peripheral edema or ascites secondary to liver disease, and Trial 156-06-005 was a double-blind, placebo-controlled trial that

evaluated subjects with cirrhosis and ascites despite conventional diuretics. The completed phase 2 and phase 3 trials in China (Trial 156-08-804-01 and Trial 156-08-805-01, respectively) were placebo-controlled trials that evaluated subjects with cirrhosis and ascites despite therapy with conventional diuretics. The three completed phase 3 trials in Japan also evaluated subjects with cirrhosis and ascites despite therapy with conventional diuretics: Trial 156-08-001 was a placebo-controlled trial, Trial 156-08-002 was an open-label trial, and Trial 156-09-004 was a randomized double-blind, parallel-group trial designed to evaluate 2 dose levels of tolvaptan.

Carcinomatous Edema Program

In the carcinomatous edema program, one phase 2, multicenter, open-label, dose-finding trial (Trial 156-12-001) has been completed in Japan. This study assessed the efficacy, PK/PD, and safety of tolvaptan in subjects with volume overload associated with cancer, and determined the initial and maintenance doses expected to be safe and have an immediate effect in this population.

Chronic Renal Failure Trials

In the chronic renal failure program, two phase 2 trials have been completed in Japan in subjects with chronic renal failure: Trials 156-12-002 and 156-12-007. One phase 2, double-blind trial in Japan is ongoing:

- Trial 156-13-003 (Japan) is a phase 2, double-blind trial for subjects with chronic renal failure who are undergoing hemodialysis or hemodiafiltration.

Data for the ongoing, double-blind trial will not be presented in this IB update.

ADPKD Program

In the ADPKD program, one phase 1 trial (in the US), eight phase 2 trials (five in the US, two in Japan, and one in the Netherlands), one phase 3/4 trial in Japan and one multinational phase 3 trial have been completed. Four ADPKD trials are ongoing: one open-label, phase 3/4 trial in Japan (156-10-003), and three multinational phase 3b trials, (156-08-271, 156-13-210, and 156-13-211). Data for the ongoing, double-blind trial, 156-13-210 will not be presented in this IB update.

Phase 2 trials in ADPKD subjects included Trial 156-04-248 and Trial 156-04-249 in the US and a sister Trial 156-04-001 in Japan which investigated ascending single and multiple doses (5 days) in ADPKD subjects with well-preserved renal function. Subjects from these trials were enrolled into open-label extension trials (Trial 156-04-250 [US] and Trial 156-05-002 [Japan]) in which tolvaptan treatment continued for up to 4 years and 3 years, respectively. Trial 156-06-260 (phase 1, US) and Trial 156-09-284 (phase 2,

Netherlands) evaluated changes in renal function and TKV in ADPKD subjects with varying degrees of renal function following 8 and 21 days of tolvaptan dosing, respectively; the effect of tolvaptan withdrawal on these endpoints was studied at 21 days post-treatment in Trial 156-09-284. Trial 156-09-285 was a phase 2 US trial in ADPKD subjects with well-preserved renal function that evaluated the PK/PD and tolerability of modified-release (MR) capsules and spray-dried tablets where each regimen was administered for 7 days. Trial 156-09-290 (US), another phase 2 trial, was a double-blind, placebo-controlled trial evaluating the safety and efficacy of MR capsule and IR tablet formulations in subjects with ADPKD. Clinical conduct for this trial is complete, but final data analysis is pending; trial safety data are included in pooled exposure and pooled adverse event presentations.

The completed multinational phase 3 trial (Trial 156-04-251) was a double-blind, placebo-controlled trial evaluating the long-term safety and efficacy of tolvaptan for the treatment of ADPKD.

The following 4 trials are ongoing in the ADPKD program:

- Trial 156-08-271 (multinational) is a phase 3b open-label, long-term extension trial for subjects who previously completed a phase 1, 2, or 3 tolvaptan ADPKD or renal impairment trial, and who have a confirmed diagnosis of ADPKD.
- Trial 156-10-003 (Japan) is a phase 3/4 open-label, long-term extension trial for Japanese subjects who participated in multinational Trial 156-04-251 and who completed 3 years of tolvaptan treatment.
- Trial 156-13-210 (multinational) is a phase 3b, placebo-controlled, double-blind trial in subjects with chronic kidney disease late stage 2 to early stage 4 due to ADPKD.
- Trial 156-13-211 (multinational) is a phase 3b, open-label, long-term, extension trial for subjects with a confirmed diagnosis of ADPKD who have completed or participated in a prior ADPKD trial with tolvaptan.

There is currently no experience with tolvaptan in pediatric patients with ADPKD, although a clinical trial is in preparation.

Table 5.1-1 List of Trials by Subject Population - Phase 1 Clinical Pharmacology Trials in Healthy Subjects (N = 47)

Spray-dried Formulation			Other Formulations				
Capsules	Tablets (cont.)		Modified Release	IV + Spray Dried	SDT	^{14}C Capsule	Jet-Milled
156-95-302 [UK]	**156-01-229** [US]		156-07-262[a] [US]	156-05-254 [US]	156-08-270 [US]	156-97-202 [US]	**156-94-001** [J]
156-95-303 [UK]	156-01-233 [US]		156-07-263 [US]				156-94-002 [J]
156-95-304 [UK]	156-01-234 [US]		156-08-269 [US]				156-95-301 [UK]
156-95-305 [UK]	156-03-239 [US]		156-10-006[a] [J]				156-05-003 [J]
156-96-301 [UK]	156-03-240 [US]						156-05-004 [J]
	156-03-242 [UK]						156-05-252 [US]
Tablets	**156-03-245** [US]						156-05-253 [US]
156-96-205 [US]	**156-05-001** [J]						
156-98-201 [US]	156-05-256 [US]						Powder
156-98-202 [US]	156-06-801-01 [C]						156-14-004 [J][c]
156-98-210 [US]	156-07-002 [J]						
156-00-001 [J]	**156-KOA-0801** [K]						
156-00-002 [J]	156-10-004 [J]						
156-00-003 [J]	156-11-295 [US]						
156-01-223 [US]	156-11-807-01 [C]						
156-01-225 [US]	156-11-808-01 [C]						
156-01-226 [MN]	156-12-202[b] [US]						

C = China; cont. = continued; IV = intravenous; J = Japan; K = Korea; MN = multinational; S-D = spray-dried; SDT = slow disintegration tablet; UK = United Kingdom; US = United States.

Data shown are trial number and country (in brackets). **Bolded** trial number represents a placebo-controlled trial.

[a] Trial employed both S-D and modified-release formulations.

[b] Trial employed both S-D and oral suspension formulations.

[c] Trial employed both S-D and 1% powder formulations.

Table 5.1-2 List of Trials by Subject Population - Trials by Disease State (N = 58)

Hyponatremia	Heart Failure		Hepatic Cirrhosis	ADPKD or Renal Impairment	Carcinomatous Edema
Clinical Pharmacology **156-96-201** $[US]_2$ **156-96-203** $[US]_2$ (**156-12-203**) $[MN]_{1b}$ Efficacy **156-97-204** $[US]_2$ **156-02-235** $[US]_3$ **156-03-238** $[MN]_3$ **156-04-246** $[US]_3$ **156-07-802-01** $[C]_2$ **156-08-275** $[US]_{3b}$ **156-KOB-1101i** $[K]_4$ (**156-KOB-1201i**) $[K]_4$ Open-label Safety 156-03-244 $[MN]_3$ (156-09-101) $[MN]_4$	Cardiac Edema - Clinical Pharmacology **156-97-251** $[US]_2$ Cardiac Edema - Efficacy **156-97-252** $[US]_2$ **156-00-222** $[US]_2$ **156-03-001** $[J]_2$ **156-06-002** $[J]_3$ 156-06-004 $[J]_3$ 156-06-006 $[J]_3$ **156-12-809-01 $[C]_3$** **156-TWA-1101i $[T]_3$** Cardiac Edema - Safety **156-10-005** $[J]_4$	HF - Clinical Pharmacology **156-00-221** $[US]_2$ 156-01-231 $[US]_2$ **156-04-247** $[MN]_2$ HF - Efficacy **156-98-213** $[MN]_2$ **156-00-220** $[MN]_2$ **156-01-232** $[US]_2$ **156-03-236** $[US]_3$	Hepatic Edema 156-03-002 $[J]_2$ **156-06-005** $[J]_2$ **156-08-001** $[J]_3$ 156-08-002 $[J]_3$ **156-08-804-01** $[C]_2$ **156-08-805-01** $[C]_3$ 156-09-004 $[J]_3$ Hepatic Impairment - Clinical Pharmacology 156-09-806-01 $[C]_1$	Clinical Pharmacology 156-04-001 $[J]_2$ **156-04-248** $[US]_2$ 156-04-249 $[US]_2$ 156-06-260 $[US]_1$ 156-09-282 $[US]_1$ 156-09-284 $[N]_2$ 156-09-285[a] $[US]_2$ Efficacy 156-04-250 $[US]_2$ **156-04-251** $[MN]_3$ 156-05-002 $[J]_2$ (156-08-271) $[MN]_{3b}$ 156-09-003[b] $[J]_{3/4}$ **156-09-290**[a,c] $[US]_2$ (156-10-003)[b] $[J]_{3/4}$ (**156-13-210**) $[MN]_{3b}$ (156-13-211) $[MN]_{3b}$ Chronic Renal Failure 156-12-002 $[J]_2$ 156-12-007 $[J]_2$ (**156-13-003**) $[J]_2$	Clinical Pharmacology and Efficacy 156-12-001 $[J]_2$

ADPKD = autosomal dominant polycystic kidney disease; C = China; HF = heart failure; J = Japan; K = Korea; MN = multinational; N = Netherlands; S-D = spray-dried; T = Taiwan; US = United States.

Note: All trials in disease states used the spray-dried (S-D) tablet formulation unless otherwise indicated. Data shown are trial number, country (in brackets), and trial phase (subscript numeral). **Bolded** trial number represents a placebo-controlled trial. ( ) represents ongoing trial. Preliminary safety data through 31 Mar 2015 will be provided for ongoing, open-label trials, but they will not be included with pooled safety or exposure data.

[a]Trial employed both S-D and modified-release formulations.
[b]Trial is conducted as a phase 4 trial after approval of tolvaptan for ADPKD in Japan.
[c]Trial is completed with final data analyses pending. Trial safety data are included in pooled exposure and pooled adverse event presentations.

5.2 Pharmacokinetics and Product Metabolism in Humans

The pharmacokinetic/pharmacodynamic trials conducted for spray-dried tolvaptan tablets have included single- and multiple-dose safety and tolerability trials; an absolute bioavailability trial; food effect trials; drug interaction trials with furosemide, hydrochlorothiazide, ketoconazole, grapefruit juice, rifampin, lovastatin, amiodarone, warfarin, and digoxin; a single-dose absorption, distribution, metabolism, and excretion (ADME) trial with ^{14}C-labeled tolvaptan; special population trials including age/gender, Japanese versus Caucasian men, subjects with hyponatremia secondary to liver disease, and renal impairment; trials in subjects with stable heart failure, hepatic edema, and ADPKD; and relative bioavailability trials of other formulations compared with the spray-dried tablet. Five trials have investigated an MR capsule formulation (4 single- and multiple-dose trials in healthy subjects and one trial in subjects with ADPKD). A single trial investigated an oral suspension compared to spray-dried tablet in healthy subjects.

5.2.1 Pharmacokinetics

5.2.1.1 Absorption

- A standard high-fat meal or Japanese standard meal does not have a clinically meaningful effect on tolvaptan pharmacokinetics following 15-, 30-, or 60-mg doses. (Trials 156-03-242, 156-05-256, 156-07-002)
- For a 90-mg dose, a standard high-fat meal increases C_{max} 1.9-fold but has no effect on AUC. (Trial 156-11-295)
- The mean absolute bioavailability of tolvaptan following oral administration as a 30-mg tablet was 56%, range 42 to 80%. (Trial 156-05-254)

5.2.1.2 Distribution

- Tolvaptan is primarily bound to serum albumin and α_1-acid glycoprotein (Section 5.2.1.5).

5.2.1.3 Metabolism

- Tolvaptan is extensively metabolized, with unchanged drug accounting for less than 3% of the radioactivity in plasma. (Trial 156-97-202)
- Tolvaptan has 14 detectable metabolites in the plasma. DM-4103 alone accounted for 52.5% of the plasma radioactivity. (Trial 156-97-202)

- Following single oral tolvaptan doses, the metabolite DM-4103 had a mean half-life of approximately 180 hours and had measurable plasma concentrations up to 456 hours postdose (Trial 156-97-202). Following multiple oral 30-mg tolvaptan doses QD, DM-4103 concentrations accumulated and mean plasma trough concentrations reached approximately 1450 ng/mL at Week 12 and remained at that level through the end of the trial at Week 54. (Trial 156-01-232) Following split-dose regimens of 90/30, 60/30 mg or 45/15 mg to subjects with ADPKD, steady-state DM-4103 concentrations up to 30 µg/mL were observed. (Trial 156-04-251) However, DM-4103 is not pharmacologically active. In an animal toxicity trial in male rats, DM-4103 did not show any notable toxicity following single subcutaneous doses of either 100 mg/kg or 500 mg/kg (Section 4.3.7.4.1).
- CYP3A4 is the predominant pathway for tolvaptan metabolism.[1,2,3]

5.2.1.4 Elimination

- The R(+) and S(-) enantiomers of tolvaptan have equipotent affinity for the V_2 receptor (Section 4.1.1.1). Concentrations of the S(-) enantiomer are higher than the R(+) enantiomer but the elimination of each enantiomer appears to be similar. The concentrations of R(+) and S(-) enantiomers on Day 1 are similar to those determined after multiple oral doses for 28 days. (Trial 156-95-305)
- Results from the ^{14}C ADME trial showed 99% recovery of the radioactivity of ^{14}C-tolvaptan, with 40% in urine and 59% in feces. (Trial 156-97-202)
- Renal clearance of tolvaptan is less than 1% of total body clearance. (Trials 156-97-202, 156-01-229)
- The major analytes in urine were DM-4107 and DM-4111, which accounted for 23.3% and 14.1% of urinary radioactivity, respectively. (Trial 156-97-202)
- The major metabolites in feces were tolvaptan and DM-4107, which accounted for 31.9% (or about 19% of the total dose) and 20.6% of fecal radioactivity, respectively. (Trial 156-97-202)

5.2.1.5 In Vitro Human Studies

- The human plasma protein binding of ^{14}C-tolvaptan was 98.0% or higher. In human plasma, ^{14}C-tolvaptan was bound mainly to serum albumin and α_1-acid glycoprotein. Diazepam, digitoxin, and warfarin had no effect on the human serum albumin binding of tolvaptan.[4]
- Tolvaptan and DM-4103 did not affect human plasma protein binding of propranolol, lidocaine, and spironolactone.[5] Furosemide, spironolactone, propranolol, dispyramide, lidocaine, and warfarin did not affect the plasma protein binding of tolvaptan, DM-4103, or DM-4107.[6]

- The following tolvaptan metabolites were produced by human liver microsomes: DM-4103, DM-4104, DM-4105, DM-4107, DM-4110, DM-4111, MOP-21826, and 3 unknown metabolites. Most metabolites were thought to be catalyzed by one enzyme, CYP3A4/5.[3]
- DM-4103, DM-4104, DM-4105, DM-4107, and tolvaptan were produced from MOP-21826. DM-4107 was produced from DM-4104. DM-4103 was produced from DM-4105. It was considered that DM-4103 was produced from tolvaptan by way of MOP-21826 and DM-4105.[7]
- The human liver S9 did not catalyze the metabolism of DM-4103.[8]
- It appears that tolvaptan is a substrate of P-glycoprotein (P-gp, and multidrug resistance 1 [MDR1]).[9].
- Studies were conducted to assess the potential of tolvaptan, DM-4103, and DM-4107 to inhibit P-gp, breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP)1B1, OATP1B3, organic cation transporter (OCT)1, OCT2, organic anion transporter (OAT)1, OAT3, multidrug and toxin extrusion (MATE)1, MATE2-K, and bile salt export pump (BSEP).[9,10,11,12,13,14]

  According to a maximum expected concentration in a transporter site based on the EMA drug-drug interaction guideline, tolvaptan concentrations in ADPKD patients may have the potential to inhibit P-gp, BCRP and OCT1. DM-4103 concentrations in ADPKD patients may have the potential to inhibit OATP1B1, OATP1B3, OCT1, OAT3, and BSEP. Tolvaptan and DM-4103 in ADPKD patients showed little potential for inhibition of OAT1, OCT2, MATE1, and MATE2-K.
- Statins are substrates of OATP1B1 and OATP1B3, and no change was observed in the adverse event profile in subjects receiving statins concomitantly with tolvaptan compared with subjects receiving tolvaptan alone in the pivotal 156-04-251 ADPKD trial. Furosemide is a substrate of OAT3, and no change was observed in the adverse event profile in subjects receiving furosemide concomitantly with tolvaptan compared with subjects receiving tolvaptan alone in CHF trials.

5.2.1.6 Single- and Multiple-dose Pharmacokinetics

- Tolvaptan pharmacokinetics were linear for single oral doses ranging from 5 to 480 mg, although C_{max} showed a less than proportional increase with increasing dose. Mean C_{max} values were 374 ng/mL and 915 ng/mL for single doses of 60 and 240 mg, respectively. (Trial 156-98-210) A similar pattern of less than proportional increases in C_{max} were observed at doses of 300, 360, 420 and 480 mg; mean C_{max} values were 994, 996, 1301 and 1073 ng/mL, respectively. (Trial 156-01-229) Tolvaptan plasma concentrations show less than dose proportional increases with increasing doses ranging from 3.75 to 15 mg; the slopes of the log C_{max} or log AUC_{∞} versus log dose plot were 0.85 for each plot. (Trial 156-12-202)
- Following multiple oral doses, tolvaptan pharmacokinetics were linear for doses of 30 and 60 mg given QD for 28 days (Trial 156-95-305), but doses of 300 mg QD for

5 days exhibited less than proportional increases. Mean C_{max} and area under the concentration-time curve during a dosing interval (τ) at steady-state (AUC_{τ}) for the 300-mg dose were only 4.2- and 6.4-fold higher, respectively, when compared to 30 mg. (Trial 156-03-245)

- t_{max} ranges from 1 to 4 hours.*
- Following single oral doses, the $t_{1/2,z}$ of tolvaptan increases with increasing dose with mean values around 3 hours for a 15 mg dose and 12 hours for 120 to 480 mg doses. The increases in tolvaptan $t_{1/2,z}$ with increasing dose may be due to continued absorption of tolvaptan from the gastrointestinal tract.*
- The mean apparent clearance of drug from plasma after extravascular administration (CL/F) ranges from 3.5 to 8.6 mL/min/kg for single dose trials* and ranges from 3.2 to 8.9 mL/min/kg following multiple doses of 30 and 60 mg. (Trials 156-95-305, 156-98-202, 156-00-003, 156-03-245)
- Accumulation of tolvaptan is minimal. (Trials 156-95-305, 156-98-202, 156-00-003, 156-03-245)
- DM-4103 concentrations accumulate ($t_{1/2,z}$ approximately 180 hours) following tolvaptan dosing and by 8 weeks steady state is reached and levels are 12 times higher than tolvaptan concentrations (Section 5.2.1.3). (Trials 156-97-202, 156-98-210, 156-01-232, 156-04-250)

*(Trials 156-96-205, 156-96-301, 156-98-201, 156-98-202, 156-98-210, 156-00-001, 156-00-003, 156-01-229, 156-03-234, 156-03-240, 156-03-242, 156-12-202)

5.2.1.7 Drug Interactions

5.2.1.7.1 Cytochrome P450

Tolvaptan is a sensitive CYP3A4 substrate with no inhibitory activity at CYP3A4 or CYP2C9.

- Coadministration of ketoconazole significantly inhibited the metabolism of tolvaptan. Upon coadministration with ketoconazole, mean C_{max} and AUC_{∞} of tolvaptan increased 3.5-fold (range 2.08 to 7.39) and 5.4-fold (range 3.50 to 7.71), respectively. Mean CL/F decreased by 83%. (Trial 156-98-201)
- Tolvaptan C_{max} and AUC_{∞} increased 1.9-fold (range 0.96 to 2.61) and 1.6-fold (range 1.11 to 2.11), respectively, when administered with 240 mL grapefruit juice. There was no change in $t_{1/2,z}$. (Trial 156-03-240)
- When a single 240-mg dose of tolvaptan was administered with rifampin at steady state (600 mg QD), tolvaptan C_{max} and AUC_t were significantly decreased to 0.17-fold (range 0.11 to 0.31) and 0.13-fold (range 0.05 to 0.19), respectively, of that for tolvaptan alone. (Trial 156-03-239)

No clinically significant changes in furosemide, hydrochlorothiazide, lovastatin, warfarin (R- or S- enantiomers), or amiodarone pharmacokinetics were observed when

administered with tolvaptan. (Trials 156-96-205, 156-01-223, 156-01-233, 156-01-225, 156-01-226)

No clinically significant changes in tolvaptan pharmacokinetics were observed when administered with the above compounds.

5.2.1.7.2 P-glycoprotein (Trial 156-01-234)

- Steady-state digoxin C_{max} and AUC_{τ} values increased 1.3-fold (range 0.7 to 2.2) and 1.2-fold (range 0.9 to 1.4), respectively, when administered with tolvaptan.[9]
- Digoxin renal clearance was statistically significantly lower (59%) when administered with tolvaptan.
- Digoxin did not clinically significant change tolvaptan pharmacokinetics or pharmacodynamics.
- In vitro studies indicate that tolvaptan is a substrate and competitive inhibitor of P-gp[9] but that metabolites DM-4103 and DM-4107 have no inhibitory activity at P-gp.[10]

5.2.1.8 Special Populations

- Tolvaptan pharmacokinetics are not affected by age or gender. (Trial 156-98-202)
- For Japanese men compared to Caucasian men, tolvaptan concentrations are higher but the increase is due to lower body weight in Japanese men as clearance values adjusted for body weight are similar. (Trial 156-03-242)
- In subjects with hyponatremia due to liver disease given tolvaptan QD for 13 days, tolvaptan concentrations accumulated 1.7- to 1.8-fold and clearance was about one-third that of healthy subjects. (Trial 156-96-203)
- In subjects with renal impairment, results indicate that tolvaptan AUC_{∞} and AUC_{∞} of unbound drug ($AUC_{\infty,u}$) are 1.9-fold higher in subjects with CrCL < 30 mL/min versus those with CrCL > 60 mL/min; plasma protein binding of tolvaptan is not altered with decreasing CrCL. (Trial 156-09-282)

5.2.1.9 Disease State

5.2.1.9.1 Population Pharmacokinetic Analysis - Hyponatremia and Heart Failure With or Without Hyponatremia

Population pharmacokinetic analyses have been performed, one including subjects with hyponatremia of any origin enrolled in the hyponatremia trials and one including subjects with heart failure with or without hyponatremia enrolled in the heart failure trials. The conclusions are as follows:

- The population pharmacokinetics 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, apparent volume of distribution (V/F), and k_a, and exponential residual error. Between-subject variability and residual error were high (coefficient of variation 61 to 66% [CL/F], 42 to 49% [V/F], 114 to 124% [k_a] and 51 to 62% [random 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% decrease 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 decrease 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 subjects 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 trial (Trial 156-96-203).
- Renal impairment (as estimated by the normalized CrCL calculated from the Cockroft-Gault equation) had no effect on tolvaptan clearance in the hyponatremia analysis.
- Coadministration of CYP3A4 inducers resulted in a 45% (95% confidence interval [CI]: 7%, 84%) increase in tolvaptan oral clearance, based on data from only 5 subjects in the core hyponatremia analysis and a 75% (95% CI: 44%, 124%) increase from 11 subjects in the expanded hyponatremia analysis (hyponatremia trials and subjects with hyponatremia enrolled in heart failure trials). The heart failure database included only 17 subjects 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 trial (Trial 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 pharmacokinetics for the subject populations investigated.

5.2.1.9.2 Population Pharmacokinetic Analysis - ADPKD

The model consisted of one compartment with first-order absorption with a lag time (t_{lag}) and first-order elimination. A dose dependency in 2 pharmacokinetic parameters: the absorption rate constant K_a (decrease) and apparent volume of distribution for central compartments (V_c/F) (increase) were identified. This dose dependency agrees with the observed less than proportional increase in C_{max} and increased apparent half-life with dose. This dose dependency remained moderate at the doses used for the single pivotal trial, 60 to 120 mg/day. Population estimates for CL/F, V_c/F, $K_{a,}$ and t_{lag} were:

16.4 $L \cdot h^{-1}$, 163 L (at 120 mg), 1.4 h^{-1} (at 120 mg), and 0.24 h, respectively. Residual variability was described by a combined error model which included both additive and proportional components.

Covariate analysis revealed the following effects:

- A reduction of the CL/F when CYP3A4 inhibitors were co-administered and with increased body mass index (BMI) values, an increase of CL/F with increased eGFR determined using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula ($eGFR_{CKD-EPI}$) values;
    - The impact of BMI on CL/F ranged from −53% (for 54.7 kg/m^2) to +63% (for 15.4 kg/m^2) of the typical value.
    - A decrease in $eGFR_{CKD-EPI}$ from 72.2 to 9.79 ($mL/min/1.73\ m^2$) would result in a 32% reduction in CL/F.
    - CYP3A4 inhibitor co-administration reduced CL/F by 27%.
- A reduction of Vc/F in subjects enrolled in Japanese sites (nearly all subjects were Japanese) and with increased age;
- A 50% greater K_a in females than in males.

Other covariate effects had a less significant impact. Inter individual variability in pharmacokinetic parameters were within the expected range for such a large population: 43% in CL/F, 34% in V_c/F and 67% in K_a.

5.2.1.9.3 Subjects With Stable Heart Failure, Including Those With Extracellular Volume Expansion

- Tolvaptan median t_{max} following single or multiple 7.5- and 15-mg doses was 4.00 hours and the mean $t_{1/2,z}$ was 6.6 to 6.8 hours. (Trial 156-06-004)
- Tolvaptan concentrations accumulate between 1.0- to 2.1-fold following multiple doses of 7.5 to 30 mg. (Trials 156-01-231, 156-06-004)
- The mean value of area under the concentration-time curve from time zero to 24 hours (AUC_{0-24h}) for the 30 mg QD regimen was 103% that of the 15 mg BID regimen. (Trial 156-01-231)
- Following single and multiple (QD, 13 days) oral doses ranging from 7.5 to 60 mg, tolvaptan concentrations increased dose proportionately. Multiple doses of 90 and 120 mg showed less than dose proportional increases. (Trials 156-04-247, 156-97-251, 156-06-004)
- The $t_{1/2,z}$, CL/F, and volume of distribution (V_z/F) of tolvaptan were unchanged across dose groups upon multiple dosing of tolvaptan. CL/F was about one third that of healthy subjects. The median V_z/F was not different from healthy subjects. (Trials 156-97-251, 156-98-210)

- For multiple 30- and 60-mg doses given QD to subjects with heart failure, C_{max} values were approximately 1.2- and 1.6-fold higher, respectively, and values of AUC_{τ} were approximately 1.7- and 2.2-fold higher, respectively, when compared with healthy subjects. (Data from integrated analysis)

5.2.1.9.4 Hepatic Edema

- Following multiple 15-mg doses, tolvaptan concentrations were about 34% higher in subjects with severe hepatic disease (Child-Pugh Class C) compared to subjects with mild to moderate hepatic disease (Child-Pugh Class A or B). (Data from population pharmacokinetic analysis)
- Tolvaptan median t_{max} following single or multiple 3.75- and 7.5-mg doses was 4.00 to 5.80 hours and the mean $t_{1/2,z}$ was 8.5 to 14.5 hours. (Trial 156-09-004)
- Tolvaptan concentrations accumulate between 1.19- to 1.26-fold following multiple doses of 3.75 to 7.5 mg. (Trial 156-09-004)

5.2.1.9.5 Autosomal Dominant Polycystic Kidney Disease

- Tolvaptan concentrations increase dose proportionately and CL/F and $t_{1/2,z}$ values were within the range of that for healthy subjects for ADPKD subjects with preserved renal function. (Trials 156-04-248, 156-04-249, 156-04-001)
- The variability of pharmacokinetic parameters is almost twice that of healthy subjects. (Trials 156-04-248, 156-04-249)
- Following multiple dosing (30 to 60 mg/day), accumulation of tolvaptan is minimal. (Trials 156-04-249, 156-04-001)
- Tolvaptan concentrations are similar for Caucasian and Japanese ADPKD subjects. (Trial 156-04-001 compared to Trials 156-04-248, 156-04-249)

5.2.2 Pharmacodynamics

5.2.2.1 Healthy Subjects

- Tolvaptan's effect on urine excretion rate is saturable. Following administration of single oral tolvaptan doses of 60 to 480 mg, with and without volumetric fluid replacement, urine volume for 0 to 12 hours postdose was similar for all doses. Increases in dose sustain the time that saturation is observed; urine volume for 0 to 72 hours postdose was highly correlated with AUC_{∞} and tolvaptan dose. (Trials 156-98-210, 156-01-229)
- The onset and offset time of tolvaptan's effect on urine excretion rate is fast. (Trials 156-03-239, 156-05-254)
- Urine output for 0 to 24 hours is decreased 20% to 25% following multiple doses of tolvaptan. (Trial 156-98-202)

- Urine osmolality and free water clearance decrease and increase, respectively, with the changes observed in urine excretion rate. (Trials 156-96-205, 156-98-210, 156-01-229, 156-05-254)
- Serum sodium and plasma osmolality are increased following a single dose of tolvaptan; the maximal observed increase in serum sodium appears to be inversely correlated with 0 to 24-hour fluid balance. (Trials 156-98-210, 156-01-229)
- Plasma AVP and renin activity were increased following tolvaptan administration but no dose-related increases were observed. (Trials 156-98-202, 156-98-210, 156-01-229)
- The aquaretic action of tolvaptan was unaffected by coadministration with furosemide or hydrochlorothiazide. (Trial 156-96-205)
- Tolvaptan did not affect the natriuretic activity of furosemide or hydrochlorothiazide. (Trial 156-96-205)
- Tolvaptan administered in multiple doses of either 30 mg or 300 mg to healthy subjects did not have a significant effect on individually corrected QT interval (QTcI) compared to placebo. The mean change from baseline in QTcI was significantly lower in healthy subjects taking a single oral dose of tolvaptan (30 mg or 300 mg) compared with those taking placebo. See Section 5.4.10 for additional details. (Trial 156-03-245)

5.2.2.2 Effect of a Single 60-mg Dose in Subjects With Creatinine Clearance Less Than 30, 30 to 60, and Greater Than 60 mL/min (Trial 156-09-282)

- Despite 1.9-fold higher tolvaptan concentrations in the CrCL < 30 mL/min group, mean 24-hour CrCL for all groups decreased 4% to 11% and the change was not dependent on baseline CrCL.
- The mean maximal change in serum sodium concentration was 5 to 6 mEq/L with the median time to the maximal change much sooner, 7 hours, in the CrCL > 60 mL/min group compared to 24 and 32 hours for the CrCL 30-60 mL/min and CrCL < 30 mL/min groups, respectively.
- Increases of 0.1 to 0.3 mg/dL in mean serum creatinine concentrations and increases of 0.1 to 0.2 mEq/L in mean serum potassium concentrations were observed and were independent of baseline CrCL.
- In subjects with preserved renal function, CrCL > 60 mL/min, increases in urine output and free water clearance occurred more quickly and were larger but then returned to baseline more quickly (ie, within 24 hours) than for subjects with increasing renal impairment (CrCL 30-60 mL/min, CrCL < 30 mL/min).
- An increase in mean urinary excretion from 0 to 24 hours postdose of osmoles sodium and potassium was observed in subjects with CrCL > 60 mL/min but not in subjects with CrCL < 60 mL/min.

5.2.2.3 Comparison of Tolvaptan 15 mg BID (8 AM and 4 PM) Versus 30 mg QD in Subjects With Stable Heart Failure (Trial 156-01-231)

- Pharmacodynamic responses (changes from baseline in serum sodium, body weight, urine volume, and urine osmolality; serum potassium, magnesium, and serum osmolality; and CrCL) to 15 mg BID dosing of tolvaptan were similar to that following 30 mg QD.
- Urine volumes for 24 hours postdose on Day 7 were approximately 1200 mL lower compared with Day 1.

5.2.2.4 Comparison of Single Doses of 30 mg Tolvaptan, 80 mg Furosemide, and Placebo in Subjects With Stable Heart Failure (Trial 156-00-221)

- Compared with placebo and furosemide, tolvaptan significantly increased effective renal plasma flow (RPF) (9.00%) and renal blood flow (RBF) (9.56%) and demonstrated trends toward an increase in glomerular filtration rate (1.45%) and a decrease in renal vascular resistance (−8.24%).
- Tolvaptan did not significantly affect proximal or distal fractional reabsorption of sodium, RBF, mean arterial pressure, plasma renin activity or plasma arginine vasopressin, aldosterone, atrial natriuretic peptide, brain natriuretic peptide, or norepinephrine concentrations.
- Tolvaptan increased sodium excretion rate (23%) and clearance (35%) compared to placebo, but did not cause significant depletion as seen with furosemide. The potassium excretion rate and clearance were not affected by tolvaptan treatment in subjects with stable heart failure.
- Tolvaptan and furosemide results were similar to that for healthy subjects in the 156-96-205 trial.

5.2.2.5 Effect of Single-dose Tolvaptan on Hemodynamics in Subjects With Stable Heart Failure (Trial 156-04-247)

- For the primary endpoint of mean peak change in pulmonary capillary wedge pressure (PCWP) from 3 to 8 hours postdose, the largest treatment effect was seen in the tolvaptan 15 mg group (mean change, −6.38 mmHg compared with −4.16 mmHg in subjects receiving placebo).
- Mean values in $AUC_{0\text{-}8h}$ for change from baseline in PCWP were similar; the largest treatment effect was seen in subjects receiving 15 mg tolvaptan (mean change of −21.41 mmHg compared with −8.36 mmHg in subjects receiving placebo).
- For all tolvaptan treatment groups, a decrease in PCWP was seen as early as 2 hours after dosing, with the largest decrease observed in subjects receiving 15 mg tolvaptan. However, only subjects receiving tolvaptan continued to have decreases in PCWP

through the 8-hour time point. Over the 8-hour period, the largest mean change was −3.76 mmHg at 7 hours in subjects receiving tolvaptan 15 mg.

- At approximately 2 hours postdose, significant differences in mean urine volume were seen between tolvaptan subjects (range, 240.6 mL to 283.4 mL) and placebo subjects (87.2 mL). As anticipated, a dose-response effect on urine volume was evident in the tolvaptan group: urine output was lowest in the 15 mg tolvaptan group and highest in the 60 mg tolvaptan group.
- From 3 to 8 hours postdose, right atrial pressure showed mean changes of −3.49 to −4.35 mmHg for subjects in all tolvaptan-treatment groups and pulmonary artery pressure showed peak changes of 3.01 to −5.60 mmHg.
- No differences were seen between the tolvaptan and placebo groups in pulmonary vascular resistance, cardiac index, or systemic vascular resistance.

5.2.2.6 Subjects With Stable Heart Failure (Trial 156-97-252)

- Mean body weight was decreased (−0.35 to −1.02 kg) from Days 1 to 25 following tolvaptan administration for 25 days (30, 45, or 60 mg, QD).
- Following tolvaptan administration of 45-mg doses, edema evaluation scores were reduced marginally (mean decreases of −0.34 to −0.49 from baseline of 2.45 ± 0.88; scale 0 = absent, 3 = marked) compared with placebo.
- Compared with placebo, tolvaptan at 30-, 45-, and 60-mg doses produced significantly greater total sodium excretions and significantly greater urine volume on Day 1 of treatment and significantly reduced urine sodium concentrations (mean decreases of 40.07 to 59.22 mEq/L) and decreased urine osmolality at all time points, ie, up to Day 25 or last visit.
- Compared with placebo, tolvaptan at 30-, 45-, and 60-mg doses produced small, but significant increases (< 4 mEq/L) in serum sodium concentrations and produced numerically greater fluid balance losses.

5.2.2.7 Subjects With Hepatic Edema

- The aquaretic action of tolvaptan produced increases in urine volume and decreases in urine osmolality together with elevation in serum osmolality and serum sodium concentrations in subjects with lower limb edema or ascites secondary to hepatic disease. (Trials 156-03-002, 156-09-004)

5.2.2.8 Subjects With Hyponatremia

- Tolvaptan was more effective than fluid restriction therapy in increasing serum sodium concentration, with mean increases of 5.73 mEq/L versus 1.00 mEq/L for fluid restriction therapy. (Trial 156-97-204)
- In hyponatremic subjects with cirrhosis, tolvaptan at doses of 5, 10, 15, 30, and 60 mg resulted in higher mean increases in plasma sodium concentrations compared to

placebo. Doses of 30 and 60 mg were associated with consistently greater body weight loss compared to placebo. Lower doses of 5, 10, and 15 mg did not show consistent body weight losses. (Trial 156-96-203)

- In Trial 156-02-235, for the primary efficacy endpoints of average daily AUC of change from baseline in serum sodium concentration up to Day 4 and up to Day 30, the tolvaptan group showed a statistically significant increase up to Day 4 of 3.41 mEq/L over that for placebo, and up to Day 30 of 4.57 mEq/L over that for placebo. In Trial 156-03-238, the tolvaptan group showed an increase up to Day 4 of 4.04 mEq/L over that for placebo, and to Day 30 of 4.54 mEq/L over that for placebo.
- Increases in serum sodium were seen regardless of hyponatremia severity (< 130 mEq/L [severe] or ≥ 130 to < 135 mEq/L [mild]) or when analyzed by other subgroups (eg, by etiology [SIAD/other, cirrhosis, CHF], gender, or volume status [euvolemic, hypervolemic]). (Trials 156-02-235 and 156-03-238)
- 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. (Trials 156-02-235 and 156-03-238)

5.2.2.9 Subjects With ADPKD and Well-preserved Renal Function

- Following single oral doses of 15 to 120 mg, subjects with ADPKD respond similarly to healthy subjects. The decreases in urine osmolality and fluid balance and the increases in 24-hour urine volume and duration that urine osmolality remains < 300 mOsm/kg are comparable. (Trial 156-04-248 compared to Trials 156-95-302, 156-98-210, 156-03-234)
- For single oral doses, the increase in 24-hour urine volume is well correlated with the decrease in urine osmolality. (Trial 156-04-248)
- Following multiple oral doses (30 to 60 mg/day) for 5 days, 24-hour urine volume is approximately 1200 mL less than on Day 1 and the increase in 24-hour volume does not appear correlated with the decrease in urine osmolality. (Trial 156-04-249)
- When the 24-hour urine volume is less than 5000 mL, 24-hour urine volume appears to be negatively correlated with urine osmolality. For urine volumes greater than 5000 mL, urine osmolality appears to reach a plateau and does not show further decreases. (Trial 156-04-249)
- In Japanese subjects with ADPKD, 24-hour urine volume following multiple oral dosing (30 mg/day) was also approximately 1300 mL less than on Day 1. (Trial 156-04-001)
- Dosing 15/15 mg is more effective than 30 mg QD in increasing urine volume and reducing urine osmolality in all subjects studied. (Trials 156-04-001, 156-04-249)

5.2.2.10 Renal Function Testing and Total Kidney Volume Assessment Following Short-term Administration in Subjects With ADPKD

See Section 5.3.6.1.4 and Section 5.3.6.1.5 for summaries of pharmacodynamic endpoints and TKV in renal function testing in ADPKD subjects with varying degrees of renal function.

5.2.3 Pharmacokinetics and Pharmacodynamics

5.2.3.1 Healthy Subjects

- Tolvaptan concentrations of around 100 ng/mL are sufficient to produce a maximal increase in urine excretion rate. Following a single 30-mg dose, a maximal urine excretion rate was sustained for 8 hours. Higher doses (60 to 480 mg) increase the duration of time that the maximal urine output is sustained. Urine volume for 0 to 72 hours postdose was highly correlated with AUC_{∞} and tolvaptan dose. (Trials 156-96-205, 156-98-210, 156-01-229, 156-05-254)
- Tolvaptan concentrations below 20 ng/mL produce no measurable increase in urine excretion rate. (Trials 156-03-239, 156-05-254)
- No apparent relationship was observed between the pharmacokinetic parameter $AUC_{0\text{-}24h}$ and changes from baseline in body weight, urine sodium excretion, and urine osmolality over the same 24-hour interval. (Trial 156-97-251)
- In 8 subjects with ADPKD given ascending single oral doses of tolvaptan from 15 to 120 mg, $AUC_{0\text{-}24h}$ of tolvaptan was moderately correlated to 24-hour urine volume or change from baseline in 24-hour urine volume. (Trial 156-04-248)
- For 37 subjects with ADPKD given multiple oral doses of tolvaptan (30 to 60 mg/day), no correlation between tolvaptan $AUC_{0\text{-}24h}$ and 24-hour urine volume was observed. (Trial 156-04-249)
- No concentration dependence was seen for any ECG parameter following administration of tolvaptan (30-mg or 300-mg doses for 5 days) to healthy subjects. A plot of change from baseline in QTcI (time-matched) versus moxifloxacin concentration had a positive slope significantly different than zero. (Trial 156-03-245)
- There was no correlation between tolvaptan C_{max} or AUC_t and changes in any pharmacodynamic parameter following a single 60-mg dose given to subjects with varying degrees of renal function. (Trial 156-09-282)
- Following 45-, 60- or 90 mg doses to ADPKD subjects at steady state, no differences in renal function test (glomerular filtration rate [GFR], RPF, and filtration fraction) results were observed as tolvaptan concentrations were greater than concentrations needed to produce a maximal increase in urine output. (Trial 156-06-260 and 156-09-284)

5.2.4 Oral Suspension

5.2.4.1 Pharmacokinetics in Healthy Subjects

- When compared to plasma concentrations following a 15-mg spray-dried tablet, a 15-mg dose of the oral suspension shows a more rapid absorption as the median t_{max} is shorter, 1.00 versus 2.00 hours respectively, and the geometric mean ratio (GMR) (90% CI) for C_{max} is 1.614 (1.484 to 1.754). (Trial 156-12-202)
- Overall exposure following a 15-mg oral suspension is unchanged from that following a 15-mg spray-dried tablet as GMRs for AUC_t and AUC_∞ are 0.928 and 0.928, respectively. (Trial 156-12-202)

5.2.4.2 Pharmacodynamics in Healthy Subjects

- When compared to a 15-mg spray-dried tablet, the PD profiles of urine excretion rate, cumulative urine volume, free water clearance, urine osmolality, and serum sodium were not different for a 15-mg syrup suspension. (Trial 156-12-202)

5.2.5 Modified-release (MR) Formulation

5.2.5.1 Pharmacokinetics in Healthy Subjects

- A US FDA high-fat meal has no clinically significant effects on tolvaptan plasma concentrations. (Trial 156-07-262)
- A Japanese standard meal increases C_{max} 1.6-fold, but has little effect on AUC. (Trial 156-10-006)
- Median t_{max} ranges from 3 to 6 hours postdose. (Trials 156-07-262, 156-07-263, 156-08-269, and 156-10-006)
- C_{max} following 60 mg MR are equal to that following 45 mg of the spray-dried tablet formulation. (Trial 156-07-262)
- In a US trial, the AUC_∞ of 60 mg MR was 1.2-fold higher when compared to a split dose of 45 mg at 8 AM and 15 mg at 4 PM of the spray-dried tablet. (Trial 156-07-262)
- In a Japan trial, the C_{max} and AUC of 60 mg MR were slightly lower than those of a split dose of 45/15 mg of the spray-dried tablet. The t_{max}, $t_{1/2,z}$, and plasma concentration at 24 hours values for the MR capsule were all higher than those of the spray-dried tablet. (Trial 156-10-006)
- Mean accumulation ratios following multiple dosing ranged from 1.0 to 1.5. (Trials 156-07-263, 156-08-269, and 156-10-006)
- Following a single dose, 3 × 20 mg capsules were bioequivalent to a 1 × 60 mg capsule with respect to AUC_t (GMR of 1.04) but not to C_{max} (GMR of 0.88). (Trial 156-08-269)

5.2.5.2 Pharmacodynamics in Healthy Subjects

- When compared to a single dose, 24-hour urine volume following multiple dosing was only about 10% lower, compared to the 20% to 25% decrease seen for the spray-dried tablet. (Trial 156-08-269)
- At 12 hours postdose and onward, urine osmolality following administration of 60 mg MR was comparable to that following administration of the split dose of 45/15 mg of the spray-dried tablet. (Trial 156-10-006)

5.2.5.3 Pharmacokinetics and Pharmacodynamics in ADPKD Subjects with Well-preserved Renal Function (Trial 156-09-285)

- Following multiple dosing of 20, 60, or 120 mg QD, AUC_{τ} values increased dose proportionately, C_{max} increased less than dose proportionately with values at 120 mg only about 4.8-fold higher when compared to the 20-mg dose, and minimum plasma (or serum) concentration increased greater than dose proportionately with values at 120 mg about 10-fold higher when compared to the 20-mg dose.
- Median t_{max} was about 6 hours following multiple dosing of 20, 60, or 120 mg QD.
- Following MR 20 mg and MR 60 mg, tolvaptan concentrations were similar to those previously observed for healthy subjects (Trial 156-08-269).
- Average 24-hour urine volumes following 20, 60, and 120 mg QD dosing were 4751, 5989, and 7366 mL, respectively; corresponding changes from baseline were 1111, 2396, and 3722 mL.
- Mean responses in urine osmolality and urine volume and median scores on the ADPKD Nocturia Quality of Life, ADPKD Urinary Urgency and ADPKD Urinary Frequency Questionnaires appear to correlate with AUC_{τ} values but at the individual level responses are highly variable.
- Individual changes from baseline in urine volume do not correlate with changes from baseline in ADPKD Nocturia Quality of Life, ADPKD Urinary Urgency and ADPKD Urinary Frequency Questionnaire scores.
- Following doses of MR 120 mg and 90/30 mg doses of the spray-dried tablet, changes from baseline in scores for the ADPKD Nocturia Quality of Life, ADPKD Urinary Urgency, and ADPKD Urinary Frequency Questionnaires range from no change to the maximal possible change, indicating that subjects have highly individual responses to the urinary side effects of tolvaptan.

5.2.6 Formulation Trials

- In a dosage strength equivalence trial of spray-dried tablets, 4 × 15 mg tablets, 2 × 30 mg tablets, and 1 × 60 mg tablet were compared and found to be bioequivalent. (Trial 156-01-233)

- In a dosage strength equivalence trial of spray-dried tablets, 3 × 30 mg commercial tablets were compared to 1 × 90 mg proposed commercial tablet and found to be bioequivalent. (Trial 156-11-295)
- Two dosage forms of the spray-dried formulation (ie, capsules and tablets) were compared. The relative bioavailability of the tablet to the capsule formulation ranged from 88% to 90%. (Trial 156-96-301)
- A single dose of jet-milled formulation of tolvaptan was directly compared to a spray-dried formulation of tolvaptan in a trial with 4 healthy male subjects. (Trial 156-95-301)
- Tolvaptan formulated as 50- and 150-mg jet-milled tablets were studied for dose strength equivalence (3 × 50 mg versus 1 × 150 mg) and dose proportionality (150-, 300-, and 450-mg doses) following single doses (Trials 156-05-253 and 156-05-004). A relative bioequivalence trial comparing the 150-mg tablet to the spray-dried tablet in a multiple dose trial was also conducted. (Trial 156-05-252)
- Tolvaptan formulated as 60-mg MR capsules (3 versions) was compared to a 45/15 mg split-dose regimen of spray-dried tablets. The effect of a high-fat meal or Japanese standard meal on 60-mg MR capsules or on three 20-mg capsules was also determined. (Trials 156-07-262 and 156-10-006)
- Dose strength equivalence between the selected 60 mg MR formulation (MR-3) from Trial 156-07-262 and 20 mg MR capsules was determined. (Trial 156-08-269)
- Relative bioavailability and food effect of tolvaptan formulated as 20-mg slow disintegration tablets (SDT, 3 versions) was determined. The pharmacokinetics and pharmacodynamics following multiple doses of 20-mg SDT-3 were determined. (Trial 156-08-270)
- Relative bioavailability of tolvaptan formulated as a 1 mg/mL oral suspension was determined by comparing to a 15-mg spray-dried tablet. (Trial 156-12-202) The oral suspension will be studied in pediatric clinical trials; see Section 5.2.4 for a pharmacokinetic/pharmacodynamic summary.
- Relative bioavailability of tolvaptan formulated as 15 mg of a 1% (w/w) powder was compared to a 15-mg tablet in healthy adult Japanese males, and was found to be bioequivalent. (Trial 156-14-004)

5.3 Efficacy

5.3.1 Hyponatremia

Thirteen trials involving either exclusive evaluation of subjects with hyponatremia (10 trials - all subjects in each trial have hyponatremia: 156-96-201, 156-96-203, 156-97-204, 156-02-235, 156-03-238, 156-04-246, 156-07-802-01, 156-08-275, 156-KOB-1101i, and the long-term extension trial 156-03-244), or substantial subpopulations of subjects with hyponatremia (from 3 CHF/cardiac edema trials - not all subjects in these trials had hyponatremia: 156-97-252, 156-98-213, and 156-03-236)

were conducted. Three trials in the pediatric population for hyponatremia are planned, but currently no data are available.

Briefly, tolvaptan has consistently shown a beneficial effect in hyponatremic subjects, regardless of etiology, by improving serum sodium concentrations, in many cases to normalization. In subjects with volume overload and hyponatremia and receiving optimal standard heart failure therapy, the effect of tolvaptan on serum sodium is combined with a reduction in fluid overload, as shown by greater decreases in body weight as compared with placebo. Additionally, subjects with liver disease responded to higher doses of tolvaptan with reductions in body weight. Tolvaptan was approved for the treatment of hyponatremia in the US (May 2009) and Europe (Aug 2009).

Details from the pivotal trials (Trials 156-02-235 and 156-03-238) that were the basis of the approval for hyponatremia in the US can be found in the US package insert (see Table 5.5-1) and are summarized briefly below.

Results from a total of 424 subjects with euvolemic or hypervolemic hyponatremia (serum sodium < 135 mEq/L) resulting from a variety of underlying causes (eg, heart failure, liver cirrhosis, SIADH, and others) who were treated for 30 days with tolvaptan (titrated dose) or placebo demonstrated that:

- Compared to placebo, tolvaptan caused a statistically greater increase in serum sodium ($p < 0.0001$) based on average daily AUC for change in serum sodium from baseline to Day 4 and from baseline to Day 30 (primary endpoint).
- For subjects with serum sodium concentrations of < 130 mEq/L or < 125 mEq/L, the effects at Day 4 and Day 30 remained significant. This effect was also seen across all disease etiology subsets (eg, CHF, cirrhosis, and SIADH/other).
- In subjects with hyponatremia (defined as < 135 mEq/L), serum sodium concentration increased to a significantly greater degree in tolvaptan-treated subjects compared to placebo-treated subjects as early as 8 hours after the first dose, and the change was maintained for 30 days.
- The percentage of subjects requiring fluid restriction (defined as ≤ 1 liter/day at any time during the treatment period) was also significantly less ($p < 0.0017$) in the tolvaptan-treated group (30/215, 14%) as compared with the placebo-treated group (51/206, 25%).
- Within 7 days of tolvaptan discontinuation, serum sodium concentrations in tolvaptan-treated patients declined to levels similar to those of placebo-treated patients.

In the open-label follow-on trial (156-03-244), 111 subjects, 94 of them hyponatremic (serum sodium < 135 mEq/L) and previously on tolvaptan or placebo therapy, were given tolvaptan 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 tolvaptan, and were sustained for at least a year.

Trial 156-08-275 was designed to compare tolvaptan (15, 30, 60 mg QD) to placebo plus fluid restriction on length of hospital stay and symptoms in subjects hospitalized with dilutional hyponatremia. In this phase 3b, randomized, single-blind, parallel group trial, 66 subjects received tolvaptan and 55 subjects received placebo. No significant difference was observed in the time to discharge ($p = 0.9495$) or change from baseline in Clinical Global Impression-Severity score ($p = 0.1460$) between the tolvaptan and placebo treatment groups. Based on the futility analysis of the primary endpoint, the trial was terminated early.

Trial 156-KOB-1101i, a phase 4 randomized, single-blind, placebo-controlled trial was conducted in Korea to assess the effects of tolvaptan on control of hyponatremia and extracellular fluid in cirrhotic patients with ascites. A total of 41 subjects (21 subjects in the tolvaptan group and 20 subjects in the placebo group) received their randomized treatment except for one subject who was randomized to tolvaptan, but received placebo. This trial was terminated early because the decision was made to exclude liver cirrhosis patients from local labeling due to safety concerns in this population; thus, the statistical tests were not performed as planned. Analysis of the Full Analysis Set showed that the changes in serum sodium from baseline to Day 14 were 2.9 (± 4.8) mEq/L and 1.7 (± 4.8) mEq/L for the tolvaptan and placebo groups, respectively.

5.3.2 Heart Failure

5.3.2.1 Cardiac Edema

Five trials were conducted in Japan for the indication of cardiac edema in subjects with extracellular volume expansion secondary to CHF (Trials 156-03-001, 156-06-002, 156-06-004, 156-06-006, and 156-10-005). Additionally, one phase 3 trial was conducted in China (156-12-809-01), and one phase 3 trial was conducted in Taiwan (156-TWA-1101i) for the indication of cardiac edema. Three previously conducted US trials (Trials 156-97-251, 156-97-252, and 156-00-222) from the heart failure program (described below) are also relevant to the cardiac edema program.

Briefly, in subjects with cardiac edema that had not resolved with furosemide treatment, tolvaptan (15, 30, and 45 mg) significantly reduced body weight and dose-dependently increased urine volume. Congestive symptoms such as lower limb edema and jugular

venous distension also improved with tolvaptan compared with placebo. Tolvaptan was approved in Japan (Oct 2010) for the adjunct treatment of volume overload in heart failure.

5.3.2.1.1 Trial 156-97-251: Sequential-cohort, Ascending-dose, Efficacy, Safety, and Pharmacokinetics of Tolvaptan in Subjects With Congestive Heart Failure With Extracellular Volume (US)

A total of 55 subjects with CHF and extracellular volume were treated with 10, 15, 30, 60, 90, or 120 mg tolvaptan or placebo for up to 13 days.

Body Weight: Tolvaptan showed a tendency to be efficacious in this subject population as demonstrated by mean decreases from baseline in body weight in tolvaptan treatment groups at doses of 15 to 120 mg (−0.1 to −2.9 kg) and in the placebo group (−0.2 to −1.9 kg) during the treatment period.

Urine Osmolality: Mean decreases in 24-hour urine sodium concentration and urine osmolality were observed in all tolvaptan treatment groups and in the placebo group. The mean decreases of urine osmolality and 24-hour sodium excretion for the tolvaptan treatment groups were −50.5 to −333.7 mOsm/kg and −22.7 to −128.9 mEq/L, respectively; these decreases were greater than that of the placebo group (mean decreases of −23.5 to −97.9 mOsm/kg and −0.1 to −35.0 mEq/L, respectively).

Urine Output: Mean increases in 24-hour urine volume were found in all treatment groups. The increases of urine volume were greater for the tolvaptan treatment groups (mean increases of 521.8 to 3750 mL) than for the placebo group (mean increases of 13.7 to 177.9 mL).

5.3.2.1.2 Trial 156-97-252: Dose-defining, Efficacy and Safety Trial of Tolvaptan in Subjects With Extracellular Volume Expansion Secondary to Congestive Heart Failure (US)

This trial included 254 subjects with stable chronic heart failure and signs of mild/moderate volume overload. Subjects were on stable furosemide therapy, which was maintained throughout the duration of the trial, and randomized to tolvaptan 30, 45, or 60 mg, or placebo QD for 25 days.

Body Weight: Mean decreases from baseline in body weight were observed on Day 1 of tolvaptan treatment at all doses and were maintained throughout the trial. These changes (mean decreases of 0.35 to 1.02 kg) were statistically significantly different from that of placebo treatment (mean increases from baseline of 0.32 to 0.59 kg).

Urine Output: In tolvaptan subjects, an apparent dose-related mean increase in urine production (3908.8 to 4596.97 mL) was observed. These mean urine volumes were significantly greater than those for the placebo-treated subjects (2328.03 mL) ($p < 0.05$).

The urine output results were supported by findings of secondary efficacy variables, ie, edema size measurements, urine osmolality, and urine sodium excretion.

5.3.2.1.3 Trial 156-00-222: Effects of Tolvaptan When Compared to Furosemide and the Combination of Tolvaptan and Furosemide in Subjects With Congestive Heart Failure (US)

After a 2-day diuretic washout period, 83 patients with stable CHF and signs of mild/moderate volume overload were randomized to tolvaptan 30 mg, placebo, furosemide 80 mg, or the combination of tolvaptan 30 mg and furosemide 80 mg QD for 7 days.

Body Weight: The results showed that tolvaptan, at a dose of 30 mg, significantly ($p < 0.05$) reduced body weight (mean changes from baseline of −0.41 kg to −1.38 kg) compared with placebo (mean changes from baseline of −0.31 kg to 1.21 kg) at all time points.

Urine Output: There was a statistically significant ($p < 0.001$) mean increase in urine volume in the tolvaptan group compared with the placebo and furosemide groups at all visits. The increase in urine volume with the combination of tolvaptan plus furosemide was also statistically significant when compared to furosemide alone ($p < 0.001$) at all visits.

Urine Sodium Excretion: Tolvaptan alone did not have an effect on urinary sodium excretion when compared with placebo; however, tolvaptan plus furosemide reduced the urinary sodium excretion when compared with furosemide alone.

5.3.2.1.4 Trial 156-03-001: A Dose-ranging Trial of Tolvaptan in Treatment of Cardiac Edema Secondary to Congestive Heart Failure (Japan)

A total of 122 subjects with extracellular volume expansion secondary to CHF whose condition had not been resolved by the use of furosemide (at 40 mg/day or more) received 7-day repeated oral administration of tolvaptan at 15, 30, and 45 mg or placebo.

Body Weight: For body weight, mean reductions were observed from the day after first administration in all tolvaptan groups. Decreases in body weight following 7-day repeated administration of tolvaptan 15, 30, and 45 mg were significantly greater than those seen in the placebo group; the degree of change was similar across all tolvaptan doses, however.

Urine Volume: The 24-hour cumulative urine volume on Day 1 was 1806 mL in the placebo group, 2749 mL in the tolvaptan 15 mg group, 3355 mL in the tolvaptan 30 mg group, and 3749 mL in the tolvaptan 45 mg group. Urine volume increased dose-dependently after the first day of administration.

Congestive Symptoms: The number of subjects in the tolvaptan groups with improvement over baseline of congestive symptoms, such as lower limb edema and pulmonary congestion, was larger than in the placebo group.

5.3.2.1.5 Trial 156-06-002: Double-blind, Placebo-controlled Trial of Tolvaptan in the Treatment of Cardiac-induced Edema (Congestive Heart Failure) (Japan)

A total of 110 subjects with CHF and extracellular volume expansion despite having used conventional diuretic therapy received 7-day repeated oral administration of tolvaptan 15 mg or placebo.

Body Weight: Change in body weight (mean ± standard deviation [SD]) from baseline at the time of final trial drug administration was −1.54 ± 1.61 kg in the tolvaptan 15 mg group and −0.45 ± 0.93 kg in the placebo group. Body weight in the tolvaptan 15 mg group decreased significantly in comparison with the placebo group ($p < 0.0001$ by t-test), and the difference in the mean change between the tolvaptan 15 mg group and the placebo group was −1.09 kg (95% CI: −1.58 to −0.60 kg). These results confirmed the superiority of tolvaptan 15 mg to placebo for the treatment of cardiac edema. Body weight in the tolvaptan 15 mg group decreased from Day 1 of administration, and the decrease was observed throughout the treatment period. The amount of decrease in body weight in the tolvaptan 15 mg group gradually became smaller upon completion of drug administration.

Congestive Symptoms: Congestive symptoms accompanying extracellular volume expansion (jugular venous distension and lower limb edema) improved in the tolvaptan 15 mg group. Excluding subjects who had no jugular venous distension from baseline until the time of final trial drug administration, the change in jugular venous distention from baseline was −2.03 ± 2.81 cm in the tolvaptan 15 mg group and −0.51 ± 1.18 cm in the placebo group ($p = 0.0317$ by t-test), and the difference between the two groups was −1.52 cm (95% CI: −2.91 to −0.14 cm).

Excluding subjects who had no lower limb edema from baseline until the time of final trial drug administration, the improvement rate for lower limb edema was 63.9% (23/36) in the tolvaptan 15 mg group and 42.1% (16/38) in the placebo group. The improvement rate in the tolvaptan 15 mg group tended to be higher than that in the placebo group ($p = 0.0681$ by Fisher's exact test).

Urine Volume / Fluid Balance: Urine volume and fluid intake increased from Day 1 to Day 7 in the tolvaptan 15 mg group; however, the increase in urine volume was larger than the increase in fluid intake, and the difference between fluid intake and urine volume showed a large negative value compared with the placebo group.

5.3.2.1.6 Trial 156-06-004: A Clinical Pharmacological Trial of Tolvaptan in the Treatment of Cardiac Edema (Congestive Heart Failure) (Japan)

A total of 20 subjects with CHF associated with extracellular volume expansion despite the use of conventional diuretics were randomized to receive 7-day repeated oral administration of tolvaptan at 7.5 or 15 mg/day (10 subjects each group).

Body Weight: Change in body weight at the time of final trial drug administration (using last observation carried forward) was −1.68 ± 1.83 kg in the 7.5 mg group and −2.14 ± 1.45 kg in the 15 mg group, and the decrease was greater in the 15 mg group than in the 7.5 mg group throughout the treatment period. Change in body weight on Day 1 was −0.57 ± 0.58 kg in the 7.5 mg group and −1.13 ± 0.66 kg in the 15 mg group, with the 15 mg group showing a marked decrease from the start of administration.

Urine Volume / Fluid Balance: Urine volume was increased at 0 to 4 hours postdose in both the tolvaptan 7.5 and 15 mg groups and was highest at 4 to 8 hours postdose. Although the increase in urine volume was seen only until 4 to 8 hours postdose in the 7.5 mg group, in the 15 mg group the increase in urine volume continued to be seen until 8 to 12 hours postdose, indicating that the aquaretic action of tolvaptan was sustained for a longer time by administration at 15 mg. No increase in urine volume was observed at 12 to 24 hours postdose in either group. The largest increase in urine volume was seen on Day 1, with a smaller increase on Day 7. On Day 7, although the 15 mg group showed a greater aquaretic effect at 4 to 8 hours postdose, no notable differences between the 2 groups were observed for any other period.

Change from the baseline in the difference between fluid intake and urine volume showed negative values from 0 to 4 hours postdose on Day 1 in both the 7.5 and 15 mg groups, and the largest negative values were seen at 4 to 8 hours postdose. The 15 mg group showed larger negative values than the 7.5 mg group until 12 hours postdose on Day 1, but almost no difference between the 2 groups was seen at 12 to 24 hours postdose. On Day 7 the negative values were smaller than those on Day 1 in both groups.

Urine Electrolytes: Tolvaptan did not affect the excretion of urine electrolytes (sodium, potassium, calcium, and magnesium), urine uric acid, or urine creatinine.

5.3.2.1.7 Trial 156-06-006: A Phase 3 Open-label Trial of Tolvaptan in Cardiac Edema Subjects (Japan)

A total of 51 subjects were enrolled and treated in two 7-day periods with 15 mg tolvaptan (Period 1) and 15 or 30 mg tolvaptan (Period 2).

Body Weight: Change in body weight (mean ± SD) at Baseline 1 (prior to tolvaptan administration) for the tolvaptan group was −1.95 ± 1.98 kg at Day 7 and −1.90 ± 2.19 at the end of treatment, and decrease in body weight was observed from Day 1 of tolvaptan administration.

The improvement rate of lower limb edema in the overall tolvaptan group, excluding subjects in whom lower limb edema was not observed from Baseline 1 to the end of treatment, was 80.6% (25/31 subjects) at Day 7 and 80.6% (29/36) at the end of the trial, and the resolution rates at these times were 61.3% (19/31) and 58.3% (21/36), respectively.

The changes in body weight from Baseline 1 in subjects in the 15 mg/day continued administration group, who showed symptoms of either lower limb edema, jugular venous distention, or pulmonary congestion at the end of treatment Period 1 and thus continued to receive administration of tolvaptan at 15 mg/day for 7 more days, were −1.55 ± 2.13 kg at Day 7 and −1.31 ± 2.95 kg at the end of the trial. The improvement rate for the 15 mg/day continued administration group, excluding subjects in whom lower limb edema was not observed from Baseline 1 to the end of treatment, was 44.4% (4/9) at Day 7 and 66.7% (6/9) at the end of trial, and the resolution rates (resolution rate 2) at these times were 11.1% (1/9) and 22.2% (2/9), respectively.

The changes in body weight for 2 subjects in the 30 mg/day dose escalation group were −1.00 kg and −2.00 kg at Day 7, respectively, and −1.00 kg and −4.80 kg at Day 14, respectively. For lower limb edema, pulmonary congestion, jugular venous distention, and hepatomegaly, continued administration of tolvaptan at the increased dose after Day 7 was also clinically effective.

Serum Sodium: Serum sodium concentration for the entire tolvaptan population increased from Day 1, but by Day 7 it had returned to almost the same value as that at Baseline 1. Similar results were seen in subjects with baseline serum sodium concentrations < 135 mEq/L.

In subjects of the 15 mg/day continued administration group, who showed symptoms of either lower limb edema, jugular venous distention, or pulmonary congestion at the end of treatment Period 1 and thus continued to receive administration of tolvaptan at 15 mg/day for 7 more days, serum sodium concentration increased slightly from Day 1,

but returned to the Baseline 1 value by Day 7, and no clear change was observed from Day 8 onward.

5.3.2.1.8 Trial 156-12-809-01: A Randomized, Double-blind, Placebo-controlled Trial Evaluating Tolvaptan in the Treatment of Cardiac Edema Despite Use of Conventional Therapy (China)

A total of 244 subjects with cardiac edema despite having received current diuretic treatment received a 7-day repeated oral administration of tolvaptan 15 mg or placebo. A total of 124 subjects received Investigational Medicinal Product (IMP) in the tolvaptan group and 120 received IMP in the placebo group; 123 subjects in the tolvaptan group were analyzed for efficacy and 120 subjects in the placebo group were analyzed for efficacy.

Body Weight: The change from baseline in body weight was −1.482 ± 1.947 kg in the tolvaptan 15 mg group and 0.540 ± 1.506 kg in the placebo group (95% CI −0.942; $p < 0.0001$. After the final dosing, the average value of body weight loss in the tolvaptan 15 mg group was statistically significantly greater than that in the placebo group.

5.3.2.1.9 Trial 156-TWA-1101i: A Multicenter, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of Tolvaptan in the Treatment of Cardiac-induced Edema in Patients With Heart Failure (Taiwan)

A total of 91 subjects with stabilized heart failure and cardiac-induced edema were enrolled in the trial and received a 4-day repeated oral administration of tolvaptan 15 mg or placebo. A total of 46 subjects received IMP in the tolvaptan group, and 45 subjects received IMP in the placebo group; all 91 subjects were in the intent-to-treat (ITT) population, 81 subjects were in the per-protocol population, and 91 subjects were in the safety population.

Body Weight: The mean change from baseline in body weight was −1.36 ± 2.13 kg in the tolvaptan 15 mg group, and −0.59 ± 1.27 kg in the placebo group ($p < 0.0001$ by paired t-test). Furthermore, the significant difference in the mean change between the two groups was −0.78 kg ($p = 0.0394$; 95% CI: −1.52 to −0.04 kg). Tolvaptan significantly decreased body weight in subjects, and demonstrated a greater improvement over placebo in the resolution of congestion signs and symptoms accompanying volume overload.

5.3.2.2 Heart Failure and Extracellular Volume Expansion

Nine phase 2 trials in the US and Argentina and one multinational phase 3 trial (with embedded 3-in-1 trials) have been completed to evaluate the effectiveness of tolvaptan

for the treatment of volume overload in subjects with CHF. Two early phase 2 trials (Trials 156-97-251 and 156-97-252) were multicenter, randomized, double-blind, placebo-controlled, dose-ranging trials. Brief results of these two trials are presented in Section 5.3.2.1.1 and Section 5.3.2.1.2, respectively. Four subsequent phase 2 efficacy trials (Trials 156-98-213, 156-00-220, 156-00-222 and 156-01-232) were conducted in the US, the first to evaluate the effects of tolvaptan on the acute and chronic outcomes of subjects with worsening CHF, the second to assess the effects of tolvaptan on the chronic outcomes of subjects with CHF, the third comparing the effects of tolvaptan, placebo, furosemide and the combination of tolvaptan plus furosemide in subjects with CHF (results for Trial 156-00-222 are presented in Section 5.3.2.1.3), and the fourth to evaluate the effects of tolvaptan on left ventricular end-diastolic volume. Additionally, one phase 2 trial (Trial 156-00-221) was conducted to determine the renal mechanism of action of tolvaptan in subjects with stable heart failure, and one phase 2 trial (Trial 156-01-231) was conducted to assess the effects of dose regimen on tolvaptan pharmacokinetics/pharmacodynamics; brief results of these trials are presented in Section 5.2.2.4 and Section 5.2.1.9, respectively. One phase 2 multinational double-blind placebo-controlled trial (Trial 156-04-247) evaluated the effects of tolvaptan on hemodynamic parameters; results of this trial are presented with pharmacodynamic results in Section 5.2.2.5. The phase 3 trial (with two embedded short-term efficacy trials) (Trial 156-03-236) evaluated the short- and long-term efficacy and safety of tolvaptan in subjects hospitalized with worsening CHF. Combined, these 10 trials have included a total of 3144 subjects exposed to tolvaptan in doses ranging from 10 to 120 mg.

Briefly, tolvaptan has consistently shown a beneficial effect in subjects with heart failure and extracellular volume expansion by improving fluid balance through the induction of increased urine volume. These trials are individually described in the following sections.

5.3.2.2.1 Trial 156-98-213: Effects of Tolvaptan on Acute and Chronic Outcomes of Subjects With Worsening Congestive Heart Failure (US and Argentina)

The population evaluated in this trial was composed of 319 subjects hospitalized with acute exacerbation of chronic heart failure (New York Heart Association [NYHA] Class III to IV with an ejection fraction < 40% and presence of fluid overload) at the time of randomization. Subjects received optimal standard therapy and either placebo or one of 3 doses of tolvaptan (30, 60, or 90 mg QD) as inpatients for up to 10 days, followed by a 7-week outpatient period.

Body Weight: A significant mean decrease in body weight (the primary endpoint) was observed in the tolvaptan groups versus placebo. These mean changes were not dose dependent and ranged between –1.99 and -2.24 kg in the tolvaptan subjects versus -0.88 kg in the placebo group. The differences observed acutely over placebo were also maintained over time and remained statistically significant ($p < 0.05$) for the 30 mg and 60 mg tolvaptan groups up until the time of hospital discharge. The results demonstrate a clinically relevant and favorable effect of the compound in subjects hospitalized with decompensated heart failure.

Serum Sodium: Tolvaptan at all 3 doses produced significant ($p < 0.05$) increases in serum sodium concentrations compared with placebo. Mean changes in serum sodium ranged between 2.74 and 4.03 mEq/L in the tolvaptan subjects versus −0.14 mEq/L in the placebo-treated group. Changes in serum sodium for nonhyponatremic subjects were transient and returned toward baseline over time.

Mortality: The on-therapy mortality rates were 8.7% (7/80) for the placebo-treated subjects and 5.4% (13/239) for the tolvaptan subjects. Within the tolvaptan groups, the rates were 3.8% (3/78), 9.5% (8/84), and 2.5% (2/77) at 30, 60, and 90 mg, respectively. The mortality benefit was not dose related, but was more evident in high-risk subjects and appeared to be lost upon discontinuation of IMP.

5.3.2.2.2 Trial 156-00-220: Effects of Tolvaptan on the Chronic Outcomes of Subjects With Congestive Heart Failure (US and Argentina)

The efficacy and safety of 6 months of treatment with 3 doses of tolvaptan (15, 30, and 60 mg) or placebo in conjunction with conventional therapy were assessed in 330 subjects with NYHA Class II to IV CHF.

Clinical Status: There were no statistically significant differences between groups for the primary efficacy variable of clinical status (ie, very much worse, much worse, worse, unchanged, improved, much improved, or very much improved) at Month 6. The clinical status of the majority of subjects in any treatment group either improved or remained unchanged at Month 6 (15 mg: 50/82 or 61.0%; 30 mg: 49/80 or 61.3%; 60 mg: 51/80 or 63.8%; placebo: 51/84 or 60.7%). A smaller but clinically significant population of subjects in each treatment group had clinical status that was much worsened at Month 6 (15 mg: 28/82 or 34.1%; 30 mg: 20/80 or 25%; 60 mg: 24/80 or 30.0%; placebo: 21/84 or 25%).

Body Weight: Statistically significant mean reductions in body weight were seen in all tolvaptan treatment groups versus placebo at Week 1 and in the 30 and 60 mg groups

versus placebo at Week 2. There were no statistically significant mean reductions in body weight versus placebo at any other time points in the trial.

5.3.2.2.3 Trial 156-01-232: Effects of Tolvaptan on Left Ventricular Dilatation and Function in Patients With Heart Failure and Left Ventricular Systolic Dysfunction (US)

This trial assessed the effects of oral tolvaptan, in addition to standard therapy, on left ventricular dilatation and function in 240 subjects with heart failure (NYHA Class II or III and ejection fraction of ≤ 30%) and left ventricular systolic dysfunction. Eligible subjects were randomized to receive either placebo or 30 mg of tolvaptan QD for 54 weeks. Radionuclide ventriculograms were performed at Weeks 54 and 55.

For the primary efficacy variable of change from baseline to Week 54 in left ventricular end-diastolic volume index, the difference from placebo showed a trend toward improvement for the 30 mg tolvaptan group; however, the differences were not statistically significant.

For the secondary radionuclide ventriculogram parameters of left ventricular end-systolic volume index, left ventricular ejection fraction, right ventricular end-diastolic volume index, right ventricular end-systolic volume index, and right ventricular ejection fraction, the changes from baseline to Week 54 showed a trend for improvement in all parameters for the tolvaptan 30 mg group; however, no statistically significant differences from placebo were observed.

5.3.2.2.4 Trial 156-03-236: Acute Symptomatic Improvement and Long-term Efficacy and Safety of Oral Tolvaptan Tablets in Subjects Hospitalized With Worsening Congestive Heart Failure (International)

This phase 3 multicenter, randomized, double-blind, placebo-controlled trial 2072 subjects hospitalized with worsening CHF (NYHA Class III or IV with ejection fraction ≤ 40% and signs of extracellular volume expansion were randomized to tolvaptan and 2061 were randomized to placebo. Of these, 2063 subjects were exposed to daily oral doses of tolvaptan 30 mg and 2055 subjects were exposed to placebo. Subjects participated in an in-hospital period of up to 10 days followed by an outpatient period. The minimum duration of exposure was 60 days and the maximum duration for each subject was event driven. Subjects continued to receive their conventional therapy during the trial, which may have included diuretics, digoxin, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB), hydralazine, nitrates, and beta-blockers.

This protocol was a 3-in-1 design, consisting of a Primary Outcome Trial (hereafter referred to as the Long-term Outcome Trial) and 2 distinct embedded trials (hereafter referred to as Short-term Clinical Status Trials A and B). The primary objective of embedded Short-term Clinical Status Trials A and B was to compare the efficacy of tolvaptan or placebo in conjunction with optimal (as determined by the investigator) current therapy on the composite of change from baseline in patient-assessed global clinical status at Inpatient Day 7 or Discharge, if earlier, and change from baseline in body weight at Inpatient Day 7 or Discharge, if earlier. The primary objectives of the Long-term Outcome Trial were to compare the efficacy of tolvaptan or placebo in conjunction with optimal (as determined by the investigator) current therapy on the time to all-cause mortality in subjects hospitalized with worsening CHF and to compare the efficacy of tolvaptan or placebo in conjunction with optimal (as determined by the investigator) current therapy on the time to first occurrence of cardiovascular mortality or hospitalization for heart failure.

Efficacy Results for the Short-term Clinical Status Trial A: The results of the efficacy analyses for Short-term Clinical Status Trial A are summarized in Table 5.3.2.2.4-1. For Trial A, the mean composite for the tolvaptan 30 mg group was greater than the mean composite for the placebo group ($p = 0.0005$, 95% CI = 0.03 to 0.11). Mean (SD) body weight reduction was greater with tolvaptan 30 mg compared with placebo on Inpatient Day 7 or Discharge (if earlier) (−3.35 kg [3.27] versus −2.73 kg [3.34]; $p < 0.0001$, 95% CI = −0.89 to −0.36), whereas improvements in patient-assessed global clinical status were not different between the groups.

Additional secondary efficacy endpoints for Trial A demonstrated significant improvements in the tolvaptan 30 mg group over placebo. Mean (SD) body weight reduction was greater with tolvaptan 30 mg on Inpatient Day 1 (−1.71 kg [1.80] versus −0.99 kg [1.83]; $p < 0.0001$, 95% CI = −0.87 to −0.56), consistent with the Inpatient Day 7/Discharge findings. Pedal edema (for subjects with pedal edema at baseline) at Inpatient Day 7 or Discharge (if earlier) improved by at least 2 points for more subjects receiving tolvaptan 30 mg compared with placebo, although the difference did not reach statistical significance (570 [73.8%] versus 555 [70.2%]; $p = 0.0653$, 95% CI = 0.496 to 0.547 for distribution of scores across 7 categories of improvement, worsening, or no change). More subjects receiving tolvaptan 30 mg (686 [76.7%]) versus subjects receiving placebo (646 [70.6%]) reported improvement in patient-assessed dyspnea at Inpatient Day 1 ($p = 0.0004$, 95% CI = 0.517 to 0.565 for distribution of scores across 7 categories of improvement, worsening, or no change) among those with dyspnea at baseline.

Table 5.3.2.2.4-1 Summary of Efficacy Results for Short-term Clinical Status Trial A in Trial 156-03-236

Endpoint	Tolvaptan 30 mg (N = 1018)	Placebo (N = 1030)	P-value (95% CI)
Primary			
Composite primary endpoint at Inpatient Day 7[a], mean (SD) [No.]	1.06 (0.43) [893]	0.99 (0.44) [901]	0.0005[b] (0.03, 0.11)
Secondary			
Patient-assessed global clinical status at Inpatient Day 7[a], mean (SD) [No.]	18.25 (22.26) [903]	17.73 (22.47) [910]	0.5131[c] (−1.09, 2.18)
Change in body weight (kg) at Inpatient Day 7[a], mean (SD) [No.]	−3.35 (3.27) [997]	−2.73 (3.34) [1007]	< 0.0001[c] (−0.89, −0.36)
Change in body weight (kg) at Inpatient Day 1, mean (SD) [No.]	−1.71 (1.80) [978]	−0.99 (1.83) [997]	< 0.0001[c] (−0.87, −0.56)
Change in pedal edema at Inpatient Day 7[a], n (%) showing improvement ≥ 2 points [No.][d]	570 (73.8) [772]	555 (70.2) [790]	0.0653[e] (0.496, 0.547)
Patient-assessed dyspnea status at Inpatient Day 1, n (%) showing improvement [No.][d]	686 (76.7) [894]	646 (70.6) [915]	0.0004[e] (0.517, 0.565)

ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; No. = number of subjects; SD = standard deviation.

[a] Assessed at Discharge if before Inpatient Day 7.

[b] P-value was derived from an ANOVA model with treatment as a factor.

[c] P-value was derived from an ANCOVA model with treatment and (pooled) clinical center as factors and baseline value as covariate.

[d] Subjects with symptoms (as assessed by the physician) at baseline.

[e] P-value was derived from van Elteren test, for distribution across 7 categories of improvement, worsening, and no change.

Efficacy Results for the Short-term Clinical Status Trial B: The results of the efficacy analyses for Short-term Clinical Status Trial B are summarized in Table 5.3.2.2.4-2. The primary efficacy endpoint was the composite, at Inpatient Day 7 or Discharge (if earlier), of change from baseline in patient-assessed global clinical status and change from baseline in body weight. For Trial B, the mean composite for the tolvaptan 30 mg group was greater than the mean composite for the placebo group ($p < 0.0001$, 95% CI = 0.06 to 0.13). Change from baseline in body weight on Inpatient Day 7 or Discharge (if earlier) was a secondary efficacy endpoint. Mean (SD) body weight reduction was greater with tolvaptan 30 mg compared with placebo on Inpatient Day 7 or Discharge (if earlier) (–3.77 kg [3.59] versus −2.79 kg [3.46]; $p < 0.0001$, 95% CI = −1.20 to −0.63), whereas improvements in patient-assessed global clinical status were not different between the groups.

Additional secondary efficacy endpoints for Trial B demonstrated significant improvements in the tolvaptan 30 mg group over placebo. Mean (SD) body weight reduction was greater with tolvaptan 30 mg on Inpatient Day 1 (−1.82 kg [2.01] versus −0.95 kg [1.85]; p < 0.0001, 95% CI = −1.00 to −0.67), consistent with the Inpatient Day 7/Discharge findings. Pedal edema (for subjects with pedal edema at baseline) at Inpatient Day 7 or Discharge (if earlier) improved by at least 2 points for more significantly more subjects receiving tolvaptan 30 mg compared with placebo (610 [73.7%] versus 570 [70.8%]; p = 0.0202, 95% CI = 0.503 to 0.553 for distribution of scores across 7 categories of improvement, worsening, or no change). More subjects receiving tolvaptan 30 mg (678 [72.1%]) versus subjects receiving placebo (597 [65.3%]) reported improvement in patient-assessed dyspnea at Inpatient Day 1 (p = 0.0002, 95% CI = 0.520 to 0.566 for distribution of scores across 7 categories of improvement, worsening, or no change) among those with dyspnea at baseline.

Table 5.3.2.2.4-2 Summary of Efficacy Results for Short-term Clinical Status Trial B in Trial 156-03-236

Endpoint	Tolvaptan 30 mg (N = 1018)	Placebo (N = 1030)	P-value (95% CI)
Primary			
Composite primary endpoint at Inpatient Day 7[a], mean (SD) [No.]	1.07 (0.42) [923]	0.97 (0.43) [892]	< 0.0001[b] (0.06, 0.13)
Secondary			
Patient-assessed global clinical status at Inpatient Day 7[a], mean (SD) [No.]	18.72 (21.71) [931]	18.28 (21.59) [900]	0.5188[c] (−1.05, 2.08)
Change in body weight (kg) at Inpatient Day 7[a], mean (SD) [No.]	−3.77 (3.59) [1031]	−2.79 (3.46) [1008]	< 0.0001[c] (−1.20, −0.63)
Change in body weight (kg) at Inpatient Day 1, mean (SD) [No.]	−1.82 (2.01) [1021]	−0.95 (1.85) [1002]	< 0.0001[c] (−1.00, −0.67)
Change in pedal edema at Inpatient Day 7[a], n (%) showing improvement ≥ 2 points [No.][d]	610 (73.7) [828]	570 (70.8) [805]	0.0202[e] (0.503, 0.553)
Change in patient-assessed dyspnea at Inpatient Day 1, n (%) showing improvement [No.][d]	678 (72.1) [941]	597 (65.3) [914]	0.0002[e] (0.520, 0.566)

ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; No. = number of subjects; SD = standard deviation.

[a] Assessed at Discharge if before Inpatient Day 7.

[b] P-value was derived from an ANOVA model with treatment as a factor.

[c] P-value was derived from an ANCOVA model with treatment and (pooled) clinical center as factors and baseline value as covariate.

[d] Subjects with symptoms (as assessed by the physician) at baseline.

[e] P-value was derived from van Elteren test, for distribution across 7 categories of improvement, worsening, and no change.

Efficacy Results for the Long-term Outcome Trial: Results for the primary and secondary morbidity and mortality efficacy endpoints for the Long-term Outcome Trial are summarized in Table 5.3.2.2.4-3. During a mean follow-up of 0.9 years, 537/2072 subjects (25.9%) in the tolvaptan 30 mg group and 543/2061 (26.4%) in the placebo group died (Hazard Ratio [HR] = 0.981, 95% CI = 0.866 to 1.112, p = 0.6845) (Table 5.3.2.2.4-3). The upper limit of the CI for the mortality difference was within the prespecified noninferiority margin of 1.25. During a mean follow-up of 0.7 years, the composite of first occurrence of cardiovascular mortality or hospitalization for heart failure occurred in 871/2072 (42.0%) tolvaptan 30 mg group subjects and 829/2061 (40.2%) placebo group subjects (HR = 1.040, 95% CI = 0.946 to 1.144, p = 0.5451) (Table 5.3.2.2.4-3).

Secondary endpoints of time to first occurrence of cardiovascular mortality/morbidity, incidence of cardiovascular mortality, and incidence of clinical worsening heart failure were also not different in the 2 treatment groups.

Table 5.3.2.2.4-3 Summary of Primary and Secondary Morbidity and Mortality Efficacy Endpoints for the Long-term Outcome Trial in Trial 156-03-236

Endpoint	Events (%)		Hazard Ratio (CI)	P-value
	Tolvaptan 30 mg (N = 2072)	Placebo (N = 2061)		
Primary				
Time to all-cause mortality	537 (25.92)	543 (26.35)	0.981 (0.866, 1.112)	0.6845[a]
Time to CV mortality or heart failure hospitalization	871 (42.04)	829 (40.22)	1.040 (0.946, 1.144)	0.5451[a]
Secondary				
Time to CV mortality/ morbidity	1006 (48.55)	958 (46.48)	1.041 (0.953, 1.138)	0.5257[a]
Incidence of CV mortality	421 (20.32)	408 (19.80)	--	0.6673[b]
Incidence of clinical worsening of heart failure[c]	757 (36.53)	739 (35.86)	--	0.6194[b]

CI = confidence interval; CV = cardiovascular; IV = intravenous.

[a] Based on Peto-Peto-Wilcoxon test.

[b] Derived by using Cochran-Mantel-Haenszel test, stratified by geographic regions.

[c] Clinical worsening of heart failure was defined as any of the following: hospitalization for heart failure; unscheduled visit for heart failure to an emergency department, outpatient clinic, or observation unit associated with need for IV therapy for heart failure; or death due to heart failure.

Tolvaptan 30 mg significantly improved secondary endpoints of patient-assessed dyspnea at Inpatient Day 1 (for subjects with physician-assessed dyspnea at baseline), body weight at Inpatient Day 1, and pedal edema at Inpatient Day 7 (for subjects with baseline

pedal edema) relative to placebo. In subjects with hyponatremia (baseline serum sodium < 134 mEq/L), serum sodium concentrations significantly increased in the tolvaptan 30 mg group compared with the placebo group. Improvement in the Kansas City Cardiomyopathy Questionnaire Overall Summary Score at Outpatient Week 1 was not different between the 2 treatment groups.

5.3.3 Hepatic Cirrhosis

Seven trials that included evaluation of efficacy of tolvaptan in subjects with hepatic edema have been completed. Efficacy data for three phase 2 trials and four phase 3 trials conducted in either Japan (phase 2: Trials 156-03-002 and 156-06-005; phase 3: Trials 156-08-001, 156-08-002, and 156-09-004) or China (phase 2: Trial 156-08-804-01; phase 3: 156-08-805-01) are described in Section 5.3.3.1 to Section 5.3.3.7. Tolvaptan (7.5 mg tablet) was approved in Japan (Sep 2013) for the adjunct treatment of body fluid retention in hepatic cirrhosis patients when adequate response is not obtained with other diuretics (eg, loop diuretics).

5.3.3.1 Trial 156-03-002: An Open-label Dose-ranging Trial of Tolvaptan in Treatment of Hepatic Edema (Japan)

Tolvaptan was orally administered in a dose-titration manner (15, 30, and 60 mg/day for 3 days each) to 18 subjects with lower-limb edema or ascites secondary to hepatic disease whose condition had not been resolved by the use of furosemide (at 40 mg/day or more).

Improvement Rate of Hepatic Edema: Improvement of hepatic edema (the primary outcome variable) was evaluated based on improvements in lower limb edema and ascites. Out of 17 subjects included in the efficacy analysis population, 4 subjects were judged to be “markedly improved” and 11 subjects were judged to be “improved.”

The mean improvement rate of hepatic edema following administration of individual maximum doses (15, 30, and 60 mg) was 88.2%, and the rates following 3-day repeated administrations of 15 mg (Day 3), 30 mg (Day 6), and 60 mg (Day 9) were 64.7%, 80.0%, and 90.9%, respectively.

Abdominal Circumference: Abdominal circumference (mean ± SD) was reduced after administration of tolvaptan. The changes in abdominal circumference following 3-day repeated administrations of 15 mg (Day 3), 30 mg (Day 6), and 60 mg (Day 9) were −2.78 ± 2.50, -3.79 ± 3.37, and -5.97 ± 4.56 cm, respectively.

Body Weight: For body weight, reductions of 1 kg or more were observed from Day 2 (at 24 hours from the administration on Day 1). The changes in body weight (mean ± SD) following 3-day repeated administrations of 15 mg (at 24 hours from the administration on Day 3), 30 mg (at 24 hours from the administration on Day 6), and 60 mg (at 24 hours from the administration on Day 9) were −1.62 ± 0.93, −2.61 ± 1.17, and −3.41 ± 2.08 kg, respectively.

5.3.3.2 Trial 156-06-005: A Placebo-controlled Trial of Tolvaptan in the Treatment of Hepatic Edema (Japan)

The efficacy, safety, and dose-response relationship were investigated in 104 subjects with cirrhosis and ascites despite conventional diuretics receiving 7-day repeated oral administration of tolvaptan at 7.5, 15, and 30 mg/day or placebo.

Body Weight: Change in body weight from baseline to the end of treatment (mean ± SD) was −0.36 ± 2.06 kg in the placebo group, −2.31 ± 2.35 kg in the 7.5 mg group, −1.88 ± 2.45 kg in the 15 mg group, and −1.67 ± 1.46 kg in the 30 mg group. No dose-response relationship was observed.

Change in abdominal circumference from baseline to the end of treatment was −1.00 ± 2.76 cm in the placebo group, −2.98 ± 3.22 cm in the 7.5 mg group, −2.42 ± 3.96 cm in the 15 mg group, and −2.62 ± 2.83 cm in the 30 mg group.

Urine Volume: Change in 24-hour cumulative urine volume from baseline was greater in all tolvaptan groups than in the placebo group from Day 1 to Day 7, and was greatest on Day 1. Mean urine volume at Day 1 was 1811.3 mL in the placebo group, 2874.0 mL in the 7.5 mg group, 2999.4 mL in the 15 mg group, and 4119.3 mL in the 30 mg group. The mean 24-hour cumulative urine volume from Day 1 to the end of treatment was 1727.0 mL in the placebo group, 2478.5 mL in the 7.5 mg group, 2692.0 mL in the 15 mg group, and 3662.7 mL in the 30 mg group.

5.3.3.3 Trial 156-08-001: A Placebo-controlled Trial of Tolvaptan in the Treatment of Hepatic Edema (Japan)

A total of 164 liver cirrhosis patients with ascites (despite having received conventional diuretic therapy) were randomized to receive either tolvaptan at 7.5 mg or placebo for 7 days to investigate the efficacy and safety of repeated oral administration of tolvaptan for treatment of hepatic edema.

Body Weight: Treatment with tolvaptan at 7.5 mg resulted in a significantly greater decrease in mean body weight compared with placebo: mean changes in body weight (mean ± SD) from baseline to the end of treatment were −1.95 ± 1.77 kg in the tolvaptan 7.5 mg group and −0.44 ± 1.93 kg in the placebo group (point estimate for the difference was −1.51 kg [95% CI: −2.08 to −0.93 kg], $p < 0.0001$).

Ascites: Treatment with tolvaptan at 7.5 mg resulted in a significantly greater decrease in ascites volume compared with placebo: mean changes in ascites volume from baseline to the end of treatment (using last observation carried forward [LOCF]) were −492.4 ± 760.3 mL in the tolvaptan 7.5 mg group and −191.8 ± 690.8 mL in the placebo group (point estimate for the difference was −300.7 mL [95% CI: −526.2 to −75.1 mL], $p = 0.0093$). The ascites improvement rate at the end of treatment (LOCF) was 56.3% in the tolvaptan 7.5 mg group and 25.6% in the placebo group ($p = 0.0001$).

Abdominal Circumference: Treatment with tolvaptan at 7.5 mg resulted in a greater decrease in mean abdominal circumference compared to placebo: mean changes (mean ± SD) from baseline to the end of treatment (LOCF) were −3.38 ± 3.56 cm in the tolvaptan 7.5 mg group and −1.11 ± 3.67 cm in the placebo group (point estimate for the difference was −2.27 cm [95% CI: −3.40 to −1.14 mL], $p = 0.0001$).

Clinical Symptoms: Clinical symptoms associated with ascites (bloated feeling, impaired appetite, malaise, sensation of pressure when in decubitus position, feeling of difficulty breathing, and general condition) showed greater improvement in the tolvaptan 7.5 mg group compared with the placebo group.

Lower Limb Edema: Lower limb edema improvement rate at final IMP administration was greater in the tolvaptan 7.5 mg group (54.8%) compared with the placebo group (28.3%) ($p = 0.0168$).

Serum Sodium: Serum sodium concentration in the tolvaptan 7.5 mg group increased continually from Day 1 to Day 7 of IMP administration (including subjects with baseline serum sodium < 135 mEq/L).

Urine Volume: Urine volume and fluid intake both showed continued increase from Day 1 until Day 7 in the tolvaptan 7.5 mg group; increases in the tolvaptan 7.5 mg group were greater than those observed in the placebo group. Fluid balance showed a greater negative value in the tolvaptan 7.5 mg group than in the placebo group.

5.3.3.4 Trial 156-08-002: An Open-label Trial of Tolvaptan in Patients With Hepatic Edema (Japan)

A total of 51 subjects with liver cirrhosis and with ascites despite having received conventional diuretic therapy were treated with tolvaptan at 7.5 mg once daily for 7 days followed by an additional 7-day administration of tolvaptan at either 7.5 mg/day or 15 mg/day if the diuretic effect at 7.5 mg/day was judged to be insufficient. A total of 30 subjects continued administration of tolvaptan at 7.5 mg/day and 13 subjects escalated the dose of tolvaptan to 15 mg/day.

Body Weight: Body weight decreased in all subjects who received 7-day administration of tolvaptan at 7.5 mg/day. Change in body weight from baseline 1 was −1.41 ± 1.67 kg (mean ± SD, same hereafter) by the end of the initial 7-day treatment period and body weight decrease was observed from Day 1.

Abdominal Circumference: Change in abdominal circumference as −2.52 ± 2.66 cm (mean ± SD, same hereafter) by the end of the initial 7-day treatment period.

Ascites: Ascites improvement rate was 53.1% (26/49 subjects) at the end of the initial 7-day treatment period. Improvement rate of abdominal distension accompanied by ascites was 69.2% (27/39 subjects) at the end of the initial 7-day treatment period.

Lower Limb Edema: Improvement rate of lower limb edema excluding the subjects showing no symptoms of lower limb edema from baseline 1 to the end of the initial 7-day treatment period was 50% (16/32 subjects).

In the group continuing the administration of tolvaptan at 7.5 mg/day for an additional 7 days, an extension of treatment beyond the initial 7-days demonstrated further improvements in changes in body weight and abdominal circumference, clinical symptoms associated with ascites, and lower limb edema improvement rate. For other parameters, the improvement observed by Day 7 was sustained.

Body Weight: Changes from baseline 1 in body weight at Day 7 and at the final IMP administration by the end of the 14-day treatment period were respectively −2.22 ± 1.55 kg and −2.97 ± 2.57 kg.

Abdominal Circumference: Changes from baseline 1 in abdominal circumference at Day 7 and at the end of the 14-day treatment period were respectively −3.62 ± 2.01 cm and −5.07 ± 3.52 cm.

Ascites: Ascites improvement rates at Day 7 and at the end of the 14-day treatment period were respectively 65.5% (19/29 subjects) and 70.0% (21/30 subjects).

Improvement rate of abdominal distension accompanied by ascites at Day 7 and at the end of the 14-day treatment period were both 76.0% (19/25 subjects).

Lower Limb Edema: Improvement rate of lower limb edema at Day 7 and at the end of the 14-day treatment period excluding subjects showing no symptoms from baseline 1 to the end of the 14-day treatment period were respectively 63.6% (14/22 subjects) and 68.2% (15 /22 subjects).

In the group escalating to 15 mg/day in the second 7-day treatment period, no greater effect of IMP administration at the increased dose at Day 8 onward was observed compared to the effect by Day 7.

5.3.3.5 Trial 156-08-804-01: A Placebo-controlled Trial of Tolvaptan in the Treatment of Hepatic Edema (China)

A total of 181 subjects with cirrhotic ascites despite routine diuretic therapy were randomized to receive 15 or 30 mg of tolvaptan or placebo once daily for 7 days to evaluate the efficacy and safety of tolvaptan tablets on the basis of routine therapy in the treatment of cirrhotic ascites and to investigate the dose response of tolvaptan.

Body Weight: The decrease in body weight change from baseline after 7 days of treatment was significantly greater in the tolvaptan groups compared with the placebo group (analysis of variance [ANOVA], $p < 0.0001$), but was similar between the 2 tolvaptan groups (ANOVA, $p > 0.05$). Tolvaptan was also superior to placebo for the secondary efficacy endpoints of the decrease in the body weight change rate, the decrease in the abdominal circumference change and change rate, and ascites improvement rate.

Urine Volume: Tolvaptan significantly increased urine volume with a dose-dependent effect observed in the 15 mg group and 30 mg group, and was significantly higher in the 30 mg group.

Serum Sodium: Both tolvaptan 15 mg and 30 mg increased the serum sodium concentration effectively but did not affect serum potassium concentration. At the end of treatment, the change from baseline in serum sodium concentration in the tolvaptan groups were statistically different from that in placebo group ($p < 0.0001$), although there was no difference between the 2 tolvaptan groups. In a subgroup of subjects with serum sodium concentration < 135 mmol/L, both tolvaptan groups showed significant increases in serum sodium concentrations compared with the placebo group, without affecting serum potassium.

5.3.3.6 Trial 156-08-805-01: A Double-blind, Placebo-controlled Parallel Trial of Tolvaptan in the Treatment of Cirrhosis With Ascites (China)

A total of 535 subjects with liver cirrhosis and ascites and using conventional diuretic therapy were randomized to receive either tolvaptan 7.5 mg, 15 mg, or placebo, in conjunction with routine diuretic therapy for 7 days to evaluate the safety and efficacy of tolvaptan tablets for the treatment of cirrhosis with ascites.

Body Weight and Abdominal Circumference: Tolvaptan tablets at 7.5 mg and 15 mg for 7 consecutive days effectively decreased body weight and abdominal circumference. On Day 8, the change in body weight was −1.19 ± 2.23 kg in the placebo group, −1.95 ± 2.40 kg in the tolvaptan 7.5 mg group, and −2.19 ± 2.50 kg in the tolvaptan 15 mg group. The differences between each tolvaptan group and the placebo group were statistically significant ($p = 0.026$ for tolvaptan 7.5 mg vs placebo and $p = 0.001$ for tolvaptan 15 mg vs placebo). The rate of decline in body weight at each time point was also statistically significantly higher in each of the tolvaptan groups compared with the placebo group ($p < 0.05$).

On Day 5 (after 4 days of drug administration), the change in abdominal circumference was −0.97 ± 2.67 cm in the placebo group, −1.97 ± 2.71 cm in the tolvaptan 7.5 mg group, and −2.31 ± 2.95 cm in the tolvaptan 15 mg group; on Day 8 (after 7 days of drug administration), the change in abdominal circumference was −1.72 ± 3.51 cm in the placebo group, −2.73 ± 3.44 cm in the tolvaptan 7.5 mg group, and −3.22 ± 3.82 cm in the tolvaptan 15 mg group. The decline in abdominal circumference was statistically significantly higher in each of the tolvaptan groups than that of the placebo group ($p < 0.05$).

Ascites: On Day 4 of drug administration, the percentage of subjects with improved ascites was 23.7% in the placebo group, 38.6% in the tolvaptan 7.5 mg group, and 44.5% in the tolvaptan 15 mg group. On Day 7 of drug administration, the percentage of subjects with improved ascites was 40.8% in the placebo group, 50.3% in the tolvaptan 7.5 g group, and 53.5% in the tolvaptan 15 g group. On Day 4 of drug administration, the difference between each of the tolvaptan groups and the placebo group was statistically significant ($p < 0.03$); however, on Day 7 of drug administration, the differences did not reach statistical significance.

5.3.3.7 Trial 156-09-004: A Parallel-group Trial of Tolvaptan in the Treatment of Hepatic Edema (Japan)

A total of 40 subjects with liver cirrhosis and ascites (despite having received conventional diuretic therapy) were randomized to receive either tolvaptan at 3.75 or 7.5 mg/day for 7 days to investigate the pharmacodynamics, pharmacokinetics, efficacy, and safety of repeated oral administration of tolvaptan for treatment of hepatic edema.

Body Weight: Body weight (mean ± SD) decreased from baseline on Day 1 in both the 3.75 mg/day group (−0.42 ± 0.38 kg) and the 7.5 mg/day group (−0.74 ± 0.91 kg). Body weight continued to decrease until the end of the treatment period (Day 7) in the 7.5 mg/day group (a mean decrease of 1.0 kg or more was observed from Day 3), whereas in the 3.75 mg/day group body weight became nearly constant from Day 4 onward (when a mean decrease of 1.0 kg or more was observed).

Urine Volume and Fluid Balance: Urine volume increased from Day 1 in both the 3.75 mg/day group and the 7.5 mg/day group. Diuretic action continued for a longer period of time in the 7.5 mg/day group than in the 3.75 mg/day group. Change in fluid balance showed the greatest negative values at 4 to 8 hours postdose on Day 1 in both groups. Urine osmolality decreased after administration in both groups, demonstrating the aquaretic action of tolvaptan.

5.3.4 Carcinomatous Edema

One trial was conducted in Japan to investigate the efficacy, PK/PD, and safety of tolvaptan in subjects with carcinomatous edema.

5.3.4.1 Trial 156-12-001: A Multicenter, Open-label, Dose-finding Trial of OPC-41061 to Investigate Efficacy, Pharmacokinetics, Pharmacodynamics, and Safety in Patients With Carcinomatous Edema (Japan)

A total of 43 subjects with volume overload associated with cancer were administered IMP in this trial. Tolvaptan was administered first by dose-escalation until the daily urine volume increased by 500 mL or more from the end of the pretreatment observation period. The tolvaptan dose was then fixed and IMP administration continued for 6 consecutive days at that dose. Treatment was for a maximum of 11 days.

Body Weight: The time profiles of the change in body weight from baseline at each analysis point consistently showed a decrease for all doses from the first day of IMP administration in the dose-escalation period until the completion of IMP administration.

Pharmacokinetics: The mean C_{max} and AUC_{24h} of tolvaptan after a 7-day repeated administration increased dose-dependently. Plasma drug concentration reached steady state within 5 days from the start of administration.

Pharmacodynamics: Daily fluid balance at the final treatment showed a negative value, indicating that tolvaptan contributed to an increase in urine volume. Serum sodium concentration and serum osmolarity also both increased.

Safety: The incidence of TEAEs in this trial was 74.4% (32/43 subjects). TEAEs with an incidence of at least 5% for all doses were vomiting, abdominal distension, constipation, thirst, blood osmolarity increased, and renal impairment. The incidence of adverse drug reactions (ADRs) was 32.6% (14/43 subjects). ADRs with an incidence of at least 5% for all doses were blood osmolarity increased, thirst, and renal impairment. There were no significant safety findings.

5.3.5 Chronic Renal Failure

Two phase 2 trials evaluating subjects with chronic renal failure have been completed in Japan.

5.3.5.1 Trial 156-12-002: A Multicenter, Open-label, Dose-finding Trial of OPC-41061 to Investigate Efficacy, Pharmacokinetics, Pharmacodynamics and Safety in Patients With Chronic Renal Failure who are Undergoing Peritoneal Dialysis (Japan)

A total of 20 subjects with chronic renal failure undergoing peritoneal dialysis were dosed in the dose-escalation period, and 7 subjects entered and completed the repeated administration period. The duration of treatment was individualized for each subject. The dose-escalation period duration was dependent on the number of dose escalations per subject; each dose level consisted of a 2-day period for the 4 dose levels for a maximum length of 8 days. The repeated-administration period was started after at least a 14-day washout period before a 2-day pre-observation period, followed by 5 days of dosing, and 1 postdose day.

Urine Volume: On repeated-administration Day 1, a mean (± SD) increase in daily urine volume of 409.3 ± 219.6 mL was observed overall for all dose strengths combined. Thereafter, the mean increase in daily urine volume was not maintained at that level, but had a tendency to be increased over baseline.

Pharmacokinetics: During the dose-escalation period, mean plasma concentrations of tolvaptan increased dose-dependently at all time points, and mean plasma concentrations of DM-4103 and DM-4107 increased dose-dependently or administration day-dependently at all time points. During the repeated-administration period, mean

plasma concentrations of tolvaptan, DM-4103, and DM4107 increased dose-dependently at all time points.

Pharmacodynamics: Mean urine osmolality decreased below baseline starting on the repeated-administration Day 1. This decline was maintained during the repeated-administration period and returned to baseline after the end of IMP administration.

Safety: No deaths or serious TEAEs were reported. Tolvaptan was safe and well-tolerated for short-term administration.

5.3.5.2 Trial 156-12-007: A Phase 2, Multicenter, Open-label, Dose-finding Trial to Investigate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of OPC-41061 in Patients With Chronic Renal Failure Undergoing Hemodialysis or Hemodiafiltration (Japan)

A total of 23 subjects with chronic renal failure undergoing hemodialysis or hemodiafiltration were treated with open-label tolvaptan at a starting dose of 7.5 mg/day and increased stepwise (7.5 mg/day to 15 mg/day to 30 mg/day to 60 mg/day) until the dose for intermittent administration was determined. Following a confirmation period for advancement to intermittent administration, a once-daily, 4-day intermittent administration of tolvaptan occurred.

Daily Urine Volume: Daily urine volume increased from baseline to Days 1, 8, 15, and 22 of the dose-titration period; the changes in daily urine volume (mean ± SD) were 334.3 ± 293.6 mL at 7.5 mg, 593.2 ± 326.7 mL at 15 mg, 670.7 ± 463.1 mL at 30 mg, and 213.5 mL at 60 mg. Daily urine volume increased after tolvaptan administration in the dose-titration period and in the intermittent administration period (in those subjects who advanced to the intermittent administration period).

Interdialytic Weight Gain: Body weight gain between dialysis sessions (separated by 2 off-dialysis days) was decreased from baseline after tolvaptan administration in the intermittent administration period; the mean ± SD of body weight gain between dialysis sessions was 2.09 ± 1.37 kg at baseline, 1.29 ± 1.37 kg after tolvaptan administration. Body weight gain between dialysis sessions (separated by 1 off-dialysis day) was decreased from baseline after tolvaptan administration in the intermittent administration period; the mean ± SD of body weight gain between dialysis sessions was 1.53 ± 0.85 kg at baseline, and 1.12 ± 1.14 kg after tolvaptan administration.

Total Volume of Fluid Removed by Dialysis per Week: Total volume of fluid removed by dialysis per week was decreased from baseline after tolvaptan administration in the intermittent administration period; the mean ± SD of total volume of fluid removed

by dialysis per week was 5568.1 ± 2984.9 mL at baseline and 4143.1 ± 3404.4 mL after tolvaptan administration.

Assessment of Whether Target Weight (Dry Weight) was Achieved by Dialysis: Administration of tolvaptan increased the number of times target body weight (dry weight) was achieved following dialysis in the intermittent administration period.

Pharmacokinetics: Mean plasma tolvaptan concentration reached a maximum at 4 hours postdose in the dose-titration period, and between 4 and 8 hours postdose in the intermittent administration period. The mean plasma concentrations of tolvaptan and metabolites (DM-4103 and DM-4107) increased dose-dependently in the dose-titration and intermittent administration periods.

Pharmacodynamics: Daily fluid balance was negative during the dose-titration and intermittent administration periods, indicating that the daily urine volume exceeded the daily fluid intake during tolvaptan administration. Urine osmolality tended to be decreased from baseline in the dose-titration and intermittent administration periods.

Safety: There were no deaths, serious adverse events (SAEs), or subjects who discontinued the trial due to TEAEs. Tolvaptan appeared to be safe and well-tolerated at a dose up to 60 mg/day in subjects with chronic renal failure who were undergoing hemodialysis or hemodiafiltration.

5.3.6 Autosomal Dominant Polycystic Kidney Disease

Eleven trials involving the exclusive evaluation of subjects with ADPKD have been completed, including 7 short-term and 4 long-term ADPKD trials:

- Short-term ADPKD trials include three single- and multiple-ascending dose trials (Trials 156-04-001, 156-04-248, 156-04-249), two trials which evaluated subjects with renal impairment (Trials 156-06-260 and 156-09-284), and two trials using the MR formulation, which is no longer in development (Trials 156-09-285 and 156-09-290). Data from Trial 156-09-284, which included evaluation of PK and PD parameters, is discussed in Section 5.3.6.1.5. Trial 156-09-290, compared MR capsule and IR tablet formulations in subjects with ADPKD; clinical conduct for this trial is complete, but final data analysis is pending.
- Completed long-term ADPKD trials include the multinational, double-blind, placebo-controlled Trial 156-04-251 and three open-label extension Trials 156-04-250, 156-05-002, and 156-09-003.

Briefly, the published results of long-term treatment of tolvaptan on TKV and renal function in the phase 3 placebo-controlled Trial 156-04-251 showed that over a 3-year period, tolvaptan slowed the increase in TKV and the decline in kidney function compared with placebo in patients with ADPKD (Section 5.3.6.2.2).[15] Tolvaptan has consistently shown a beneficial effect in subjects with ADPKD by improving eGFR (Section 5.3.6.2.1). The results of a study which examined the pooled results from subjects in long-term Trials 156-04-250 and 156-05-002 in comparison with matched historical controls suggests that tolvaptan therapy significantly and safely slowed ADPKD kidney growth and eGFR decline with a magnitude that could delay volume-related outcomes, including end-stage renal disease.[16] The short-term effects of tolvaptan on renal function and volume in subjects with ADPKD, as evaluated in Trial 156-06-260 (Section 5.3.6.1.4)[17] and in Trial 156-09-284[18,19]have also been published. Tolvaptan was approved in Japan (Mar 2014) for suppression of progression of ADPKD in patients with increased kidney volume and a rapid rate of increase.

5.3.6.1 Short-term Trials in Autosomal Dominant Polycystic Kidney Disease

5.3.6.1.1 Trial 156-04-001: A Dose Finding Study of Tolvaptan in Autosomal Dominant Polycystic Kidney Disease Patients (Japan)

Eighteen subjects with ADPKD were evaluated in this trial. Subjects in Group I received single doses of 15 and 30 mg (Periods I and II, respectively) and 15 mg BID for 5 days (Period III), with treatments separated by a washout period of 1 to 3 weeks. Subjects in Group II received single doses of 15 and 30 mg (Periods I and II, respectively) and 30 mg QD for 5 days (Period III). The primary pharmacodynamic variable was urine osmolality.

Urine Osmolality: Urine osmolality decreased following single administration of tolvaptan in Periods I (15 mg) and II (30 mg), and the time courses of Periods I and II were similar. In Period III (repeated administration), urine osmolality decreased following administration of tolvaptan in both Group I (15 mg BID) and Group II (30 mg QD), and the patterns of decrease following single administrations did not change following repeated administration. The duration of low urine osmolality (< 300 mOsm/kg) was longer for Group I (15 mg BID) than for Group II (30 mg QD).

Urine Volume: Urine volume increased from the predosing value following single administration of 15 mg (Period I) and 30 mg (Period II), and repeated administrations (Period III) of 15 mg BID (Group I) and 30 QD (Group II). However, changes in urine volume from predosing values on the fifth administration day were smaller than on the first administration day in Period III.

It was concluded that tolvaptan decreased urine osmolality and provided aquaretic effect without having any effect on electrolytes, renal function, or the number of urine voids and fluid intakes during the night. The same daily dose (30 mg/day) was administered via a BID and QD regimen, and the number of subjects for which the pharmacological effects were judged to be inadequate was fewer in the BID regimen group than in the QD regimen group, and the results indicated that duration of V_2-receptor inhibition was longer in the BID regimen group than in the QD regimen group.

5.3.6.1.2 Trial 156-04-248: A Phase 2, Randomized, Double-blind, Placebo-controlled, Ascending Dose Study to Determine the Safety, Pharmacokinetics, and Pharmacodynamics of Orally Administered Tolvaptan Tablets in Male and Female Adults Diagnosed With Autosomal Dominant Polycystic Kidney Disease (US)

Eleven subjects with ADPKD (as confirmed by imaging) received placebo or single ascending doses of tolvaptan 15, 30, 60, or 120 mg, all separated by a washout period. The primary pharmacodynamic variable was urine osmolality.

Urine Osmolality: Urine osmolality AUC from time zero to 28 hours (AUC_{0-28h}) showed a dose-dependent decrease following single oral dosing of 15 to 120 mg of tolvaptan, and the change from baseline in urine osmolality AUC_{0-28h} was highly negatively correlated with the change from baseline in urine volume. The duration that urine osmolality remained < 300 mOsm/kg was greater for tolvaptan-treated subjects compared with placebo-treated subjects, with the duration increasing with increasing dose.

Urine Volume: A dose-related increase in urine volume from 0 to 24-hours postdose was observed. The mean number of times a subject got out of bed between 16 to 24 hours postdose, compared to placebo, increased for tolvaptan doses greater than 15 mg.

5.3.6.1.3 Trial 156-04-249: A Phase 2, In-patient, Double-blind, Randomized, Parallel-arm Study to Determine the Safety, Pharmacokinetics, Pharmacodynamics and Tolerability of Multiple QD/BID Doses of Orally Administered Tolvaptan Tablets in Male and Female Adults Diagnosed With Autosomal Dominant Polycystic Kidney Disease (US)

A total of 37 subjects with ADPKD (as confirmed by imaging) and normal to moderately impaired renal function were enrolled and treated in 2 cohorts in this trial. Subjects in the first cohort were randomized to one of 3 tolvaptan regimens: 15/15 mg, 30/15 mg, or 30/30 mg. Subjects in the second cohort were randomized to one of the latter 3 dosing regimens or to a fourth regimen, 30 mg AM + placebo PM (referred to as 30 mg QD). All subjects received tolvaptan or placebo for 5 consecutive days. The primary pharmacodynamic variable was urine osmolality.

Urine Osmolality: A split-dose regimen of tolvaptan 15/15 mg was more effective than 30 mg QD in reducing urine osmolality as measured by urine osmolality $AUC_{0\text{-}28h}$. A split-dose regimen of 30/30 mg was more effective than 15/15 mg or 30/15 mg. Following multiple oral doses (30 to 60 mg/day) for 5 days, mean 24-hour urine volume is approximately 1200 mL less than on Day 1 and mean urine osmolality $AUC_{0\text{-}24h}$ is increased approximately 15%.

Urine Volume: Following multiple oral doses (30 to 60 mg/day) for 5 days, tolvaptan produced a bigger increase in mean 24-hour urine volume on Day 1 compared with Day 5; mean 24-hour urine volume was approximately 1200 mL less than on Day 1.

Fluid Balance: Twenty-four-hour fluid balance on Day 1 showed a dose-dependent response; fluid balance decreased as the tolvaptan daily dose increased from 30 to 45 to 60 mg. Fluid balance became more positive by Day 5 as fluid intake increased and urine volume decreased.

5.3.6.1.4 Trial 156-06-260: Short-term Trial in Subjects With Autosomal Dominant Polycystic Kidney Disease and Varying Degrees of Renal Function (US)

Trial 156-06-260 was designed to evaluate the effect of a 45/15 mg split-dose regimen of oral tolvaptan tablets on renal function in subjects with ADPKD. A total of 20 subjects with ADPKD with varying degrees of renal function were enrolled into this trial in the US in one of 3 groups as follows:

- Group A (estimated creatinine clearance determined using the Cockcroft-Gault formula [$eCrCL_{CG}$] ≥ 60 mL/min and normal blood pressure, who had never received any medication for hypertension [Subgroup A1] or $eCrCL_{CG}$ ≥ 60 mL/min and high blood pressure, currently receiving an ACE inhibitor and/or an ARB as their primary antihypertension medication [Subgroup A2])
- Group B ($eCrCL_{CG}$ 45 to < 60 mL/min; could have been taking either an ACE inhibitor or an ARB)
- Group C ($eCrCL_{CG}$ 30 to < 45 mL/min; could have been taking either an ACE inhibitor or an ARB)

All subjects received a daily split-dose regimen of tolvaptan (45 mg AM/15 mg PM) for 8 days. The primary pharmacodynamic outcome variables were GFR as determined by iothalamate clearance, RBF and RPF as determined by para-amino-hippurate (PAH) clearance, and filtration fraction (defined as GFR/RPF). In addition, RBF was also determined by magnetic resonance imaging (MRI). A post-hoc determination of TKV was performed from the MRI data.

Modest (approximately 9%) reductions in GFR were seen overall in the 3 $eCrCL_{CG}$ categories, with the ≥ 60 mL/min category showing a 16% decrease in subjects who were not hypertensive and no change in those with hypertension (and receiving renin-angiotensin system inhibition). Change from baseline in RBF as measured by either MRI or PAH clearance varied widely around zero. For subjects with measured GFR < 60 mL/min, RBF by MRI showed small positive changes, whereas small negative changes were observed using PAH clearance, possibly because of lower than expected tubular excretion of PAH with declining renal function. Filtration fraction appeared minimally reduced across groups, but its estimation may also have been affected by reduced PAH. Most estimates of renal clearance, including serum cystatin C concentrations, showed changes consistent with the slight (9%) decrease in measured GFR, with the notable exception of uric acid. Clearance of uric acid was reduced to a proportionally greater extent, 20% to 25%. This is consistent with an effect of tolvaptan

reducing distal reabsorption of sodium and sodium dependent uric acid reabsorption. This is similar to the mechanism by which certain diuretics are thought to increase serum uric acid. These preliminary findings support the hypothesized actions of vasopressin in modulating renal function.

Statistically significant decreases from baseline in TKV were observed overall (mean [SD] percent change from baseline of 1.9 [2.4], p = 0.0040), and in Subgroup A2 (mean [SD] percent change from baseline −3.9 [1.5], p = 0.0014).

5.3.6.1.5 Trial 156-09-284: Short-term Trial in Subjects With Autosomal Dominant Polycystic Kidney Disease and Varying Degrees of Renal Function (Netherlands)

Trial 156-09-284 was an open-label trial to assess the effect of maximally-tolerated doses of tolvaptan at steady state on renal function in subjects with ADPKD with varying degrees of renal function. Twenty-nine subjects with ADPKD were enrolled; all subjects had a medical history of hypertension and 24 of the 29 subjects enrolled were taking ACE inhibitors/ARBs for control. Subjects were administered a daily split-dose regimen of tolvaptan for 3 weeks; concomitant medications taken once daily were taken with or prior to the morning tolvaptan dose. The dose was up-titrated weekly, as tolerated, starting at 45 mg AM/15 mg PM (45/15 mg) and progressing to 60 mg AM/30 mg PM (60/30 mg) and 90 mg AM/30 mg PM (90/30 mg) as tolerated. Inclusion was stratified for eGFR using the 4-variable modification of diet in renal disease (MDRD) equation ($eGFR_{MDRD}$), with 3 strata: > 60, 30 to 60, and < 30 mL/min/1.73 m^2. Subjects with $eGFR_{MDRD} \geq 30$ mL/min/1.73 m^2 were enrolled first, followed by $eGFR_{MDRD} < 30$ mL/min/1.73 m^2 subjects. Twenty-seven subjects completed the trial, 26 titrating to 90/30 mg and one titrating to 60/30 mg; two subjects withdrew due to TEAEs (dry mouth, polyuria [a serious TEAE]). Pharmacodynamic endpoints were assessed at baseline, on Day 21 of treatment and at 21 days after treatment.

The primary pharmacodynamic outcome variables were GFR as determined by iothalamate clearance, RPF as determined by para-amino-hippurate (PAH) clearance, and filtration fraction (defined as GFR/RPF). A secondary finding was modest (approximately 8%), but significant, reductions in measured GFR seen in subjects with $eGFR_{MDRD}$ of > 60 and 30 to 60 mL/min/1.73 m^2; a non-significant decrease of −2.1% was seen in subjects with $eGFR_{MDRD}$ of < 30 mL/min/1.73 m^2. The percent change from baseline in effective renal plasma flow, as measured by clearance of hippuran, decreased as baseline measured GFR decreased and was highly correlated with the percent change in measured GFR. Filtration fraction appeared minimally reduced across groups but for all subjects combined the decreases were statistically significant. Tolvaptan-induced

changes in urine output and free water clearance were larger as renal function increased. Total kidney volume was slightly reduced after 3 weeks of tolvaptan treatment, mean changes were −4.6, −4.5 and −1.9% in subjects with $eGFR_{MDRD}$ of > 60, 30 to 60 and < 30 mL/min/1.73 m^2, respectively; at 21 days posttreatment, mean changes were still negative but not significantly different from baseline. Changes in creatinine and uric acid clearances paralleled the changes in measured GFR but uric acid clearance was reduced by a greater than proportional extent, about 20%, in subjects with eGFR > 30 mL/min/1.73 m^2. Copeptin, cystatin C, creatinine, osmole, sodium, and uric acid concentrations were increased following tolvaptan administration while albumin, aldosterone, plasma renin, potassium, and urea concentrations were not; at 21 days post treatment, all concentrations were similar to baseline values.[18,19]

5.3.6.2 Long-term Trials in Autosomal Dominant Polycystic Kidney Disease

5.3.6.2.1 Trial 156-04-250: A Phase 2, Multi-center, Open-label Study to Determine Long-term Safety, Tolerability, and Efficacy of Split-dose Oral Regimens of Tolvaptan Tablets in a Range of 30 to 120 mg/day in Patients With Autosomal Dominant Polycystic Kidney Disease (US)

A total of 46 subjects with ADPKD who had completed a previous tolvaptan ADPKD trial (either Trial 156-04-248 or Trial 156-04-249) were enrolled in this trial. Tolvaptan doses were initially titrated weekly beginning with a 30/15 mg split-dose regimen and then sustained for up to 60 days. Options for titration included 15/15 mg, 30/15 mg, 45/15 mg, 60/30 mg, and 90/30 mg. Subjects continued split-dose regimens of 45/15 mg or 60/30 mg up to Month 36, followed by an off-treatment period with the option to enter an extension period for an additional 12 months. Acquisition of pilot efficacy data was a secondary objective of the trial.

Trough urine osmolality prior to the first daily dose decreased from baseline throughout the course of the trial and was sustained through 36 months in both treatment groups. Mean urine osmolality for the total population was maintained at < 300 mOsm/kg throughout the 36 months of the trial.

Total renal volume decreased from baseline through Month 2 in the tolvaptan 60/30 mg group and through Month 12 in the tolvaptan 45/15 mg group. At Month 36, renal volume increased from baseline in both groups, with a higher mean (SD) percent increase seen in the tolvaptan 45/15 mg group (9.86% [11.81%]) compared with the tolvaptan 60/30 mg group (5.06% [9.77%]; p = 0.0553).

Estimated GFR tended to decrease from baseline in both groups at each visit, with similar mean decreases seen at Month 36 in the tolvaptan 45/15 mg group compared with the tolvaptan 60/30 mg group.

No effect was seen with tolvaptan dosing over 36 months on hypertension assessments, renal pain, or abdominal girth. Few clinically significant events were reported via the PKD Outcomes Survey.

5.3.6.2.2 Trial 156-04-251: A Phase 3, Multicenter, Double-blind, Placebo-controlled, Parallel-arm Trial to Determine Long-term Safety and Efficacy of Oral Tolvaptan Tablet Regimens in Adult Subjects With Autosomal Dominant Polycystic Kidney Disease (Multinational)

Trial 156-04-251 was the pivotal trial in the ADPKD program. It evaluated the long-term efficacy of tolvaptan in adult subjects with ADPKD through the rate of TKV change (%) for tolvaptan subjects compared with placebo. The key secondary objective evaluated long-term efficacy through a composite of clinical outcome events (ie, progressive hypertension, renal pain, albuminuria, and renal function). A third important secondary objective evaluated the rate of renal function change.

This trial was conducted in 1445 subjects at 129 trial sites in 15 countries. A total of 1444 subjects received at least one dose of IMP; 961 subjects received tolvaptan and 483 subjects received placebo. During a 3-week titration phase, IMP doses were titrated in weekly intervals to the highest tolerated levels given in split-dose regimens of 45 mg AM/15 mg PM (45/15 mg), 60 mg AM/30 mg PM (60/30 mg), or 90 mg AM/30 mg PM (90/30 mg). Subjects continued in the maintenance phase at their highest tolerated dose for up to Month 36. Subjects were allowed to down-titrate at any time, as indicated for safety or tolerability. During maintenance, investigators could increase a subject's dosage up to the maximum dose of 90/30 mg with medical monitor approval if any changes suggested that a higher dose could be tolerated.

Rate of Kidney Volume Change: Total kidney volume increased over the 3-year period by 2.8% per year (95% CI, 2.5 to 3.1) in the tolvaptan group compared with 5.5% per year (95% CI, 5.1 to 6.0) in the placebo group, for a difference of −2.7% per year (95% CI, −3.3 to −2.1, $p < 0.0001$), representing a treatment effect of 49.2% in the ITT population. The ratio of the geometric means of growth rate was 0.97 (95% CI, 0.97 to 0.98; $p < 0.0001$) (Figure 5.3.6.2.2-1). The mixed-model repeated-measures (MMRM) analysis was consistent with the primary analysis: least-squares mean TKV growth over the 3-year period for tolvaptan (9.56%) was halved relative to placebo (18.75%), for a treatment group difference of −9.2% (95% CI, −11.1 to −7.3; $p < 0.0001$). The MMRM

analysis showed that the effect of treatment on TKV growth was greatest in the first year and included negative cyst growth for the tolvaptan group (−1.65%) compared with positive cyst growth in the placebo group (4.62%), for a treatment effect of −6.27% ($p < 0.0001$). During the second and third years, kidney enlargement progressed in both groups; this progression was significantly slower in tolvaptan subjects compared with placebo subjects (2.93% vs 11.10% for a treatment effect of −8.17% by Month 24 and 9.56% vs 18.75% for a treatment effect of −9.19% by Month 36; each, $p < 0.0001$). The effects of tolvaptan persisted into the second and third year of therapy, with a year-to-year accrual of effect over time, leading to continued incremental separation from placebo over the entire 3-year duration of therapy. When restricted to subjects who were taking the IMP at the time of image acquisition, this same analysis showed a higher between-group difference during the third year (Figure 5.3.6.2.2-1).

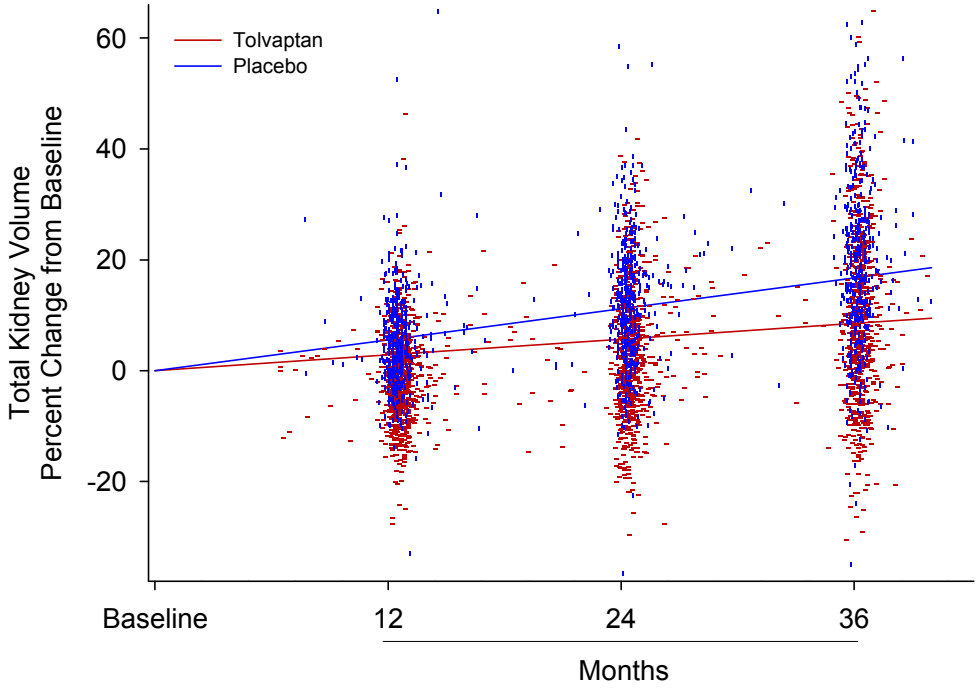

Figure 5.3.6.2.2-1 Effect of Tolvaptan on the Rate of Total Kidney Volume Change (Normalized as a Percentage)

When evaluated by subgroup, tolvaptan had a beneficial effect on TKV in all subgroups including the following: sex, age (< 35 years versus ≥ 35 years), baseline TKV (< 1000 mL versus ≥ 1000 mL), baseline estimated creatinine clearance (< 80 mL/min versus ≥ 80 mL/min), and hypertension status (absent versus present).

Key Secondary Composite (progressive hypertension, renal pain, albuminuria, and renal function): Events relating to renal function, renal pain, hypertension, and albuminuria comprised the prospectively defined key secondary composite endpoint and were defined as progression past a clinically relevant threshold. The key secondary composite endpoint was time to multiple events. This endpoint, tested after the primary endpoint, favored tolvaptan. In this analysis, fewer ADPKD-related events per 100 person-years of follow-up were observed in the tolvaptan group compared with the placebo group (44 versus 50 events; HR, ie, intensity ratio), 0.87; 95% CI, 0.78 to 0.97; p = 0.0095). The analysis of time to first event confirmed these results (HR, 0.83; 95% CI, 0.72 to 0.94; p = 0.0051). An analysis using the events adjudicated by an independent committee also confirmed the results of the key secondary composite endpoint (HR, 0.85; 95% CI 0.76 to 0.95, p = 0.0044). The result was driven predominantly by events directly attributable to ADPKD, namely those relating to renal function decline with 2 versus 5 events per 100 person-years of follow-up for tolvaptan versus placebo (HR, 0.39; 95% CI, 0.26 to 0.57; p < 0.0001) and renal pain with 5 versus 7 events per 100 person-years of follow-up for tolvaptan versus placebo (HR, 0.64; 95% CI, 0.47 to 0.89; p = 0.0071). This reflects a relative improvement of 61.4% in renal function decline and 35.8% in renal pain. No evidence for an effect of treatment was seen in hypertension or albuminuria events.

Slope of Renal Function: The slope of renal function decline using the reciprocal of the serum creatinine level, from the end of dose escalation to Month 36, also favored tolvaptan treatment, with an estimated slope of −2.61 $(mg/mL)^{-1}$ yr^{-1} versus an estimated slope for placebo of −3.81 $(mg/mL)^{-1}$ yr^{-1} with a treatment effect of 1.20 $(mg/mL)^{-1}$ yr^{-1} (95% CI, 0.62 to 1.78; p < 0.0001). This result, which represents a relative improvement of 31.6%, was confirmed using other methods of estimating renal function, $eCrCL_{CG}$, eGFR determined using the MDRD formula ($eGFR_{MDRD}$), and $eGFR_{CKD\text{-}EPI}$. In an MMRM sensitivity analysis, a comparison of data from pretreatment baseline and post-treatment visits showed an increase in 1/serum creatinine of 4.93 $(mg/mL)^{-1}$ over the 3-year period for tolvaptan, as compared with placebo (95% CI, 2.96 to 6.89; p < 0.0001). This corresponds to an increase in the mean serum creatinine level from 1.05 mg/dL to 1.21 mg/dL in the tolvaptan group, compared with an increase from 1.04 mg/dL to 1.27 mg/dL in the placebo group (mean difference, −0.09 mg/dL; 95% CI, −0.13 to −0.06; p < 0.0001). The MMRM analysis showed a significant benefit of tolvaptan from the first year (treatment effect, 2.02 $[mg/mL]^{-1}$; p = 0.0005) and increasing through the third year (treatment effect, 3.68 $[mg/mL]^{-1}$; p < 0.0001). Analysis by prespecified subgroups suggested a beneficial effect of tolvaptan on renal

function in all relevant subgroups tested. These effects were statistically significant in favor of tolvaptan among older subjects (≥ 35 years) and among Caucasian subjects and those with hypertension, TKV ≥ 1000 mL, or microalbuminuria.

5.3.6.2.3 Trial 156-05-002: A Long-term Administration Study of OPC-41061 in Patients With Autosomal Dominant Polycystic Kidney Disease (Extension of Study 156-04-001) (Japan)

A total of 17 subjects with ADPKD who completed Trial 156-04-001 and whose safety was confirmed in that trial were enrolled and received tolvaptan 15 mg BID (morning and evening) for up to 3 years. The primary pharmacodynamic variable was urine osmolality. Efficacy variables included combined renal volume (right and left kidneys) and renal function tests (CrCL, eGFR, and cystatin C).

Urine Osmolality: Urine osmolality during the long-term administration of tolvaptan decreased compared with baseline in most subjects.

Renal Function and Total Renal Volume: The renal function test values in a few subjects worsened slightly, but the combined renal volume showed no increase from baseline in most subjects.

5.3.6.2.4 Trial 156-09-003: A Long-term Administration Trial of OPC-41061 in Patients With Autosomal Dominant Polycystic Kidney Disease (ADPKD) (2) [Extension of Trial 156-05-002] (Japan)

A total of 13 subjects with ADPKD who completed Trial 156-05-002 or who were withdrawn for reasons other than an adverse event (AE) were enrolled and received tolvaptan initially at a dose of 15 mg BID (morning and evening). After approval of the revised protocol, tolvaptan was initiated at a dose of 45 mg in the morning and 15 mg in the evening. Subjects were titrated to a daily split-dose of 60/30 mg and then to 90/30 mg, dependent on tolerability. Duration of treatment ranged from 205 to 1651 days.

Renal Function and Total Kidney Volume: In most subjects, renal function test values gradually declined, but TKV did not show marked changes.

Safety: Adverse events and potentially drug-related AEs were reported in all 13 subjects. Long-term administration was not associated with an increase in the occurrence of any AEs. Most of the events resolved through appropriate measures. Serious AEs were reported in 6 subjects, but there were no SAEs that occurred in 2 or more subjects, and all of the SAEs were either resolved or resolving. An AE leading to discontinuation occurred in 1 subject. No clinically significant changes in clinical laboratory values, vital signs, body weight, or 12-lead ECGs were observed. Long-term administration of tolvaptan in ADPKD subjects was considered safe in this population.

5.4 Safety

All adverse events were coded by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA®), version 17.0.

For the purpose of this update, the pooled exposure data includes data from a total of 93 trials (Section 5.4.1.1). Exposure data for 4 completed open-label, long-term trials (Trial 156-03-244 in subjects with hyponatremia and Trials 156-04-250, 156-05-002, and 156-09-003 in subjects with ADPKD) are presented separately by indication (Section 5.4.1.2).

Subjects are included in the pooled safety database if they received at least one oral dose of tolvaptan. The pooled safety database comprises data from a total of 91 trials (Table 5.4.2-1). Safety data were unavailable for pooling for 2 trials comprising 30 subjects in early phase 1 trials conducted in Japan (Trials 156-94-001 and 156-94-002) using the jet-milled formulation; safety data from these trials are representative of the data in the pooled database. Further, safety data are presented separately by indication for 4 completed open-label, long-term trials (Trial 156-03-244 in subjects with hyponatremia and Trials 156-04-250, 156-05-002, and 156-09-003 in subjects with ADPKD).

For Trial 156-03-236, subjects were followed for 14 days after discontinuation of trial medication. The data presented herein for Trial 156-03-236 includes adverse events that started up to 7 days after discontinuation of trial medication, which is the usual follow-up period for the tolvaptan trials. Data from Trial 156-03-236 are represented as a pooled population from the long-term outcomes portion of this trial.

5.4.1 Exposure

5.4.1.1 Pooled Exposure Data for 93 Trials

As of 31 Mar 2015, pooled exposure data are available from 93 trials, including 7373 subjects worldwide who were exposed to oral doses of tolvaptan. Thus, the extent of exposure to oral tolvaptan by dose in the pooled database (N = 7373) summarized in Table 5.4.1.1-1 comprises 3115 subjects in trials for heart failure, 511 subjects in trials for hyponatremia, 961 subjects in the pivotal long-term ADPKD trial (Trial 156-04-251), 270 subjects in short-term trials for ADPKD or renal impairment, 437 subjects in trials for cardiac edema, 855 subjects in trials for hepatic edema, 43 subjects in trials for chronic renal failure, 43 subjects in a trial for carcinomatous edema, 37 subjects with renal impairment in a phase 1 trial, and 1101 healthy subjects in clinical pharmacology trials. For overall exposure, subjects in crossover or sequential trials are counted once for exposure to any oral tolvaptan dose.

A total of 7373 subjects were exposed to oral tolvaptan in doses ranging from 3.75 to 480 mg (Table 5.4.1.1-1) for a total of 1,577,067 days of exposure. The median exposure for all doses of all oral formulations combined was 25 days, with a mean exposure of 214 days (± 334 days).

In addition, 14 healthy subjects were also exposed to a single 1-mg intravenous (IV) dose of tolvaptan in the phase 1 bioavailability Trial 156-05-254 (data are included in the pooled safety database and further details are provided in Section 5.4.1.2.1).

Table 5.4.1.1-1 Exposure to Oral Tolvaptan by Dose in 93 Trials in the Pooled Database

Dose	Total subjects exposed[a]	Mean exposure (days)	SD (days)	Minimum (days)	Maximum (days)
3.75 mg	33	4	3	1	7
5 mg	18	5	4	1	13
7.5 mg	409	7	3	1	14
10 mg	18	9	7	1	27
15 mg	1044	17	41	1	198
30 mg	3000	215	214	1	934
3.75 to 30 mg	43	8	2	1	10
45 mg	107	16	10	1	26
60 mg	706	26	49	1	177
7.5 to 60 mg	43	7	2	2	11
15 to 60 mg[b]	478	16	12	1	34
90 mg	265	22	25	1	113
120 mg	82	6	4	1	13
180 mg	11	1	1	1	2
240 mg	27	2	0	1	2
300 mg	49	4	1	1	5
360 mg	6	1	0	1	1
420 mg	6	1	0	1	1
480 mg	6	1	0	1	1
60 to 120 mg	961	887	370	1	1139
< 60 mg jet-milled[c]	20	1	0	1	2
60 mg jet-milled	16	1	0	1	2
100 mg jet-milled	6	1	0	1	1
150 mg jet-milled	59	5	3	2	8
300 mg jet-milled	28	1	0	1	1
450 mg jet-milled	28	1	0	1	1
MR 20 mg	27	6	1	5	7
MR 40 mg	17	7	0	6	7
MR 50 mg	45	52	12	6	67
MR 60 mg	87	5	3	1	9
MR 80 mg	44	51	15	2	70
MR 120 mg	12	7	0	7	7
SDT 20 mg	28	4	1	3	5
SDT 60 mg	10	6	2	1	6
Powder 15 mg	40	1	0	1	1
Oral suspension 15 mg	14	1	0	1	1

Table 5.4.1.1-1	**Exposure to Oral Tolvaptan by Dose in 93 Trials in the Pooled Database**				
Dose	**Total subjects exposed[a]**	**Mean exposure (days)**	**SD (days)**	**Minimum (days)**	**Maximum (days)**
Any oral dose	7373	211	337	1	1139
Placebo/other[d]	4346	263	334	1	1165
Furosemide 80 mg	41	4	3	1	7

ADPKD = autosomal dominant polycystic kidney disease; MR = modified release; SD = standard deviation; SDT = slow disintegration tablet; UK = United Kingdom; US = United States.

Note: Of the 93 trials in the pooled exposure analysis, 89 were completed and 4 were terminated. Subjects are included in the pooled safety analysis if they received at least 1 dose of tolvaptan.

[a]Subjects in crossover/sequential trials are included under each dose received and are counted only once in the “Any oral dose” category.

[b]Subjects who received titrated doses from 15 to 60 mg.

[c]Includes 1 mg, 3 mg, 10 mg, and 30 mg doses from Trial 156-94-001.

[d]Other includes placebo, fluid restriction, hydrochlorothiazide, ketoconazole, lovastatin, warfarin, amiodarone, digoxin, rifampin, and moxifloxacin.

Trials: 156-95-301, 156-95-302, 156-95-303, 156-95-304, 156-95-305, 156-96-301, and 156-03-242 (healthy subjects phase 1 UK); 156-96-205, 156-97-202, 156-98-201, 156-98-202, 156-98-210, 156-01-223, 156-01-225, 156-01-229, 156-01-233, 156-01-234, 156-03-239, 156-03-240, 156-03-245, 156-05-252, 156-05-253, 156-05-254, 156-05-256, 156-07-262, 156-07-263, 156-08-269, 156-08-270, 156-11-295, 156-12-202 (healthy subjects phase 1 US); 156-01-226 (healthy subjects phase 1 US and Argentina); 156-94-001, 156-94-002, 156-00-001, 156-00-002, 156-00-003, 156-05-001, 156-05-003, 156-05-004, 156-07-002, 156-10-004, 156-10-006, and 156-14-004 (healthy subjects phase 1 Japan); 156-06-801-01, 156-11-807-01, and 156-11-808-01 (healthy subjects phase 1 China); 156-KOA-0801 (healthy subjects phase 1 Korea); 156-09-806-01 (hepatic impairment phase 1 China); 156-06-260 (ADPKD phase 1 US); 156-09-282 (renal impairment phase 1 US); 156-96-201, 156-96-203, 156-97-204, 156-02-235, 156-03-238, 156-04-246, 156-07-802-01, and 156-08-275 (hyponatremia phase 2/3); 156-KOB-1101i (hyponatremia phase 4 Korea); 156-97-251, 156-97-252, 156-98-213, 156-00-220, 156-00-221, 156-00-222, 156-01-231, 156-01-232, 156-03-236, and 156-04-247 (heart failure phase 2/3); 156-04-001, 156-04-248, 156-04-249, 156-04-251, 156-09-284, 156-09-285, 156-09-290 (ADPKD phase 2/3); 156-03-001, 156-06-002, 156-06-004, 156-06-006, and 156-12-809-01 (cardiac edema phase 2/3 Japan and China); 156-10-005 (cardiac edema phase 4 Japan); 156-03-002, 156-06-005, 156-08-001, 156-08-002, and 156-09-004 (hepatic edema phase 2/3 Japan); 156-08-804-01 and 156-08-805-01 (hepatic edema phase 2/3 China), 156-12-001 (carcinomatous edema, phase 2 Japan), 156-12-002 and156-12-007 (chronic renal failure phase 2 Japan), and 156-TWA-1101i (cardiac edema phase 3 Taiwan).

5.4.1.2 Exposure Data by Disease State

The pooling strategy for exposure by disease state is the same as for the pooling strategy for analysis of TEAEs by disease state (Table 5.4.2-1), except that for ADPKD trials, short-term Trials 156-06-260, 156-09-284, and 156-09-285 are pooled with the other short-term ADPKD trials (Trials 156-04-001, 156-04-248, and 156-04-249) for exposure; whereas, for safety, they are presented separately.

5.4.1.2.1 Exposure in Healthy Subjects

In the 47 pooled trials in healthy subjects, a total of 1101 healthy subjects were exposed to oral tolvaptan in doses ranging from 5 to 480 mg (Table 5.4.1.2.1-1) for a total of 4435 days of exposure. The median exposure for all doses of all oral formulations combined was 2 days, with a mean exposure of 4 days (± 4 days).

In addition, 14 healthy subjects who received a single 30-mg dose of oral tolvaptan in a phase 1 bioavailability trial (Trial 156-05-254) in the US were also exposed to a single 1-mg IV dose of tolvaptan.

Table 5.4.1.2.1-1 Exposure to Oral Tolvaptan by Dose in 47 Pooled Trials in Healthy Subjects

Dose	Total subjects exposed	Mean exposure (days)	SD (days)	Minimum (days)	Maximum (days)
3.75 mg	14	1	0	1	1
5 mg	6	1	0	1	1
7.5 mg	66	3	3	1	8
10 mg	6	1	0	1	1
15 mg	62	1	0	1	2
30 mg	273	4	5	1	28
45 mg	6	1	0	1	1
60 mg	313	5	5	1	28
90 mg	112	2	2	1	8
120 mg	28	3	3	1	8
180 mg	11	1	1	1	2
240 mg	27	2	0	1	2
300 mg	49	4	1	1	5
360 mg	6	1	0	1	1
420 mg	6	1	0	1	1
480 mg	6	1	0	1	1
< 60 mg	20	1	0	1	2
60 mg JM	16	1	0	1	2
100 mg JM	6	1	0	1	1
150 mg JM	59	5	3	2	8
300 mg JM	28	1	0	1	1
450 mg JM	28	1	0	1	1
MR 20 mg	10	5	0	5	5
SDT 20 mg	28	4	1	3	5
MR 60 mg	70	5	3	1	9
SDT 60 mg	10	6	2	1	6
Powder 15 mg	40	40	0	1	1
Oral suspension 15 mg	14	1	0	1	1
Any oral dose	1101	4	5	1	28
Placebo/other	300	5	5	1	28
Furosemide 80 mg	6	1	0	1	1

JM = jet-milled; MR = modified release; SD = standard deviation; SDT = slow disintegration tablet.
Note: Subjects are included in the pooled safety analysis if they received at least 1 dose of tolvaptan.

Trials: 156-95-301, 156-95-302, 156-95-303, 156-95-304, 156-95-305, 156-96-301, and 156-03-242 (healthy subjects phase 1 UK); 156-96-205, 156-97-202, 156-98-201, 156-98-202, 156-98-210, 156-01-223, 156-01-225, 156-01-229, 156-01-233, 156-01-234, 156-03-239, 156-03-240, 156-03-245, 156-05-252, 156-05-253, 156-05-254, 156-05-256, 156-07-262, 156-07-263, 156-08-269, 156-08-270, 156-11-295, 156-12-202 (healthy subjects phase 1 US); 156-01-226 (healthy subjects phase 1 US and Argentina); 156-94-001, 156-94-002, 156-00-001, 156-00-002, 156-00-003, 156-05-001, 156-05-003, 156-05-004, 156-07-002, 156-10-004, 156-10-006, and 156-14-004 (healthy subjects phase 1 Japan); 156-06-801-01, 156-11-807-01, and 156-11-808-01 (healthy subjects phase 1 China); 156-KOA-0801 (healthy subjects phase 1 Korea).

5.4.1.2.2 Exposure in Hyponatremia Trials

In the 9 pooled trials in subjects with hyponatremia, a total of 511 subjects were exposed to oral tolvaptan in doses ranging from 5 to 60 mg (Table 5.4.1.2.2-1) for a total of 8339 days of exposure. The median exposure for all doses of all oral formulations combined was 13 days, with a mean exposure of 16 days (± 11 days).

Table 5.4.1.2.2-1 Exposure to Oral Tolvaptan by Dose in 9 Pooled Hyponatremia Trials

Dose	Total subjects exposed	Mean exposure (days)	SD (days)	Minimum (days)	Maximum (days)
5 mg	12	6	3	3	13
10 mg	7	13	7	2	27
15mg	11	16	8	5	27
30 mg	9	16	6	8	26
45 mg	1	9	--	9	9
60 mg	11	12	4	3	20
15 to 60 mg[a]	460	17	12	1	34
Any oral dose	511	16	11	1	34
Placebo/other	469	16	12	1	36

SD = standard deviation.
Note: Subjects are included in the pooled safety analysis if they received at least 1 dose of tolvaptan.
[a]Subjects who received titrated doses from 15 to 60 mg.
Trials: 156-96-201, 156-96-203, 156-97-204, 156-02-235, 156-03-238, 156-04-246, 156-07-802-01, 156-08-275, and 156-KOB-1101i.

Long-term exposure (up to 264 weeks of treatment with titrated tolvaptan [15 mg, 30 mg, or 60 mg]) in subjects with hyponatremia in the open-label Trial 156-03-244 is presented in Table 5.4.1.2.2-2. Of the 111 subjects enrolled in the open-label trial, the majority of subjects were exposed to oral tolvaptan for a minimum of > 56 to 58 weeks (79/111, 71.2%) and nearly half were exposed to tolvaptan for a minimum of > 98 to 106 weeks (55/111, 49.5%). A total of 12/111 (10.8%) subjects were exposed to tolvaptan for > 202 to 214 weeks. Six of 111 subjects (5.4%) had > 214 weeks of exposure to tolvaptan. Exposure during this open-label trial was similar between the prior treatment

groups. Fifty-five subjects received placebo in the parent trial and were exposed to tolvaptan for the first time in this trial.

Table 5.4.1.2.2-2 Long-term Extent of Exposure to Titrated Tolvaptan in Subjects with Hyponatremia (Trial 156-03-244)

Duration of Exposure, Weeks	Prior Treatment (Parent Trial)[a]				Tolvaptan	
	Tolvaptan		Placebo			
	n (%)	Average Daily Dose (mg)	n (%)	Average Daily Dose (mg)	n (%)	Average Daily Dose (mg)
1 day to 2 (weeks)[b]	56 (100.0)	21.73	55 (100.0)	21.67	111 (100.0)	21.70
> 2 to 4	55 (98.2)	28.13	53 (96.4)	26.42	108 (97.3)	27.29
> 4 to 8	53 (94.6)	29.61	53 (96.4)	27.26	106 (95.5)	28.44
> 8 to 12	48 (85.7)	31.03	51 (92.7)	28.49	99 (89.2)	29.72
> 12 to 16	47 (83.9)	31.47	48 (87.3)	29.29	95 (85.6)	30.37
> 28 to 32	44 (78.6)	35.11	42 (76.4)	30.66	86 (77.5)	32.94
> 44 to 48	41 (73.2)	33.83	41 (74.5)	32.64	82 (73.9)	33.23
> 56 to 58[c]	39 (69.6)	34.04	40 (72.7)	32.71	79 (71.2)	33.36
> 74 to 82	33 (58.9)	33.43	28 (50.9)	32.10	61 (55.0)	32.81
> 98 to 106[d]	28 (50.0)	33.95	27 (49.1)	32.35	55 (49.5)	33.17
> 130 to 142	24 (42.9)	32.75	20 (36.4)	30.71	44 (39.60)	31.82
> 166 to 178	18 (32.1)	34.67	15 (27.3)	32.81	33 (29.7)	33.83
> 202 to 214	6 (10.7)	32.5	6 (10.9)	37.47	12 (10.8)	34.99
> 214	3 (5.4)	20.0	3 (5.5)	25.00	6 (5.4)	22.50
Any exposure	56 (100.0)	33.17	55 (100.0)	31.77	111 (100.0)	32.48

Note: Although duration of exposure was summarized for all weekly increments, only select exposure intervals are shown above.

[a] Parent trials were 156-02-235 and 156-03-238.

[b] Initial dose titration occurred during first 2 weeks of the trial.

[c] Subjects who completed Week 58 could have elected not to continue in the first trial extension.

[d] Subjects who completed Week 106 could have elected not to continue in the second trial extension.

5.4.1.2.3 Exposure in Heart Failure Trials

In 10 pooled trials in subjects with heart failure, a total of 3115 subjects were exposed to oral tolvaptan in doses ranging from 10 to 120 mg (Table 5.4.1.2.3-1) for a total of 676,345 days of exposure. The median exposure for all doses of oral tolvaptan combined was 169 days, with a mean exposure of 217 days (± 207 days).

Table 5.4.1.2.3-1 Exposure to Oral Tolvaptan by Dose in 10 Pooled Heart Failure Trials

Dose	Total subjects exposed	Mean exposure (days)	SD (days)	Minimum (days)	Maximum (days)
10 mg	5	12	1	10	13
15 mg	132	95	80	1	198
30 mg	2549	252	211	1	934
45 mg	62	24	4	2	26
60 mg	278	59	65	1	177
90 mg	82	38	23	2	92
120 mg	7	13	0	13	13
Any oral dose	3115	217	207	1	934
Placebo/other	2502	260	213	1	927
Furosemide 80 mg	35	4	3	1	7

SD = standard deviation.
Note: Subjects are included in the pooled safety analysis if they received at least 1 dose of tolvaptan.
Trials: 156-97-251, 156-97-252, 156-98-213, 156-00-220, 156-00-221, 156-00-222, 156-01-231, 156-01-232, 156-03-236, 156-04-247.

5.4.1.2.4 Exposure in Cardiac Edema Trials

In 7 pooled trials in subjects with cardiac edema, a total of 437 subjects were exposed to oral tolvaptan in doses ranging from 7.5 to 45 mg (Table 5.4.1.2.4-1) for a total of 2755 days of exposure. The median exposure for all doses of oral tolvaptan combined was 7 days, with a mean exposure of 6 days (± 2 days).

Table 5.4.1.2.4-1 Exposure to Oral Tolvaptan by Dose in 7 Pooled Cardiac Edema Trials

Dose	Total subjects exposed	Mean exposure (days)	SD (days)	Minimum (days)	Maximum (days)
7.5 mg	10	7	1	3	7
15 mg	364	6	2	1	14
30 mg	36	7	1	2	7
45 mg	29	6	2	1	7
Any oral dose	437	6	2	1	14
Placebo/other	302	6	2	1	13

SD = standard deviation.
Note: Subjects are included in the pooled safety analysis if they received at least 1 dose of tolvaptan.
Trials: 156-03-001, 156-06-002, 156-06-004, 156-06-006, 156-10-005, 156-TWA-1101i, and 156-12-809-01.

5.4.1.2.5 Exposure in Hepatic Cirrhosis Trials

In 8 pooled trials in subjects with hepatic edema, a total of 855 subjects were exposed to oral tolvaptan in doses ranging from 3.75 to 60 mg (Table 5.4.1.2.5-1) for a total of 5965 days of exposure. The median exposure for all doses of oral tolvaptan combined was 7 days, with a mean exposure of 7 days (± 2 days).

Table 5.4.1.2.5-1 Exposure to Oral Tolvaptan by Dose in 8 Pooled Hepatic Cirrhosis Trials

Dose	Total subjects exposed	Mean exposure (days)	SD (days)	Minimum (days)	Maximum (days)
3.75 mg	19	7	1	1	7
7.5 mg	333	7	2	1	14
15 mg	409	7	1	1	7
≤ 15 mg	748	7	2	1	14
30 mg	89	6	1	1	7
15 to 60 mg[a]	18	7	3	1	9
Any oral dose	855	7	2	1	14
Placebo/other	245	6	1	1	7

SD = standard deviation.
Note: Subjects are included in the pooled safety analysis if they received at least 1 dose of tolvaptan.
[a]Subjects who received titrated doses from 15 to 60 mg.
Trials: 156-03-002, 156-06-005, 156-08-001, 156-08-002, 156-08-804-01, 156-08-804-01, 156-09-004, 156-09-806-01.

5.4.1.2.6 Exposure in Carcinomatous Edema Trial

Trial 156-12-001 was conducted in subjects with volume overload associated with cancer. A total of 43 subjects were exposed to oral tolvaptan in doses ranging from 3.75 to 30 mg. The median exposure for all doses was 8 days, with a mean exposure of 8 days (± 2 days) (Table 5.4.1.2.6-1).

Table 5.4.1.2.6-1 Exposure to Oral Tolvaptan by Dose in Carcinomatous Edema (Trial 156-12-001)

Dose	Total subjects exposed	Mean exposure (days)	SD (days)	Minimum (days)	Maximum (days)
3.75 to 30 mg/day	43	8	2	1	10

SD = standard deviation

5.4.1.2.7 Exposure in Chronic Renal Failure Trials

In 2 pooled trials in subjects with chronic renal failure, a total of 43 subjects were exposed to oral tolvaptan in doses ranging from 7.5 to 60 mg. The median exposure for all doses was 7 days, with a mean exposure of 7 days (± 2 days) (Table 5.4.1.2.7-1).

Table 5.4.1.2.7-1 Exposure to Oral Tolvaptan by Dose in 2 Pooled Chronic Renal Failure Trials					
Dose	**Total subjects exposed**	**Mean exposure (days)**	**SD (days)**	**Minimum (days)**	**Maximum (days)**
7.5 to 60 mg/day	43	7	2	2	11

SD = standard deviation.
Trials: 156-12-002 and 156-12-007.

5.4.1.2.8 Exposure in ADPKD or Renal Impairment Trials

Long-term Placebo-controlled Trial in Adult Subjects With ADPKD (Trial 156-04-251)

In the pivotal long-term double-blind placebo-controlled trial of tolvaptan in adult subjects with ADPKD (Trial 156-04-251), a total of 961 subjects were exposed to oral tolvaptan tablets (spray-dried formulation) in doses ranging from 60 to 120 mg for a total of 852101 exposure days. The median exposure for all doses was 1081 days, with a mean exposure of 887 days (± 370 days).

Table 5.4.1.2.8-1 Exposure to Oral Tolvaptan by Dose in the Pivotal Long-term ADPKD Trial (Trial 156-04-251)					
Dose	**Total subjects exposed**	**Mean exposure (days)**	**SD (days)**	**Minimum (days)**	**Maximum (days)**
60 - 120 mg	961	887	370	1	1139
Placebo/other	483	987	253	6	1165

ADPKD = autosomal dominant polycystic kidney disease; SD = standard deviation.

Short Term Ascending Dose ADPKD Trials (Single and Multiple Dose)

In the short-term ascending dose trials, a total of 63 subjects were exposed to oral tolvaptan tablets in doses ranging from 15 to 120 mg for a total of 388 days of exposure. The median exposure for all doses of oral formulation combined was 5 days, with a mean exposure of 6 days (±3 days) (Table 5.4.1.2.8-2).

Table 5.4.1.2.8-2 Short Term Ascending Dose ADPKD Trials					
Dose	**Total subjects exposed**	**Mean exposure (days)**	**SD (days)**	**Minimum (days)**	**Maximum (days)**
15 mg	26	1	0	1	1
30 mg	44	6	3	1	11
45 mg	9	5	0	5	5
60 mg	18	3	2	1	5
120 mg	8	1	0	1	1
Any oral dose	63	6	3	4	12
Placebo/other	3	4	0	4	4

Trials: 156-04-001, 156-04-248 and 156-04-249.
ADPKD = autosomal dominant polycystic kidney disease; SD = standard deviation.

Short-term ADPKD Trials With or Without Renal Impairment

In 7 pooled short-term trials in subjects with ADPKD with or without renal impairment, a total of 270 subjects were exposed to oral tolvaptan in doses ranging from 15 to 120 mg (Table 5.4.1.2.8-3) for a total of 8627 days of exposure. The median exposure for all doses of all oral formulations combined was 21 days, with a mean exposure of 32 days (± 23 days).

Table 5.4.1.2.8-3 Exposure to Oral Tolvaptan by Dose in 7 Pooled Short-term ADPKD Trials

Dose	Total subjects exposed	Mean exposure (days)	SD (days)	Minimum (days)	Maximum (days)
15 mg	26	1	0	1	1
30 mg	44	6	3	1	11
45 mg	9	5	0	5	5
60 mg	67	6	2	1	14
90 mg	71	36	26	2	113
120 mg	47	7	3	1	9
MR 20 mg	17	7	0	7	7
MR 40 mg	17	7	0	6	7
MR 50 mg	45	52	12	6	67
MR 60 mg	17	7	0	7	8
MR 80 mg	44	51	15	2	70
MR 120 mg	12	7	0	7	7
Any oral dose	270	32	23	2	113
Placebo/other	45	49	17	4	62

ADPKD = autosomal dominant polycystic kidney disease; MR = modified release; SD = standard deviation.
Note: Subjects are included in the pooled safety analysis if they received at least 1 dose of tolvaptan.
Trials: 156-04-001, 156-04-248, 156-04-249, 156-06-260, 156-09-284, 156-09-285, and 156-09-290.

For the 3 open-label trials that assessed long-term safety of tolvaptan in subjects with ADPKD, exposure for the titration period in Trial 156-04-250 is presented separately in Table 5.4.1.2.8-4, whereas the long-term exposure for the fixed-dose period in this trial was pooled with the long-term exposure in Trial 156-05-002 (Table 5.4.1.2.8-5). In Trial 156-04-250, open-label treatment with oral tolvaptan was titrated (tolvaptan was administered in the range of 30 to 120 mg/day during the 2-month titration period), after which subjects were randomized to receive a fixed split-dose (AM/PM) QD regimen (45/15 mg or 60/30 mg) for 36 months. In Trial 156-05-002 (an extension trial for subjects who had participated in Trial 156-04-001), subjects received oral 15 mg tolvaptan BID for 36 months, and in Trial 156-09-003 (an extension trial for subjects who participated in Trial 156-05-002), 13 subjects received oral tolvaptan from 30 to 120 mg daily for 205 to 1651 days.

Table 5.4.1.2.8-4 Exposure to Tolvaptan During the Titration Period in 46 Subjects with ADPKD (Trial 156-04-250)		
Dose (AM/PM)	**n**	**Down-titrated n (reduced dose)**
15/15 mg	1 (starting dose)	0
30/15 mg	45 (starting dose)	2 (15/15 mg)
30/15 mg	1 (up-titration)	0
45/15 mg	44 (up-titration)	0
60/30 mg	44 (up-titration)	16 (45/15 mg)
90/30 mg	28 (up-titration)	7 (60/30 mg)

ADPKD = autosomal dominant polycystic kidney disease.

Table 5.4.1.2.8-5 Long-term Extent of Exposure to Tolvaptan in Subjects With ADPKD (Trials 156-04-250 and 156-05-002)					
Dose (AM/PM)	**Total subjects exposed[a]**	**Mean exposure (days)**	**SD (days)**	**Minimum (days)**	**Maximum (days)**
15/15 mg	17	903	396	59	1138
45/15 mg	22	1126	502	26	1400
60/30 mg	24	1197	361	66	1415
Any oral dose	63	1093	434	26	1415

ADPKD = autosomal dominant polycystic kidney disease; SD = standard deviation.
[a]Subjects are included if they received at least one dose of tolvaptan.

Renal Impairment Without ADPKD

In support of the ADPKD program, Trial 156-09-282 determined the effect of varying degrees of renal function on the pharmacokinetics and pharmacodynamics of tolvaptan in 37 subjects without ADPKD. All 37 subjects received a single 60-mg oral dose of tolvaptan.

5.4.2 Treatment-emergent Adverse Events

The pooling strategy for the presentation of TEAEs across tolvaptan trials and for the various disease states is depicted in Table 5.4.2-1.

Table 5.4.2-1 Pooling Strategy for Analysis of Treatment-emergent Adverse Events by Disease State

Subject Population (Number of trials pooled)	Trials Included in Pooling
Overall Pooled Safety Analysis (N = 91)	All trials in healthy subjects and all trials in disease states (Table 5.1-1 and Table 5.1-2, respectively) except: • Phase 1 - 156-94-001, 156-94-002 • Open-label, long-term: 156-03-244, 156-04-250, 156-05-002, 156-09-003 (data are presented individually for each trial) • 8 ongoing trials: Open label or observational: 156-09-101, 156-10-003, 156-08-271, 156-13-211 and Double-blind: 156-12-203, 156-13-003, 156-KOB-1201i, 156-13-210
Healthy Subjects (N = 47)	All trials in healthy subjects (Table 5.1-1)
Hyponatremia (N = 9)	156-96-201, 156-96-203, 156-97-204, 156-02-235, 156-03-238, 156-04-246, 156-07-802-01, 156-08-275, 156-KOB-1101i (Note: Trial 156-03-244 is presented separately)
Cardiac Edema (N = 7)	156-03-001, 156-06-002, 156-06-004, 156-06-006, 156-10-005, 156-12-809-01, 156-TWA-1101i
Heart Failure (N = 10)	156-97-251, 156-97-252, 156-98-213, 156-00-220, 156-00-221, 156-00-222, 156-01-231, 156-01-232, 156-03-236, 156-04-247
Hepatic Edema (N = 8)	156-03-002, 156-06-005, 156-08-001, 156-08-002, 156-08-804-01, 156-08-805-01, 156-09-004, 156-09-806-01
Carcinomatous edema (N = 1)	156-12-001
Chronic renal failure (N = 2)	156-12-002, 156-12-007
ADPKD • Long-term, placebo-controlled (N = 1) • Short-term, ascending dose (N = 3) • Open-label long-term (N = 3)	156-04-251 156-04-001, 156-04-248, 156-04-249 156-04-250, 156-05-002, 156-09-003 (Note: Data are presented individually for 2 ADPKD trials that focused on renal function [156-06-260, 156-09-284]; one supportive trial in subjects with renal impairment [156-09-282]; and for two ADPKD trials of the MR formulation (also presented by individual trial [156-09-285 and 156-09-290])

ADPKD = autosomal dominant polycystic kidney disease; MR = modified-release.

Across the 91 trials included in the pooled safety analysis (ie, regardless of indication or phase), the most common TEAEs (≥ 3% incidence) in the All Oral Tolvaptan Dose group

(all oral formulations combined) are summarized in Table 5.4.2-2; data for the placebo/other and furosemide treatment groups are included for comparison. Common TEAEs (≥ 3% incidence) for the Any Oral Tolvaptan Spray-dried Dose group (spray-dried tablet or capsule formulation only) are summarized by dose in Table 5.4.2-3. A similar summary is presented in Table 5.4.2-4 for alternative oral tolvaptan formulations (ie, jet-milled, modified-release, slow-disintegration tablets, and oral suspension) by dose and combined. The TEAEs reported with administration of the IV formulation of tolvaptan (14 patients who were also exposed to the tolvaptan 30 mg oral spray-dried tablets in Trial 156-05-254) are not included in these tables; one TEAE (nasopharyngitis) was reported for 1/14 patients exposed to IV tolvaptan. The IV formulation is not discussed further in this IB.

Thirst was the most common TEAE for tolvaptan subjects across all oral doses and formulations combined (25.4% of tolvaptan-treated subjects overall in the pooled analysis, see Table 5.4.2-2) and was either the most common or among the most common across healthy subjects and the 5 disease states with completed trials. The one exception was in one trial of subjects with ADPKD who received a 45/15 mg split dose of tolvaptan for 7 days, in which thirst was reported for only 1/20 subject (5.0%) (Section 5.4.2.7.4, Trial 156-06-260). Across the 5 disease states, the incidence of thirst was lowest (< 15%) in subjects in the pooled short-term ADPKD trials (9.5%, Table 5.4.2.7.2-1), in one trial of subjects with ADPKD who received a 45/15 mg split dose of tolvaptan for 7 days (Trial 156-06-260 as mentioned above), in the pooled hyponatremia trials (14.3%, Table 5.4.2.2-1), and in the long-term open-label extension trial in subjects with hyponatremia (12.6%, Table 5.4.2.2-2). Other common TEAEs in the All Tolvaptan Oral Dose group (by ≥ 3% incidence and greater than that of placebo) were dry mouth, pollakiuria, polyuria, headache, dizziness, constipation, fatigue, nocturia, nasopharyngitis, increased blood creatinine, and decreased appetite (Table 5.4.2-2).

Table 5.4.2-2 Most Common Treatment-emergent Adverse Events With at Least 3% Incidence in the All Tolvaptan Oral Dose Group (Summary of All Oral Formulations), in the Pooled Trials Analyzed for Safety

Adverse Event	All TLV Oral Dose[a] (N = 7343) n (%)	Placebo/ Other (N = 4334) n (%)	Furosemide 80 mg (N = 41) n (%)
Any adverse event	5945 (81.0)	3412 (78.7)	17 (41.5)
Thirst	1830 (24.9)	206 (4.8)	2 (4.9)
Dry mouth	771 (10.5)	158 (3.6)	2 (4.9)
Pollakiuria	715 (9.7)	81 (1.9)	0 (0.0)
Polyuria	662 (9.0)	101 (2.3)	0 (0.0)
Headache	642 (8.7)	344 (7.9)	3 (7.3)
Cardiac failure	606 (8.3)	585 (13.5)	0 (0.0)
Nausea	547 (7.4)	400 (9.2)	1 (2.4)
Dizziness	507 (6.9)	293 (6.8)	2 (4.9)
Cardiac failure congestive	476 (6.5)	409 (9.4)	1 (2.4)
Constipation	477 (6.5)	260 (6.0)	0 (0.0)
Diarrhoea	456 (6.2)	299 (6.9)	1 (2.4)
Fatigue	415 (5.7)	177 (4.1)	0 (0.0)
Hypertension	407 (5.5)	257 (5.9)	0 (0.0)
Nocturia	399 (5.4)	75 (1.7)	0 (0.0)
Hypotension	351 (4.8)	288 (6.6)	1 (2.4)
Nasopharyngitis	333 (4.5)	190 (4.4)	0 (0.0)
Insomnia	328 (4.5)	230 (5.3)	0 (0.0)
Vomiting	316 (4.3)	220 (5.1)	1 (2.4)
Back pain	310 (4.2)	203 (4.7)	0 (0.0)
Blood creatinine increased	308 (4.2)	166 (3.8)	0 (0.0)
Urinary tract infection	310 (4.2)	247 (5.7)	1 (2.4)
Dyspnoea	283 (3.9)	178 (4.1)	0 (0.0)
Chest pain	282 (3.8)	194 (4.5)	0 (0.0)
Renal pain	278 (3.8)	177 (4.1)	0 (0.0)
Cough	277 (3.8)	233 (5.4)	0 (0.0)
Hypokalaemia	271 (3.7)	254 (5.9)	0 (0.0)
Hyperkalaemia	264 (3.6)	177 (4.1)	0 (0.0)
Oedema peripheral	248 (3.4)	191 (4.4)	1 (2.4)
Anaemia	247 (3.4)	221 (5.1)	0 (0.0)
Abdominal pain	243 (3.3)	160 (3.7)	0 (0.0)
Pyrexia	231 (3.1)	160 (3.7)	1 (2.4)
Decreased appetite	230 (3.1)	89 (2.1)	0 (0.0)
Bronchitis	224 (3.1)	182 (4.2)	0 (0.0)
Upper respiratory tract infection	217 (3.0)	151 (3.5)	0 (0.0)
Hyperuricaemia	218 (3.0)	145 (3.3)	0 (0.0)

TLV = tolvaptan; UK = United Kingdom; US = United States.

[a]Subjects are counted once for each dose received and once for the Any Tolvaptan Oral Dose category.

Trials: 156-95-301, 156-95-302, 156-95-303, 156-95-304, 156-95-305, 156-96-301, and 156-03-242 (healthy subjects phase 1 UK); 156-96-205, 156-97-202, 156-98-201, 156-98-202, 156-98-210, 156-01-223, 156-01-225, 156-01-229, 156-01-233, 156-01-234, 156-03-239, 156-03-240, 156-03-245, 156-05-252, 156-05-253, 156-05-254, 156-05-256, 156-07-262, 156-07-263, 156-08-269, 156-08-270, 156-11-295, and 156-12-202 (healthy subjects phase 1 US); 156-01-226 (healthy subjects phase 1 US and Argentina); 156-00-001, 156-00-002, 156-00-003, 156-05-001, 156-05-003, 156-05-004, 156-07-002, 156-10-004, 156-10-006, and 156-14-004 (healthy subjects phase 1 Japan); 156-06-801-01, 156-11-807-01, and 156-11-808-01 (healthy subjects phase 1 China); 156-KOA-0801 (healthy subjects phase 1 Korea); 156-09-806-01 (hepatic impairment phase 1 China); 156-06-260

(ADPKD phase 1 US); 156-09-282 (renal impairment phase 1 US); 156-96-201, 156-96-203, 156-97-204, 156-02-235, 156-03-238, 156-04-246, 156-07-802-01, and 156-08-275 (hyponatremia phase 2/3); 156-KOB-1101i (hyponatremia phase 4 Korea); 156-97-251, 156-97-252, 156-98-213, 156-00-220, 156-00-221, 156-00-222, 156-01-231, 156-01-232, 156-03-236, and 156-04-247 (heart failure phase 2/3); 156-04-248, 156-04-249, 156-04-001, 156-04-251, 156-09-284, 156-09-285, and 156-09-290 (ADPKD phase 2/3); 156-03-001, 156-06-002, 156-06-004, 156-06-006, and 156-12-809-01 (cardiac edema phase 2/3 Japan and China); 156-10-005 (cardiac edema phase 4 Japan); 156-03-002, 156-06-005, 156-08-001, 156-08-002, 156-09-004 (hepatic edema phase 2/3 Japan); 156-08-804-01, 156-08-805-01 (hepatic edema phase 2/3 China), 156-12-001 (carcinomatous edema, phase 2, Japan), 156-12-002, 156-12-007 (chronic renal failure, phase 2, Japan), and 156-TWA-1101i (cardiac edema, phase 3, Taiwan).

Table 5.4.2-3 Most Common Treatment-emergent Adverse Events With at Least 3% Incidence in the Any Tolvaptan Spray-dried Capsule/Tablet Group by Dose, in the Pooled Trials Analyzed for Safety

Adverse Event	Dose of Tolvaptan Spray-dried (S-D) Capsule/Tablet						Any Oral TLV S-D Dose[a] (N = 7129) n (%)
	≤ 15 mg (N = 1481) n (%)	30 mg (N = 3000) n (%)	45 mg (N = 107) n (%)	60 mg (N = 706) n (%)	15 to 60 mg (N = 478) n (%)	> 60 mg (N = 1386) n (%)	
Any adverse event	1009 (68.1)	2483 (82.8)	87 (81.3)	529 (74.9)	398 (83.3)	1264 (91.2)	N/A[b]
Thirst	214 (14.4)	521 (17.4)	37 (34.6)	242 (34.3)	77 (16.1)	664 (47.9)	1763 (24.7)
Dry mouth	110 (7.4)	260 (8.7)	13 (12.1)	116 (16.4)	57 (11.9)	193 (13.9)	747 (10.5)
Pollakiuria	70 (4.7)	165 (5.5)	15 (14.0)	103 (14.6)	32 (6.7)	294 (21.2)	683 (9.6)
Headache	38 (2.6)	193 (6.4)	3 (2.8)	73 (10.3)	21 (4.4)	291 (21.0)	618 (8.7)
Polyuria	7 (0.5)	95 (3.2)	4 (3.7)	75 (10.6)	10 (2.1)	431 (31.1)	621 (8.7)
Cardiac failure	33 (2.2)	544 (18.1)	2 (1.9)	11 (1.6)	10 (2.1)	4 (0.3)	606 (8.5)
Nausea	41 (2.8)	280 (9.3)	3 (2.8)	46 (6.5)	29 (6.1)	131 (9.5)	532 (7.5)
Dizziness	55 (3.7)	226 (7.5)	7 (6.5)	42 (5.9)	31 (6.5)	136 (9.8)	497 (7.0)
Cardiac failure congestive	29 (2.0)	380 (12.7)	6 (5.6)	38 (5.4)	9 (1.9)	14 (1.0)	476 (6.7)
Constipation	61 (4.1)	243 (8.1)	7 (6.5)	30 (4.2)	30 (6.3)	95 (6.9)	473 (6.6)
Diarrhoea	52 (3.5)	193 (6.4)	3 (2.8)	31 (4.4)	23 (4.8)	148 (10.7)	450 (6.3)
Fatigue	27 (1.8)	142 (4.7)	9 (8.4)	55 (7.8)	26 (5.4)	149 (10.8)	407 (5.7)
Hypertension	5 (0.3)	58 (1.9)	0 (0.0)	3 (0.4)	4 (0.8)	331 (23.9)	402 (5.6)
Nocturia	7 (0.5)	15 (0.5)	1 (0.9)	37 (5.2)	1 (0.2)	306 (22.1)	367 (5.1)
Hypotension	11 (0.7)	255 (8.5)	3 (2.8)	14 (2.0)	27 (5.6)	39 (2.8)	351 (4.9)
Insomnia	33 (2.2)	192 (6.4)	0 (0.0)	9 (1.3)	21 (4.4)	70 (5.1)	327 (4.6)
Nasopharyngitis	29 (2.0)	56 (1.9)	2 (1.9)	8 (1.1)	5 (1.0)	223 (16.1)	328 (4.6)
Blood creatinine increased	49 (3.3)	87 (2.9)	1 (0.9)	12 (1.7)	11 (2.3)	144 (10.4)	305 (4.3)
Urinary tract infection	20 (1.4)	156 (5.2)	4 (3.7)	15 (2.1)	19 (4.0)	92 (6.6)	307 (4.3)
Back pain	17 (1.1)	112 (3.7)	2 (1.9)	17 (2.4)	11 (2.3)	146 (10.5)	306 (4.3)
Vomiting	40 (2.7)	142 (4.7)	3 (2.8)	12 (1.7)	14 (2.9)	92 (6.6)	308 (4.3)
Dyspnoea	20 (1.4)	186 (6.2)	10 (9.3)	23 (3.3)	12 (12.5)	31 (2.2)	282 (4.0)
Chest pain	13 (0.9)	188 (6.3)	6 (5.6)	18 (2.5)	12 (2.5)	45 (3.2)	282 (4.0)
Renal pain	0 (0.0)	2 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	272 (19.6)	275 (3.9)
Cough	21 (1.4)	139 (4.6)	6 (5.6)	11 (1.6)	13 (2.7)	86 (6.2)	276 (3.9)
Hypokalaemia	47 (3.2)	182 (6.1)	1 (0.9)	7 (1.0)	24 (5.0)	10 (0.7)	271 (3.8)
Hyperkalaemia	38 (2.6)	171 (5.7)	3 (2.8)	15 (2.1)	21 (4.4)	12 (0.9)	264 (3.7)
Oedema peripheral	19 (1.3)	89 (3.0)	3 (2.8)	12 (1.7)	38 (7.9)	83 (6.0)	246 (3.5)
Anaemia	19 (1.3)	172 (5.7)	1 (0.9)	9 (1.3)	13 (2.7)	33 (2.4)	247 (3.5)

Table 5.4.2-3 Most Common Treatment-emergent Adverse Events With at Least 3% Incidence in the Any Tolvaptan Spray-dried Capsule/Tablet Group by Dose, in the Pooled Trials Analyzed for Safety

Adverse Event	Dose of Tolvaptan Spray-dried (S-D) Capsule/Tablet						Any Oral TLV S-D Dose[a] (N = 7129) n (%)
	≤ 15 mg (N = 1481) n (%)	30 mg (N = 3000) n (%)	45 mg (N = 107) n (%)	60 mg (N = 706) n (%)	15 to 60 mg (N = 478) n (%)	> 60 mg (N = 1386) n (%)	
Abdominal pain	20 (1.4)	113 (3.8)	0 (0.0)	13 (1.8)	15 (3.1)	80 (5.8)	241 (3.4)
Pyrexia	45 (3.0)	97 (3.2)	0 (0.0)	7 (1.0)	27 (5.6)	49 (3.5)	228 (3.2)
Decreased appetite	23 (1.6)	80 (2.7)	1 (0.9)	26 (3.7)	15 (3.1)	79 (5.7)	226 (3.2)
Bronchitis	7 (0.5)	145 (4.8)	0 (0.0)	5 (0.7)	5 (1.0)	61 (4.4)	223 (3.1)
Hyperuricaemia	22 (1.5)	150 (5.0)	0 (0.0)	1 (0.1)	3 (0.6)	40 (2.9)	218 (3.1)
Upper respiratory tract infection	27 (1.8)	79 (2.6)	2 (1.9)	11 (1.6)	4 (0.8)	91 (6.6)	214 (3.0)
Pain in extremity	11 (0.7)	122 (4.1)	0 (0.0)	13 (1.8)	8 (1.8)	57 (4.1)	212 (3.0)

S-D = spray-dried; TLV = tolvaptan; UK = United Kingdom; US = United States.

[a] Subjects are counted once for each dose received and once for the Any TLV Spray-dried Oral Dose Capsule/Tablet category. Subjects who received the jet-milled and MR formulations of tolvaptan are not included. See Table 5.4.2-2, Any Tolvaptan Oral Dose group (N = 7171), for all adverse events experienced by all tolvaptan-treated subjects in the pooled safety database.

[b] N/A = a meaningful number is not available for this group; some subjects received more than one dosage of tolvaptan, therefore, the total number of subjects who experienced an adverse event is not the sum of all dosage groups.

Trials: 156-95-302, 156-95-303, 156-95-304, 156-95-305, 156-96-301, and 156-03-242 (healthy subjects phase 1 UK); 156-96-205, 156-97-202, 156-98-201, 156-98-202, 156-98-210, 156-01-223, 156-01-225, 156-01-229, 156-01-233, 156-01-234, 156-03-239, 156-03-240, 156-03-245, 156-05-252, 156-05-254, 156-05-256, 156-07-262, 156-11-295, and 156-12-202 (healthy subjects phase 1 US); 156-01-226 (healthy subjects phase 1 US and Argentina); 156-00-001, 156-00-002, 156-00-003, 156-05-001, 156-05-003, 156-07-002, 156-10-004, 156-14-004 (healthy subjects phase 1 Japan); 156-06-801-01, 156-11-807-01, and 156-11-808-01 (healthy subjects phase 1 China); 156-KOA-0801 (healthy subjects phase 1 Korea); 156-09-806-01 (hepatic impairment phase 1 China); 156-06-260 (ADPKD phase 1 US); 156-09-282 (renal impairment phase 1 US); 156-96-201, 156-96-203, 156-97-204, 156-02-235, 156-03-238, 156-04-246, 156-07-802-01, and 156-08-275 (hyponatremia phase 2/3); 156-KOB-1101i (hyponatremia phase 4 Korea); 156-97-251, 156-97-252, 156-98-213, 156-00-220, 156-00-221, 156-00-222, 156-01-231, 156-01-232, 156-03-236, and 156-04-247 (heart failure phase 2/3); 156-04-248, 156-04-249, 156-04-001, 156-04-251. 156-09-284, 156-09-285, and 156-09-290 (ADPKD phase 2/3); 156-03-001, 156-06-002, 156-06-004, 156-06-006, and 156-12-809-01 (cardiac edema phase 2/3 Japan and China); 156-10-005 (cardiac edema phase 4 Japan); 156-03-002, 156-06-005, 156-08-001, 156-08-002, 156-09-004 (hepatic edema phase 2 Japan); 156-08-804-01 and 156-08-805-01 (hepatic edema phase 2/3 China), 156-12-001 (carcinomatous edema phase 2 Japan), 156-12-002 and 156-12-007 (chronic renal failure phase 2 Japan), 156-14-004 (bioequivalence phase 1 Japan), and 156-TWA-1101i (cardiac edema phase 2 Taiwan).

Table 5.4.2-4 Most Common Treatment-emergent Adverse Events With at Least 3% Incidence in the Any Tolvaptan Group of Alternative Oral Formulations by Dose, in the Pooled Trials Analyzed for Safety

Adverse Event	Dose and Formulation of Tolvaptan													15 mg P (N=40) n (%)	Any non-S-D TLV Oral Dose[a] (N = 291) n (%)
	60 mg JM (N = 4) n (%)	150 mg JM (N = 59) n (%)	300 mg JM (N = 28) n (%)	450 mg JM (N = 28) n (%)	20 mg MR (N = 27) n (%)	20 mg SDT (N = 28) n (%)	40 mg MR (N = 17) n (%)	50 mg MR (N = 45) n (%)	60 mg MR (N = 87) n (%)	60 mg SDT (N = 10) n (%)	80 mg MR (N = 44) n (%)	120 mg MR (N = 12) n (%)	15 mL Oral Susp (N = 14) n (%)		
Any adverse event	1 (25.0)	30 (50.8)	12 (42.9)	9 (32.1)	9 (33.3)	12 (42.9)	10 (58.8)	30 (66.7)	53 (60.9)	1 (10.0)	33 (75.0)	8 (66.7)	5 (35.7)	1 (2.5)	N/A[b]
Thirst	0 (0.0)	12 (20.3)	3 (10.7)	2 (7.1)	3 (11.1)	0 (0.0)	3 (17.6)	15 (33.3)	30 (34.5)	0 (0.0)	15 (34.1)	2 (16.7)	3 (21.4)	0 (0.0)	83 (27.2)
Polyuria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.4)	0 (0.0)	5 (29.4)	11 (24.4)	22 (25.3)	0 (0.0)	11 (25.0)	4 (33.3)	0 (0.0)	0. (0.0)	53 (17.4)
Pollakiuria	0 (0.0)	3 (5.1)	2 (7.1)	3 (10.7)	2 (7.4)	5 (17.9)	2 (11.8)	8 (17.8)	1 (1.1)	0 (0.0)	9 (20.5)	2 (16.7)	0 (0.0)	0. (0.0)	32 (10.5)
Nocturia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	2 (11.8)	14 (31.1)	1 (1.1)	0 (0.0)	14 (31.8)	1 (8.3)	0 (0.0)	0. (0.0)	32 (10.5)
Headache	1 (25.0)	7 (11.9)	3 (10.7)	1 (3.6)	0 (0.0)	0 (0.0)	2 (11.8)	1 (2.2)	8 (9.2)	0 (0.0)	1 (2.3)	1 (8.3)	2 (14.3)	0. (0.0)	26 (8.5)
Dry mouth	0 (0.0)	3 (5.1)	0 (0.0)	2 (7.1)	1 (3.7)	2 (7.1)	1 (5.9)	7 (15.6)	2 (2.3)	0 (0.0)	7 (15.9)	0 (0.0)	1 (7.1)	0. (0.0)	24 (7.9)
Polydipsia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	2 (11.8)	7 (15.6)	0 (0.0)	0 (0.0)	6 (13.6)	2 (16.7)	0 (0.0)	0. (0.0)	17 (5.6)
Nausea	0 (0.0)	1 (1.7)	1 (3.6)	1 (3.6)	0 (0.0)	2 (7.1)	0 (0.0)	2 (4.4)	5 (5.7)	0 (0.0)	1 (2.3)	2 (16.7)	1 (7.1)	0. (0.0)	15 (4.9)
Dizziness	0 (0.0)	3 (5.1)	2 (7.1)	1 (3.6)	0 (0.0)	0 (0.0)	1 (5.9)	2 (4.4)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	0. (0.0)	11 (3.6)

JM = jet-milled; MR = modified release; SDT = slow disintegration tablet; P = powder; TLV = tolvaptan; UK = United Kingdom; US = United States.

[a] JM, MR, SDT, oral suspension, or P.

[b] N/A = a meaningful number is not available. The total number of subjects who received any tolvaptan JM, MR, or SDT formulations combined and reported any adverse event is not available.

Trials: 156-95-301 (healthy subjects phase 1 UK); 156-97-202, 156-05-252, 156-05-253, 156-05-254, 156-07-262, 156-07-263, 156-08-269, 156-08-270, and 156-12-202 (healthy subjects phase 1 US); 156-05-003, 156-05-004, 156-10-006, and 156-14-004 (healthy subjects phase 1 Japan); 156-09-285, and 156-09-290 (ADPKD phase 2).

5.4.2.1 Treatment-emergent Adverse Events in Healthy Subjects

The incidences of TEAEs reported by at least 3% of subjects in the All Tolvaptan Oral Doses group, the Any Tolvaptan MR Oral Dose group, and the oral suspension group from pooled phase 1 trials in healthy subjects are shown in Table 5.4.2.1-1. The pooled trials include Trial 156-01-226, an interaction trial in subjects with a history of arrhythmia and who were on maintenance amiodarone therapy, but were otherwise healthy. The most commonly reported TEAEs (by > 10% incidence in the All Tolvaptan Oral Doses group or the Any Tolvaptan MR Oral Dose group and greater than placebo) in healthy subjects treated with tolvaptan were thirst, pollakiuria, and headache for the All Tolvaptan Oral Doses group and thirst and headache for the Any Tolvaptan MR Oral Dose group and the Tolvaptan Oral Syrup group. In the tolvaptan oral suspension group, the most common TEAEs (by ≥ 10% incidence and greater than placebo) were thirst and headache. Headache was the most commonly reported TEAE in the placebo subjects.

Four of these trials in healthy subjects were trials of the MR oral capsule formulation conducted in the US and Japan: a relative bioavailability trial using 3 MR formulations (MR-1, MR-2, MR-3) in comparison to the tolvaptan IR formulation (Trial 156-07-262), a pharmacokinetic/pharmacodynamic trial following multiple dosing of the MR-3 formulation (Trial 156-07-263), a dose strength equivalence trial of the MR-3 formulation with an arm comparing single doses and an arm evaluating pharmacokinetics/pharmacodynamics after multiple doses (Trial 156-08-269), and a trial evaluating the pharmacokinetics/pharmacodynamics and safety of the MR-3 formulation in healthy male subjects following single-dose administration (including assessment of food effect and comparison with the IR tablet formulation), and after repeated oral dose administration (Trial 156-10-006). The TEAE data are presented in Table 5.4.2.1-1 for the MR formulations combined due to their similarity of chemical composition. Generally the adverse event profiles are consistent between the Any Tolvaptan MR Oral Dose group and the All Tolvaptan Oral Doses group, with thirst being the TEAE most frequently reported in either. Polyuria and headache were the other most commonly reported TEAEs (ie, by ≥ 10% incidence) in MR oral formulation subjects; whereas in the All Tolvaptan Oral Doses group, pollakiuria and headache were the other most commonly reported TEAEs.

Table 5.4.2.1-1 Treatment-emergent Adverse Events With at Least 3% Incidence in the All Tolvaptan Oral Dose Group and/or Any Tolvaptan MR Oral Dose Group From Pooled Phase 1 Trials in Healthy Subjects Analyzed for Safety

Adverse Events	All Tolvaptan Oral Doses[a] (N = 1071) n (%)	Placebo/ Other (N = 288) n (%)	Any Tolvaptan MR Oral Dose[b] (N = 70) n (%)	Tolvaptan 15 mL Oral Suspension (N = 14) n (%)	Furosemide 80 mg (N = 6) n (%)
Any adverse event	630 (58.8)	105 (36.5)	48 (68.6)	5 (35.7)	1 (16.7)
Thirst	324 (30.3)	10 (3.5)	30 (42.9)	3 (21.4)	0 (0.0)
Pollakiuria	153 (14.3)	13 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	107 (10.0)	26 (9.0)	7 (10.0)	2 (14.3)	1 (16.7)
Dry mouth	95 (8.9)	10 (3.5)	2 (2.9)	1 (7.1)	1 (16.7)
Polyuria	80 (7.5)	0 (0.0)	21 (30.0)	0 (0.0)	0 (0.0)
Dizziness	48 (4.5)	17 (5.9)	1 (1.4)	1 (7.1)	1 (16.7)
Nausea	43 (4.0)	15 (5.2)	4 (5.7)	1 (7.1)	1 (16.7)
Fatigue	34 (3.2)	6 (2.1)	1 (1.4)	0 (0.0)	0 (0.0)
Nasal congestion	14 (1.3)	4 (1.4)	3 (4.3)	0 (0.0)	0 (0.0)
Somnolence	9 (0.8)	0 (0.0)	3 (4.3)	0 (0.0)	0 (0.0)

MR = modified release; SDT = slow disintegration tablet; UK = United Kingdom; US = United States.

[a] Includes spray-dried doses of 5, 10, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420, and 480 mg: jet-milled doses of 150, 300, and 450 mg; MR doses of 20 and 60 mg; SDT doses of 20 and 60 mg, and 1% powder doses of 15 mg. Subjects are counted once per term for any tolvaptan dose received.

[b] This subset of the All Tolvaptan group includes MR doses of 20 mg and 60 mg in Trials 156-07-262, 156-07-263, 156-08-269, and 156-10-006.Trials: 156-95-301, 156-95-302, 156-95-303, 156-95-304, 156-95-305, 156-96-301, and 156- 03-242 (UK); 156-96-205, 156-97-202, 156-98-201, 156-98-202, 156-98-210, 156-01-223, 156-01-225, 156-01-229, 156-01-233, 156-01-234, 156-03-239, 156-03-240, 156-03-245, 156-05-252, 156-05-253, 156-05-254, 156-05-256, 156-07-262, 156-07-263, 156-08-269, 156-08-270, 156-11-295, and 156-12-202 (US); 156-01-226 (US and Argentina); 156-00-001, 156-00-002, 156-00-003, 156-05-001, 156-05-003, 156-05-004, 156-07-002, 156-10-004, 156-10-006, and 156-14-004 (Japan); 156-06-801-01, 156-11-807-01, and 156-11-808-01 (China); 156-KOA-0801 (Korea).

5.4.2.2 Treatment-emergent Adverse Events in Hyponatremia Trials

The hyponatremia program comprised 835 subjects from 12 short-term trials involving either exclusive evaluation of subjects with hyponatremia (9 trials 156-96-201, 156-96-203, 156-97-204, 156-02-235, 156-03-238, 156-04-246, 156-07-802-01, 156-08-275, 156-KOB-1101i) or substantial subpopulations of subjects with hyponatremia (3 CHF trials: 156-97-252, 156-98-213, and 156-03-236). TEAEs reported by at least 3% of subjects treated with tolvaptan at any oral dose in the 9 trials that exclusively evaluated subjects with hyponatremia (511 subjects) are presented Table 5.4.2.2-1 and the TEAEs experienced by at least 3% of the 324 subjects in the 3 CHF trials is presented with all 3115 tolvaptan-treated subjects in CHF trials in Table 5.4.2.3.2-1.

For the 511 subjects in exclusively hyponatremia trials, the most commonly reported TEAEs (> 5% incidence in the All Tolvaptan Oral Doses group) in the tolvaptan subjects were thirst, dry mouth, peripheral oedema, nausea, dizziness, fatigue, constipation, headache, ascites, diarrhoea, pollakiuria, asthenia, hypotension, pyrexia, and hypokalaemia. The most commonly reported TEAEs (> 5% incidence) in the placebo subjects were peripheral oedema, diarrhoea, headache, ascites, vomiting, dyspnoea, nausea, and hypotension.

Table 5.4.2.2-1 Treatment-emergent Adverse Events With at Least 3% Incidence in the All Tolvaptan Group in Trials in Hyponatremia

Adverse Events	All Tolvaptan Oral Doses[a] (N = 511) n (%)	Placebo (N = 469) n (%)
Any adverse event	423 (82.8)	350 (74.6)
Thirst	73 (14.3)	19 (4.1)
Dry mouth	61 (11.9)	17 (3.6)
Oedema peripheral	40 (7.8)	38 (8.1)
Nausea	36 (7.0)	25 (5.3)
Dizziness	35 (6.8)	21 (4.5)
Fatigue	32 (6.3)	23 (4.9)
Constipation	32 (6.3)	18 (3.8)
Headache	30 (5.9)	29 (6.2)
Ascites	30 (5.9)	28 (6.0)
Diarrhoea	27 (5.3)	30 (6.4)
Pollakiuria	28 (5.5)	9 (1.9)
Asthenia	27 (5.3)	14 (3.0)
Hypotension	27 (5.3)	24 (5.1)
Pyrexia	26 (5.1)	12 (2.6)
Hypokalaemia	26 (5.1)	19 (4.1)
Urinary tract infection	23 (4.5)	15 (3.2)
Hyperkalaemia	23 (4.5)	19 (4.1)
Vomiting	20 (3.9)	27 (5.8)
Insomnia	18 (3.5)	14 (3.0)
Decreased appetite	18 (3.5)	5 (1.1)
Cough	17 (3.3)	12 (2.6)
Abdominal distention	16 (3.1)	8 (1.7)
Abdominal pain	16 (3.1)	14 (3.0)
Dyspnoea	16 (3.1)	25 (5.3)

[a] Doses of 5, 10, 15, 30, 45, 60 mg, and 15 to 60 mg titrated dose. Subjects are counted once per term for any tolvaptan dose received.

Trials: 156-96-201, 156-96-203, 156-97-204, 156-02-235, 156-03-238, 156-04-246, 156-07-802-01, 156-08-275, and 156-KOB-1101i.

The most common TEAEs experienced by at least 10% of all subjects with hyponatremia in the open-label, long-term trial, Trial 156-03-244, were hyponatremia, peripheral oedema, diarrhoea, anaemia, urinary tract infection, nausea, headache, fatigue, thirst, hypokalaemia, pneumonia, ascites, hypotension, dizziness, congestive cardiac failure, back pain, and pollakiuria (Table 5.4.2.2-2).

Table 5.4.2.2-2 Treatment-emergent Adverse Events With at Least 5% Incidence in the Total Population Regardless of Causality in the Long-term, Open-label, Hyponatremia Extension Trial (Trial 156-03-244)

Adverse Event	Prior Treatment (Parent Trial)		Tolvaptan (N = 111) n (%)
	Tolvaptan (N = 56) n (%)	Placebo (N = 55) n (%)	
Any adverse event	52 (92.9)	53 (96.4)	105 (94.6)
Hyponatremia	12 (21.4)	13 (23.6)	25 (22.5)
Oedema peripheral	11 (19.6)	11 (20.0)	22 (19.8)
Diarrhoea	10 (17.9)	10 (18.2)	20 (18.0)
Anaemia	8 (14.3)	12 (21.8)	20 (18.0)
Urinary tract infection	8 (14.3)	11 (20.0)	19 (17.1)
Nausea	8 (14.3)	11 (20.0)	19 (17.1)
Headache	10 (17.9)	5 (9.1)	15 (13.5)
Fatigue	7 (12.5)	8 (14.5)	15 (13.5)
Thirst	5 (8.9)	9 (16.4)	14 (12.6)
Hypokalaemia	5 (8.9)	9 (16.4)	14 (12.6)
Pneumonia	11 (19.6)	2 (3.6)	13 (11.7)
Ascites	7 (12.5)	6 (10.9)	13 (11.7)
Hypotension	7 (12.5)	6 (10.9)	13 (11.7)
Dizziness	7 (12.5)	6 (10.9)	13 (11.7)
Cardiac failure congestive	5 (8.9)	7 (12.7)	12 (10.8)
Back pain	5 (8.9)	7 (12.7)	12 (10.8)
Pollakiuria	4 (7.1)	8 (14.5)	12 (10.8)
Chest pain	5 (8.9)	6 (10.9)	11 (9.9)
Dyspnoea	5 (8.9)	6 (10.9)	11 (9.9)
Renal failure	4 (7.1)	7 (12.7)	11 (9.9)
Vomiting	3 (5.4)	8 (14.5)	11 (9.9)
Musculoskeletal pain	6 (10.7)	4 (7.3)	10 (9.0)
Cardiac failure	4 (7.1)	5 (9.1)	9 (8.1)
Bronchitis	7 (12.5)	2 (3.6)	9 (8.1)
Insomnia	4 (7.1)	5 (9.1)	9 (8.1)
Cough	2 (3.6)	7 (12.7)	9 (8.1)
Depression	6 (10.7)	2 (3.6)	8 (7.2)
Arthralgia	5 (8.9)	3 (5.5)	8 (7.2)
Gastroenteritis	2 (3.6)	6 (10.9)	8 (7.2)
Constipation	1 (1.8)	7 (12.7)	8 (7.2)
Abdominal pain	4 (7.1)	4 (7.3)	8 (7.2)
Oedema	5 (8.9)	3 (5.5)	8 (7.2)
Contusion	4 (7.1)	3 (5.5)	7 (6.3)
Dyspnoea exertional	4 (7.1)	3 (5.5)	7 (6.3)
Encephalopathy	3 (5.4)	4 (7.3)	7 (6.3)

Table 5.4.2.2-2 Treatment-emergent Adverse Events With at Least 5% Incidence in the Total Population Regardless of Causality in the Long-term, Open-label, Hyponatremia Extension Trial (Trial 156-03-244)

Adverse Event	Prior Treatment (Parent Trial)		Tolvaptan (N = 111) n (%)
	Tolvaptan (N = 56) n (%)	Placebo (N = 55) n (%)	
Fall	3 (5.4)	4 (7.3)	7 (6.3)
Hyperkalaemia	3 (5.4)	4 (7.3)	7 (6.3)
Ecchymosis	2 (3.6)	5 (9.1)	7 (6.3)
Chronic obstructive pulmonary disease	5 (8.9)	1 (1.8)	6 (5.4)
Epistaxis	5 (8.9)	1 (1.8)	6 (5.4)
Hypothyroidism	4 (7.1)	2 (3.6)	6 (5.4)
Nasopharyngitis	3 (5.4)	3 (5.5)	6 (5.4)
Dyspepsia	4 (7.1)	2 (3.6)	6 (5.4)
Lethargy	4 (7.1)	2 (3.6)	6 (5.4)
Gastrointestinal haemorrhage	4 (7.1)	2 (3.6)	6 (5.4)
Decreased appetite	3 (5.4)	3 (5.5)	6 (5.4)
Upper respiratory tract infection	4 (7.1)	2 (3.6)	6 (5.4)
Atrial fibrillation	3 (5.4)	3 (5.5)	6 (5.4)
Muscle spasms	2 (3.6)	4 (7.3)	6 (5.4)
Nasal congestion	2 (3.6)	4 (7.3)	6 (5.4)
Pain in extremity	2 (3.6)	4 (7.3)	6 (5.4)
Hypertension	5 (8.9)	1 (1.8)	6 (5.4)
Peripheral arterial occlusive disease	3 (5.4)	3 (5.5)	6 (5.4)
Pyrexia	2 (3.6)	4 (7.3)	6 (5.4)
Asthenia	1 (1.8)	5 (9.1)	6 (5.4)

Note: Parent trial = Trial 156-02-235 or Trial 156-03-238.
Subjects are counted once for any multiple occurrences of a MedDRA term.

5.4.2.3 Treatment-emergent Adverse Events in Heart Failure Trials

5.4.2.3.1 Cardiac Edema

The most commonly reported adverse events (incidence ≥ 3% in the Any Tolvaptan Oral Dose group) observed in subjects with cardiac edema (Trials 156-03-001, 156-06-002, 156-06-004, 156-06-006. 156-10-005, 156-TWA-1101i, and 156-12-809-01) are presented in Table 5.4.2.3.1-1. In the 80.8% of tolvaptan subjects that experienced adverse events, thirst, increased blood urea and increased blood uric acid were reported most frequently (19.7%, 8.0% and 8.0%, respectively, compared with 2.3%, 3.6%, and 4.0% in the placebo group). Other frequent adverse events (≥ 5% in the Any Tolvaptan Oral Dose group and greater than placebo) reported in tolvaptan subjects included increased blood uric acid, constipation, increased blood creatinine, and increased blood potassium.

Table 5.4.2.3.1-1 Most Common Treatment-emergent Adverse Events With at Least 3% Incidence in the Any Oral Tolvaptan Group in Trials in Cardiac Edema

Adverse Events	Tolvaptan Dose				Any Tolvaptan Oral Dose (N = 437) n (%)	Placebo (N = 302) n (%)
	7.5 mg (N = 10) n (%)	15 mg (N = 364) n (%)	30 mg (N = 36) n (%)	45 mg (N = 29) n (%)		
Any adverse event	10 (100.0)	286 (78.6)	34 (94.4)	24 (82.8)	353 (80.8)	202 (66.9)
Thirst	4 (40.0)	58 (15.9)	9 (25.0)	15 (51.7)	86 (19.7)	7 (2.3)
Blood urea increased	2 (20.0)	29 (9.1)	2 (5.6)	2 (6.9)	35 (8.0)	11 (3.6)
Blood uric acid increased	0 (0.0)	29 (8.0)	4 (11.1)	2 (6.9)	35 (8.0)	12 (4.0)
Constipation	0 (0.0)	24 (6.6)	6 (16.7)	2 (6.9)	32 (7.3)	10 (3.3)
Cardiac failure	0 (0.0)	28 (7.7)	1 (2.8)	1 (3.4)	30 (6.9)	34 (11.3)
Blood creatinine increased	2 (20.0)	21 (5.8)	1 (2.8)	0 (0.0)	24 (5.5)	7 (2.3)
Blood potassium increased	1 (10.0)	19 (5.2)	2 (5.6)	2 (6.9)	24 (5.5)	10 (3.3)
Pollakiuria	1 (10.0)	17 (4.7)	1 (2.8)	1 (3.4)	20 (4.6)	0 (0.0)
Dry mouth	0 (0.0)	18 (4.9)	0 (0.0)	0 (0.0)	18 (4.1)	3 (1.0)
Dehydration	0 (0.0)	5 (1.4)	3 (8.3)	6 (20.7)	14 (3.2)	5 (1.7)
Dizziness	0 (0.0)	11 (3.0)	1 (2.8)	2 (6.9)	13 (3.2)	5 (1.7)
Nasopharyngitis	2 (20.0)	9 (2.5)	1 (2.8)	1 (3.4)	13 (3.0)	10 (3.3)
Hyperuricaemia	0 (0.0)	15 (4.1)	0 (0.0)	0 (0.0)	15 (3.4)	13 (4.3)
Diarrhoea	0 (0.0)	9 (2.5)	3 (8.3)	1 (3.4)	13 (3.0)	6 (2.0)
Hypokalaemia	0 (0.0)	13 (3.6)	0 (0.0)	0 (0.0)	13 (3.0)	16 (5.3)

Subjects are counted once per term for any tolvaptan dose received.
Trials: 156-03-001, 156-06-002, 156-06-004, 156-06-006, 156-10-005, 156-TWA-1101i, and 156-12-809-01.

5.4.2.3.2 Congestive Heart Failure

Table 5.4.2.3.2-1 shows the TEAEs reported by at least 3% of subjects treated with tolvaptan in the All Tolvaptan Oral Doses group in the pooled heart failure trials. The most commonly reported TEAEs (by > 5% incidence and greater than that of placebo) in tolvaptan subjects were thirst, dry mouth, dizziness, dyspnoea, chest pain, hyperkalaemia, headache, fatigue, pollakiuria, and ventricular tachycardia. The most commonly reported TEAEs (by > 5% incidence) seen in placebo subjects were cardiac failure, congestive cardiac failure, nausea, hypotension, dizziness, constipation, diarrhoea, insomnia, hypokalaemia, cough, anaemia, chest pain, headache, urinary tract infection, renal failure, hyperkalaemia, pneumonia, vomiting, dyspnoea, bronchitis, atrial fibrillation, and ventricular tachycardia.

Table 5.4.2.3.2-1 Treatment-emergent Adverse Events With at Least 3% Incidence in the All Tolvaptan Group in Trials in Congestive Heart Failure

Adverse Events	All Tolvaptan Oral Doses[a] (N = 3115) n (%)	Placebo (N = 2502) n (%)
Any adverse event	2696 (86.5)	2117 (84.6)
Cardiac failure	565 (18.1)	538 (21.5)
Thirst	536 (17.2)	56 (2.2)
Cardiac failure congestive	460 (14.8)	398 (15.9)
Nausea	315 (10.1)	284 (11.4)
Hypotension	290 (9.3)	247 (9.9)
Dry mouth	286 (9.2)	54 (2.2)
Dizziness	256 (8.2)	203 (8.1)
Constipation	255 (8.2)	209 (8.4)
Dyspnoea	234 (7.5)	141 (5.6)
Chest pain	216 (6.9)	170 (6.8)
Diarrhoea	213 (6.8)	187 (7.5)
Insomnia	208 (6.7)	186 (7.4)
Hyperkalaemia	208 (6.7)	149 (6.0)
Headache	207 (6.6)	161 (6.4)
Hypokalaemia	193 (6.2)	207 (8.3)
Anaemia	186 (6.0)	172 (6.9)
Fatigue	181 (5.8)	99 (4.0)
Pollakiuria	181 (5.8)	29 (1.2)
Urinary tract infection	180 (5.8)	158 (6.3)
Ventricular tachycardia	167 (5.4)	129 (5.2)
Renal failure	164 (5.3)	153 (6.1)
Cough	160 (5.1)	179 (7.2)
Vomiting	156 (5.0)	140 (5.6)
Bronchitis	156 (5.0)	136 (5.4)
Pneumonia	152 (4.9)	147 (5.9)
Hyperuricaemia	148 (4.8)	119 (4.8)
Atrial fibrillation	141 (4.5)	134 (5.4)
Pain in extremity	141 (4.5)	115 (4.6)
Back pain	129 (4.1)	102 (4.1)
Anxiety	122 (3.9)	100 (4.0)
Gout	120 (3.9)	96 (3.8)
Abdominal pain	117 (3.8)	98 (3.9)
Hypoglycaemia	113 (3.6)	80 (3.2)
Oedema peripheral	109 (3.5)	103 (4.1)
Blood creatinine increased	103 (3.3)	73 (2.9)
Pyrexia	101 (3.2)	84 (3.4)
Polyuria	100 (3.2)	14 (0.6)
Renal failure acute	99 (3.2)	106 (4.2)
Asthenia	97 (3.1)	99 (4.0)

Table 5.4.2.3.2-1 Treatment-emergent Adverse Events With at Least 3% Incidence in the All Tolvaptan Group in Trials in Congestive Heart Failure		
Adverse Events	**All Tolvaptan Oral Doses[a] (N = 3115) n (%)**	**Placebo (N = 2502) n (%)**
Upper respiratory tract infection	98 (3.1)	98 (3.9)
Hyperglycaemia	96 (3.1)	80 (3.2)
Depression	95 (3.0)	88 (3.5)
Arthralgia	95 (3.0)	78 (3.1)
Decreased appetite	92 (3.0)	68 (2.7)

[a]Doses of 10, 15, 30, 45, 60, 90, and 120 mg. Subjects are counted once per term for any tolvaptan dose received.

Trials: 156-97-251, 156-97-252, 156-98-213, 156-00-220, 156-00-221, 156-00-222, 156-01-231, 156-01-232, 156-03-236, and 156-04-247.

5.4.2.4 Treatment-emergent Adverse Events in Hepatic Edema Trials

Eight trials in subjects with hepatic edema have been completed and analyzed (5 were conducted in Japan and 3 were conducted in China). The most commonly reported TEAEs (incidence ≥ 3% in the Any Tolvaptan Oral Dose group) observed in subjects with hepatic edema are presented in Table 5.4.2.4-1. In the 71.0% of tolvaptan subjects who experienced TEAEs, thirst, dry mouth, and pollakiuria were reported most frequently (19.6%, 11.2%, and 7.4%, respectively, compared with 3.7%, 5.3%, and 0.4% in the placebo group).

Table 5.4.2.4-1 Treatment-emergent Adverse Events With at Least 3% Incidence in the Any Oral Tolvaptan Group in Trials in Hepatic Edema

Adverse Events	Tolvaptan Dose					Any Tolvaptan Oral Dose[b] (N = 855) n (%)	Placebo (N = 245) n (%)
	3.75 mg (N = 19) n (%)	7.5 mg (N = 333) n (%)	15 mg (N = 409) n (%)	30 mg (N = 89) n (%)	15 to 60 mg[a] (N = 18) n (%)		
Any adverse event	14 (73.7)	228 (68.5)	284 (69.4)	69 (77.5)	18 (100.0)	607 (71.0)	142 (58.0)
Thirst	3 (15.8)	43 (12.9)	71 (17.4)	36 (40.4)	15 (83.3)	168 (19.6)	9 (3.7)
Dry mouth	1 (5.3)	26 (7.8)	52 (12.7)	17 (19.1)	0 (0.0)	96 (11.2)	13 (5.3)
Pollakiuria	0 (0.0)	17 (5.1)	16 (3.9)	22 (24.7)	8 (44.4)	63 (7.4)	1 (0.4)
Pyrexia	2 (10.5)	16 (4.8)	17 (4.2)	4 (4.5)	2 (11.1)	41 (4.8)	12 (4.9)
Hepatic encephalopathy	1 (5.3)	17 (5.1)	16 (3.9)	2 (2.2)	1 (5.6)	37 (4.3)	11 (4.5)
Constipation	0 (0.0)	18 (5.4)	13 (3.2)	3 (3.4)	2 (11.1)	36 (4.2)	9 (3.7)
Blood uric acid increased	0 (0.0)	7 (2.1)	13 (3.2)	12 (13.5)	3 (16.7)	35 (4.1)	1 (0.4)
Diarrhoea	0 (0.0)	15 (4.5)	13 (3.2)	4 (4.5)	1 (5.6)	33 (3.9)	12 (4.9)
Hypokalaemia	0 (0.0)	11 (3.3)	18 (4.4)	4 (4.5)	0 (0.0)	33 (3.9)	9 (3.7)
Insomnia	1 (5.3)	12 (3.6)	7 (1.7)	8 (9.0)	4 (22.2)	32 (3.7)	1 (0.4)
Blood urea increased	0 (0.0)	13 (3.9)	13 (3.2)	4 (4.5)	0 (0.0)	30 (3.5)	14 (5.7)
Dizziness	0 (0.0)	11 (3.3)	14 (3.4)	4 (4.5)	1 (5.6)	30 (3.5)	2 (0.8)
Abdominal distension	0 (0.0)	8 (2.4)	17 (4.2)	0 (0.0)	1 (5.6)	26 (3.0)	9 (3.7)

[a] Subjects received titrated doses from 15 to 60 mg.

[b] Subjects are included in the pooled safety analysis if they received at least one dose of tolvaptan.

Trials: 156-03-002, 156-06-005, 156-08-001, 156-08-002, 156-08-804-01, 156-08-805-01, 156-09-004, and 156-09-806-01.

5.4.2.5 Treatment -emergent Adverse Events in Carcinomatous Edema

In subjects with carcinomatous edema in Trial 156-12-001, TEAEs were experienced by 32 of the 43 subjects (74.4%). The most commonly reported TEAEs (incidence ≥ 3% in the Any Tolvaptan Oral Dose group) are presented in Table 5.4.2.5-1. Vomiting (11.6%) was the most commonly reported TEAE.

Table 5.4.2.5-1 Treatment-emergent Adverse Events With at Least 3% Incidence in the Any Tolvaptan Oral Dose Group in Trial 156-12-001

Adverse Event	Any Tolvaptan Oral Dose (N=43) n (%)
Any adverse event	32 (74.4)
Vomiting	5 (11.6)
Abdominal distension	3 (7.0)
Constipation	3 (7.0)
Thirst	3 (7.0)
Blood osmolality increased	3 (7.0)
Renal impairment	3 (7.0)
Neutropenia	2 (4.7)
Dyspepsia	2 (4.7)
Nausea	2 (4.7)
Pyrexia	2 (4.7)
Abnormal hepatic function	2 (4.7)
Blood urea increased	2 (4.7)
Decreased appetite	2 (4.7)
Hyperuricaemia	2 (4.7)
Cancer pain	2 (4.7)
Insomnia	2 (4.7)
Pollakiuria	2 (4.7)
Hypoxia	2 (4.7)

5.4.2.6 Treatment-emergent Adverse Events in Chronic Renal Failure

There were 43 subjects in total who received at least one dose of tolvaptan in one of the 2 chronic renal failure trials (156-12-002 and 156-12-007). Of these 43 subjects, 26 subjects (60.5%) experienced at least 1 TEAE. The most common TEAEs (incidence ≥ 3% in the Any Tolvaptan Oral Dose group) are presented in Table 5.4.2.6-1, and included thirst, constipation, nasopharyngitis, and decreased blood sodium.

Table 5.4.2.6-1	**Treatment-emergent Adverse Events with at Least 3% Incidence in the Any Tolvaptan Oral Dose Group in Chronic Renal Failure Trials**
Adverse Event	**Any Tolvaptan Oral Dose (N=43) n (%)**
Any adverse event	26 (60.5)
Thirst	6 (14.0)
Constipation	4 (9.3)
Nasopharyngitis	4 (9.3)
Blood sodium decreased	4 (9.3)
Nephrogenic anaemia	3 (7.0)
Malaise	3 (7.0)
Hyperkalaemia	3 (7.0)
Shunt stenosis	2 (4.7)
Hyponatraemia	2 (4.7)
Arthralgia	2 (4.7)
Pollakiuria	2 (4.7)
Pruritus	2 (4.7)
Hypotension	2 (4.7)

Trials: 156-12-002 and 156-12-007.

5.4.2.7 Treatment-emergent Adverse Events in ADPKD or Renal Impairment Trials

5.4.2.7.1 Long-term, Double-blind, Placebo-controlled ADPKD Trial

Table 5.4.2.7.1-1 shows the TEAEs reported by at least 3% of subjects treated with tolvaptan at any dose in the long-term, double-blind, placebo-controlled, multinational trial in subjects with ADPKD (Trial 156-04-251). The most commonly reported TEAEs (≥ 10% incidence in the Any Tolvaptan Oral Dose group) in this 36-month trial were thirst, polyuria, hypertension, nocturia, renal pain, headache, pollakiuria, nasopharyngitis, dry mouth, blood creatinine increased, back pain, diarrhoea, fatigue, dizziness, nausea, and polydipsia. In the placebo group, the most commonly reported TEAEs (≥ 10% incidence) were hypertension, renal pain, headache, nasopharyngitis, thirst, back pain, polyuria, blood creatinine increased, hematuria, urinary tract infection, nocturia, dry mouth, nausea, and diarrhoea.

Table 5.4.2.7.1-1 Treatment-emergent Adverse Events With at Least 3% Incidence in the Any Tolvaptan Oral Dose Group in the Long-term, Double-blind, Placebo-controlled ADPKD Trial (Trial 156-04-251)

Adverse Events	Any Tolvaptan Oral Dose[a] (N = 961) n (%)	Placebo (N = 483) n (%)
Any adverse event	942 (98.0)	472 (97.7)
Thirst	532 (55.4)	99 (20.5)
Polyuria	369 (38.4)	83 (17.2)
Hypertension	325 (33.8)	178 (36.9)
Nocturia	281 (29.2)	63 (13.0)
Renal pain	266 (27.7)	173 (35.8)
Headache	245 (25.5)	123 (25.5)
Pollakiuria	223 (23.2)	26 (5.4)
Nasopharyngitis	220 (22.9)	111 (23.0)
Dry mouth	154 (16.0)	60 (12.4)
Blood creatinine increased	140 (14.6)	71 (14.7)
Back pain	138 (14.4)	89 (18.4)
Fatigue	132 (13.7)	47 (9.7)
Diarrhoea	131 (13.6)	53 (11.0)
Dizziness	109 (11.3)	42 (8.7)
Nausea	102 (10.6)	59 (12.2)
Polydipsia	100 (10.4)	17 (3.5)
Urinary tract infection	88 (9.2)	65 (13.5)
Upper respiratory tract infection	87 (9.1)	42 (8.7)
Vomiting	82 (8.5)	40 (8.3)
Constipation	81 (8.4)	12 (2.5)
Oedema peripheral	79 (8.2)	43 (8.9)
Dyspepsia	78 (8.1)	16 (3.3)
Influenza	78 (8.1)	38 (7.9)
Cough	78 (8.1)	38 (7.9)
Haematuria	75 (7.8)	69 (14.3)
Decreased appetite	69 (7.2)	5 (1.0)
Arthralgia	69 (7.2)	29 (6.0)
Abdominal pain	63 (6.6)	33 (6.8)
Abdominal pain upper	60 (6.2)	42 (8.7)
Bronchitis	59 (6.1)	36 (7.5)
Asthenia	58 (6.0)	27 (5.6)
Gastroenteritis	56 (5.8)	22 (4.6)
Sinusitis	56 (5.8)	23 (4.8)
Insomnia	55 (5.7)	23 (4.8)
Myalgia	51 (5.3)	16 (3.3)
Abdominal distension	50 (5.2)	18 (3.7)
Oropharyngeal pain	50 (5.2)	18 (3.7)
Dry skin	49 (5.1)	9 (1.9)
Weight decreased	46 (4.8)	17 (3.5)
Weight increased	46 (4.8)	19 (3.9)
Pyrexia	45 (4.7)	43 (8.9)
Gastrooesophageal reflux disease	43 (4.5)	16 (3.3)
Chest pain	43 (4.5)	12 (2.5)

Table 5.4.2.7.1-1 Treatment-emergent Adverse Events With at Least 3% Incidence in the Any Tolvaptan Oral Dose Group in the Long-term, Double-blind, Placebo-controlled ADPKD Trial (Trial 156-04-251)

Adverse Events	Any Tolvaptan Oral Dose[a] (N = 961) n (%)	Placebo (N = 483) n (%)
Rash	41 (4.3)	9 (1.9)
Alanine aminotransferase increased	40 (4.2)	17 (3.5)
Hyperuricaemia	40 (4.2)	9 (1.9)
Pain in extremity	42 (4.4)	29 (6.0)
Depression	42 (4.4)	21 (4.3)
Aspartate aminotransferase increased	37 (3.9)	16 (3.3)
Muscle spasms	36 (3.7)	17 (3.5)
Musculoskeletal pain	35 (3.6)	16 (3.3)
Palpitations	35 (3.6)	6 (1.2)
Pruritus	34 (3.5)	13 (2.7)
Abdominal discomfort	32 (3.3)	11 (2.3)
Anaemia	30 (3.1)	26 (5.4)
Anxiety	30 (3.1)	8 (1.7)
Hypotension	30 (3.1)	15 (3.1)

ADPKD = autosomal dominant polycystic kidney disease.
[a]Doses of 60 - 120 mg. Subjects are counted once per term for any tolvaptan dose received.

5.4.2.7.2 Short-term Ascending Dose ADPKD Trials (Single- and Multiple-dose)

Table 5.4.2.7.2-1 shows the TEAEs reported by at least 3% of subjects treated with tolvaptan at any dose in the pooled short-term, single- and multiple-ascending dose ADPKD trials. The most commonly reported TEAEs (≥ 5% incidence in the Any Tolvaptan Oral Dose group) were dry mouth, headache, thirst, fatigue, dizziness, and nausea.

Table 5.4.2.7.2-1 Treatment-emergent Adverse Events With at Least 3% Incidence in the Any Tolvaptan Oral Dose Group in Short-term Trials in ADPKD

Adverse Events	Any Tolvaptan Oral Dose[a] (N = 63) n (%)	Placebo (N = 3) n (%)
Any adverse event	38 (60.3)	2 (66.7)
Dry mouth	14 (22.2)	0 (0.0)
Headache	9 (14.3)	1 (33.3)
Thirst	6 (9.5)	0 (0.0)
Fatigue	5 (7.9)	1 (33.3)
Dizziness	4 (6.3)	2 (66.7)
Nausea	4 (6.3)	0 (0.0)
Dysgeusia	3 (4.8)	0 (0.0)
Nasopharyngitis	3 (4.8)	0 (0.0)
Constipation	2 (3.2)	0 (0.0)
Blood creatine phosphokinase increased	2 (3.2)	0 (0.0)
Somnolence	2 (3.2)	0 (0.0)
Insomnia	2 (3.2)	0 (0.0)

ADPKD = autosomal dominant polycystic kidney disease.
[a]Doses of 15, 30, 45, 60, and 120 mg. Subjects are counted once per term for any tolvaptan dose received.
Trials: 156-04-001, 156-04-248, and 156-04-249.

5.4.2.7.3 Long-term, Open-label, ADPKD Extension Trials

For the 2 open-label trials that assessed long-term safety of tolvaptan in subjects with ADPKD, a summary of TEAEs for the titration period in Trial 156-04-250 is presented separately, whereas a summary of TEAEs for the fixed-dose period in this trial was pooled with the TEAEs in Trial 156-05-002. The trial design for Trial 156-04-250 included a 2-month titration period in which tolvaptan was administered in the range of 30 to 120 mg/day as a split-dose regimen. This period allowed the identification of subjects who would respond to tolvaptan treatment in terms of urine osmolality and who were able to tolerate tolvaptan treatment. Table 5.4.2.7.3-1 shows the TEAEs reported for at least 5% of subjects treated with tolvaptan at any dose during the titration period in Trial 156-04-250. The most frequently reported TEAEs during the titration period (ie, those reported by > 10% of subjects) were pollakiuria, thirst, nocturia, polyuria, fatigue, dizziness, upper respiratory tract infection, sinusitis, renal pain, headache, and dry skin.

Table 5.4.2.7.3-1 Treatment-emergent Adverse Events With at Least 5% Incidence During the Titration Period in Subjects With ADPKD in Trial 156-04-250

Adverse Events	Any Tolvaptan Oral Dose (Titration Period) (N = 46) n (%)
Any adverse event	46 (100.0)
Pollakiuria	22 (47.8)
Thirst	19 (41.3)
Nocturia	11 (23.9)
Polyuria	10 (21.7)
Fatigue	9 (19.6)
Dizziness	6 (13.0)
Upper respiratory tract infection	5 (10.9)
Sinusitis	5 (10.9)
Renal pain	5 (10.9)
Headache	5 (10.9)
Dry skin	5 (10.9)
Nausea	4 (8.7)
Hypotension	4 (8.7)
Dyspepsia	4 (8.7)
Diarrhoea	4 (8.7)
Constipation	4 (8.7)
Hypertension	4 (8.7)
Weight decreased	3 (6.5)
Urinary tract infection	3 (6.5)
Flatulence	3 (6.5)
Dry mouth	3 (6.5)
Abdominal pain	3 (6.5)
Polydipsia	3 (6.5)

ADPKD = autosomal dominant polycystic kidney disease.
Note: Subjects are counted once per term for any tolvaptan dose received.

Safety data for the fixed-dose period in Trial 156-04-250 were pooled with data for Trial 156-05-002. Of note, the subjects included in these trials were not naive to tolvaptan, and their previous experience taking tolvaptan may have affected the reported TEAEs in these trials. The TEAEs reported for at least 5% of subjects treated with tolvaptan at any dose are summarized in Table 5.4.2.7.3-2. The most frequently reported TEAEs (ie, those reported by > 10% of total subjects) over a long-term period of up to 36 months were thirst, renal pain, nasopharyngitis, polyuria, hypertension, fatigue, dizziness, nocturia, pollakiuria, diarrhoea, back pain, headache, sinusitis, abdominal pain, upper respiratory tract infection, urinary tract infection, anaemia, palpitations, peripheral oedema, and arthralgia.

Table 5.4.2.7.3-2 Treatment-emergent Adverse Events With at Least 5% Incidence in the Any Tolvaptan Group in Long-term Open-label Trials in Subjects with ADPKD

Adverse Events	Tolvaptan 15/15 mg (N = 17) n (%)	Tolvaptan 45/15 mg (N = 22) n (%)	Tolvaptan 60/30 mg (N = 24) n (%)	Any Tolvaptan Oral Dose (N = 63) n (%)
Any adverse event	17 (100.0)	22 (100.0)	24 (100.0)	63 (100.0)
Thirst	9 (52.9)	3 (13.6)	12 (50.0)	24 (38.1)
Renal pain	0 (0.0)	10 (45.5)	9 (37.5)	19 (30.2)
Nasopharyngitis	13 (76.5)	2 (9.1)	1 (4.2)	16 (25.4)
Polyuria	1 (5.9)	6 (27.3)	7 (29.2)	14 (22.2)
Hypertension	5 (29.4)	4 (18.2)	4 (16.7)	13 (20.6)
Fatigue	1 (5.9)	6 (27.3)	6 (25.0)	13 (20.6)
Dizziness	2 (11.8)	8 (36.4)	3 (12.5)	13 (20.6)
Nocturia	2 (11.8)	8 (36.4)	3 (12.5)	13 (20.6)
Pollakiuria	2 (11.8)	3 (13.6)	7 (29.2)	12 (19.0)
Diarrhoea	2 (11.8)	5 (22.7)	4 (16.7)	11 (17.5)
Back pain	3 (17.6)	4 (18.2)	3 (12.5)	10 (15.9)
Headache	4 (23.5)	3 (13.6)	3 (12.5)	10 (15.9)
Sinusitis	2 (11.8)	3 (13.6)	4 (16.7)	9 (14.3)
Abdominal pain	1 (5.9)	2 (9.1)	5 (20.8)	8 (12.7)
Upper respiratory tract infection	0 (0.0)	2 (9.1)	6 (25.0)	8 (12.7)
Urinary tract infection	1 (5.9)	1 (4.5)	6 (25.0)	8 (12.7)
Anaemia	1 (5.9)	4 (18.2)	2 (8.3)	7 (11.1)
Palpitations	3 (17.6)	3 (13.6)	1 (4.2)	7 (11.1)
Oedema peripheral	1 (5.9)	3 (13.6)	3 (12.5)	7 (11.1)
Arthralgia	1 (5.9)	3 (13.6)	3 (12.5)	7 (11.1)
Abdominal distension	1 (5.9)	3 (13.6)	2 (8.3)	6 (9.5)
Chest pain	1 (5.9)	3 (13.6)	2 (8.3)	6 (9.5)
Bronchitis	1 (5.9)	3 (13.6)	2 (8.3)	6 (9.5)
Contusion	6 (35.3)	0 (0.0)	0 (0.0)	6 (9.5)
Polydipsia	0 (0.0)	5 (22.7)	1 (4.2)	6 (9.5)
Dyspnoea	0 (0.0)	1 (4.5)	5 (20.8)	6 (9.5)
Dry eye	0 (0.0)	3 (13.6)	2 (8.3)	5 (7.9)
Blood antidiuretic hormone increased	5 (29.4)	0 (0.0)	0 (0.0)	5 (7.9)
Insomnia	1 (5.9)	1 (4.5)	3 (12.5)	5 (7.9)
Nausea	1 (5.9)	1 (4.5)	2 (8.3)	4 (6.3)
Blood creatinine increased	2 (11.8)	1 (4.5)	1 (4.2)	4 (6.3)
Blood uric acid increased	4 (23.5)	0 (0.0)	0 (0.0)	4 (6.3)
Dehydration	3 (17.6)	0 (0.0)	1 (4.2)	4 (6.3)
Musculoskeletal pain	2 (11.8)	1 (4.5)	1 (4.2)	4 (6.3)
Flank pain	0 (0.0)	2 (9.1)	2 (8.3)	4 (6.3)
Neck pain	2 (11.8)	1 (4.5)	1 (4.2)	4 (6.3)
Pain in extremity	2 (11.8)	2 (9.1)	0 (0.0)	4 (6.3)
Dry skin	2 (11.8)	2 (9.1)	0 (0.0)	4 (6.3)

ADPKD = autosomal dominant polycystic kidney disease.
Note: Subjects are counted once per term for any tolvaptan dose received.
Trials: 156-04-250 and 156-05-002.

5.4.2.7.4 Short-term Pharmacokinetic/Pharmacodynamic Trials Focusing on Renal Function

Three open-label trials that focused on renal function have been conducted as part of the ADPKD program. Adverse event data were grouped according to the following categories based on the subjects' baseline eGFR: < 30 mL/min; 30 to 60 mL/min; and > 60 mL/min.

Trial 156-09-282 determined the effect of varying degrees of renal function on the pharmacokinetics and pharmacodynamics of tolvaptan in subjects without ADPKD. All subjects received a single, oral 60-mg dose of tolvaptan. The TEAEs reported for 2 or more subjects treated with tolvaptan are summarized in Table 5.4.2.7.4-1. The most frequently reported TEAEs (ie, those reported by ≥ 10% of total subjects) were thirst, pollakiuria, and dry mouth.

Table 5.4.2.7.4-1 Treatment-emergent Adverse Events in Two or More Subjects in the Total Tolvaptan Group in Subjects With Renal Impairment but Without ADPKD (Trial 156-09-282)

Adverse Events	Estimated Glomerular Filtration Rate			Total (N = 37) n (%)
	< 30 mL/min (N = 12) n (%)	30 to 60 mL/min (N = 11) n (%)	> 60 mL/min (N = 14) n (%)	
Any adverse event	10 (83.3)	7 (63.6)	9 (64.3)	26 (70.3)
Thirst	3 (25.0)	4 (36.4)	3 (21.4)	10 (27.0)
Pollakiuria	1 (8.3)	3 (27.3)	5 (35.7)	9 (24.3)
Dry mouth	1 (8.3)	3 (27.3)	1 (7.1)	5 (13.5)
Diarrhoea	2 (16.7)	0 (0.0)	0 (0.0)	2 (5.4)
Hyperglycaemia	1 (8.3)	1 (9.1)	0 (0.0)	2 (5.4)
Hypoglycaemia	2 (16.7)	0 (0.0)	0 (0.0)	2 (5.4)
Headache	1 (8.3)	1 (9.1)	0 (0.0)	2 (5.4)

ADPKD = autosomal dominant polycystic kidney disease; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CrCL = creatinine clearance; eGFR = estimated glomerular filtration rate; TEAE = treatment-emergent adverse events.

Note: The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) method; results shown here are slightly different from those reported in the clinical study report based on CrCL values.

Note: All subjects with TEAEs of hyperglycaemia and hypoglycaemia had a history of diabetes mellitus.

Trial 156-06-260 evaluated the effect of a 45/15 mg split-dose regimen of oral tolvaptan tablets on renal function in subjects with ADPKD. Subjects received tolvaptan 45/15 mg for 7 days and 45 mg of tolvaptan on Day 8. The most frequently reported TEAEs (ie, those reported by ≥ 10% of total subjects) were polyuria, polydipsia, nocturia, dry mouth,

and headache (Table 5.4.2.7.4-2). The incidence of thirst was very low (1/20 subjects, 5.0%).

Table 5.4.2.7.4-2 Treatment-emergent Adverse Events in Two or More Subjects in the Total Tolvaptan Group in Subjects With ADPKD (Trial 156-06-260)

Adverse Events	Estimated Glomerular Filtration Rate			Total (N = 20) n (%)
	< 30 mL/min (N = 3) n (%)	30 to 60 mL/min (N = 5) n (%)	> 60 mL/min (N = 12) n (%)	
Any adverse event	3 (100.0)	5 (100.0)	12 (100.0)	20 (100.0)
Polyuria	3 (100.0)	5 (100.0)	12 (100.0)	20 (100.0)
Polydipsia	3 (100.0)	5 (100.0)	10 (83.3)	18 (90.0)
Nocturia	2 (66.7)	5 (100.0)	10 (83.3)	17 (85.0)
Dry mouth	0 (0.0)	4 (80.0)	5 (41.7)	9 (45.0)
Headache	0 (0.0)	1 (20.0)	2 (16.7)	3 (15.0)

ADPKD = autosomal dominant polycystic kidney disease; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate.
Note: The eGFR was calculated using the CKD-EPI method; results shown here are slightly different from those reported in the clinical study report based on the Cockroft-Gault method for eGFR categories of 30 to < 45, 45 to < 60, and ≥ 60 mL/min.

Trial 156-09-284 assessed the effect of maximally-tolerated doses of tolvaptan (45/15 mg split dose for one week, followed by titration to 60/30 mg and then to 90/30 mg, as tolerated) at steady state on renal function in subjects with ADPKD with varying degrees of renal function. Subjects received tolvaptan treatment for 3 weeks. The most frequently reported TEAEs (ie, those reported by ≥ 10% of total subjects) were thirst, polyuria, nocturia, dry mouth, decreased appetite, fatigue, headache, nausea, dizziness, and renal pain (Table 5.4.2.7.4-3).

Table 5.4.2.7.4-3 Treatment-emergent Adverse Events in Two or More Subjects in the Total Tolvaptan Group in Subjects With ADPKD (Trial 156-09-284)

Adverse Events	Estimated Glomerular Filtration Rate			Total (N = 29) n (%)
	< 30 mL/min (N = 8) n (%)	30 to 60 mL/min (N = 7) n (%)	> 60 mL/min (N = 14) n (%)	
Any adverse event	8 (100.0)	7 (100.0)	14 (100.0)	29 (100.0)
Thirst	7 (87.5)	7 (100.0)	14 (100.0)	28 (96.6)
Polyuria	6 (75.0)	7 (100.0)	13 (92.9)	26 (89.7)
Nocturia	6 (75.0)	5 (71.4)	9 (64.3)	20 (69.0)
Dry mouth	5 (62,5)	3 (42.9)	8 (57.1)	16 (55.2)
Decreased appetite	2 (25.0)	1 (14.3)	4 (28.6)	7 (24.1)
Fatigue	2 (25.0)	2 (28.6)	2 (14.3)	6 (20.7)
Headache	2 (25.0)	1 (14.3)	3 (21.4)	6 (20.7)
Nausea	2 (25.0)	0 (0.0)	2 (14.3)	4 (13.8)
Dizziness	1 (12.5)	1 (14.3)	2 (14.3)	4 (13.8)
Renal pain	1 (12.5)	0 (0.0)	3 (21.4)	4 (13.8)
Anaemia	1 (12.5)	0 (0.0)	1 (7.1)	2 (6.9)
Abdominal distension	0 (0.0)	0 (0.0)	2 (14.3)	2 (6.9)
Abdominal pain	0 (0.0)	0 (0.0)	2 (14.3)	2 (6.9)
Diarrhoea	0 (0.0)	1 (14.3)	1 (7.1)	2 (6.9)
Oedema	2 (25.0)	0 (0.0)	0 (0.0)	2 (6.9)
Pyrexia	0 (0.0)	0 (0.0)	2 (14.3)	2 (6.9)
Hypernatraemia	1 (12.5)	1 (14.3)	0 (0.0)	2 (6.9)
Insomnia	2 (25.0)	0 (0.0)	0 (0.0)	2 (6.9)
Dyspnoea	1 (12.5)	0 (0.0)	1 (7.1)	2 (6.9)
Flushing	1 (12.5)	0 (0.0)	1 (7.1)	2 (6.9)

ADPKD = autosomal dominant polycystic kidney disease; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; MDRD = modification of diet in renal disease.

Note: The eGFR was calculated using the CKD-EPI method; results shown here are slightly different from those reported in the clinical study report based on the MDRD equation for eGFR categories of < 30, 30 to 60, and > 60 mL/min/1.73 m^2.

5.4.2.7.5 ADPKD Trials Using the Modified-release Formulation

Trial 156-09-285 compared the IR and MR formulations of tolvaptan and evaluated different doses and dose regimens of tolvaptan MR capsules. The TEAEs reported for 2 or more subjects in the total tolvaptan group are summarized in Table 5.4.2.7.5-1. The most frequently reported TEAEs (ie, those reported by > 10% of total subjects) were polyuria, thirst, polydipsia, nocturia, pollakiuria, nausea, headache, and micturition urgency. The overall incidence of TEAEs was similar for the tolvaptan IR 90/30 mg split-dose group and the MR 120 mg group.

Table 5.4.2.7.5-1 Treatment-emergent Adverse Events in Two or More Subjects in the Total Tolvaptan Group in Subjects With ADPKD (Trial 156-09-285)

Adverse Events	Tolvaptan Dose and Formulation					Total (N = 25) n (%)
	MR 20 mg (N = 17) n (%)	MR 20/20 mg (N = 17) n (%)	MR 60 mg (N = 17) n (%)	MR 120 mg (N = 12) n (%)	IR 90/30 mg (N = 12) n (%)	
Any adverse event	5 (29.4)	10 (58.8)	6 (35.3)	8 (66.7)	7 (58.3)	21 (84.0)
Polyuria	2 (11.8)	5 (29.4)	1 (5.9)	4 (33.3)	5 (41.7)	15 (60.0)
Thirst	1 (5.9)	3 (17.6)	2 (11.8)	2 (16.7)	1 (8.3)	8 (32.0)
Polydipsia	1 (5.9)	2 (11.8)	0 (0.0)	2 (16.7)	3 (25.0)	7 (28.0)
Nocturia	1 (5.9)	2 (11.8)	1 (5.9)	1 (8.3)	3 (25.0)	7 (28.0)
Pollakiuria	2 (11.8)	2 (11.8)	1 (5.9)	2 (16.7)	0 (0.0)	5 (20.0)
Nausea	0 (0.0)	0 (0.0)	1 (5.9)	2 (16.7)	1 (8.3)	4 (16.0)
Headache	0 (0.0)	2 (11.8)	1 (5.9)	1 (8.3)	0 (0.0)	4 (16.0)
Micturition urgency	2 (11.8)	2 (11.8)	0 (0.0)	1 (8.3)	0 (0.0)	3 (12.0)
Vomiting	0 (0.0)	0 (0.0)	1 (5.9)	1 (8.3)	0 (0.0)	2 (8.0)
Feeling cold	1 (5.9)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	2 (8.0)
Dehydration	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	1 (8.3)	2 (8.0)
Alopecia	1 (5.9)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.0)
Dry skin	0 (0.0)	1 (5.9)	0 (0.0)	1 (8.3)	0 (0.0)	2 (8.0)

ADPKD = autosomal dominant polycystic kidney disease; IR = immediate release; MR = modified release.

Note: Data are shown by dose group and total for the combined 2 groups of patients who were enrolled in the parallel 3-period crossover groups (12 subjects in Group 1 and 13 subjects in Group 2).

Trial 156-09-290 compared the efficacy, tolerability, and safety of tolvaptan MR (50 and 80 mg doses) and IR (60/30 mg split-dose) formulations in subjects with ADPKD. The TEAEs reported for 2 or more subjects in the total tolvaptan group are summarized in Table 5.4.2.7.5-2. The most frequently reported TEAEs (ie, those reported by > 10% of total subjects) were thirst, nocturia, polyuria, pollakiuria, polydipsia, and dry mouth. The overall incidence of TEAEs was greater in the IR 60/30 mg dose group than in either of the MR dose groups.

Table 5.4.2.7.5-2 Treatment-emergent Adverse Events in Two or More Subjects in the Total Tolvaptan Group in Subjects With ADPKD (Trial 156-09-290)

Adverse Events	Tolvaptan Dose and Formulation			Any Tolvaptan Oral Dose (N = 133) n (%)	Placebo (N = 42) n (%)
	IR 60/30 mg (N = 44) n (%)	MR 50 mg (N = 45) n (%)	MR 80 mg (N = 44) n (%)		
Any adverse event	38 (86.4)	30 (66.7)	33 (75.0)	101 (75.9)	22 (52.4)
Thirst	19 (43.2)	15 (33.3)	15 (34.1)	49 (36.8)	6 (14.3)
Nocturia	18 (40.9)	14 (31.1)	14 (31.8)	46 (34.6)	3 (7.1)
Polyuria	13 (29.5)	11 (24.4)	11 (25.0)	35 (26.3)	3 (7.1)
Pollakiuria	12 (27.3)	8 (17.8)	9 (20.5)	29 (21.8)	3 (7.1)
Polydipsia	5 (11.4)	7 (15.6)	6 (13.6)	18 (13.5)	2 (4.8)
Dry mouth	2 (4.5)	7 (15.6)	7 (15.9)	16 (12.0)	1 (2.4)
Fatigue	6 (13.6)	3 (6.7)	2 (4.5)	11 (8.3)	1 (2.4)
Headache	7 (15.9)	1 (2.2)	1 (2.3)	9 (6.8)	1 (2.4)
Hypertension	3 (6.8)	2 (4.4)	2 (4.5)	7 (5.3)	2 (4.8)
Nausea	2 (4.5)	2 (4.4)	1 (2.3)	5 (3.8)	4 (9.5)
Decreased appetite	2 (4.5)	1 (2.2)	2 (4.5)	5 (3.8)	1 (2.4)
Renal pain	2 (4.5)	2 (4.4)	1 (2.3)	5 (3.8)	3 (7.1)
Constipation	2 (4.5)	1 (2.2)	1 (2.3)	4 (3.0)	0 (0.0)
Vomiting	2 (4.5)	1 (2.2)	1 (2.3)	4 (3.0)	2 (4.8)
Nasopharyngitis	0 (0.0)	3 (6.7)	1 (2.3)	4 (3.0)	1 (2.4)
Dizziness	2 (4.5)	2 (4.4)	0 (0.0)	4 (3.0)	1 (2.4)
Urinary tract infection	0 (0.0)	1 (2.2)	2 (4.5)	3 (2.3)	2 (4.8)

5.4.3 Deaths

5.4.3.1 Deaths in Completed Trials

For the 91 trials included in the pooled safety analysis, the overall frequency of death due to TEAEs was lower for tolvaptan subjects (553/7343; 7.5%) compared with placebo subjects (527/4334; 12.2%).

Trials in Healthy Subjects

No deaths occurred in the completed phase 1 trials in healthy subjects.

Hyponatremia Trials

In the 9 pooled hyponatremia trials, 20/511 (3.9%) of tolvaptan-treated subjects and 20/469 (4.3%) of placebo subjects died as a result of TEAEs. Table 5.4.3.1-1 provides a list of all TEAEs resulting in death experienced by any tolvaptan subject in the pooled hyponatremia trials. In the tolvaptan group, the most common TEAE resulting in death, reported for more than 1 subject, was respiratory failure (3 subjects, 0.6%). In the placebo group, the most common TEAEs (reported by more than 1 subject) resulting in death in the hyponatremia trials were sepsis and death (2 subjects, 0.4% each).

Table 5.4.3.1-1	**List of Treatment-emergent Adverse Events Resulting in Death Experienced by Any Tolvaptan Subject in Trials in Hyponatremia (Pooled Safety Analysis)**
System Organ Class	**MedDRA Preferred Term**
Cardiac disorders	Cardiac arrest, cardiac failure, cardiac failure chronic
General disorders and administration site conditions	Multi-organ failure, sudden cardiac death
Hepatobiliary disorders	Hepatic failure, hepatorenal syndrome
Infections and infestations	Peritonitis bacterial
Injury, poisoning, and procedural complications	Cervical vertebral fracture
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	Lung neoplasm malignant, non-Hodgkin's lymphoma
Nervous system disorders	Cerebral ischaemia, encephalopathy, hepatic encephalopathy
Renal and urinary disorders	Renal failure acute
Respiratory, thoracic, and mediastinal disorders	Pulmonary embolism, respiratory arrest, respiratory failure
Vascular disorders	Circulatory collapse

MedDRA = Medical Dictionary for Regulatory Activities.
Trials: 156-96-201, 156-96-203, 156-97-204, 156-02-235, 156-03-238, 156-04-246, 156-07-802-01, 156-08-275, and 156-KOB-1101i.

In the completed long-term, open-label extension trial in subjects with hyponatremia (Trial 156-03-244, not included in the pooled safety analysis), there were 19/111 (17.1%) deaths in tolvaptan subjects. The most common TEAEs (reported for more than 1 subject) resulting in death were cardiac failure (5 subjects, 4.5%) and renal failure (2 subjects, 1.8%). Other TEAEs that resulted in death reported for 1 subject each included: cardiac arrest, cardio-respiratory arrest, gastrointestinal haemorrhage, oesophageal varices haemorrhage, hepatic cirrhosis, hepatorenal syndrome, pneumonia, sepsis, urosepsis, cerebral haemorrhage, respiratory failure, and haemorrhagic infarction.

Cardiac Edema Trials

In completed cardiac edema trials (Trials 156-03-001, 156-06-002, 156-06-004, 156-06-006, 156-10-005, 156-TWA-1101i and 156-12-809-01), the incidence of death was similar in the tolvaptan group (8/437, 1.8%) and the placebo group (7/302, 2.3%). The adverse events leading to death reported in tolvaptan subjects were cardiac failure (2 subjects), sudden death (2 subjects), and cerebral artery embolism, acute renal failure, chronic renal failure, and congestive cardiac failure (1 subject each).

Congestive Heart Failure Trials

In the 10 pooled congestive heart failure trials, 508/3115 (16.3%) tolvaptan and 494/2502 (19.7%) placebo subjects died as a result of TEAEs. The most common TEAEs (≥ 1% incidence in the All Tolvaptan Oral Doses group) resulting in death in tolvaptan subjects

in the heart failure trials were cardiac failure (98/3115, 3.1%), congestive cardiac failure (58/3115, 1.9%), sudden death (50/3115, 1.6%), sudden cardiac death (44/3115, 1.4%), and cardiac arrest (34/3115, 1.1%). In the placebo group, the most common TEAEs (≥ 1% incidence) resulting in death in the heart failure trials were cardiac failure (108/2502, 4.3%), congestive cardiac failure (48/2502, 1.9%), sudden death (48/2502, 1.9%), and sudden cardiac death (44/2502, 1.8%). Table 5.4.3.1-2 provides a list of all TEAEs resulting in death experienced by any tolvaptan subject in the pooled heart failure trials.

Table 5.4.3.1-2 List of Treatment-emergent Adverse Events Resulting in Death Experienced by Any Tolvaptan Subject in Trials in Congestive Heart Failure (Pooled Safety Analysis)

System Organ Class	MedDRA Preferred Term
Cardiac disorders	Acute myocardial infarction, angina pectoris, aortic valve incompetence, arrhythmia, arteriosclerosis coronary artery, atrioventricular block complete, bradycardia, cardiac arrest, cardiac asthma, cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, cardiorespiratory arrest, cardiogenic shock, cardiomyopathy, cardiopulmonary failure, cardiovascular insufficiency, ischaemic cardiomyopathy, myocardial infarction, pulseless electrical activity, ventricular fibrillation, ventricular tachycardia
Gastrointestinal disorders	Abdominal pain, duodenal ulcer perforation, gastric ulcer haemorrhage, gastrointestinal haemorrhage, haematemesis
General disorders and administration site conditions	Cardiac death, death, multi-organ failure, sudden cardiac death, sudden death
Hepatobiliary disorders	Cholestasis
Infections and infestations	Abdominal sepsis, bacterial infection, erysipelas, gastroenteritis, peritonitis, pneumonia, respiratory tract infection, sepsis, septic shock, urinary tract infection
Injury, poisoning, and procedural complications	Post-procedural complication, subdural haematoma
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	Breast cancer metastatic, hepatic cancer, hepatic neoplasm, lung neoplasm, lung neoplasm malignant, metastases to central nervous system, metastatic neoplasm, non-Hodgkin's lymphoma, oesophageal carcinoma, pancreatic neoplasm, renal neoplasm
Nervous system disorders	Cerebrovascular accident, haemorrhagic stroke, hypoglycaemic coma, ischaemic stroke
Renal and urinary disorders	Anuria, renal failure, renal failure acute, renal failure chronic, renal impairment
Respiratory, thoracic, and mediastinal disorders	Acute pulmonary oedema, chronic obstructive pulmonary disease, haemothorax, pulmonary embolism, pulmonary haemorrhage, pulmonary oedema, respiratory arrest, respiratory failure
Vascular disorders	Haemorrhage, shock haemorrhagic

MedDRA = Medical Dictionary for Regulatory Activities.
Trials: 156-97-251, 156-97-252, 156-98-213, 156-00-220, 156-00-221, 156-00-222, 156-01-231, 156-01-232, 156-03-236, and 156-04-247.

Hepatic Cirrhosis Trials

In completed and analyzed Japanese and Chinese trials in subjects with hepatic edema (Trials 156-03-002, 156-06-005, 156-08-001, 156-08-002, 156-08-804-01, 156-08-805-01, 156-09-004, and 156-09-806-01), there were 17/855 (2.0%) deaths in tolvaptan subjects and 6/245 (2.4%) deaths in placebo subjects. In the tolvaptan group, the most common TEAEs resulting in death (reported for more than 1 subject) were upper gastrointestinal hemorrhage (3 subjects, 0.4%), hepatic cancer (2 subjects, 0.2%), and haemorrhagic shock (2 subjects, 0.2%). In the placebo group, the most common TEAE (reported by more than 1 subject) resulting in death was hepatic failure (2 subjects, 0.8%). Table 5.4.3.1-3 provides a list of all TEAEs resulting in death experienced by any tolvaptan subject in the pooled hepatic cirrhosis trials.

Table 5.4.3.1-3 List of Treatment-emergent Adverse Events Resulting in Death Experienced by Any Tolvaptan Subject in Trials in Hepatic Cirrhosis (Pooled Safety Analysis)

System Organ Class	MedDRA Preferred Term
Cardiac disorders	Cardiac failure
Gastrointestinal disorders	Intra-abdominal haemorrhage, oesophageal varices haemorrhage, upper gastrointestinal haemorrhage
General disorders and administration site conditions	Multi-organ failure
Hepatobiliary disorders	Cirrhosis alcoholic, hepatic failure, hepatic function abnormal, hepatorenal syndrome
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	Gastric cancer, hepatic neoplasm malignant
Renal and urinary disorders	Renal failure, renal impairment
Respiratory, thoracic, and mediastinal disorders	Respiratory failure
Vascular disorders	Shock haemorrhagic

MedDRA = Medical Dictionary for Regulatory Activities.
Trials: 156-03-002, 156-06-005, 156-08-001, 156-08-002, 156-08-804-01, 156-08-805-01, 156-09-004, and 156-09-806-01.

Carcinomatous Edema Trial

There were no deaths reported during the completed carcinomatous edema trial, Trial 156-12-001. However, 2 patients died during the follow-up investigation after trial completion, and it was concluded that relationship to the IMP could not be ruled out for the worsening of bile duct cancer which was cause of death in one of these subjects. The cause of death in the other subject was worsening of gastric cancer, which was judged to be a SAE.

Chronic Renal Failure Trials

No deaths were reported in the completed chronic renal failure trials (Trials 156-12-002 and 156-12-007).

ADPKD Trials

No deaths were reported in the completed long-term, placebo-controlled trial in ADPKD (Trial 156-04-251). Among the completed open-label long-term trials in ADPKD (Trials 156-04-250, 156-05-002 and 156-09-003), one tolvaptan-treated subject died due to subarachnoid haemorrhage (Trial 156-05-002). No deaths were reported in the completed short-term ascending dose trials in ADPKD (Trials 156-04-001, 156-04-248, and 156-04-249), the completed trials in subjects with renal impairment (Trials 156-06-260, 156-09-282, and 156-09-284), nor in the completed trials using the tolvaptan MR formulation (Trials 156-09-285 and 159-09-290).

5.4.3.2 Deaths in Ongoing Trials

Among the 4 ongoing trials as of the cutoff date of 31 Mar 2015, a total of 77 deaths have been reported, including 14 deaths in the ongoing ADPKD Trial 156-08-271 and 63 deaths in the ongoing hyponatremia Trial 156-09-101. The preliminary causes of death are listed by preferred term in Table 5.4.3.2-1 (note that a given subject may have had more than one cause of death).

Table 5.4.3.2-1 Deaths in Ongoing Tolvaptan Trials	
Population (Trial Number)	**Preferred Term (Number of Subjects)**
Hyponatremia (156-09-101)	Death (8), lung neoplasm malignant (5), small cell lung cancer extensive stage (4), malignant neoplasm progression (3), rapid correction of hyponatremia (3), sepsis (3), small cell lung cancer (3), dyspnoea (2), metastatic neoplasm (2), neoplasm progression (2), respiratory failure (2), acute respiratory failure (1), adenocarcinoma (1), arrhythmia (1), bronchial carcinoma (1), bronchopneumonia (1), cardiac failure (1), cervix carcinoma (1), craniopharyngioma (1), disease progression (1), haematemesis (1), hepatic cirrhosis (1), hepatic failure (1), hypothermia (1), multi-organ failure (1), myocardial infarction (1), neutropenia (1), peripheral embolism (1), pharyngeal haemorrhage (1), pneumonia aspiration (1), small cell lung cancer metastatic (1), small intestinal obstruction (1), suicide attempt (1), tachycardia (1), transitional cell carcinoma (1), urosepsis (1), ventricular tachycardia (1)
ADPKD (156-08-271, 156-10-003, 156-13-211)	156-08-271: Cardiac arrest (2), subarachnoid haemorrhage (2), atrial fibrillation (1), cervix carcinoma (1), drug hypersensitivity (1), endometrial cancer (1), gun shot wound (1), intracranial aneurysm (1), myocardial infarction (1), pancreatitis necrotising (1), urosepsis (1), wound infection (1) 156-10-003: None 156-13-211: None

ADPKD = autosomal dominant polycystic kidney disease.

5.4.4 Serious Treatment-emergent Adverse Events

A serious TEAE is defined as any event that is fatal, life threatening, requires or prolongs hospitalization, leads to significant disability/incapacity, involves a congenital anomaly or birth defect, or is medically significant.

5.4.4.1 Serious Treatment-emergent Adverse Events in Completed Trials

For the 91 trials included in the pooled safety analysis, the overall incidence of serious TEAEs was lower in tolvaptan subjects than in subjects who received placebo (1895/7343 [25.8%] for tolvaptan versus 1587/4334 [36.6%] for placebo). For furosemide-treated subjects, 2/41 (4.9%) experienced serious TEAEs.

Trials in Healthy Subjects

No serious TEAEs were reported in the completed and analyzed phase 1 trials conducted in Argentina, China, Korea, UK, or US/Multinational; however, 2 serious TEAEs (sinus arrest and bradycardia) were reported in a single subject in a Japanese phase 1 trial in healthy subjects (Trial 156-00-001). No serious TEAEs occurred in healthy subjects taking the MR formulation or the oral suspension formulation of tolvaptan.

Hyponatremia Trials

In the pooled hyponatremia trials, 114/511 (22.3%) of tolvaptan-treated subjects, and 94/469 (20.0%) of subjects who received placebo experienced serious TEAEs. Serious TEAEs, regardless of causality, reported at an incidence of ≥ 1% in the All Tolvaptan Oral Doses group, are reported for the pooled hyponatremia trials in Table 5.4.4.1-1.

Table 5.4.4.1-1 Serious Treatment-emergent Adverse Events With at Least 1% Incidence in the All Tolvaptan Group in Trials in Hyponatremia (Pooled Safety Analysis)

Adverse Events	All Tolvaptan Oral Doses[a] (N = 511) n (%)	Placebo (N = 469) n (%)
Any serious TEAE	114 (22.3)	94 (20.0)
Cardiac failure congestive	8 (1.6)	6 (1.3)
Ascites	7 (1.4)	2 (0.4)
Renal failure acute	7 (1.4)	5 (1.1)
Cardiac failure	6 (1.2)	4 (0.9)
Respiratory failure	6 (1.2)	1 (0.2)
Dehydration	5 (1.0)	1 (0.2)
Sepsis	5 (1.0)	3 (0.6)

[a]Doses of 5, 10, 15, 30, 45, 60 mg, and 15 to 60 mg titrated dose. Subjects are counted once per term for any tolvaptan dose received.
Trials: 156-96-201, 156-96-203, 156-97-204, 156-02-235, 156-03-238, 156-04-246, 156-07-802-01, 156-08-275, and 156-KOB-1101i.

In the long-term, open-label extension trial in subjects with hyponatremia (Trial 156-03-244, not included in the pooled safety analysis), serious TEAEs were experienced by 76/111 (68.5%) of all subjects and the serious TEAEs that were reported by ≥ 2% of all subjects are presented in Table 5.4.4.1-2. The most common serious TEAEs (> 5%) experienced by all subjects were hyponatremia and pneumonia (10/111, 9.0% each), cardiac failure (7/111, 6.3%), and congestive cardiac failure (7/111, 6.3%).

Table 5.4.4.1-2 Serious Treatment-emergent Adverse Events by 2% or Greater Incidence in All Subjects with Hyponatremia in the Long-term, Open-label Extension Trial 156-03-244

Adverse Events	Prior Treatment (Parent Trial)		Tolvaptan (N = 111) n (%)
	Tolvaptan (N = 56) n (%)	Placebo (N = 55) n (%)	
Any serious TEAE	37 (66.1)	39 (70.9)	76 (68.5)
Hyponatremia	4 (7.1)	6 (10.9)	10 (9.0)
Pneumonia	9 (16.1)	1 (1.8)	10 (9.0)
Cardiac failure	3 (5.4)	4 (7.3)	7 (6.3)
Cardiac failure congestive	3 (5.4)	4 (7.3)	7 (6.3)
Ascites	4 (7.1)	1 (1.8)	5 (4.5)
Gastrointestinal haemorrhage	4 (7.1)	1 (1.8)	5 (4.5)
Chest pain	2 (3.6)	3 (5.5)	5 (4.5)
Encephalopathy	1 (1.8)	4 (7.3)	5 (4.5)
Anaemia	1 (1.8)	3 (5.5)	4 (3.6)
Renal failure	1 (1.8)	3 (5.5)	4 (3.6)
Urinary tract infection	3 (5.4)	0 (0.0)	3 (2.7)
Hyperkalaemia	2 (3.6)	1 (1.8)	3 (2.7)
Depression	2 (3.6)	1 (1.8)	3 (2.7)
Syncope	2 (3.6)	1 (1.8)	3 (2.7)
Atrial fibrillation	1 (1.8)	2 (3.6)	3 (2.7)
Coronary artery disease	1 (1.8)	2 (3.6)	3 (2.7)
Hip fracture	1 (1.8)	2 (3.6)	3 (2.7)
Renal failure acute	1 (1.8)	2 (3.6)	3 (2.7)

MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse events.
Note: Parent trial = Trial 156-02-235 or Trial 156-03-238.
Subjects are counted once, per term, for the most severe of multiple occurrences of a specific MedDRA preferred term.

Cardiac Edema Trials

In completed trials in subjects with cardiac edema (Trials 156-03-001, 156-06-002, 156-06-004, 156-06-006, 156-10-005, and 156-12-809-01), 39/391 (10.0%) subjects receiving tolvaptan experienced serious TEAEs compared to 41/257 (16.0%) subjects in the placebo group. Cardiac failure was the most frequently reported serious TEAE (15/391, 3.8% tolvaptan subjects). Other serious TEAEs reported were sudden death, acute renal failure, chronic renal failure, and epistaxis (each reported in 2 tolvaptan subjects), and acute cardiac failure, congestive cardiac failure, intracardiac thrombus, ventricular tachycardia, cataract, diabetic retinal oedema, inguinal hernia, large intestinal polyp, vomiting, pyrexia, increased C-reactive protein, occult blood positive, osteoarthritis, cerebral artery embolism, embolic stroke, transient ischemic attack,

chronic obstructive pulmonary disease, and exertional dyspnoea (each reported by 1 tolvaptan subject).

Congestive Heart Failure Trials

In the 10 completed congestive heart failure trials, 1475/3115 (47.4%) of tolvaptan subjects and 1321/2502 (52.8%) of placebo subjects experienced serious TEAEs. Table 5.4.4.1-3 lists the serious TEAEs, regardless of causality, reported at an incidence of ≥ 1% in the All Tolvaptan group in the completed heart failure trials.

Table 5.4.4.1-3 Serious Treatment-emergent Adverse Events With at Least 1% Incidence in the All Tolvaptan Group in Trials in Congestive Heart Failure (Pooled Safety Analysis)

Adverse Events	All Tolvaptan Oral Doses[a] (N = 3115) n (%)	Placebo (N = 2502) n (%)
Any serious TEAE	1475 (47.4)	1321 (52.8)
Cardiac failure	471 (15.1)	445 (17.8)
Cardiac failure congestive	368 (11.8)	313 (12.5)
Pneumonia	85 (2.7)	69 (2.8)
Ventricular tachycardia	72 (2.3)	47 (1.9)
Renal failure acute	62 (2.0)	69 (2.8)
Renal failure	54 (1.7)	60 (2.4)
Chest pain	53 (1.7)	34 (1.4)
Sudden death	50 (1.6)	48 (1.9)
Cardiac arrest	49 (1.6)	27 (1.1)
Sudden cardiac death	44 (1.4)	44 (1.8)
Atrial fibrillation	39 (1.3)	41 (1.6)
Angina unstable	37 (1.2)	38 (1.5)
Cerebrovascular accident	37 (1.2)	34 (1.4)
Syncope	37 (1.2)	27 (1.1)
Hypotension	36 (1.2)	27 (1.1)
Dehydration	36 (1.2)	26 (1.0)
Cardiogenic shock	34 (1.1)	25 (1.0)
Anaemia	30 (1.0)	30 (1.2)

TEAE = treatment-emergent adverse events.

[a]Doses of 10, 15, 30, 45, 60, 90, and 120 mg. Subjects are counted once per term for any tolvaptan dose received.

Trials: 156-97-251, 156-97-252, 156-98-213, 156-00-220, 156-00-221, 156-00-222, 156-01-231, 156-01-232, 156-03-236, and 156-04-247.

Hepatic Cirrhosis Trials

In completed Japanese and Chinese trials in subjects with hepatic edema (Trials 156-03-002, 156-06-005, 156-08-001, 156-08-002, 156-08-804-01, 156-08-805-01, 156-09-004, and 156-09-806-01), serious TEAEs were reported in 64/855 (7.5%) tolvaptan subjects and 26/245 (10.6%) placebo subjects. The most

frequently reported serious TEAEs reported (reported for ≥ 1% of tolvaptan-treated subjects were hepatic encephalopathy (17/855 [2.0%] subjects), and upper gastrointestinal haemorrhage (10/855 [1.2%] subjects). Table 5.4.4.1-4 lists the serious TEAEs, regardless of causality, reported by two or more subjects in the All Tolvaptan Oral Doses group in the completed hepatic edema trials.

Table 5.4.4.1-4 Serious Treatment-emergent Adverse Events Reported by Two or More Subjects in the All Tolvaptan Oral Dose Group in Trials in Hepatic Edema (Pooled Safety Analysis)

Adverse Events	All Tolvaptan Oral Doses[a] (N = 855) n (%)	Placebo/Other (N = 245) n (%)
Any serious TEAE	64 (7.5)	26 (10.6)
Hepatic encephalopathy	17 (2.0)	4 (1.6)
Upper gastrointestinal haemorrhage	10 (1.2)	7 (2.9)
Renal impairment	3 (0.4)	1 (0.4)
Hepatic cancer	2 (0.2)	1 (0.4)
Hepatocellular carcinoma	2 (0.2)	0 (0.0)
Ascites	2 (0.2)	0 (0.0)
Intra-abdominal haemorrhage	2 (0.2)	0 (0.0)
Hepatic cirrhosis	2 (0.2)	0 (0.0)
Peritonitis	2 (0.2)	0 (0.0)
Peritonitis bacterial	2 (0.2)	0 (0.0)
Haemorrhagic shock	2 (0.2)	0 (0.0)

TEAE = treatment-emergent adverse events.

[a]Doses of 3.75, 7.5, 15, 30, and 60 mg. Subjects are counted once per term for any tolvaptan dose received.

Trials: 156-03-002, 156-06-005, 156-08-001, 156-08-002, 156-08-804-01, 156-08-805-01, 156-09-004, and 156-09-806-01.

Carcinomatous Edema

In Trial 156-12-001, there was 1 SAE reported; gastric cancer which occurred in 1 subject, but relationship to the IMP was ruled out. The severity assessment of the event was changed from “non-serious” to “serious” after completion of the trial, and it was concluded that relationship to the IMP could not be ruled out.

Chronic Renal Failure

In Trials 156-12-002 and 156-12-007 there were no SAEs reported during the course of either trial.

ADPKD Trials

In the completed long-term placebo-controlled trial in ADPKD (Trial 156-04-251) serious TEAEs were reported in 184/961 (19.1%) tolvaptan subjects and 96/483 (19.9%)

placebo subjects. The most frequently reported serious TEAEs (reported for ≥ 0.5% of tolvaptan-treated subjects) were increased alanine aminotransferase and increased aspartate aminotransferase (9/961, 0.9% subjects); chest pain (8/961, 0.8% subjects); renal cyst infection (6/961, 0.6% subjects); and pyelonephritis and headache (5/961, 0.5% subjects, each). Table 5.4.4.1-5 lists the serious TEAEs, regardless of causality, reported by 3 or more subjects in the tolvaptan group in the completed Trial 156-04-251.

Table 5.4.4.1-5 Serious Treatment-emergent Adverse Events Reported by 3 or More Subjects in the All Tolvaptan Oral Dose Group in the Long-term Placebo-controlled ADPKD Trial (Trial 156-04-251)

Adverse Events	All Tolvaptan Oral Doses[a] (N = 961) n (%)	Placebo (N = 483) n (%)
Any serious TEAE[b]	184 (19.1)	96 (19.9)
Alanine aminotransferase increased	9 (0.9)	2 (0.4)
Aspartate aminotransferase increased	9 (0.9)	2 (0.4)
Chest pain	8 (0.8)	2 (0.4)
Renal cyst infection	6 (0.6)	4 (0.8)
Pyelonephritis	5 (0.5)	6 (1.2)
Headache	5 (0.5)	0 (0.0)
Transaminases increased	4 (0.4)	0 (0.0)
Intracranial aneurysm	4 (0.4)	1 (0.2)
Haematuria	4 (0.4)	1 (0.2)
Atrial fibrillation	3 (0.3)	1 (0.2)
Dehydration	3 (0.3)	2 (0.4)
Renal cyst haemorrhage	3 (0.3)	4 (0.8)
Hepatic function abnormal	3 (0.3)	0 (0.0)
Menorrhagia	3 (0.3)	0 (0.0)
Uterine prolapse	3 (0.3)	0 (0.0)
Hypotension	3 (0.3)	1 (0.2)
Abdominal pain	3 (0.3)	2 (0.4)
Fatigue	3 (0.3)	0 (0.0)
Pneumonia	3 (0.3)	0 (0.0)

TEAE = treatment-emergent adverse events.

[a]Doses of 60 to 120 mg. Subjects are counted once per term for any tolvaptan dose received.

[b]Regardless of treatment period.

Among the 2 completed open-label, long-term trials in ADPKD (Trials 156-04-250 and 156-05-002), serious TEAEs were reported in 14/63 (22.2%) tolvaptan subjects. Serious TEAEs reported for more than one tolvaptan-treated subject were atrial fibrillation and renal pain (2/63 [3.2%] subjects each). All other serious TEAEs were reported for 1/63 (1.6%) subjects each (tachycardia, polycystic liver disease, abdominal pain, epiploic appendagitis, chest pain, cholelithiasis, ruptured hepatic cyst, diverticulitis,

pyelonephritis, malignant melanoma in situ, benign pituitary tumor, uterine leiomyoma, subarachnoid haemorrhage, transient ischemic attack, dyspnoea, and rash). No serious TEAEs were reported in the completed short-term ascending dose trials in ADPKD (Trials 156-04-001, 156-04-248, and 156-04-249). Among the trials in subjects with renal impairment (Trial 156-06-260, 156-09-282, and 156-09-284), serious TEAEs were reported for 2 tolvaptan-treated subjects: 1 subject had angina pectoris and 1 subject had polyuria (both in Trial 156-09-284). No serious TEAEs have been reported in the trial of the tolvaptan MR formulation (Trial 156-09-285).

In the completed, long-term, extension Trial 156-09-003, 9 SAEs were reported in 6/13 (46.2%) of tolvaptan subjects. Serious TEAEs were reported in 1 subject each: retinal vein occlusion, abdominal pain, large intestinal polyp, pyrexia, hepatic cyst infection, pyelonephritis, uterine leiomyoma, alcoholism, and hypertension. An individual subject could have had multiple SAEs.

5.4.4.2 Adverse Events From Completed Trials That Were Reclassified as Serious

As requested by the Medicines and Healthcare products Regulatory Agency Pharmacovigilance Inspection Report 11515/122759-003 from December 2011, findings D 3.1.5), all non-serious cases from all interventional trials performed by Otsuka or partner companies for all Otsuka compounds with an approved or pending Marketing Authorization in the European Economic Area were retrospectively medically reviewed with regard to seriousness and/or expectedness. As a result of this medical review of events in completed trials of tolvaptan, 11 events in 9 tolvaptan-treated subjects were upgraded from nonserious to serious because the event terms were unlisted as expected TEAEs in the IB (Table 5.4.4.2-1). Because this review and reclassification was done after database lock and clinical trial report finalization for the affected trials (with the exception of Trial 156-04-251), these events are not classified as serious in the pooled safety database.

Table 5.4.4.2-1	**Adverse Events Originally Classified as Nonserious in Completed Trials of Tolvaptan That Were Upgraded to Serious by the Sponsor**	
Trial (Program)	**Subject Number**	**Events by Preferred Term**
156-01-232 (Heart failure)	022-1030	Respiratory failure
156-03-236 (Heart failure)	007-3489	Atrioventricular block complete
	068-9968	Myocardial infarction
	100-7529	Bladder perforation
	134-9100	Respiratory arrest
	157-8577	Respiratory failure
	358-1006	Ischaemic stroke
156-03-244 (Hyponatremia)	039-4051	Sepsis, cardiac failure congestive
156-04-251 (ADPKD)	115-4402	Malignant melanoma, malignant melanoma in situ

ADPKD = autosomal dominant polycystic kidney disease.

5.4.4.3 Serious Treatment-emergent Adverse Events in Ongoing Trials

Among the 4 ongoing trials as of the cutoff date of 31 Mar 2015, serious TEAEs have been reported for 424 subjects. A summary of serious TEAEs reported for ≥ 3 subjects by disease state in the 4 ongoing trials is presented in Table 5.4.4.3-1. Subjects may have had more than one serious TEAE.

Table 5.4.4.3-1 Serious Treatment-emergent Adverse Events Occurring in 3 or More Subjects by Disease State in Ongoing Tolvaptan Trials	
Population (Trial Number)	**Preferred Term (Number of Subjects)**
Hyponatremia (156-09-101)	Rapid correction of hyponatremia (47), pneumonia (11), general physical health deterioration (11), lung neoplasm malignant (10), sepsis (8), death (8), malignant neoplasm progression (8), pyrexia (8), blood sodium decreased (7), dyspnoea (7), urinary tract infection (7), confusional state (6), respiratory failure (6), nausea (5), hyponatremia (5), vomiting (3), cardiac failure (5), convulsion (5), leukopenia (5), pleural effusion (5), anaemia (4), chronic obstructive pulmonary disease (4), depression (4), neutropenia (4), small cell lung cancer (4), small cell lung cancer extensive stage (4), oedema (3), pancytopenia (3), asthenia (3), C-reactive protein increased (3), diabetes mellitus (3), dizziness (3), fall (3), febrile neutropenia (3), hypokalaemia (3), infection (3), neoplasm progression (3)
ADPKD (156-08-271, 156-10-003, 156-13-211)	Renal cyst infection (17), renal cyst haemorrhage (15), blood creatinine increased (13), alanine aminotransferase increased (10), chronic kidney disease (10), renal impairment (9), intracranial aneurysm (8), pyelonephritis (8), transaminases increased (7), aspartate aminotransferase increased (6), inguinal hernia (6), acute kidney injury (5), hepatic cyst (5), sepsis (5), abdominal pain (4), anaemia (4), atrial fibrillation (4), cerebrovascular accident (4), depression (3), diverticulitis (4), liver function test abnormal (3), urinary tract infection (4), abdominal hernia (3), gamma-glutamyltransferase increased (3), intervertebral disc protrusion (3), joint dislocation (3), myocardial infarction (3), pulmonary embolism (3), renal cyst (3), renal failure (3), renal pain (4), urosepsis (3)

ADPKD = autosomal dominant polycystic kidney disease.

5.4.5 Discontinuation of Investigational Medicinal Product Due to Adverse Events

5.4.5.1 Discontinuation of Investigational Medicinal Product Due to Adverse Events in Completed Trials

In the 91 trials in the pooled safety analysis, the overall frequency of discontinuations of IMP due to TEAEs was similar between tolvaptan-treated subjects (560/7343, 7.6%) and placebo-treated subjects (260/4334, 6.0%). For furosemide-treated subjects, 2/41 (4.9%) discontinued IMP due to TEAEs. No TEAE resulted in discontinuation of IMP for more than 1% of tolvaptan- or placebo-treated subjects and no TEAE resulted in discontinuation of IMP for more than 1 furosemide-treated subject. The most common TEAEs (≥ 0.4% in the Any Tolvaptan Oral Dose group) that resulted in discontinuation of IMP were polyuria (51/7343 tolvaptan subjects [0.7%] and 1/4334 placebo subjects [0.0%]); cardiac failure (30/7343 tolvaptan subjects [0.4%] and 33/4334 placebo subjects [0.8%]); and congestive cardiac failure (28/7343 tolvaptan subjects [0.4%] and 14/4334 placebo subjects [0.3%]). The only TEAEs that resulted in discontinuation of

IMP for furosemide-treated subjects were acute cardiac failure and ECG change (1/41 subjects [2.4%] each).

Trials in Healthy Subjects

In the pooled phase 1 trials in healthy subjects, 14/1071 (1.3%) of tolvaptan-treated subjects discontinued IMP due to TEAEs compared with none of the placebo subjects or furosemide-treated subjects. The TEAEs resulting in discontinuation included 1 event each of atrial fibrillation, tachycardia, ventricular tachycardia, upper abdominal pain, rectal haemorrhage, hypersensitivity, nasopharyngitis, pneumonia, sinusitis, dizziness, delusion, and maculopapular rash, and 2 events of pruritic rash. All of the TEAEs resulting in discontinuation occurred in subjects taking the spray-dried formulation of tolvaptan, with the exception of moderate hypersensitivity (dryness around the eyes, skin rash on neck, and itching), which occurred in one subject taking the MR formulation of tolvaptan; the investigator considered the moderate hypersensitivity possibly related to the investigational product.

Hyponatremia Trials

In the pooled hyponatremia trials, 49/511 (9.6%) of tolvaptan and 40/469 (8.5%) of placebo-treated subjects discontinued IMP as a result of TEAEs. In tolvaptan subjects, the most frequently reported TEAEs resulting in discontinuation (reported by 2 or more subjects) were liver transplant (ie, hospitalization of subjects on waiting list) (3/511; 0.6%); followed by cardiac arrest, cardiac failure, ascites, malignant lung neoplasm, encephalopathy, and hepatic encephalopathy (2/511; 0.4% each). In placebo-treated subjects, the most frequently reported adverse events resulting in discontinuation (reported by 2 or more subjects) were acute renal failure (4/469; 0.9%); hepatic encephalopathy (3/469; 0.6%); and cardiac failure, vomiting, increased blood creatinine, hyponatremia, and rash (2/469; 0.4%).

In the long-term, open label extension trial in subjects with hyponatremia (Trial 156-03-244, not included in the pooled safety analysis), 19/111 (17.1%) of subjects discontinued IMP due to TEAEs and the percentage was similar for subjects who previously received tolvaptan or placebo in the parent trials. Two subjects discontinued IMP due to cardiac failure (2/111 subjects, 1.8%) and the following TEAEs resulted in discontinuation of IMP for 1/111 (0.9%) subjects each: ventricular tachycardia, vertigo, gastrointestinal haemorrhage, oesophageal varices haemorrhage, vomiting, gait disturbance, irritability, hepatic cirrhosis, increased blood creatinine, increased blood sodium, decreased appetite, bladder cancer, aphasia, psychotic disorder, renal failure, pruritus, and haemorrhagic infarction.

Cardiac Edema Trials

In the completed cardiac edema trials in Japan (Trials 156-03-001, 156-06-002, 156-06-004, 156-06-006, and 156-10-005), China (156-12-809-01), and Taiwan (156-TWA-1101i), a total of 36/437 (8.2%) subjects discontinued due to TEAEs in the tolvaptan group and 23/302 (7.6%) in the placebo group. In tolvaptan subjects, the most frequently reported adverse events resulting in discontinuation (reported by ≥ 2 subjects) were increased blood sodium (9/437, 2.1%), increased blood potassium (4/437 subjects, 0.9%), and cardiac failure, chest pain, dehydration, chronic renal impairment, and renal failure (2/437 subjects each, 0.5%). Other adverse events resulting in discontinuation in 1/473 (0.2%) subjects each in the tolvaptan group were acute cardiac failure, abdominal distension, malaise, sudden death, ischaemic hepatitis, pneumonia, increased blood creatinine, decreased blood pressure, increased blood urea, decreased blood volume, hyponatremia, cerebral artery embolism, depression, acute renal failure, exertional dyspnoea, and palmar-plantar erythrodysaesthesia syndrome.

Heart Failure Trials

In the pooled heart failure trials, 268/3115 (8.6%) of tolvaptan subjects and 161/2502 (6.4%) of placebo-treated subjects discontinued IMP as a result of TEAEs. Cardiac failure and congestive cardiac failure were the most common causes of discontinuation in both treatment groups. In the tolvaptan group, congestive cardiac failure and cardiac failure were reported by 27/3115 (0.9%) and 26/3115 (0.8%) subjects, respectively; in the placebo group, congestive cardiac failure and cardiac failure were reported by 13/2502 (0.5%) and 20/2502 (0.8%) and subjects, respectively.

Hepatic Cirrhosis Trials

In the pooled Japanese and Chinese hepatic edema trials (Trials 156-03-002, 156-06-005, 156-08-001, 156-08-002, 156-08-804-01, 156-08-805-01, 156-09-004, and 156-09-806-01), 34/855 (4.0%) tolvaptan subjects discontinued IMP compared with 11/245 (4.5%) placebo subjects. The most frequently reported TEAEs resulting in discontinuation of IMP (reported by ≥ 2 subjects) in tolvaptan-treated subjects were hepatic encephalopathy (6/855, 0.7%); dehydration (4/855, 0.5%); dizziness (3/855, 0.4%); and palpitations, abdominal distension, malaise, increased blood sodium, pollakiuria, and rash (2/855, 0.2% each). Other TEAEs resulting in discontinuation of IMP in tolvaptan-treated subjects by 1/855 (0.1%), each, were ventricular extrasystoles, nausea, upper gastrointestinal haemorrhage, vomiting, fatigue, obstructive hernia, peripheral oedema, thirst, peritonitis, rib fracture, decreased blood albumin, increased blood chloride, increased blood creatinine, increased blood potassium, decreased blood

pressure, irregular heart rate, decreased appetite, hypernatraemia, hyponatraemia, insomnia, chronic renal failure, pneumothorax, upper respiratory tract inflammation, and Henoch-Schonlein purpura. The TEAEs that led to discontinuation of IMP in placebo-treated subjects were abdominal distension (6/245, 2.4%); oedema due to hepatic disease (2/245, 0.8%); and ascites, upper gastrointestinal haemorrhage, pyrexia, sepsis, and tachypnoea (1/245, 0.4%, each).

Chronic Renal Failure Trials

In the 2 completed chronic renal failure trials (156-12-002 and 156-12-007) there were 2 subjects who discontinued (both from Trial 156-12-002) due to a TEAE: one subject with blood sodium decreased, and one subject with hyperkalaemia.

Carcinomatous Edema Trial

In the carcinomatous edema Trial 156-12-001, there were no subjects who discontinued due to a TEAE.

ADPKD Trials

In the completed long-term placebo-controlled trial in ADPKD (Trial 156-04-251) TEAEs leading to discontinuation of IMP (regardless of treatment period) were reported in 148/961 (15.4%) tolvaptan subjects and 24/483 (5.0%) placebo subjects. The difference in the rate of discontinuations of IMP due to TEAEs between tolvaptan and placebo is primarily attributable to adverse events of aquaresis and hepatic dysfunction. The most frequently reported TEAEs leading to discontinuation of IMP, reported for 2 or more tolvaptan-treated subjects were polyuria (40/961, 4.2%); pollakiuria (15/961, 1.6%); nocturia (9/961, 0.9%); thirst, and abnormal hepatic function (6/961, 0.6% each); fatigue (5/961, 0.5%); increased alanine aminotransferase, increased aspartate aminotransferase, and increased blood creatinine (4/961, 0.4% each); nausea, asthenia, depression, insomnia, and hypertension (3/961, 0.3%, each); and abdominal discomfort, constipation, abnormal liver function test, polydipsia, arthralgia, renal pain, and headache (2/961, 0.2%, each). The most frequently reported TEAEs leading to discontinuation of IMP reported for 2 or more placebo-treated subjects were renal pain (3/483, 0.6%) and headache (2/483, 0.4%).

Among the completed open-label, long-term trials in ADPKD (Trials 156-04-250 and 156-05-002), 7/63 (11.1%) tolvaptan-treated subjects discontinued IMP. The TEAEs leading to discontinuation were eye swelling, benign pituitary tumour, transient ischemic attack, acute renal failure, renal impairment, subarachnoid hemorrhage, and increased blood creatinine in 1/63 (1.6%) subject each. In the completed, long-term extension trial

156-09-003, a TEAE leading to discontinuation occurred in 1 subject who experienced alcoholism.

No subject discontinued IMP due to TEAEs in the completed short-term trials in ADPKD (Trials 156-04-001, 156-04-248, and 156-04-249). Among the trials in subjects with renal impairment (Trial 156-06-260, 156-09-282, and 156-09-284), 2 tolvaptan-treated subjects discontinued IMP due to TEAEs: 1 subject had dry mouth and 1 subject had polyuria (both in Trial 156-09-284). In trials of the tolvaptan MR formulation, 7/133 (5.3%) of subjects in Trial 156-09-290 discontinued IMP due to TEAEs; no subjects discontinued IMP due to TEAEs in Trial 156-09-285. The TEAEs leading to discontinuation of IMP in Trial 156-09-290 in the tolvaptan group were sinus tachycardia, increased blood creatinine, abnormal liver function test, increased transaminases, abnormal weight loss, dehydration, polydipsia, and polyuria (1 subject each). In subjects treated with the MR formulation, TEAEs leading to discontinuation of IMP were sinus tachycardia, increased blood creatinine, increased transaminases, abnormal weight loss, and dehydration.

5.4.5.2 Discontinuation of Investigational Medicinal Product Due to Adverse Events in Ongoing Trials

Among the 4 ongoing trials as of the cutoff date of 31 Mar 2015, 183 subjects have discontinued IMP due to TEAEs. A summary of TEAEs resulting in discontinuation of IMP in 2 or more subjects, by disease state in the ongoing trials is presented in Table 5.4.5.2-1.

Table 5.4.5.2-1 Treatment-emergent Adverse Events Resulting in Discontinuation of Investigational Medicinal Product in 2 or More Subjects by Disease State in Ongoing Tolvaptan Trials

Population (Trial Number)	Preferred Term (Number of Subjects)
Hyponatremia (156-09-101)	Rapid correction of hyponatremia (7), death (4), small cell lung cancer (4), dyspnoea (2), lung neoplasm malignant (2), urinary tract infection (2)
ADPKD (156-08-271, 156-10-003, 156-13-211)	Polyuria (39), nocturia (38), thirst (30), blood creatinine increased (12), dizziness (9), fatigue (9), pollakiuria (7), renal impairment (7), headache (5), nausea (4), polydipsia (4), dehydration (3), dry mouth (3), hypernatremia (3), insomnia (3), abdominal distension (2), acute kidney injury (2), diarrhoea (2), micturition urgency (2), orthostatic hypotension (2)

ADPKD = autosomal dominant polycystic kidney disease.
Note: A subject could have more than 1 TEAE that resulted in IMP discontinuation.

5.4.6 Other Adverse Event Findings

See Section 5.4.11.

5.4.7 Clinical Laboratory Assessment Results

Clinical laboratory abnormalities that were considered by the investigators to be clinically significant were reported as adverse events. Adverse events related to abnormal clinical laboratory findings reported with an incidence of at least 1% in the All Tolvaptan Oral Doses group for all pooled trials are shown in Table 5.4.7-1. The most frequently reported event for the tolvaptan group was increased blood creatinine with an incidence of 4.2% (308/7343) in the tolvaptan group and 3.89% (166/4334) in the placebo group. The most frequently reported event for the placebo group was hypokalaemia, with an incidence of 3.7% (271/7343) in the tolvaptan group and 5.9% (254/4334) in the placebo group. Increased blood creatinine and increased uric acid, as well as increased aspartate aminotransferase and increased alanine aminotransferase (particularly in the ADPKD population), are important laboratory parameters to monitor during tolvaptan treatment.

Table 5.4.7-1 Treatment-emergent Adverse Events Related to Clinical Laboratory Abnormalities With at Least 1% Incidence in the All Tolvaptan Group in the Pooled Trials

Adverse Events	All Tolvaptan Oral Doses[a] (N = 7343) n (%)	Placebo (N = 4334) n (%)	Furosemide 80 mg (N = 41) n (%)
Blood creatinine increased	308 (4.2)	166 (3.8)	0 (0.0)
Hypokalaemia	271 (3.7)	254 (5.9)	0 (0.0)
Hyperkalaemia	264 (3.6)	177 (4.1)	0 (0.0)
Anaemia	247 (3.4)	221 (5.1)	0 (0.0)
Hyperuricaemia	218 (3.0)	145 (3.3)	0 (0.0)
Blood uric acid increased	197 (2.7)	76 (1.8)	0 (0.0)
Haematuria	162 (2.2)	125 (2.9)	0 (0.0)
Blood urea increased	164 (2.2)	111 (2.6)	0 (0.0)
Hypoglycaemia	141 (1.9)	96 (2.2)	0 (0.0)
Hyperglycaemia	121 (1.6)	93 (2.1)	0 (0.0)
Hyponatremia	103 (1.4)	90 (2.1)	0 (0.0)
Hypernatraemia	100 (1.4)	19 (0.4)	0 (0.0)
Blood potassium increased	90 (1.2)	40 (0.9)	0 (0.0)
Blood glucose increased	90 (1.2)	44 (1.0)	1 (2.4)
Gamma-glutamyl transferase increased	83 (1.1)	63 (1.5)	0 (0.0)
Aspartate aminotransferase increased	76 (1.0)	49 (1.1)	0 (0.0)
Alanine aminotransferase increased	71 (1.0)	38 (0.9)	0 (0.0)

ADPKD = autosomal dominant polycystic kidney disease; MR = modified-release; SDT = slow-disintegration tablet; UK = United Kingdom; US = United States.

[a] Includes spray-dried doses of 3.75, 5, 7.5, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420, and 480 mg; jet-milled doses of 60, 150, 300, and 450 mg; MR doses of 20, 40, 60, and 120 mg; SDT

doses of 20 and 60 mg, and powder doses of 15 mg. Subjects are counted once per term for any tolvaptan dose received.

Trials: 156-95-301, 156-95-302, 156-95-303, 156-95-304, 156-95-305, 156-96-301, and 156-03-242 (healthy subjects phase 1 UK); 156-96-205, 156-97-202, 156-98-201, 156-98-202, 156-98-210, 156-01-223, 156-01-225, 156-01-229, 156-01-233, 156-01-234, 156-03-239, 156-03-240, 156-03-245, 156-05-252, 156-05-253, 156-05-254, 156-05-256, 156-07-262, 156-07-263, 156-08-269, 156-08-270, 156-11-295, and 156-12-202 (healthy subjects phase 1 US); 156-01-226 (healthy subjects phase 1 US and Argentina); 156-00-001, 156-00-002, 156-00-003, 156-05-001, 156-05-003, 156-05-004, 156-07-002, 156-10-004, 156-10-006, and 156-14-004 (healthy subjects phase 1 Japan); 156-06-801-01, 156-11-807-01, 156-11-808-01 (healthy subjects phase 1 China); 156-KOA-0801 (healthy subjects phase 1 Korea); 156-09-806-01 (hepatic impairment phase 1 China); 156-06-260 (ADPKD phase 1 US); 156-09-282 (renal impairment phase 1 US); 156-96-201, 156-96-203, 156-97-204, 156-02-235, 156-03-238, 156-04-246, 156-07-802-01, and 156-08-275 (hyponatremia phase 2/3); 156-KOB-1101i (hyponatremia phase 4 Korea); 156-97-251, 156-97-252, 156-98-213, 156-00-220, 156-00-221, 156-00-222, 156-01-231, 156-01-232, 156-03-236, and 156-04-247 (heart failure phase 2/3); 156-04-001, 156-04-248, 156-04-249, 156-04-251, 156-09-284, 156-09-285, 156-09-290 (ADPKD phase 2/3); 156-03-001, 156-06-002, 156-06-004, 156-06-006, and 156-12-809-01 (cardiac edema phase 2/3 Japan and China); 156-TWA-1101i (cardiac edema phase 3 Taiwan), 156-10-005 (cardiac edema phase 4 Japan); 156-03-002, 156-06-005, 156-08-001, 156-08-002, 156-09-004 (hepatic edema phase 2/3 Japan); 156-08-804-01 and 156-08-805-01 (hepatic edema phase 2/3 China), 156-12-001 (carcinomatous edema Japan), and 156-12-002, 156-12-007 (chronic renal failure phase 2 Japan).

5.4.8 Physical Examination

Clinically significant physical examination findings in tolvaptan trials were reported as TEAEs (Section 5.4.2).

5.4.9 Vital Signs

In the pooled trials, adverse events related to vital signs abnormalities that occurred in ≥ 1% of tolvaptan subjects were hypertension, hypotension, pyrexia, weight increased, and weight decreased (Table 5.4.9-1).

Table 5.4.9-1 Treatment-emergent Adverse Events Related to Vital Sign Abnormalities With at Least 1% Incidence in the All Tolvaptan Group in the Pooled Trials

Adverse Events	All Tolvaptan Oral Doses[a] (N = 7343) n (%)	Placebo (N = 4334) n (%)	Furosemide 80 mg (N = 41) n (%)
Hypertension	407 (5.5)	257 (5.9)	0 (0.0)
Hypotension	351 (4.8)	288 (6.6)	1 (2.4)
Pyrexia	231 (3.1)	160 (3.7)	1 (2.4)
Weight increased	113 (1.5)	65 (1.5)	0 (0.0)
Weight decreased	74 (1.0)	34 (0.8)	0 (0.0)

[a] Includes spray-dried doses of 3.75, 5, 7.5, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420, and 480 mg; jet-milled doses of 60, 150, 300, and 450 mg; MR doses of 20, 40, 60, and 120 mg; SDT doses of 20 and 60 mg, and powder doses of 15 mg. Subjects are counted once per term for any tolvaptan dose received.

Trials: 156-95-301, 156-95-302, 156-95-303, 156-95-304, 156-95-305, 156-96-301, and 156-03-242 (healthy subjects phase 1 UK); 156-96-205, 156-97-202, 156-98-201, 156-98-202, 156-98-210, 156-01-223, 156-01-225, 156-01-229, 156-01-233, 156-01-234, 156-03-239, 156-03-240, 156-03-245, 156-05-252, 156-05-253, 156-05-254, 156-05-256, 156-07-262, 156-07-263, 156-08-269, 156-08-270, 156-11-295, and 156-12-202 (healthy subjects phase 1 US); 156-01-226 (healthy subjects phase 1 US and Argentina); 156-00-001, 156-00-002, 156-00-003, 156-05-001, 156-05-003, 156-05-004, 156-07-002, 156-10-004, 156-10-006, and 156-14-004 (healthy subjects phase 1 Japan); 156-06-801-01, 156-11-807-01, 156-11-808-01 (healthy subjects phase 1 China); 156-KOA-0801 (healthy subjects phase 1 Korea); 156-09-806-01 (hepatic impairment phase 1 China); 156-06-260 (ADPKD phase 1 US); 156-09-282 (renal impairment phase 1 US); 156-96-201, 156-96-203, 156-97-204, 156-02-235, 156-03-238, 156-04-246, 156-07-802-01, and 156-08-275 (hyponatremia phase 2/3); 156-KOB-1101i (hyponatremia phase 4 Korea); 156-97-251, 156-97-252, 156-98-213, 156-00-220, 156-00-221, 156-00-222, 156-01-231, 156-01-232, 156-03-236, and 156-04-247 (heart failure phase 2/3); 156-04-001, 156-04-248, 156-04-249, 156-04-251, 156-09-284, 156-09-285, 156-09-290 (ADPKD phase 2/3); 156-03-001, 156-06-002, 156-06-004, 156-06-006, and 156-12-809-01 (cardiac edema phase 2/3 Japan and China); 156-TWA-1101i (cardiac edema phase 3 Taiwan), 156-10-005 (cardiac edema phase 4 Japan); 156-03-002, 156-06-005, 156-08-001, 156-08-002, 156-09-004 (hepatic edema phase 2/3 Japan); 156-08-804-01 and 156-08-805-01 (hepatic edema phase 2/3 China), 156-12-001 (carcinomatous edema Japan), and 156-12-002, 156-12-007 (chronic renal failure phase 2 Japan).

5.4.10 Electrocardiogram

Electrocardiogram abnormalities that were considered by the investigators to be clinically significant were reported as adverse events. The most common adverse events (≥ 1%) related to ECG abnormalities in the All Tolvaptan Oral Doses group in the pooled trials were ventricular tachycardia (2.5% for tolvaptan, 3.1% for placebo, and none for furosemide); atrial fibrillation (2.1% for tolvaptan, 3.2% for placebo, and none for furosemide); and ventricular extrasystoles (1.0% for tolvaptan, 1.1% for placebo, and none for furosemide). Adverse events related to ECG abnormalities reported with an incidence of at least 1% in the All Tolvaptan Oral Doses group in the pooled trials are shown in Table 5.4.10-1.

In Trial 156-03-242 in healthy subjects, one subject had a change from baseline in QTc > 60 msec (QTc = 480 msec on Day 1, hour 2 of the trial); however this value reflected an electronic reading that was determined to be erroneous by manual reading. Another subject had a ventricular rate of 103 bpm (representing a > 25% increase from baseline). Both of these events were considered by the sponsor to be clinically relevant changes from baseline; however, neither was reported as an adverse event by the investigator.

Electrocardiogram data integrating 51 single- and multiple-dose trials in healthy subjects and subjects with heart failure, hyponatremia, cardiac edema, hepatic edema, or ADPKD were centrally analyzed, and there was no evidence that tolvaptan posed any risk in terms of cardiac safety defined by its effects on the 12-lead ECG.

Table 5.4.10-1	**Treatment-emergent Adverse Events Related to Electrocardiogram Abnormalities With at Least 1% Incidence in the All Tolvaptan Group in the Pooled Trials**		
Adverse Events	**All Tolvaptan Oral Doses[a] (N = 7343) n (%)**	**Placebo (N = 4334) n (%)**	**Furosemide 80 mg (N = 41) n (%)**
Ventricular tachycardia	180 (2.5)	135 (3.1)	0 (0.0)
Atrial fibrillation	156 (2.1)	138 (3.2)	0 (0.0)
Ventricular extrasystoles	76 (1.0)	48 (1.1)	0 (0.0)

ADPKD = autosomal dominant polycystic kidney disease; MR = modified-release; SDT = slow-disintegration tablet; UK = United Kingdom; US = United States.

[a] Includes spray-dried doses of 3.75, 5, 7.5, 10, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420, and 480 mg; jet-milled doses of 60, 150, 300, and 450 mg; MR doses of 20 , 40, 60, and 120 mg; SDT doses of 20 and 60 mg and powder doses of 15 mg. Subjects are counted once per term for any tolvaptan dose received.

Trials: 156-95-301, 156-95-302, 156-95-303, 156-95-304, 156-95-305, 156-96-301, and 156-03-242 (healthy subjects phase 1 UK); 156-96-205, 156-97-202, 156-98-201, 156-98-202, 156-98-210, 156-01-223, 156-01-225, 156-01-229, 156-01-233, 156-01-234, 156-03-239, 156-03-240, 156-03-245, 156-05-252, 156-05-253, 156-05-254, 156-05-256, 156-07-262, 156-07-263, 156-08-269, 156-08-270, 156-11-295, and 156-12-202 (healthy subjects phase 1 US); 156-01-226 (healthy subjects phase 1 US and Argentina); 156-00-001, 156-00-002, 156-00-003, 156-05-001, 156-05-003, 156-05-004, 156-07-002, 156-10-004, and 156-10-006, and 156-14-004 (healthy subjects phase 1 Japan); 156-06-801-01, 156-11-807-01, 156-11-808-01 (healthy subjects phase 1 China); 156-KOA-0801 (healthy subjects phase 1 Korea); 156-09-806-01 (hepatic impairment phase 1 China); 156-06-260 (ADPKD phase 1 US); 156-09-282 (renal impairment phase 1 US); 156-96-201, 156-96-203, 156-97-204, 156-02-235, 156-03-238, 156-04-246, 156-07-802-01, and 156-08-275 (hyponatremia phase 2/3); 156-KOB-1101i (hyponatremia phase 4); 156-97-251, 156-97-252, 156-98-213, 156-00-220, 156-00-221, 156-00-222, 156-01-231, 156-01-232, 156-03-236, and 156-04-247 (heart failure phase 2/3); 156-04-001, 156-04-248, 156-04-249, 156-04-251, 156-09-284, 156-09-285, 156-09-290 (ADPKD phase 2/3); 156-03-001, 156-06-002, 156-06-004, 156-06-006, and 156-12-809-01 (cardiac edema phase 2/3 Japan and China); 156-TWA-1101i (cardiac edema, phase 3,Taiwan), 156-10-005 (cardiac edema phase 4 Japan); 156-03-002, 156-06-005, 156-08-001, 156-08-002, 156-09-004 (hepatic edema phase 2/3 Japan); 156-08-804-01 and 156-08-805-01 (hepatic edema phase 2/3 China), 156-12-001 (carcinomatous edema, phase 2, Japan), and 156-12-002, 156-12-007 (chronic renal failure, phase 2, Japan).

In Trial 156-03-245 in healthy subjects (a trial specifically designed to study the effect of tolvaptan on QTc), the mean change from baseline in QTcI was not statistically significantly different in subjects taking multiple oral doses of either 30 mg or 300 mg tolvaptan compared to subjects taking placebo, whereas the change from baseline in QTcI was statistically significantly higher in subjects taking single and multiple oral doses of 400 mg moxifloxacin compared to those taking placebo. The mean change from baseline in QTcI was statistically significantly lower in subjects taking a single oral dose of either 30 mg or 300 mg tolvaptan compared to subjects taking placebo. The changes from mean baseline in mean QTcI following either single (Day 1) or multiple QD (Day 5) oral

doses of 30 or 300 mg tolvaptan, 400 mg moxifloxacin, or placebo are summarized in Table 5.4.10-2.

Table 5.4.10-2 Mean Change in QTcI from Mean Baseline and 95% Confidence Intervals in Trial 156-03-245 in Healthy Subjects

	Mean Change (msec)	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	-

ANCOVA = analysis of covariance; CI = confidence interval; QTcI = individually corrected QT interval.

[a]Derived from ANCOVA with factors of treatment group and gender, and covariate baseline for least squares mean difference from placebo. $P < 0.05$ is considered significant.

5.4.11 Other Safety Variables

5.4.11.1 Heart Failure and Hyponatremia Populations

Exploratory analyses relating to special safety topics of interest were performed on the pooled population of subjects with heart failure in multiple-dose trials and in the pooled population of subjects with hyponatremia in multiple-dose, placebo-controlled trials. In these analyses, adverse events or combinations of adverse events were evaluated as medical concepts, rather than unique terms. In this population, tolvaptan is associated with small increases in serum creatinine concentrations. The magnitude of the increase in creatinine is relatively consistent and does not change markedly with duration or worsen at any specific time point. The increase was not associated with increases in adverse events associated with renal function (renal failure, acute renal failure, chronic renal failure) or increased all-cause mortality.

Adverse events relating to glucose control were also explored. The analyses performed suggest that rates of events related to glucose abnormalities are inconsistent and arise from small subsets of subject data. An apparent signal exists for hyperglycemia associated with tolvaptan treatment in the hyponatremia subgroup; however, the numbers of subjects reporting these events are small and the clinical consequences generally appear benign. While there is no consistent association with any particular disease

etiology, timeframe, dose, or other indicator of drug effect, the association between tolvaptan use and occurrence of hyperglycemia cannot be excluded.

In addition, an analysis of long-term events was carried on using pooled data from Trials 156-03-236 and 156-01-232, which were the only 2 trials in the Heart Failure development program with treatment durations ≥ 54 weeks. It was noted that the incidence of gout was increased over time in the tolvaptan 30 mg group relative to placebo. Further analyses were performed, which took into account the subjects' baseline gout history and history of uric acid increase/hyperuricaemia. While the results were not statistically different between the groups when factoring for history of gout or history of uric acid increase/hyperuricaemia, tolvaptan 30 mg subjects had a 1.3 times greater risk of gout if having a history of gout. Because of the small sample size, an association between gout and increased uric acid cannot be completely ruled out. Subjects with a gout history should be monitored when taking tolvaptan.

5.4.11.2 Cardiac Edema Population

Based on evaluation of the effect of short-term administration of tolvaptan on mid- to long-term prognosis in heart failure patients with volume overload in whom adequate response is not obtained with other diuretics in a completed phase 4 Trial 156-10-005, there was no marked difference in the cumulative incidence of events observed between the tolvaptan group and the placebo group, except in the initial stage of IMP administration during which a larger number of events were reported in the placebo group. There was no marked difference in survival/mortality at Week 26 between the tolvaptan group and the placebo group, suggesting that short-term administration of tolvaptan does not worsen the mid- to long-term prognosis in heart failure patients with volume overload in whom adequate response is not obtained with other diuretics.

5.4.11.3 ADPKD Population

An imbalance in the proportion of subjects with elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values (tolvaptan > placebo) was observed in Trial 156-04-251, although no hepatotoxicity was noted in nonclinical toxicity studies including repeated-dose toxicity and carcinogenicity studies. Based on central laboratory data, the incidence of elevated transaminase levels for tolvaptan subjects (> 3 times the upper limit of normal [ULN]) was approximately 3- to 4-fold higher than for placebo subjects. In an effort to further clarify these finding, a full risk assessment of hepatic events and laboratory abnormalities was undertaken, including supplemental and exploratory analyses conducted by the sponsor. Additionally, a Hepatic Adjudication Committee was formed for ongoing review of cases of transaminase elevations in Trial 156-04-251 and other studies. Transient hepatocellular injury was identified as a risk of

tolvaptan treatment in some subjects with ADPKD; however, transaminase elevations associated with tolvaptan treatment were transient, reversible, and were not associated with fulminant liver failure, or permanent liver injury or dysfunction. Most of the liver enzyme abnormalities were observed during the first 18 months of treatment. Expert adjudication of the cases in Trial 156-04-251 using a combined analysis of local and central laboratory data revealed that 2 subjects met “Hy’s Law” criteria for potential serious hepatocellular injury; however, no subjects experienced hepatic failure, hepatic transplantation, or death. An additional ADPKD subject in the ongoing extension Trial 156-08-271 was identified by the Hepatic Adjudication Committee as meeting the criteria for “Hy’s Law”.

As a result of these findings, for all ongoing tolvaptan trials in any indication, liver function should be monitored at baseline and then at least every 4 to 5 weeks, beginning at the end of the first month of treatment and continuing through Month 18 of treatment. Prompt interruption of IMP and additional testing should be performed per protocol should signs or symptoms suggestive of liver injury occur.

Monitoring for hepatotoxicity is ongoing. Data through 28 Feb 2014 included an additional 437 patients treated with tolvaptan for at least 18 months (ie, through the estimated window of susceptibility for hepatotoxicity). There have been no new cases meeting the criteria for “Hy’s Law” for potentially serious liver injury during this reporting interval.

See Section 6.2.11 in the Summary of Data and Guidance for the Investigator for additional details on hepatic transaminase elevations and potential hepatotoxicity in ADPKD and non-ADPKD populations.

Adverse events relating to glaucoma were evaluated in the ADPKD pivotal Trial 156-04-251. There was a higher incidence of glaucoma-related TEAEs (glaucoma, open angle glaucoma, and intraocular pressure increased) in the tolvaptan group (8/961, 0.8%, including one case that was noted after database lock and thus was not reported as a TEAE in this trial) than in the placebo group (2/483, 0.4%), which was considered potentially clinically important. Although there is no direct evidence for a causal association between tolvaptan and glaucoma, the possibility of such an association could not be excluded and appropriate eye examinations should be considered before and during treatment with tolvaptan.

Adverse events associated with neoplasms were also assessed in the ADPKD pivotal Trial 156-04-251. An increased incidence of malignant neoplasm diagnoses was observed in the tolvaptan group (16/961, 1.7%) compared with the placebo group (2/483, 0.4%), in particular basal cell carcinoma (8/961, 0.8% vs 1/483, 0.2%, respectively). It is

not clear whether there is a causal association between this observation and tolvaptan use. Skin examination and management should be considered for patients before and during treatment with tolvaptan.

See Section 6, Summary and Data Guidance for the Investigator for additional information.

5.5 Marketing Experience

Tolvaptan (IR formulation) was approved in the US on 19 May 2009. In Europe, central marketing authorization was granted on 03 Aug 2009. Tolvaptan was also approved in Hong Kong, Japan, Taiwan, Canada, Korea, China, Indonesia, Australia, Turkey, Philippines, and Thailand. A summary of the worldwide marketing authorization status as of the cutoff date (31 Mar 2015) is presented below (Table 5.5-1).

There are no records of any marketing authorization being revoked or withdrawn for safety reasons. A New Drug Application for marketing authorization in the US for the treatment of the ADPKD indication was not approved (Complete Response Letter: 28 Aug 2013). The FDA requested an additional clinical efficacy trial; Otsuka has initiated Protocol 156-13-210 to fulfill the FDA request.

Table 5.5-1 Worldwide Marketing Authorization Status				
Country	**Authorization Date**	**Indication(s)**	**Trade Name**	**URL for Region Specific Product Labeling**
United States	19 May 2009	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 and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).	SAMSCA	http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022275s014lbl.pdf
Europe*	03 Aug 2009	Treatment of adult patients with hyponatremia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH).	SAMSCA	http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000980/WC500048716.pdf
	27 May 2015[a]	JINARC is indicated for the treatment of autosomal dominant polycystic kidney disease (ADPKD) in adults with chronic kidney disease (CKD) stage 1 to 3 at initiation of treatment and evidence of rapidly progressing disease.	JINARC	http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002788/WC500187921.pdf
Hong Kong	06 Aug 2010	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 and SIADH.	SAMSCA	Not available
Japan	27 Oct 2010	Volume overload in heart failure when adequate response is not obtained with other diuretics (eg, loop diuretics).	SAMSCA	http://www.pmda.go.jp/PmdaSearch/iyakuDetail/GeneralList/2139011F1 (English translation not available)
	13 Sep 2013	Body fluid retention in hepatic cirrhosis when adequate response is not obtained with other diuretics (eg, loop diuretics).	SAMSCA	
	24 Mar 2014	Suppression of progression of autosomal dominant polycystic kidney disease (ADPKD) in patients with increased kidney volume and a rapid rate of increase.	SAMSCA	

Table 5.5-1 Worldwide Marketing Authorization Status				
Country	**Authorization Date**	**Indication(s)**	**Trade Name**	**URL for Region Specific Product Labeling**
Taiwan	23 Nov 2010	SAMSCA is indicated for the treatment of patients with hyponatremia secondary to heart failure and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).	SAMSCA	Samsca tablets 30 mg: http://www.fda.gov.tw/MLMS/ShowFile.aspx?LicId=02025295&Seq=005&Type=9 (English translation not available) Samsca tablets 15 mg: http://www.fda.gov.tw/MLMS/ShowFile.aspx?LicId=02025296&Seq=005&Type=9 (English translation not available)
Canada	25 Jul 2011	SAMSCA (tolvaptan) is indicated for the treatment of clinically important, non-hypovolemic hyponatremia, (eg, serum sodium < 130 mEq/L, or symptomatic hyponatremia).	SAMSCA	Available from : http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp"
	25 Feb 2015	JINARC™ (tolvaptan) is indicated to slow the progression of kidney enlargement in patients with autosomal dominant polycystic kidney disease (ADPKD). In ADPKD, kidney enlargement reflects renal cyst burden.	JINARC	
Republic of Korea	01 Sep 2011	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, and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).	SAMSCA	http://ezdrug.mfds.go.kr/kfda2 (official website of Korean Health Authority - available only in Korea) Direct URLs are not available

Table 5.5-1 Worldwide Marketing Authorization Status				
Country	**Authorization Date**	**Indication(s)**	**Trade Name**	**URL for Region Specific Product Labeling**
China	23 Sep 2011	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 Syndrome of Inappropriate Antidiuretic Hormone (SIADH).	SAMSCA	Not available
Indonesia	01 Nov 2011	Treatment of adult patients with hyponatremia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH). Treatment of clinically significant hypervolemic 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).	SAMSCA	Not available
Australia	15 Mar 2012	SAMSCA is indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium < 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).	SAMSCA	Available from: http://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2013-PI-01155-1
Turkey	31 Jul 2012	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 and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).	SAMSCA	http://www.titck.gov.tr/PortalAdmin/Uploads/KubKT/a78186c333604.pdf http://www.titck.gov.tr/PortalAdmin/Uploads/KubKT/5102371d55461.pdf http://www.titck.gov.tr/PortalAdmin/Uploads/KubKT/4132558f19451.pdf http://www.titck.gov.tr/PortalAdmin/Uploads/KubKT/8b951d0532395.pdf

Table 5.5-1 Worldwide Marketing Authorization Status				
Country	**Authorization Date**	**Indication(s)**	**Trade Name**	**URL for Region Specific Product Labeling**
				(English translation not available - password required for access)
Philippines	03 Jun 2013	TOLVAPTAN (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, and Syndrome of Inappropriate Antidiuretic Hormone (SIADH). Volume overload in heart failure when adequate response is not obtained with other diuretics (eg, loop diuretics)	SAMSCA	Not available
Thailand	25 Dec 2013	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 and Syndrome of Inappropriate Antidiuretic Hormone (SIADH). Volume overload in heart failure when adequate response is not obtained with other diuretics (eg, loop diuretics).	SAMSCA	Not available

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

[a]Although this authorization approval is outside the reporting period, it is included in this IB Edition for completeness

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6 Summary of Data and Guidance for the Investigator

Tolvaptan is a highly potent human AVP V_2 receptor antagonist, and it produces marked aquaresis, ie, increased excretion of free water with minimal changes in electrolyte excretion, after single and repeated oral administration. Tolvaptan alone, and when administered in combination with furosemide, produces aquaresis (confirmed in preclinical and clinical trials), resulting in a decrease in cardiac preload with no apparent effect on cardiac afterload (confirmed in preclinical studies) or renal function, or activation of the sympathetic or renin-angiotensin-aldosterone system (confirmed in preclinical and clinical trials). Consequently, tolvaptan can be expected to be useful for the treatment of the volume overload state of heart failure without having any undesirable effect on renal functions, systemic hemodynamics, or circulating neurohormones. Similarly, in clinical trials involving subjects with primary hyponatremia or hyponatremia associated with heart failure or cirrhosis, tolvaptan produced dose-dependent aquaresis resulting in a gradual increase in plasma sodium concentration. Tolvaptan was approved by the US FDA and by the EMA in 2009, and subsequently in 10 other countries for specific forms of hyponatremia. Tolvaptan was also approved by the Japanese MHLW for the adjunct treatment of volume overload in heart failure when adequate response is not obtained with other diuretics (Oct 2010); for body fluid retention in hepatic cirrhosis when adequate response is not obtained with other diuretics (Sep 2013); and for suppression of progression of ADPKD in patients with increased kidney volume and a rapid rate of increase (Mar 2014). Phase 3 development for hepatic edema has completed in China. Tolvaptan is also being developed in the US and multinationally for the indication of ADPKD; for the adjunct treatment of chronic renal failure treated with peritoneal dialysis and hematodialysis or hemodiafiltration, and for carcinomatous edema in Japan; and for cardiac edema in China and Taiwan. Health Canada approved JINARC™ (tolvaptan) in Feb 2015 to slow the progression of kidney enlargement in patients with ADPKD. Approval of JINARC in the EU for treatment of ADPKD was recommended by the CHMP during this reporting interval.

Tolvaptan oral bioavailability following a 30 mg dose was determined to be 56%. The $t_{1/2,z}$ is about 3 hours, consequently no accumulation of tolvaptan concentrations is observed following once-daily dosing. Maximal plasma concentrations (C_{max}) are obtained at 2 hours post dose as absorption occurs primarily in the upper small intestine. Low levels of continuing absorption from the lower gastrointestinal tract results in longer apparent $t_{1/2,z}$ values. A high-fat meal increases the early absorption of tolvaptan for doses above 30 mg, with an approximately 2-fold increase in C_{max} and no change in the

AUC observed for a 90-mg dose. There is no clinically meaningful effect on aquaresis as tolvaptan plasma concentrations at this dose are already higher than needed to saturate the V_2 receptor. Tolvaptan pharmacokinetics are not affected by race, age, or gender. In subjects with severe hepatic impairment (Child-Pugh Class C) compared to subjects with mild or moderate impairment (Child-Pugh Class A or B), tolvaptan concentrations are about 1.3-fold higher. In subjects with severe renal impairment (CrCL < 30 mL/min) compared to subjects with CrCL > 60 mL/min, tolvaptan concentrations are 1.9-fold higher. Neither hepatic nor renal impairment changes tolvaptan plasma protein binding, which is greater than 98%. When administered as described on the label, tolvaptan would be expected to be safe in subjects with renal impairment. In subjects with heart failure compared with healthy subjects, tolvaptan concentrations are 1.2- to 1.6-fold higher with no change in elimination half-life. In subjects with ADPKD and well preserved renal function, tolvaptan concentrations are similar to healthy subjects. Values for median t_{max}, steady-state exposure to tolvaptan, and daily urine volume at steady state following administration of MR 60 mg QD to subjects with ADPKD and eGFR of > 60 mL/min/1.73 m^2, were similar to values for healthy subjects.

For the treatment of hyponatremia, no dose adjustment is indicated in labeling for subjects with heart failure, renal or hepatic impairment as increases in serum sodium were observed in all subject populations, either in the pivotal trials in the hyponatremia program (Trials 156-02-235 and 156-03-238) (heart failure, hepatic impairment) or in the single dose renal impairment trial (Trial 156-09-282).

In clinical trials of subjects with hepatic edema that had not resolved despite routine diuretic therapy, a phase 2 trial (Trial 156-06-005) was conducted and the 7.5 mg dose was selected for phase 3 trials based on the results obtained. Three phase 3 trials in Japan and one phase 3 trial in China have been completed. In subjects with ADPKD, tolvaptan has been studied using surrogates of vasopressin action (eg, urine osmolality) and ADPKD disease progression (eg, TKV and eGFR); tolvaptan suppresses AVP action (ie, urine osmolality) for most of the day in most subjects when administered as split-dose regimens of 15/15 mg or higher, and long-term administration appears to slow the rate of TKV growth and to stabilize the rate of decline in eGFR. In clinical trials conducted to date, no gender effects have been observed.

6.1 Possible Risks and Expected Adverse Drug Reactions

Expected ADRs have been identified for use of tolvaptan in ADPKD, heart failure, cardiac edema, hepatic edema, and hyponatremia populations based on trials completed to date and are listed in Table 6.1-1 for purposes of expedited safety reporting.

For laboratory test abnormalities that are considered expected ADRs, the corresponding diagnostic terms (eg, hypernatraemia for blood sodium increased) are also considered expected ADRs because the test abnormality and the diagnosis indicate the same medical concept. Similarly, for diagnostic terms that are considered expected ADRs, if there are corresponding laboratory test abnormalities (eg, blood sodium increased for hypernatraemia), the laboratory test abnormalities are also considered expected ADRs.

New events added in Edition 20 IB update included osmotic demyelination syndrome (ODS) and those events associated with anaphylaxis (anaphylactic reaction, anaphylactic shock, hypersensitivity, and rash generalized) (see bolded ADRs in Table 6.1-1). There were no new expected ADRs in the reporting period for Edition 21.

Table 6.1-1 Expected Adverse Drug Reactions Inclusive of All Indications

Alanine aminotransferase abnormal[a]	Dizziness[a,b,c,d]	Jaundice hepatocellular[a]
Alanine aminotransferase increased[a]	Dizziness postural[c]	Liver disorder[a]
Anaphylactic reaction[f]	Dry mouth[a,b,e]	Liver function test abnormal[a]
Anaphylactic shock[f]	Dry skin[a,d]	Lymphadenopathy[b]
Aspartate aminotransferase abnormal[a]	Dysgeusia[a]	Malaise[c,d]
Aspartate aminotransferase increased[a]	Dyspnoea[b]	Micturition urgency[a,b]
Acute coronary syndrome[b]	Dyspnoea exacerbated[b]	Musculoskeletal discomfort[b]
Alopecia[a]	Dyspnoea paroxysmal nocturnal[b]	Nasal congestion[a]
Aortic aneurysm[b]	Fatigue[a,b]	Nasopharyngitis[a]
Asthenia[e]	Feeling cold[a]	Nausea[a,e]
Back pain[b]	Glucose tolerance impaired[e]	Nocturia[a]
Blood alkaline phosphatase increased[d]	Headache[a,b,c,d]	**Osmotic demyelination syndrome[f]**
Blood bilirubin abnormal[a]	Hepatic enzyme abnormal[a]	Pancytopenia[b]
Blood bilirubin increased[a]	Hepatic enzyme increased[a]	Pharyngitis[a]
Blood creatinine increased[a,b,c,d]	Hepatic function abnormal[a]	Pollakiuria[a,b,c,d,e]
Blood glucose decreased[b]	Hepatocellular injury[a]	Polydipsia[a,b,e]
Blood glucose increased[c,d,e]	Hepatotoxicity[a]	Polyuria[a,b,e]
Blood potassium increased[b,c,d,e]	Drug-induced liver injury[a]	Protein total increased[b]
Blood pressure decreased[c,d]	Hyperbilirubinaemia[a]	Pruritus[d]
Blood sodium increased[b,c,e]	Hypercreatininaemia[b,c,d]	Pyrexia[d,e]
Blood urea increased[c]	Hyperglycaemia[c,d,e]	Rapid correction of hyponatraemia[e]
Blood uric acid increased[c,d]	Hyperkalaemia[b,c,d,e]	**Rash generalized[f]**

Table 6.1-1 Expected Adverse Drug Reactions Inclusive of All Indications		
Blood urine present[c,d]	Hypernatraemia[b,c,e,f]	Skin irritation[b]
Chest pain[b]	**Hypersensitivity[f]**	Somnolence[a]
Constipation[a,c,d,e]	Hypertransaminasaemia[a]	Thirst[a,b,c,d,e]
Decreased appetite[a,d,e]	Hyperuricaemia[c,d]	Transaminases abnormal[a]
Dehydration[e]	Hypoglycaemia[b]	Transaminases increased[a]
Diabetes mellitus[b,e]	Hypotension[c,d]	Urine output increased[e]
Diabetes mellitus insulin-dependent[e]	Hypovolaemia[c,e]	Ventricular tachycardia[b]
Diabetes mellitus non-insulin-dependent[b,e]	Influenza like illness[b]	Vomiting[a,d]
Diarrhoea[a,c,d]	Insomnia[a,d]	--

ADPKD = autosomal dominant polycystic kidney disease; CHF = congestive heart failure; IR = immediate release; MR = modified release; SIADH = syndrome of inappropriate secretion of antidiuretic hormone.

Note: Bolded terms are new ADRs added in Edition 20 IB update.

Note: In addition to the indications noted below, this table also includes carcinomatous edema Trial 156-12-001 and chronic renal failure Trials 156-12-007 and 156-12-002.

[a]Patients with ADPKD: expected ADRs include events that have an incidence ≥ 2% in the pooled tolvaptan group from completed ADPKD trials or that have an incidence < 2% but are considered to be clinically significant. Trials for the ADPKD indication have been conducted using the IR tablet formulation (Trials 156-04-001, 156-04-248, 156-04-249, 156-04-250, 156-04-251, 156-05-002, 156-06-260, 156-09-284, and 156-09-003) and the MR capsule formulation (Trials 156-09-285 and 156-09-290).

[b]Patients with CHF: expected ADRs include all events that (1) occurred with a frequency greater than placebo and in at least 3% in tolvaptan-treated subjects in clinical trials in which heart failure was the primary inclusion criteria, (2) occurred with a frequency less than 3% in tolvaptan-treated subjects but are considered to have a possible causal relationship based on the mechanism of action or previous findings, (3) have a known or possible drug mechanism of action, or (4) have a temporal association. Also included are AEs that occur as part of the natural history of heart failure or due to possible contribution of concomitant medications, but for which the possibility of an index drug-related causality cannot be ruled out. Trials: 156-97-251, 156-97-252, 156-98-213, 156-00-220, 156-00-221, 156-00-222, 156-01-231, 156-01-232, 156-03-236, 156-04-247, and 156-09-290 (doses of 10, 15, 30, 45, 60, 90, and 120 mg).

[c]Patients with cardiac edema: AEs that were reported in at least 2% of subjects who received any oral tolvaptan dose and assessed as reasonably associated with tolvaptan, as well as AEs that occurred with a frequency of less than 2% in tolvaptan-treated subjects but are considered to have a possible causal relationship to tolvaptan based on the mechanism of action or previous findings, are considered expected ADRs. Trials: 156-03-001, 156-06-002, 156-06-004, 156-06-006, 156-10-005, 156-12-809-01 and 156-TWA-1101i.

[d]Patients with hepatic edema: AEs that occurred with a frequency greater than placebo and in at least 2% of tolvaptan-treated subjects are considered expected ADRs. Trials: 156-03-002, 156-06-005, 156-08-001, 156-08-002, 156-08-804-01, 156-08-805-01, 156-09-004, and 156-09-806-01.

[e]Patients with hyponatremia: AEs reported in multiple-dose, double-blind placebo-controlled clinical trials of tolvaptan in subjects with hyponatremia (N = 607, serum sodium < 135 mEq/L) of any cause (primarily liver disease, CHF, and SIADH) that occurred in ≥ 2% of subjects who received any oral tolvaptan dose and assessed as reasonably associated with tolvaptan use are considered ADRs. In addition, AEs that occurred with a frequency of less than 2% in tolvaptan-treated subjects but are considered to have a possible causal relationship based on the mechanism of action or previous

findings are also included. Trials: 156-96-201, 156-96-203, 156-97-204, 156-97-251, 157-97-252, 156-98-213, 156-00-220, 156-00-222, 156-01-232, 156-02-235, 156-03-236, 156-03-238, 156-04-246, 156-07-802-01, 156-08-275, and 156-KOB-1101i.

[f] AEs reported through postmarketing surveillance.

6.2 Precautions

6.2.1 Too Rapid Correction of Serum Sodium

Patients with very low baseline serum sodium concentrations may be at greater risk for too rapid correction of serum sodium. Too rapid correction of hyponatraemia (increase ≥ 12 mmol/L/24 hours) can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma, or death. Therefore after initiation of treatment and after titration, patients should be closely monitored for serum sodium, volume status, and neurologic status. In order to minimize the risk of too rapid correction of hyponatraemia the increase of serum sodium should be less than 10 to 12 mmol/L/24 hours and less than 18 mmol/L/48 hours. Therefore, more precautionary limits apply during the early treatment phase. If sodium correction exceeds 6 mmol/L during the first 6 hours of administration or 8 mmol/L during the first 6 to 12 hours, respectively, the possibility that serum sodium correction may be overly rapid should be considered. These patients should be monitored more frequently regarding their serum sodium and administration of hypotonic fluid is recommended. In case serum sodium increases ≥ 12 mmol/L within 24 hours or ≥ 18 mmol/L within 48 hours, tolvaptan treatment is to be interrupted or discontinued followed by administration of hypotonic fluid. Patients (non-ADPKD) should be hospitalized for the initiation of tolvaptan and serum sodium should be checked 2 to 3 times in the first 24 hours. In patients at higher risk of demyelination syndromes, for example those with hypoxia, alcoholism, advanced liver disease, or malnutrition, the appropriate rate of sodium correction may be lower than that in patients without risk factors; these patients should be very carefully managed. Patients with SIADH or very low baseline serum sodium concentrations may be at greater risk for too-rapid correction of serum sodium.

Patients who receive other treatment for hyponatraemia or medicinal products which increase serum sodium concentration prior to initiation of treatment with tolvaptan should be managed very cautiously. These patients may be at higher risk for developing rapid correction of serum sodium during the first 1 to 2 days of treatment due to potential additive effects. Coadministration of tolvaptan with other treatments for hyponatraemia, and medications that increase serum sodium concentration is not recommended. Fluid restriction during the first 24 hours of therapy with tolvaptan may increase the likelihood of overly-rapid correction of serum sodium, and should generally be avoided.

In controlled clinical trials in which tolvaptan was administered in titrated doses starting at 15 mg once daily, 7% of tolvaptan-treated subjects with a serum sodium < 130 mEq/L had an increase in serum sodium greater than 8 mEq/L at approximately 8 hours and 2% had an increase greater than 12 mEq/L at 24 hours. Approximately 1% of placebo-treated subjects with serum sodium < 130 mEq/L had a rise greater than 8 mEq/L at 8 hours and no subject had a rise greater than 12 mEq/L/24 hours. None of the subjects in these trials had evidence of ODS or related neurological sequelae, but such complications have been reported following too-rapid correction of serum sodium in the post-marketing environment (see Section 5.5). Since completion of the pivotal hyponatremia trials (Trials 156-02-235, 156-03-238), 2 events of rapid correction of hyponatremia have been reported in clinical trials; no evidence of ODS or related neurological signs or symptoms were reported as a result of these events.

6.2.2 Gastrointestinal Bleeding in Subjects With Cirrhosis

Among subjects with cirrhosis in trials of tolvaptan for the treatment of hyponatremia, gastrointestinal bleeding was reported in 6 out of 63 (10%) tolvaptan-treated subjects and 1 out of 57 (2%) placebo-treated subjects. Investigators are advised to use caution when administering tolvaptan in subjects with cirrhosis. A few reports of gastrointestinal bleeding in hyponatremic patients with cirrhosis have been received in the post-marketing environment. The reporting frequency cannot be calculated because the total number of subjects with cirrhosis treated with tolvaptan is not known. No clear causal association has been identified and the sponsor continues to monitor this potential risk.

6.2.3 Coadministration With Hypertonic Saline

There is very limited experience (one reported instance) with concomitant use of tolvaptan and hypertonic saline. Several of the patients with reported cases of ODS appeared to have received concurrent hypertonic saline. Concomitant use with hypertonic saline is not recommended.

6.2.4 Fluid and Electrolyte Balance

There have been reports of electrolyte abnormalities in subjects treated with tolvaptan. At this point in development, it is difficult to determine whether electrolyte abnormalities have a causal relationship to trial medication or whether they are more directly related to a disease state.

Fluid and electrolyte status should be monitored in all patients and particularly in those with renal and hepatic impairment. Administration of tolvaptan may cause too rapid increases in serum sodium (≥ 12 mmol/L per 24 hours); therefore, monitoring of serum

sodium in all patients should start no later than 4 to 6 hours after treatment initiation. During the first 1 to 2 days and until the tolvaptan dose is stabilized, serum sodium and volume status should be monitored at least every 6 hours.

Due to the effects of diuretics on fluid and electrolyte balance, other shifts in fluid/electrolyte balance that may not be known are possible in the presence of tolvaptan when subjects are also on diuretics. Investigators are cautioned to monitor electrolytes closely.

6.2.5 Hyperkalemia or Drugs That Increase Serum Potassium

Treatment with tolvaptan 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 tolvaptan treatment in patients with a serum potassium level > 5 mEq/L as well as those who are receiving drugs known to increase serum potassium levels.

6.2.6 Dehydration and Hypovolemia

Tolvaptan therapy increases free water clearance, which can lead to dehydration and hypovolemia if not offset by adequate water intake. Because of this risk, tolvaptan should not be administered to patients who do not have access to fluids or who cannot respond to the physiologic sensation of thirst. Patients who have impaired mobility (eg, bedridden, disabled) or who are intubated, disoriented, confused, or forgetful should not be administered tolvaptan unless measures to frequently monitor fluid status and blood sodium concentration are instituted.

6.2.7 Urgent Need to Raise Serum Sodium Concentrations Acutely

Tolvaptan has not been studied in a setting of urgent need to raise serum sodium concentrations acutely.

6.2.8 Hypernatremia

Potent aquaresis (free water clearance), especially in normonatremic patients treated with tolvaptan for heart failure, may induce hypernatremia which can lead to disturbed consciousness. During treatment initiation, patients should be frequently monitored for serum sodium and volume status. If serum sodium increases above normal range, tolvaptan should be discontinued, serum sodium should be carefully monitored and appropriate measures should be taken if necessary.

6.2.9 Urinary Outflow Obstruction

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. These patients should be carefully monitored while receiving treatment with tolvaptan.

6.2.10 Effects on Ability to Drive and to Use Machinery

There are no controlled trials evaluating the effects of tolvaptan on driving performance. When driving vehicles or using machines it should be taken into account that occasionally dizziness, asthenia, and syncope may occur.

6.2.11 Hepatic Transaminase Elevations - Potential Hepatotoxicity and "Hy's Law" Cases

ADPKD Population

Drug induced liver injury has been observed in clinical trials investigating ADPKD with long-term use of tolvaptan at higher doses than for the approved indications. Although transient hepatocellular injury was identified as a risk of tolvaptan treatment in some subjects with ADPKD, no subjects experienced hepatic failure, hepatic transplantation, or death resulting from hepatocellular injury. Expert adjudication of data through 31 Mar 2012 revealed that 3 tolvaptan subjects (2 in the pivotal trial [Trial 156-04-251] and 1 in the ongoing extension trial [Trial 156-08-271]) in the ADPKD program met the criteria for "Hy's Law" for potentially serious liver injury (ie, the subject met "Hy's Law" laboratory criteria [ALT/AST > 3 × ULN accompanied by total bilirubin (BT) > 2 × ULN, with the BT elevation occurring within 30 days of the transaminase elevation], did not have associated evidence of cholestasis [serum alkaline phosphatase < 2 × ULN], and other causes of hepatic injury were excluded by medical differential diagnosis). A clear "signature" presentation of idiosyncratic tolvaptan-induced liver injury was discerned from the data reviewed by the Hepatic Adjudication Committee. The onset of hepatocellular injury, as manifested by transaminase values > 3 × ULN, was characteristically observed after at least 3 months of treatment, although this does not preclude the possibility of an earlier onset injury. The incidence of new onset ALT elevations > 3 × ULN in tolvaptan subjects was low after 14 months. The ALT elevations associated with tolvaptan treatment were reversible (returned to ≤ 3 × ULN typically within 1 to 4 months), and were not associated with fulminant liver failure, or permanent liver injury or dysfunction. However, the Hepatic Adjudication Committee concluded that in patients with ADPKD, tolvaptan has the potential to cause liver injury capable of progression to liver failure.

No association with tolvaptan dose or exposure was found. The results did not appear to suggest an association between tolvaptan and age or gender with respect to an increased risk of potential liver injury. An association with Asian race or decreased renal function could not be ruled out based on numeric imbalances; however, it should be noted that the sample size for the at-risk cohort was small.

In addition, overall, there was increased incidence of significant elevations of ALT was observed in patients treated with tolvaptan [4.4% (42/958)] compared to those who received placebo [1.0% (5/484)]. Elevation (> 3 x ULN) of serum AST was observed in 3.1% (30/958) of patients on tolvaptan and 0.8% (4/484) patients on placebo (Trial 156-04-251). Most of the liver enzyme abnormalities were observed during the first 18 months of treatment, after which the rates of new elevations were comparable to placebo rates for the same period. The elevations gradually improved after discontinuation of tolvaptan. These findings may suggest that tolvaptan has the potential to cause irreversible and potentially fatal liver injury.

Monitoring for hepatotoxicity is ongoing. Data from 01 Apr 2012 through 28 Feb 2014 included an additional 437 patients treated with tolvaptan for at least 18 months (ie, through the estimated window of susceptibility for hepatotoxicity). There have been no new cases meeting the criteria for “Hy’s Law” for potentially serious liver injury as discussed in the Safety Report Update published in May 2014 (Appendix 3).

Assuming 10% of Hy’s Law cases will progress to acute liver failure, the estimate of incidence of acute liver failure in ADPKD patients chronically receiving treatment with tolvaptan would therefore be about 1 in 4,000. This estimate of risk is somewhat less the 1:3,000 arrived at in the prior Oct 2012 report. Whereas it is reassuring that no new Hy’s Law Cases have emerged, the number of additional patients treated through 18 months is not sufficient to assure a reduced risk of acute liver failure. Likewise, too few patients have been treated under the risk management strategy that went into effect in Nov 2012 to assess the effectiveness of this strategy.

Non-ADPKD Population

Retrospective evaluation of data from the hyponatremia and heart failure clinical development programs did not reveal an imbalance of subjects with elevated ALT between tolvaptan and placebo groups, nor were any of the subjects adjudicated as “highly likely” or “probable.” The dose difference between the non-ADPKD population analyzed (15 to 60 mg for hyponatremia and 30 mg for heart failure) and the ADPKD population (most common dose taken during the pivotal ADPKD trial was a split-dose regimen of 90 mg AM/30 mg PM) may at least partially account for the absence of a liver safety signal in the non-ADPKD trials. An association with dose seems less likely, given

that tolvaptan plasma concentrations in the heart failure population significantly overlap those observed in the ADPKD population despite the lower administered dose and the lack of an exposure response in the ADPKD population. It is also possible that subjects with ADPKD may be more susceptible to tolvaptan liver injury than other populations. In addition, no signal of tolvaptan-induced hepatotoxicity has been detected in the review of the postmarketing experience to date for any non-ADPKD indication. Although no signal for potential hepatotoxicity has been observed with tolvaptan in non-ADPKD populations, liver function should be monitored as described in the summary below for subjects in all tolvaptan clinical trials.

Summary

Based on the available evidence, the sponsor believes that in ADPKD there is a significant unmet medical need for therapies effective in preventing serious complications of disease progression, such as end-stage renal disease; therefore, the risk of hepatocellular injury should be evaluated in this context. The sponsor believes that the benefit outweighs the potential risk for tolvaptan to cause liver injury capable of progression to liver failure in the ADPKD population, and that through appropriate clinical management, patient monitoring can and should be implemented to mitigate the likelihood of progression to irreversible liver injury.

For all ongoing tolvaptan trials in any indication, liver function should be monitored at baseline and then at least every 4 to 5 weeks, beginning at the end of the first month of treatment and continuing through Month 18 of treatment. Liver function tests should be promptly performed in patients taking tolvaptan who report symptoms that may indicate liver injury, including fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, icterus, dark urine or jaundice. If liver injury is suspected, tolvaptan should be promptly discontinued, appropriate treatment should be instituted, and investigations should be performed to determine the probable cause. Tolvaptan should not be re-initiated in patients unless the cause for the observed liver injury is definitively established to be unrelated to treatment with tolvaptan.

6.2.12 Glaucoma

In a placebo-controlled clinical trial (Trial 156-04-251), tolvaptan-treated patients with ADPKD experienced a nominally higher frequency of glaucoma-related events (0.7% [7/961]) compared to placebo (0.4% [2/483]), however, the frequency of glaucoma was low in both groups and a causal relationship between tolvaptan and the glaucoma cannot be established. Appropriate eye examinations should be considered for patients during treatment with tolvaptan.

6.2.13 Skin Neoplasm

In a placebo-controlled clinical trial (Trial 156-04-251), tolvaptan-treated patients with ADPKD experienced a higher frequency of skin neoplasms (1.0%, 10/961) compared to placebo (0.2%, 1/483); events included basal cell carcinoma (0.8%, [8/961] vs 0.2% [1/483]) and melanoma (0.2% [2/961] vs 0% [0/483]). Periodic skin examinations should be considered during treatment with tolvaptan.

6.2.14 Gout

Decreased uric acid clearance by the kidney is a known effect of tolvaptan. In 2 long-term trials in the Heart Failure development program with treatment durations ≥ 54 weeks (Trials 156-03-236 and 156-01-232), it was noted that the incidence of gout increased over time in the tolvaptan 30 mg group relative to placebo. Results of a short-term open-label trial (Trial 156-06-260) in the ADPKD program showed a 20% to 25% decrease in the clearance of uric acid. Subjects with a gout history should be monitored for gout when taking tolvaptan.

6.2.15 Contraindications

Tolvaptan is contraindicated in the following patients:

- Patients with known or suspected hypersensitivity to tolvaptan or to benzazepine derivatives or to the ingredients of the IMP.
- Patients who are anuric, as tolvaptan would not be effective in patients with renal failure.
- Patients with hypovolemia.
- Patients who do not have access to fluids or who cannot respond to the physiologic sensation of thirst.
- Patients with hypernatremia.

6.2.16 Warnings

The safety and efficacy of tolvaptan in children, adolescents (under 18 years of age), and pregnant or lactating women have not been studied. Safety and efficacy trials in the pediatric population are under preparation in agreement with the authorities in the US and Europe.

Patients should notify their physician immediately if they become pregnant during therapy, and tolvaptan administration should be discontinued (see Section 6.4).

Tolvaptan has not been studied in a setting of urgent need to raise serum sodium acutely.

6.2.17 Drug Interactions

Coadministration of ketoconazole (a potent CYP3A4 inhibitor) significantly ($p < 0.05$) inhibited the metabolism of tolvaptan. Tolvaptan C_{max}, AUC, AUC_{∞}, $t_{1/2,z}$, and renal clearance were all increased in the presence of ketoconazole whereas CL/F was decreased (Trial 156-98-201). When therapy is initiated with tolvaptan in those who are also receiving CYP3A4 inhibitors, particular attention should be paid to monitoring the patient for clinical effects that may reflect high plasma concentrations of tolvaptan.

Tolvaptan C_{max} and AUC_{∞} were also increased 1.9- and 1.6-fold, respectively, when administered with 240 mL grapefruit juice. Tolvaptan $t_{1/2}$ was unchanged.

Steady-state digoxin concentrations were only modestly increased (20% increase in AUC_{τ}) when digoxin was coadministered with multiple 60-mg doses of tolvaptan (QD) (Trial 156-01-234). However, due to the narrow therapeutic window for digoxin, the clinician should be alert to the possibility of increases in digoxin concentrations.

When a single 240-mg dose of tolvaptan was administered with rifampin at steady state (600 mg QD), tolvaptan C_{max} and AUC_t were significantly decreased (83% and 87%, respectively).

In addition to its renal aquaretic effect (see Section 4.1.1.6), tolvaptan is capable of blocking extrarenal vascular vasopressin V_2 receptors involved in the release of coagulation factors (eg, von Willebrand's factor) from endothelial cells. Therefore, the effect of vasopressin analogs such as desmopressin acetate may be attenuated in patients using such analogs to prevent or control bleeding when coadministered with tolvaptan.

No clinically significant drug interactions were found when tolvaptan was administered with furosemide, hydrochlorothiazide, amiodarone, warfarin, or lovastatin.

6.2.18 Post-marketing Experience

In the post-marketing experience since the international birth date through 31 Mar 2014, 358 cases of rapid correction of hyponatremia (RCHN) have been reported and are broken down as follows: 198 spontaneous cases, 23 spontaneous cases from literature, and 136 solicited cases from post-marketing studies. One spontaneous case with the event of RCHN reported a fatal outcome. Of the 358 cases with events of RCHN, 28 cases are associated with ODS or neurological symptoms seen with ODS. In the safety database, there are 13 spontaneous reports (2 derived from literature) with either the MedDRA preferred term of ODS or demyelination, four of which do not contain the event of RCHN. A root cause analysis of cases of RCHN and ODS or associated

neurological sequelae suggested insufficient serum sodium monitoring in the first 24 to 48 hours. There was no consistent association with hypertonic saline, diuretics, fluid restriction, indication, or split dosing in these patients. The patients in this analysis had multiple risk factors for the development of RCHN and ODS and the related neurological complications. Because these reactions are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. See Section 6.2.1 for further guidance.

In addition, an analysis of global clinical trial and post-marketing cases of tolvaptan was conducted as a result of 2 post-marketing cases of anaphylaxis selected by the Pharmaceuticals and Medical Devices Agency in Japan. The analysis revealed 5 cases consistent with anaphylaxis and a causative role of tolvaptan was suspected in only 1 out of the 5 cases. The causally related event occurred just 8 hours after the first dose of tolvaptan and the patient was described as experiencing generalized itchiness, followed by generalized redness, dyspnea and a decrease in systolic blood pressure. The patient responded to treatment with oxygen and steroids and tolvaptan was discontinued. Despite there being just one case with suspected causality, in view of the importance of this potentially life threatening event, the sponsor adopted the events of anaphylaxis (including generalized rash and anaphylactic shock) as adverse drug reactions of tolvaptan. As of 31 Mar 2014, no additional cases of anaphylaxis have been identified. Should a patient develop signs or symptoms of hypersensitivity or anaphylactic reaction, tolvaptan should be withdrawn and the patient should seek immediate medical attention.

6.3 Overdosage

Single oral doses up to 480 mg and multiple doses up to 300 mg QD for 5 days have been well tolerated in trials in healthy subjects. There is no specific antidote for tolvaptan intoxication. 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/hypovolemia. Incidence and severity of rapid increases in serum sodium may be increased. The oral median lethal dosage (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 IV hypotonic fluids, while closely monitoring electrolytes and fluid balance. Electrocardiogram 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 (> 98%). Close medical supervision and monitoring should continue until the patient recovers.

6.4 Pregnancy

In embryo-fetal development studies, pregnant rats and rabbits received oral tolvaptan during organogenesis. Reduced fetal weights and delayed fetal ossification occurred at 1000 mg/kg. Signs of maternal toxicity (reduction in body weight gain and food consumption) occurred at 100 mg/kg or higher. When pregnant rabbits received oral tolvaptan at 100 mg/kg or higher, there were reductions in maternal body weight gain and food consumption at all doses, and increased abortions at 300 mg/kg or higher. At 1000 mg/kg, there were embryo-fetal lethality and teratogenicity (increased incidence of fetal microphthalmia, open eyelids, cleft palate, brachymelia, and skeletal malformations). No teratogenic effects were seen at 300 mg/kg.

As of 31 Mar 2015, 16 pregnancies have been reported in tolvaptan-treated subjects and 6 pregnancies have been reported in partners of tolvaptan-treated subjects. Among the 16 pregnancies reported in tolvaptan-treated subjects, 5 have resulted in live birth. In one case in Japan (Trial 156-10-003), the baby had neonatal jaundice which resolved. The relationship to IMP could be ruled out, per the investigator, since neonatal jaundice could commonly occur in newborns. This same baby was also noted to have bilateral renal cysts. Of the 11 remaining pregnancies in tolvaptan-treated subjects, 4 resulted in elective abortion, 4 resulted in spontaneous abortion or miscarriage, 1 subject had an ectopic pregnancy, and the outcome of the other 2 is unknown as of the date of this report. All of the 6 partner pregnancies resulted in live births with no known defects. Table 6.4-1 presents a listing of the pregnancies reported in tolvaptan trials in tolvaptan-treated subjects and partners of tolvaptan-treated subjects.

Table 6.4-1	**Listing of Pregnancies in Tolvaptan-treated Subjects or Their Partners Reported in Tolvaptan Studies**		
Trial Number	**Subject ID**	**Event**	**Outcome**
156-04-251	04251-308-0130	Pregnancy of partner	Live birth; no known defects
	04251-662-1857	Pregnancy of partner	Live birth; no known defects
	04251-510-1870	Pregnancy	Live birth; no known defects
	04251-467-2224	Pregnancy	Elective abortion
	04251-515-2231	Pregnancy	Elective abortion
	04251-711-3001	Pregnancy	Elective abortion
	04251-530-4225	Pregnancy	Spontaneous abortion
	04251-673-4537	Pregnancy	Elective abortion
156-08-271[a]	08271-155-0109	Pregnancy	Live birth; no known defects
	08271-533-1964	Pregnancy	Live birth; no known defects
	08271-550-8003	Pregnancy	Miscarriage
	08271-510-4235	Pregnancy	Unknown at time of report
	08271-550-8005	Pregnancy	Ectopic pregnancy
	08271-572-2223	Pregnancy	Unknown at time of report
156-10-003[a]	2907	Pregnancy	Live birth; no known defects
	2902	Pregnancy	Live birth; baby had neonatal jaundice which resolved; the relationship to IMP could be ruled out, per the investigator, since neonatal jaundice could commonly occur in newborns. Neonate had abnormality of bilateral renal cysts.
	2722	Pregnancy of partner	Live birth; no known defects
	2742	Pregnancy of partner	Live birth; no known defects
	2724	Pregnancy of partner	Live birth; no known defects
	2624	Pregnancy of partner	Live birth; no known defects
156-09-290	09290-191-9075	Pregnancy	Miscarriage
156-13-210[a]	147-S0056	Pregnancy	Spontaneous abortion

[a]Trial is ongoing.

Ongoing clinical trials mandate contraceptive measures for women of childbearing potential and exclude pregnant or lactating women. If pregnancy is confirmed for an enrolled subject, that subject may be discontinued from trial therapy and monitored.

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Appendix 1, Summary of Tolvaptan Clinical Trials

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Protocol No. Trial Type Phase	Principal Investigator (or No. of Sites) & Location	Trial Start; Trial Status/Date; Enrollment Actual/Goal	Trial Objectives	Trial Design and Type of Control	Test Product(s); Dosage Regimen, Route, and Formulation	No. Subjects by Arm Entered/ Treated/ Completed	Treatment Duration	Gender (%); Mean Age (Range); Race (%)	Healthy Subjects or Main Inclusion Criteria	Primary Endpoint(s)
156-95-302[1] (PK) 1	James G. Riddell, MD; United Kingdom	Aug 1995; Completed Oct 1995; 30/30	Dose ranging PK and PD	Sequential cohort dose escalation	Tolvaptan Capsule (spray-dried) PO 5 mg 10 mg 15 mg 30 mg 60 mg	 6/6/6 6/6/6 6/6/6 6/6.6 6/6/5	Single dose	M (100.0%); 26 (18-39) years; Caucasian (100.0%)	Healthy subjects	PK parameters
156-95-303[2] (PK) 1	James G. Riddell, MD; United Kingdom	Sep 1995; Completed Nov 1995; 6/6	Effect of food on tolvaptan PK	Open-label, randomized, crossover	Tolvaptan Capsule (spray-dried) PO 30 mg	 6/6/6	Two single doses, 7 days apart	M (100.0%); 34 (30-40) years; Caucasian (100.0%)	Healthy subjects	PK parameters
156-95-304[3] (PK) 1	James G. Riddell, MD; United Kingdom	Oct 1995; Completed Nov 1995; 8/8	Pilot Multiple Dose PK	Open-label	Tolvaptan Capsule (spray-dried) PO 30 mg QD 60 mg QD	 8/8/7	3 days QD with 30 mg 5 days QD with 60 mg	M (100.0%); 26 (19-32) years; Caucasian (100.0%)	Healthy subjects	PK parameters
156-95-305[4] (PK) 1	James G. Riddell, MD; United Kingdom	Nov 1995; Completed Jan 1996; 24/24	Multiple Dose Safety and PK	Randomized, double-blind, parallel, placebo-controlled	Tolvaptan Capsule (spray-dried) PO 30 mg QD 60 mg QD Placebo QD	 9/9/9 8/8/7 7/7/7	28 days	M (100.0%); 28 (20-39) years; Caucasian (100.0%)	Healthy subjects	PK parameters

Protocol No. Trial Type Phase	Principal Investigator (or No. of Sites) & Location	Trial Start; Trial Status/Date; Enrollment Actual/Goal	Trial Objectives	Trial Design and Type of Control	Test Product(s); Dosage Regimen, Route, and Formulation	No. Subjects by Arm Entered/ Treated/ Completed	Treatment Duration	Gender (%); Mean Age (Range); Race (%)	Healthy Subjects or Main Inclusion Criteria	Primary Endpoint(s)
156-96-301[5] (PK) 1	James G. Riddell, MD; United Kingdom	Feb 1996; Completed Mar 1996; 6/6	Formulation PK	Randomized, 3-period, 3-treatment crossover	Tolvaptan Capsule PO 30 mg Tablet PO 5 mg (× 6) Tablet PO 15 mg (× 2)	6/6/6	Three single doses, 7-day washout between doses	M (100.0%); 26 (20-31) years; Caucasian (100.0%)	Healthy subjects	PK parameters
156-96-205[6] (PK) 1	Aziz L. Laurent, MD; United States	Apr 1997; Completed Jun 1997; 12/12	PK/PD interactions between Tolvaptan and Furosemide and Tolvaptan and HCTZ	Open-label, parallel, randomized, 3-way crossover	Tolvaptan Tablet PO, 30 mg alone; Furosemide tablet PO, 80 mg alone; Tolvaptan Tablet PO 30 mg + Furosemide Tablet PO 80 mg Tolvaptan Tablet PO, 30 mg alone; HCTZ tablet PO, 100 mg alone; Tolvaptan Tablet PO 30 mg + HCTZ Tablet PO 100 mg	6/6/6 6/6/6	Tolvaptan 2 single doses, 2 or 4 days apart Furosemide Two single doses, 2 or 4 days apart HCTZ Two single doses, 2 or 4 days apart	M (100.0%); 24 (18-29) years; Caucasian (100.0%)	Healthy subjects	PK parameters

Protocol No. Trial Type Phase	Principal Investigator (or No. of Sites) & Location	Trial Start; Trial Status/Date; Enrollment Actual/Goal	Trial Objectives	Trial Design and Type of Control	Test Product(s); Dosage Regimen, Route, and Formulation	No. Subjects by Arm Entered/ Treated/ Completed	Treatment Duration	Gender (%); Mean Age (Range); Race (%)	Healthy Subjects or Main Inclusion Criteria	Primary Endpoint(s)
156-98-201[7] (PK) 1	Philip T. Leese, MD; United States	Sep 1998; Completed Oct 1998; 25/25	Effect of ketoconazole (CYP3A4 inhibition) on tolvaptan PK	Randomized (4:1), double-blind, placebo-controlled	Tolvaptan Tablet PO 30 mg Placebo Ketoconazole Tablet PO 200 mg QD	20/19/17 5/5/5	Tolvaptan (or placebo) 2 single doses, 4 days apart Ketoconazole 3 days	M (58.3%) F (41.7%); 30 (19-45) years; Caucasian (70.8%) Black (20.8%) Hispanic (4.2%) Other (4.2%)	Healthy subjects	PK parameters
156-98-202[8] (PK) 1	James D. Carlson, PharmD; United States	Jul 1998; Completed Sep 1998; 51/48	Effect of age and gender on tolvaptan PK	Open-label	Tolvaptan Tablet PO 60 mg	51/51/47 ≥ 65: 25/25/23 18-45: 26/26/24	Single dose, 3-day washout, 7 days QD	M (51.0%) F (49.0%); 48 (18-91) years; Caucasian (98.0%) Asian (2.0%)	Healthy subjects (adults 18-45 and elderly ≥ 65)	PK parameters
156-98-210[9] (PK) 1	Philip T. Leese, MD; United States	Dec 1998; Completed May 1999; 40/40	Determine safety, tolerability and PK	Randomized (3:1), double-blind, placebo-controlled, sequential cohort dose escalation, crossover (for with and without volumetric fluid replacement)	Tolvaptan Tablet PO 60 mg 90 mg 120 mg 180 mg 240 mg Placebo	6/6/6 6/6/6 6/6/6 6/6/5 6/6/4 10/10/9	Two single doses, 7 days apart	M (72.5%) F (27.5%); 28 (18-44) years; Caucasian (82.5%) Black (15.0%) Hispanic (2.5%)	Healthy subjects	PK parameters

Protocol No. Trial Type Phase	Principal Investigator (or No. of Sites) & Location	Trial Start; Trial Status/Date; Enrollment Actual/Goal	Trial Objectives	Trial Design and Type of Control	Test Product(s); Dosage Regimen, Route, and Formulation	No. Subjects by Arm Entered/ Treated/ Completed	Treatment Duration	Gender (%); Mean Age (Range); Race (%)	Healthy Subjects or Main Inclusion Criteria	Primary Endpoint(s)
156-00-001[10] (PK/PD) 1	Tomoko Hasunuma, MD, PhD; Japan	May 2001; Completed Feb 2002; 56/56	PK, PD, safety, and tolerance	Randomized (3:1), single-blind, placebo-controlled, sequential cohort dose escalation	Tolvaptan Tablet PO 15 mg 30 mg 45 mg 60 mg 90 mg 120 mg Placebo	 6/6/6 12/12/12 6/6/6 6/6/6 6/6/6 6/6/6 14/14/14	Single dose	M (100.0%); 24 (20-34) years; Japanese (100.0%)	Healthy subjects	PK parameters
156-00-002[11] (PK/PD) 1	Tomoko Hasunuma, MD, PhD; Japan	Jun 2002; Completed Jul 2002; 16/16	Effect of food on tolvaptan PK	Open-label, crossover	Tolvaptan Tablet PO 30 mg	16/16/14	Two single doses, 7 days apart	M (100.0%); 24 (20-33) years; Japanese (100.0%)	Healthy subjects	PK parameters
156-00-003[12] (PK/PD) 1	Tomoko Hasunuma, MD, PhD; Japan	Aug 2002; Completed Sep 2002; 18/18	PK, PD, and safety	Randomized, double-blind, placebo-controlled, parallel group	Tolvaptan Tablet PO 30 mg QD 60 mg QD Placebo QD	 6/6/6 6/6/5 6/6.6	Single oral dose, followed by 7 days QD	M (100.0%); 24 (20-31) years; Japanese (100.0%)	Healthy subjects	PK parameters
156-01-223[13] (PK) 1	Laurence A. Galitz, MD; United States	Feb 2001; Completed Mar 2001; 15/15	Effect of tolvaptan on lovastatin (CYP3A4 substrate) PK	Open-label, single-arm, 3-period sequential	Lovastatin Tablet PO 80 mg alone, with Tolvaptan Tablet PO 60 mg, with Tolvaptan Tablet PO 90 mg	15/15//15	Tolvaptan 2 single doses, 5 days apart Lovastatin Three single doses, 5-day washout between doses	M (60.0%) F (40.0%); 34 (22-44) years; Caucasian (53.3%) Hispanic (46.7%)	Healthy subjects	Lovastatin and Lovastatin β-hydroxy acid PK parameters

Protocol No. Trial Type Phase	Principal Investigator (or No. of Sites) & Location	Trial Start; Trial Status/Date; Enrollment Actual/Goal	Trial Objectives	Trial Design and Type of Control	Test Product(s); Dosage Regimen, Route, and Formulation	No. Subjects by Arm Entered/ Treated/ Completed	Treatment Duration	Gender (%); Mean Age (Range); Race (%)	Healthy Subjects or Main Inclusion Criteria	Primary Endpoint(s)
156-01-225[14] (PK) 1	Philip T. Leese, MD; United States	Jul 2001; Completed Dec 2001; 24/24	Effect of tolvaptan on warfarin PK and PD	Open-label, randomized, placebo-controlled crossover	Tolvaptan Tablet PO 60 mg QD Placebo for tolvaptan tablet PO QD Warfarin Tablet PO 25 mg	24/23/21	Tolvaptan 13 days QD Placebo 13 days QD Warfarin 3 single doses, Day 1, Day 23, Day 37	M (82.6%) F (17.4%); 30 (20-45) years; Caucasian (78.3%) Black (17.4%) Hispanic (4.3%)	Healthy subjects	C_{max} and AUC_{τ} of (R) and (S) warfarin; $C_{ss,min}$, $C_{ss,max}$, and AUC_{τ} of tolvaptan
156-01-226[15] (PK) 1	4 centers; United States and Argentina	Jan 2002; Completed Mar 2002; 22/20	Effect of tolvaptan on amiodarone PK	Open-label, single-arm, sequential	Tolvaptan Tablet PO 30 mg (Day 3) 90 mg (Day 4) Amiodarone Tablet PO 200 mg	22/21/21	Tolvaptan 2 single doses, 1 day apart Amiodarone 5 days	M (50.0%) F (50.0%); 66 (49-80) years; Caucasian (95.5%) Hispanic (4.5%)	Otherwise healthy subjects with history of arrhythmia; on oral maintenance amiodarone therapy	Amiodarone and desethyl-amiodarone $C_{ss,min}$, $C_{ss,max}$, and AUC_{τ}
156-01-229[16] (PK) 1	Philip T. Leese, MD; United States	Jan 2002; Completed May 2002; 59/54	Determine safety, tolerability, PK and PD, confirmatory MTD	Randomized (2:1), double-blind, placebo-controlled, sequential cohort dose escalation	Tolvaptan Tablet PO 180 mg 240 mg 300 mg 360 mg 420 mg 480 mg Placebo	7/5/5 7/6/6 7/6/6 6/6/6 7/6/5 6/6/6 19/18/18	Single dose	M (84.7%) F (15.3%); 29 (19-51) years; Caucasian (83.1%) Black (8.5%) Hispanic (3.4%) Asian (1.7%) Other (3.4%)	Healthy subjects	PK parameters

Protocol No. Trial Type Phase	Principal Investigator (or No. of Sites) & Location	Trial Start; Trial Status/Date; Enrollment Actual/Goal	Trial Objectives	Trial Design and Type of Control	Test Product(s); Dosage Regimen, Route, and Formulation	No. Subjects by Arm Entered/ Treated/ Completed	Treatment Duration	Gender (%); Mean Age (Range); Race (%)	Healthy Subjects or Main Inclusion Criteria	Primary Endpoint(s)
156-01-233[17] (PK) 1	Philip T. Leese, MD; United States	Jul 2002: Completed Sep 2002; 30/30	Dose strength equivalence, effect of lovastatin on tolvaptan PK	Open-label, randomized, cross-over	Periods 1 to 3: Tolvaptan Tablet PO 60 mg (×1) 30 mg (×2) 15 mg (×4) Period 4: Tolvaptan Tablet PO 60 mg (×1) with Lovastatin Tablet PO 80 mg	30/30/27	Tolvaptan Four single doses, 4-day washout between doses Lovastatin Single dose	M (76.6%) F (23.4%); 28 (18-44) years; Caucasian (66.7%) Black (23.3%) Hispanic (6.7%) Other (3.3%)	Healthy subjects	PK parameters
156-01-234[18] (PK) 1	Laurence A. Galitz, MD; United States	Nov 2002; Completed Jan 2003; 14/14	PK interaction between tolvaptan and digoxin	Open-label	Tolvaptan Tablet PO 60 mg QD Digoxin Tablet PO 0.25 mg QD	14/14/14	Tolvaptan single dose, 11-day washout, 5 days QD Digoxin One day of 0.5 mg with 0.25 mg 8 h later, 12 days QD	M (64.3%) F (35.7%); 34 (18-45) years; Caucasian (28.6%) Hispanic (50.0%) Black (21.4%)	Healthy subjects	Digoxin: C_{max}, AUC_{0-24h}, $A_{e,0-24}$; Tolvaptan: C_{max} and AUC_{0-24h}

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156-03-239[19] (PK) 1	Royce A. Morrison, MD; United States	May 2005; Completed Jun 2005; 15/15	Effect of rifampin on tolvaptan	Open-label, sequential	Tolvaptan Tablet PO 240 mg Rifampin Capsule PO 600 mg QD	15/15/15	Tolvaptan single dose, 8-day washout, single dose Rifampin 8 days QD	M (60.0%) F (40.0%); 26 (18-42) years; Caucasian (66.7%) Black (13.3%) Hispanic (6.7%) Asian (6.7%) Other (6.7%)	Healthy subjects	Tolvaptan and metabolite PK parameters
156-03-240[20] (PK) 1	D. Ronald Goldwater, MD; United States	Sep 2004; Completed Oct 2004; 20/20	Effect of grapefruit juice on tolvaptan	Open-label, randomized, 2-period crossover	Tolvaptan Tablet PO 60 mg Grapefruit juice, 240 mL PO	20/20/20	Tolvaptan single dose, 3-day washout, single dose Grapefruit juice, single dose	M (75.0%) F (25.0%); 35 (19-45) years; Black (50.0%) Caucasian (30.0%) Asian (15.0%) Other (5.0%)	Healthy subjects	Tolvaptan PK parameters
156-03-242[21] (PK) 1	Pauline Palmer, BSc, MB.BCHir; United Kingdom	Sep 2003; Completed Dec 2003; 49/48	PK comparison between Japanese and Caucasian men. Effect of US FDA high fat meal or Japanese standard meal.	Open-label, parallel-arm, randomized, 3-period, crossover	Tolvaptan Tablet PO 30 mg	24/24/22 Japanese 25/24/24 Caucasian	Three single doses, 3-day washout between doses	M (100.0%); 26.2 (20-40) years; Caucasian (51.0%) Japanese (49.0%)	Healthy subjects Japanese or Caucasian in origin	PK parameters

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156-03-245[22] (PK/PD) 1	David D. Hoelscher, MD; United States	Mar 2004; Completed Jun 2004; 172/160	Effect of single and multiple dose oral admini-stration of 30 or 300 mg tolvaptan, 400 mg moxifloxacin , or placebo on ECG QTc interval	Randomized, parallel-arm, double-blind, placebo-controlled	Tolvaptan Tablet PO 30 mg QD 300 mg QD Moxifloxacin 400 mg QD Placebo QD	 43/43/43 43/43/42 43/42/41 43/43/43	Tolvaptan 5 days QD Moxifloxacin 5 days QD Placebo single dose for tolvaptan and moxifloxacin groups, 6 days QD for placebo group	M (51.2%) F (48.8%); 28 (18-45) years; Caucasian (51.7%) Hispanic (29.7%) Black (14.5%) Asian (2.3%) Other (1.7%)	Healthy subjects	Individually corrected QTc on Day 5; tolvaptan and moxifloxacin PK parameters
156-05-001[23] (PK, PD, and safety) 1	Tomoko Hasunuma, MD, PhD; Japan	Nov 2005; Completed Jan 2006; 18/18	PK, PD, and safety	Randomized, single-blind, placebo-controlled, parallel group	Tolvaptan Tablet PO 90 mg QD 120 mg QD Placebo QD	 6/6/6 6/6/6 6/6/5	Single oral dose, followed by 7 days QD	M (100.0%); 28 (22-36) years; Japanese (100.0%)	Healthy subjects	PK parameters
156-05-256[24] (PK/PD) 1	Thomas H. Lagen, MD; United States	Jan 2006; Completed Feb 2006; 14/14	Effect of food on PK, PD, and safety	Open-label, crossover	Tolvaptan Tablet PO 60 mg	14/14/14 fed 14/14/14 fasted	2 single doses; 3-day washout between doses	M (64.3%) F (35.7%); 28 (18-45) years; Caucasian (100.0%)	Healthy subjects	PK parameters
156-06-801-01[25] (PK/PD) 1	Yishi Li; China	Oct 2006; Completed Dec 2006; 64/64	Safety, tolerance, PK and PD under fasting conditions	Stage 1: Open-label, sequential cohort, single ascending doses Stage 2: sequential cohort, multiple doses	Tolvaptan Tablets PO 15 mg 30 mg 60mg 120 mg Multiple dose: 30 mg QD 60 mg QD	 10/10/10 10/10/10 10/10/10 10/10/10 1212/12 12/12/12	Single dose 8 days (single dose [Stage 1] followed by 7-day multiple dosing [Stage 2])	M (100.0%); 23.1 (19-30) years Chinese (100.0%)	Healthy male subjects	PK parameters; serum electrolytes, fluid balance, urine volume, fluid intake

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156-07-002[26] (PK/PD) 1	Tomoko Hasunuma, MD, PhD; Japan	Feb 2008; Completed; Mar 2008 20/20	Effect of food on PK and PD of tolvaptan and safety	Randomized, open-label, crossover	Tolvaptan Tablet PO 15 mg	20/20/19	2 single doses; 2 to 6-day washout between doses	M (100.0%) 24.4 (20-36) years Japanese (100.0%)	Healthy male subjects	PK parameters
156-KOA-0801[27] (PK/PD) 1	Yu Kyungsang, MD, PhD. Korea	Dec 2009; Completed; Feb 2010 49/46	Safety, tolerance, pharmaco-kinetics and pharmaco-dynamics	Dose block-randomized, double-blind, placebo-controlled, single dose, dose-escalation	Tolvaptan Tablet PO 15 mg, 30 mg, 60 mg Placebo	7/6/6 26/24/24 6/6/6 10/10/10	1 day	Male (100.0%) 24.9 (20-45) years Korean (100.0%)	Healthy Korean male subjects	PK/PD parameters, safety outcomes
156-10-004[28] (BE) 1	Tomoko Hasunuma, MD, PhD; Japan	Apr 2011; Completed May 2011 30/30	Bioequiva-lence of the commercial tablet and clinical trial tablet formulations	Randomized, open-label, 2-period cross-over	Tolvaptan Tablet PO 7.5 mg (clinical trial formulation) Tolvaptan Tablet PO 7.5 mg (commercial formulation)	30/30/30	Two single doses separated by a period of 2 to 6 days	Male (100.0%) 28.7 (21-39) years Japanese (100.0%)	Healthy male subjects	PK parameters

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156-11-295[29] (Dose strength equivalence) 1	William Lewis, MD; United States	Oct 2011; Completed Nov 2011; 58/58	Determine dose-strength equivalence of 3 × 30-mg tablets to 90-mg tablet and food effect of 90-mg tablet	Open-label, randomized, 2-period crossover: Part 1: 3 × 30-mg vs 90-mg tablets Part 2: with and without high-fat meal	Tolvaptan Tablet PO 3 × 30 mg then 90 mg 90 mg	Part 1: 44/44/43 Part 2: 14/14/14	Parts 1 and 2: single doses separated by 96-hour washout	Part 1: M (45.5%) F (54.5%) 32.3 (19-45) years Caucasian (56.8%) Black (36.4%) American Indian or Alaska Native (2.3%) Other (4.5%) Part 2: M (71.4%) F (28.6%) 34.6 (24-44) years Caucasian (64.3%) Black (28.6%) Other (7.1%)	Healthy subjects	PK parameters (C_{max}, AUC_t, AUC_∞)
156-11-807-01[30] (PK, pharmacologic actions, and safety) 1	Pei Hu, MD; China	Jun 2011; Completed Jul 2011; 10/10	To investigate PK, pharmacologic actions, and safety of a single dose of tolvaptan 7.5 mg	Open label, single dose	Tolvaptan Tablet PO 7.5 mg	10/10/10	Single dose	Male (100.0%) 26.9 (23-30) years Asian (Chinese) (100.0%)	Healthy male subjects	PK; pharmaco-logic actions; safety

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156-11-808-01[31] (PK, pharmacologic actions, and safety) 1	Pei Hu, MD; China	Jun 2011; Completed Jun 2011; 12/12	To investigate PK, pharmacologic actions, and safety of multiple dosing of tolvaptan 7.5 mg	Open label; single and multiple dose	Tolvaptan Tablet PO 7.5 mg QD	12/12/12	8 days total Day 1: single dose Days 3 to 9: QD for 7 days	Male (100.0%) 25.1 (20-28) years Asian (Chinese) (100.0%)	Healthy male subjects	PK; pharmaco-logic actions; safety
156-07-262[32] (BA) 1	Maria J. Gutierrez, MD; United States	Jul 2007; Completed Aug 2007; 18/18	Relative BA of 3 MR formulations of tolvaptan compared to the IR formulation (tablet), effect on urine osmolality, and effect of food on BA of the MR formulation	Open-label, 4-period, randomized, incomplete crossover	Tolvaptan Capsule PO 60 mg MR-1 Tolvaptan Capsule PO 60 mg MR-2 Tolvaptan Capsule PO 60 mg MR-3 Tolvaptan Tablet PO 3 × 15 mg/ 1 × 15 mg split dose (AM/PM)	18/18/18	4 single doses; 4-day washout between doses	M (61.1%) F (38.9%); 34.7 (24-45) years; Caucasian (88.9%) Black (11.1%)	Healthy subjects	PK parameters Urine osmolality
156-07-263[33] (PK/PD 1	Maria J. Gutierrez, MD; United States	Mar 2008; Completed; Apr 2008; 10/10	PK of MR-3 formulation of tolvaptan and effect on urine osmolality	Open-label, single arm	Tolvaptan Capsule PO 60 mg MR-3 QD	10/10/10	7 days	M (50%)) F (50%) 35.1 (28-44) years Caucasian (90%) Black (10%)	Healthy subjects	PK parameters Urine osmolality

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156-08-269[34] (PK/PD) 1	Michael K. B. Corporon, MD; United States	Oct 2008; Completed; Dec 2008; 30/20	Dose strength equivalence of 3 × 20 mg vs 1 × 60 mg MR capsules and PK of multiple oral doses of 20 and 60 mg MR capsules	Open-label, 2-period, randomized crossover (Arm 1) Open-label, sequential, multiple dose (Arm 2)	Tolvaptan MR-3 Capsule PO Arm 1: 3 × 20 mg vs 1 × 60 mg Arm 2: 1 × 20 mg QD followed by 1 × 60 mg QD	10/10/10 20/20/9	Arm 1: Single dose of 3 × 20 mg and 1 × 60 mg on Days 1 and 4 respectively (72-hour washout) Arm 2: 1 × 20 mg QD for 5 days followed by 1 × 60 mg MR-3 QD for 5 days	Arm 1: M (60%), F (40%) 29.2 (21 -39) years Caucasian (80.0%) Black (10.0%) Asian (10.0%) Arm 2: M (40%), F (60%) 28.0 (20-45) years Caucasian (70.0%) Black (10.0%) Other (20.0%)	Healthy subjects	PK parameters, urine volume, urine osmolality

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156-10-006[35] (PK/PD) 1	Tomoko Hasunuma, MD, PhD; Japan	Nov 2011; Completed Dec 2011; 12/12	PK, PD, and safety of tolvaptan MR-3 capsules including food effect and comparison with IR tablet	Open-label, 4-period trial Period 1 and 2: Randomized, parallel-group, crossover Period 3 and 4: Sequential	Period 1 and 2: Tolvaptan MR-3 Capsule PO 3 × 20 mg QD Period 3: Tolvaptan Tablet PO 3 × 15 mg/ 1 × 15 mg split dose (AM/PM) Period 4: Tolvaptan MR-3 Capsule PO 3 × 20 mg QD	12/12/12	Period 1 and 2: Single dose on Day 1 Period 3: Split dose (AM/PM) on Day 1 Period 4: QD for 7 days	M (100%) 29.8 (23-39) years Japanese (100%)	Healthy subjects	PK parameters; urine osmolality
156-05-254[36] (BA) 1	Thomas L. Hunt, MD, PhD; United States	Oct 2005; Completed Dec 2005; 14/14-22	Absolute BA of tolvaptan 30-mg tablet formulation	Open-label, sequential	Single IV placebo infusion Tolvaptan single IV infusion Tolvaptan single dose 30-mg tablet PO	14/14//14 14/14/14 14/14/14	1 day IV placebo; 1 day IV tolvaptan; 1 day 30-mg tablet tolvaptan	M (50.0%) F (50.0%); 27 (19-44) years; Caucasian (42.9%) Hispanic (42.9%) Black (14.3%)	Healthy subjects	Absolute BA of tolvaptan

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156-08-270[37] (BA) 1	Nicholas Siebers, MD; United States	Jan 2009; Completed; Apr 2009; 28/28	Relative BA and effect of food on PK of 3 SDT formulations of tolvaptan (20 mg)	Open-label, 3-period, incomplete crossover (Arm 1) Open-label, multiple dose of selected SDT formulation (Arm 2)	Arm 1: Tolvaptan SDT Tablet PO 20 mg SDT-1 20 mg SDT-2 20 mg SDT-3 Arm 2: 20 mg SDT-3 QD	18/18/18 10/10/9	Arm 1: 3 single doses, 96-hour washout between doses Arm 2: 1 × 20 mg QD for 5 days followed by 3 × 20 mg QD for 5 days	Arm 1: M (66.7%), F (33.3%) 33.0 (19-44) years Caucasian (83.3%) Black (11.1%) Asian (5.6%) Arm 2: M (70%), F (30%) 32.3 (25-43) years Caucasian (40%) Black (60%)	Healthy subjects	PK parameters, urine osmolality
156-97-202[38] (PK) 1	Aziz L. Laurent, MD; United States	Jan 1998; Completed Mar 1998; 12/12	^{14}C Mass Balance	Open-label	^{14}C-OPC-41061 Capsule PO 60 mg (100 µCi)	12/12/12	Single dose	M (100.0%); 32 (25-37) years; Caucasian (100.0%)	Healthy subjects	PK profile; mass balance

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156-94-001[39] (PK/PD) 1	1 center; Japan	Aug 1994; Completed Oct 1994; 25/24	Safety, PK, PD, and tolerance	Randomized (3:1), single-blind, placebo-controlled, sequential dose escalation	Tolvaptan (jet-milled, powder) PO 1 mg 3 mg 10 mg 30 mg 60 mg 100 mg Placebo powder	25/24/24	Single dose × 2 (subjects received one low dose [1, 3, or 10 mg] and one high dose [30, 60, or 100 mg])	M (100.0%); 23 (20-29) years; Japanese (100.0%)	Healthy subjects	PK parameters
156-94-002[40] (PK/PD) 1	1 center; Japan	Jan 1995; Completed Feb 1995; 6/6	Effect of food on safety, PK, and PD	Open-label, crossover	Tolvaptan (jet-milled, powder) PO 60 mg	6/6/5	Two single doses, 2 weeks apart	M (100.0%); 24 (21-28) years; Japanese (100.0%)	Healthy subjects	PK parameters
156-95-301[41] (BA) 1	S.D. Oliver, MD; United Kingdom	Jun 1995; Completed Jul 1995; 4/4	Formulation PK	Open-label, crossover	Tolvaptan Sachet (jet-milled granules) PO 60 mg Tolvaptan Sachet (spray-dried granules) PO 60 mg	4/4/4	Two single doses, 7 days apart	M (100.0%); 32 (30-34) years; Caucasian (100.0%)	Healthy subjects	PK parameters
156-05-003[42] (PK/PD) 1	Tomoko Hasunuma, MD, PhD; Japan	May 2006; Completed Jun 2006; 12/12	PK, PD, and safety	Open-label, randomized, crossover	Tolvaptan Tablet (spray-dried) PO QD 45/15 mg split dose (AM/PM) Tolvaptan Tablet (jet-milled) PO QD 150 mg AM	12/12/12	5 days (spray-dried) 7 days (jet-milled)	M (100.0%); 26 (21-30) years; Japanese (100.0%)	Healthy subjects	PK parameters Urine osmolality

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156-05-004[43] (PK/PD) 1	Tomoko Hasunuma, MD, PhD; Japan	May 2006; Completed Jul 2006; 24/24	Effect of food PK, PD, and safety	Open-label	Tolvaptan Tablet (jet-milled) PO 150 mg 300 mg 450 mg	24/24/24	Single dose	M (100.0%); 28 (22-39) years; Japanese (100.0%)	Healthy subjects	PK parameters Urine osmolality
156-05-252[44] (BA) 1	Thomas H. Lagen, MD; United States	May 2006; Completed Jun 2006; 20/20	Relative BA of 150-mg jet-milled tablet compared to 60-mg spray-dried tablet Urine osmolality Food effect, safety, urine volume, and fluid balance	Open-label, multiple dose	Tolvaptan Tablet PO 150 mg (jet-milled tablet) QD 60 mg (spray-dried tablet) QD	20/20/18	5 days spray-dried 3-day washout 9 days jet-milled	M (75.0%) F (25.0%); 29 (18-45) years; Caucasian (55.0%) Black (40.0%) Other (5.0%)	Healthy subjects	PK parameters Urine osmolality
156-05-253[45] (PK/PD) 1	Thomas L. Hunt, MD, PhD; United States	Jun 2006; Completed Jun 2006; 20/20	Relative BA of 3 × 150-mg jet-milled tablets compared to a single 150-mg jet-milled tablet Safety, urine osmolality, urine volume, and fluid balance	Open-label, crossover	Tolvaptan Tablet PO (jet-milled) 3 × 50 mg (jet-milled) 1 × 150 mg (jet-milled) 2 × 150 mg (jet-milled) 3 × 150 mg	20/20/20	4 single doses; 3-day washout between doses	M (75.0%) F (25.0%); 29 (19-44) years; Caucasian (80.0%) Black (20.0%)	Healthy subjects	PK parameters Urine osmolality

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156-14-004[46] 1	Japan	Aug 2014; Completed Sep 2014; 40/40	Bioequivalence	Open-label, randomized, single-dose, 2-period, 2-way crossover	Tolvaptan 1% powder - 15 mg per 1500-mg sachet 15 mg tablet	40/40/40	Single administration, a total of twice on 2 separate days (once in each treatment period). Treatment periods were separated by a 2-day washout	M (100%) Asian (100%)	Healthy	PK: AUC_t, C_{max}
156-12-202[47] (BA) 1	David Krefetz, MD, United States	Apr 2013; Completed; May 2013; 14/14	Relative BA of oral suspension formulation at a dose of 15-mg tolvaptan compared with the 15-mg approved tablet formulation; PK/PD of tolvaptan following doses of 15 mg oral suspension or 3.75, 7.5, and 15 mg tablet doses	Open-label, 4 period, crossover	Tolvaptan Tablet PO 3.75 mg 7.5 mg 15 mg Tolvaptan Oral Suspension 15 mg	14/14/14 14/14/14	7 days (dosing on days 1, 3, 5, and 7 with a 48-hour washout between doses)	M (57.1%) F (42.9%) 33 (26-45) years Caucasian (28.6%) Black (57.1%) Native Hawaiian or Other Pacific Islander (7.1%) Other (7.1%)	Healthy subjects	PK parameters
156-12-203[48] (PK/PD) 1b	Multicenter; International	Apr 2013; Ongoing; 30 planned	PD, PK, and safety	Randomized, parallell group, double-blind	Tolvaptan Tablet PO 3.75 mg 7.5 mg 15 mg	NA	1 day	NA	Euvolemic hypo-natremia secondary to SIADH	Maximal increase and time to maximal increase in serum sodium

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156-96-201[49] (Efficacy and Safety) 2	3 centers; United States	Dec 1996; Terminated Aug 1997; 9/36	Dose ranging efficacy, safety, and PK	Randomized, double-blind, placebo-controlled, sequential-cohort, ascending-dose	Tolvaptan Tablet PO 5 mg QD 10 mg QD 15 mg QD 30 mg QD Placebo QD	6/6/5 0/0/0 0/0/0 0/0/0 3/3/3	4 days	M (55.6%) F (44.4%); 56 (32-84) years; Caucasian (77.8%) Hispanic (22.2%)	Hyponatremia secondary to CHF	Plasma sodium concentration
156-96-203[50] (Efficacy and Safety) 2	7 centers; United States	May 1997; Completed Apr 1999; 45/45	Dose ranging efficacy, safety and PK	Randomized (2:1), double-blind, placebo-controlled, sequential cohort, ascending-dose	Tolvaptan Tablet PO 5 mg QD 10 mg QD 15 mg QD 30 mg QD 60 mg QD Placebo QD	6/6/2 6/6/4 6/6/4 6/6/4 6/6/4 15/15/9	13 days	M (71.1%) F (28.9%); 52 (36-73) years; Caucasian (71.1%) Hispanic (24.4%) Black (2.2%) Other (2.2%)	Hyponatremia secondary to liver disease	Plasma sodium concentration
156-97-204[51] (Efficacy and Safety) 2	24 centers; United States	Jan 1998; Terminated Mar 1999; 28/90	Titration efficacy, safety, and dose characteris-tics	Randomized, open-label, active-controlled (placebo with fluid restriction), dose titration	Tolvaptan Tablet PO 10, 15, 30, 45, and 60 mg; titrated to effect, QD Placebo QD (with fluid restriction)	17/15/6 11/8/2	Up to 26 days	M (57.1%) F (42.9%); 67 (41-88) years; Caucasian (78.6%) Black 14.3%) Hispanic (7.1%)	Hyponatremia due to SIAD and other causes in euvolemic or hyper-volemic states	Plasma sodium concentration

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156-02-235[52] (Efficacy and safety) 3	42 centers; United States	Apr 2003; Completed Dec 2005; 205/240	Pivotal efficacy and safety	Randomized, double-blind, placebo-controlled	Tolvaptan Tablet PO 15 mg (with titration to 30 and 60 mg) QD Placebo QD	102/100/79 103/101/65	30 days	M (55.6%) F (44.4%); 60 (18-90) years; Caucasian (71.7%) Black (14.6%) Hispanic (10.7%) Asian (1.5%) Other (1.5%)	Hyponatremia	Two primary endpoints: Average AUC for serum sodium change from baseline over 4 and 30 days postbaseline
156-03-238[53] (Efficacy and safety) 3	72 centers; International	Nov 2003; Completed Jul 2005; 243/240	Pivotal efficacy and safety	Randomized, double-blind, placebo-controlled	Tolvaptan Tablet PO 15 mg (with titration to 30 and 60 mg) QD Placebo QD	123/123/92 120/119/89	30 days	M (60.9%) F (39.1%); 63 (27-100) years; Caucasian (93.4%) Hispanic (3.7%) Black (1.6%) Asian (0.4%) Other (0.8%)	Hyponatremia	Two primary endpoints: Average AUC for serum sodium change from baseline over 4 and 30 days postbaseline
156-04-246[54] (Efficacy and safety) 3	Multicenter; US	Sep 2007; Completed; Mar 2009; 57/60	Efficacy and safety	Randomized, double-blind, placebo-controlled, crossover	Tolvaptan Tablet PO 15 mg (with titration up to 60mg) QD Placebo QD	29/29/26 28/28/27	30 days	M (40.4%) F (59.6%) 71.2 (50 - 87) years Caucasian (96.5) Black (1.8%) American Indian or Alaska Native (1.8%)	Elderly subjects (≥ 50 years of age) with chronic, otherwise asymptomatic hyponatremia	Shift in neurocog-nitive composite for hyponatremia for tolvaptan relative to placebo

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156-07-802-01[55] (Efficacy and Safety) 2	49 centers, China	May 2008; Completed; Jul 2009; 241/240	Efficacy and safety	Randomized, double-blind, placebo-controlled	Tolvaptan Tablets PO 15, 30, or 60 mg QD (given as titrated dose) Placebo QD	122/122/93 119/119/82	7 days	Tolvaptan: M (63.1%), F (36.9%) 58.2 (19-81) years Placebo: M (63.9%), F (36.1%) 58.1 (22-83) years Asian (Chinese) (100%)	Hyponatremia in non-hypovolemic and non-acute states	Serum sodium
156-08-275[56] (Safety and efficacy) 3b	Multicenter; United States	Oct 2010 Terminated; Apr 2013; 124/400	Superiority of tolvaptan over fluid restriction in reducing medically-necessary length of hospital stay	Randomized, single-blind subject and symptom-rater, placebo-controlled, parallel group	Tolvaptan Tablet PO 15, 30, or 60 mg QD (titrated) Placebo QD	66/66/53 58/55/48	7 days	Tolvaptan: M (49.2%), F (50.8%) 66.7 (26-97) years Caucasian (68.5%) Black (18.5%) Asian (5.6%) Other (5.6%) Native Hawaiian or other Pacific Islander (1.6%)	Dilutional hyponatremia	Time to hospital discharge from treatment initiation through Day 45 post-first dose

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156-KOB-1101i[57] (Efficacy and Safety) 4	Multicenter, Korea	Apr 2012; Terminated Apr 2013; 42/74	Efficacy of tolvaptan in improvement of serum sodium and excretion of extracellular fluid in cirrhotic patients with hyponatremia and ascites	Single-blind, placebo-controlled, stratified, randomized	Tolvaptan Tablet PO Titration: 15 mg QD 30 mg QD 60 mg QD Placebo QD	21/21/14 21/20/14	14 days	M (70.7%)[b] F (29.3%); 55 (40-76) years; Asian (100.0%)	Liver cirrhosis patients with hyponatremia and ascites	Change in serum sodium from baseline to Day 14
156-KOB-1201i[58] (Safety and Efficacy) 4	Multicenter; Korea	Nov 2012; Ongoing; 100 planned	Efficacy and safety of tolvaptan for increasing serum sodium levels in patients with heart failure	Multicenter, randomized, double-blind, placebo-controlled, parallel group	Tolvaptan Tablet PO Titration: 15 mg QD 30 mg QD 60 mg QD Placebo QD	NA	60 days	NA	Hyponatremia in patients hospitalized with worsening heart failure	Average daily AUC of change from baseline to Day 4 in serum sodium
156-03-244[59] (Long-term safety) 3	Multicenter; International	May 2004; Completed; Oct 2009; 111/Up to 200	Long-term safety and natural history of disease	Open-label, extension of 156-02-235 and 156-03-238	Tolvaptan Tablet PO 15 mg QD, 30 mg QD, or 60 mg QD (given as titrated dose)	111/111/47	Up to 214 weeks	M (49.5%), F (50.5%) 64.6 (27-92) years Caucasian (94.0%) Black (5.0%) Hispanic (1.0%)	Hyponatremia	AEs and change from baseline in selected laboratory parameters

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156-09-101[60] (Safety) 4	Multicenter International	Nov 2010; Completed;[a] Nov 2014; 252	Monitor and document the drug utilization patterns of tolvaptan in routine medical practice, and collect information on the safety of tolvaptan in a real-life setting	Observational, Drug Utilization Survey and Post-Authorization Safety Study	Dose and regimen prescribed by physician	252/252/41	As prescribed by physician (chronically-treated subjects observed for a minimum of 12 months after treatment initiation)	M (49.6%) F (50.4%) 70.6 (26-96) years Caucasion (98.4%) Asian (1.2%) Unknown (0.4%)	Subjects prescribed tolvaptan for treatment of SIADH	Survey: individual prescription-level data collected from hospital pharmacies. Safety study: sodium levels and adverse events.
156-97-251[61] (Efficacy and Safety) 2	10 centers; United States	Sep 1997; Completed Mar 1999; 55/54	Efficacy, safety, and PK	Randomized (2:1), double-blind, placebo-controlled, sequential cohort, ascending-dose	Tolvaptan Tablet PO 10 mg QD 15 mg QD 30 mg QD 60 mg QD 90 mg QD 120 mg QD Placebo QD	 5/5/4 6/6/6 6/6/6 6/6/5 6/6/6 7/7/7 19/19/16	13 days	M (61.8%) F (38.2%); 64.4 (44-86) years; Caucasian (81.8%) Black (16.4%) Other (1.8%)	Hospitalized patients with CHF with extracellular volume expansion	Body weight
156-97-252[62] (Efficacy and Safety) 2	30 centers; United States	Mar 1998; Completed Jan 1999; 254/240	Efficacy, safety, and dose characteristics	Randomized, double-blind, placebo-controlled	Tolvaptan Tablet PO 30 mg QD 45 mg QD 60 mg QD Placebo QD	 64/64/59 64/62/59 63/61/48 63/62/55	25 days	M (64.2%) F (35.8%); 67 (29-94) years; Caucasian (73.6%) Black (24.0%) Hispanic (2.0%) Asian (0.4%)	Patients with extracellular volume expansion secondary to CHF	Body weight

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156-00-222[63] (Efficacy and safety) 2	18 centers; United States	Oct 2000; Completed May 2001; 83/80	Furosemide comparator efficacy and safety	Randomized, double-blind, placebo-controlled	Tolvaptan Tablet PO 30 mg QD Furosemide Tablet PO 80 mg QD Tolvaptan 30 mg + Furosemide 80 mg, QD Placebo QD	20/19/18 22/22/20 20/20/19 21/21/20	7 days	M (80.7%) F (19.3%); 59 (24-82) years; Caucasian (59.0%) Black (27.7%) Hispanic (12.1%) Asian (1.2%)	CHF	Change from baseline in body weight
156-03-001[64] (Efficacy and safety) 2	51 centers; Japan	Aug 2004; Completed Jan 2006; 122/120	Efficacy, safety, and dose character-istics	Randomized, double-blind, placebo-controlled	Tolvaptan Tablet PO 15 mg QD 30 mg QD 45 mg QD Placebo QD	29/29/28 34/34/29 29/29/21 30/30/26	7 days	M (69.5%) F (30.5%); Placebo: 68 (41-79) years; Tolvaptan: 65 (31-79) years; Japanese (100.0%)	Hospitalized patients with extracellular volume expansion secondary to CHF	Change from baseline in body weight
156-06-002[65] (Safety & efficacy) 3	Multicenter; Japan	May 2007; Completed; April 2008; 110/110	Safety and efficacy	Randomized, double-blind, placebo-controlled, parallel group	Tolvaptan Tablet PO 15 mg QD Placebo QD	53/53/45 57/57/51	7 days	M (67.3%) F (32.7%) Tolvaptan 71 (41-85) years Placebo 71 (35-85) years Japanese (100.0%)	Subjects with extracellular volume expansion secondary to CHF despite the use of a diuretic	Change from baseline in body weight

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156-06-004[66] (Safety & efficacy) 3	Multicenter: Japan	Sep 2007; Completed; Jun 2008; 20/20	PK, PD, safety and efficacy	Randomized, double-blind, parallel group	Tolvaptan Tablet PO 7.5 mg QD 15 mg QD	 10/10/9 10/10/10	7 days	M (72.5%) F (27.5%) 70.5 (41-84) years Japanese (100.0%)	CHF subjects with extracellular volume expansion despite the use of furosemide	PK/PD parameters; body weight, lower limb edema, other edema, jugular venous distension, hepatomegaly, pulmonary rales, third cardiac sound, pulmonary congestion, and cardiothoracic ratio
156-06-006[67] (Safety & efficacy) 3	Multicenter; Japan	Oct 2007; Completed; Jun 2008 68/50	Plasma drug concentration, safety, efficacy	Open-label, uncontrolled	Tolvaptan Tablet PO Period 1: 15 mg QD Period 2: 15 mg QD 30 mg QD	 68/52/24 (16 subjects from Period 1 entered Period 2) 14/14/12 2/2/2	7 days in each period (14 days total)	M (72.5%) F (27.5%) 70.5 (41-84) years Japanese (100.0%)	CHF subjects with extracellular volume expansion despite conventional diuretic therapy	Change from baseline in body weight

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156-10-005[68] (Safety and efficacy) 4	Multicenter, Japan	Oct 2011; Completed Feb 2014; 105/111	Effect of short-term administration of tolvaptan on the mid- to long-term prognosis of heart failure patients with volume overload	Randomized, double-blind, placebo-controlled, parallel-group comparison	Tolvaptan Tablet PO 15 mg QD Placebo QD	53/50/42 52/50/47	Maximum of 14 days with no interruption of administration permitted	M (66%) F (34%) 73.8 (52-85) years Asian (100.0%)	CHF subjects with extracellular volume expansion despite conventional diuretic therapy	Time to event occurrence (CV mortality or worsening of heart failure) over a 26-week observation period
156-12-809-01[69] (Safety and Efficacy) 3	Multicenter, China	Aug 2012; Completed Jul 2013; 244/240	Efficacy and safety of short-term administration of tolvaptan on body fluid retention in CHF patients after current diuretic treatment	Randomized, double-blind, placebo-controlled, parallel group comparison	Conventional diuretic therapy plus: Tolvaptan Tablet PO 15 mg QD Placebo QD	 124/124/113 120/120/99	7 days	M (63.0%) F (37.0%); 64.7 (18-85) years; Asian (100.0%)	CHF patients with body fluid retention after receiving current diuretic therapy	Change from baseline in body weight
156-TWA-1101i[70] (Safety and efficacy) 3	Multicenter, Taiwan	Jul 2012; Completed May 2014; 91/74	Efficacy and safety of short-term administration of tolvaptan in HF patients after acute exacerbation of cardiac-induced volume retention	Randomized, double-blind, placebo-controlled, parallel group comparison	Tolvaptan Tablet PO 15 mg QD Placebo QD	46/46/44 45/45/41	4 days	Tolvaptan M (71.7%) F (28.3%) 68.0 (37-85) years Placebo M (73.3%) F (26.7%) 65.6 (29-84) years Asian (100.0%)	Stabilized heart failure patients after acute exacerbation of cardiac-induced volume congestion	Change from baseline in body weight

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156-00-221[71] (PD) 2	William Smith, MD; United States	Nov 2000; Completed Feb 2002; 14/14	Renal mechanism of action	Open-label, randomized, placebo-controlled, crossover	Tolvaptan Tablet PO 30 mg Placebo Furosemide Tablet PO 80 mg	14/14/13	Tolvaptan Single dose (Day 1 or 3) Placebo Single dose (Day 1 or 3) Furosemide Single dose (Day 5)	M (71.4%) F (28.6%); 56 (45-70) years; Caucasian (50.0%) Black (50.0%)	Mild to moderate CHF	Glomerular filtration rate, proximal fractional reabsorption of sodium, distal fractional reabsorption of sodium, effective renal plasma flow, renal blood flow, and renal vascular resistance
156-01-231[72] (PK/PD) 2	10 centers; United States	May 2002; Completed Sep 2002; 40/40	Effect of dose regimen on tolvaptan PK/PD	Randomized, double-blind, parallel group	Tolvaptan Tablet PO 30 mg QD 15 mg BID	21/21/20 19/19/19	7 days	M (75.0%) F (25.0%); 53 (27-84) years; Caucasian (45.0%) Hispanic (32.5%) Black (22.5%)	CHF	PK/PD parameters

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156-04-247[73] (PK/PD) 2	48 centers; International	Feb 2005 Completed Dec 2006; 181/180	Effect of tolvaptan on hemodynamic parameters	Randomized, double-blind, placebo-controlled	Tolvaptan, Tablet PO 15 mg 30 mg 60 mg Placebo	 44/44/44 43/43/43 46/46/45 48/48/45	Single dose	M (79.6%) F (20.4%) 60 (26-89) years Caucasian (70.7%) Black (23.2%) Hispanic (3.9%) Asian (1.1%) Other (1.1%)	Heart failure and left ventricular dysfunction	Peak change from baseline in pulmonary capillary wedge pressure; Tolvaptan PK parameters
156-98-213[74] (Efficacy and Safety) 2	46 centers; United States and Argentina	Feb 2000; Completed Sep 2001; 319/320	Efficacy and safety	Randomized, double-blind, placebo-controlled	Tolvaptan Tablet PO 30 mg QD 60 mg QD 90 mg QD Placebo QD	 78/78/48 84/84/40 77/76/45 80/79/56	Up to 61 days	M (70.2%) F (29.8%); 62 (18-89) years; Caucasian (48.9%) Black (22.9%) Hispanic (26.1%) Asian (0.6%) Other (1.5%)	Patients hospitalized with worsening CHF	Inpatient: body weight at 24 hours; outpatient: worsening of heart failure; overall: clinical worsening of heart failure
156-00-220[75] (Efficacy and Safety) 2	67 centers; United States and Argentina	Apr 2000; Completed Dec 2001; 330/320	Efficacy and safety	Randomized, double-blind, placebo-controlled	Tolvaptan Tablet PO 15 mg QD 30 mg QD 60 mg QD Placebo QD	 82/82/65 82/82/59 82/81/65 84/84/71	Up to 169 days	M (67.6%) F (32.4%); 65 (28-92) years; Caucasian (79.7%) Black (10.6%) Hispanic (7.9%) Asian (0.6%) Other (1.2%)	Patients with CHF	Clinical status at 6 months

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156-01-232[76] (Efficacy and safety) 2	38 centers; United States	Jul 2002; Completed Aug 2004; 240/240	Cardiac remodeling efficacy and safety	Randomized, double-blind, placebo-controlled	Tolvaptan Tablet PO 30 mg QD Placebo QD	120/120/91 120/120/89	1 year	M (81.7%) F (18.3%); 64 (29-87) years; Caucasian (87.1%) Black (9.2%) Hispanic (2.9%) Other (0.8%)	Heart failure and left ventricular dysfunction	Reduction in left ventricular end diastolic volume at Week 54

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156-03-236[77] (Efficacy and safety) 3	432 centers; International	Oct 2003; Completed Jul 2006; 4133/3600 (event driven)	Pivotal efficacy and safety including short-term symptomatic improvement (Short-term Clinical Status Trials A and B); and long-term safety (morbidity/ mortality) (Long-term Outcome Trial)	Randomized, double-blind, placebo-controlled with embedded 3-in-1 trials	Tolvaptan Tablet PO 30 mg QD Placebo QD	2072/2063/ 1231 2061/2055 1235	Minimum of 60 days or up to Day 7/Discharge for inpatient studies	M (74.4%) F (25.6%); 66 (18-94) years; Caucasian (85.5%) Black (7.5%) Hispanic (4.9%) Asian (0.2%) Other (1.9%)	Subjects hospitalized for worsening heart failure	Composite of change from baseline in patient-assessed global clinical status and change from baseline in body weight at Inpatient Day 7 or discharge, if earlier (Short-term Clinical Status Trials A and B); and Time to all-cause mortality; Time to first CV mortality or hospital-ization for heart failure (Long-term Outcome Trial)
156-03-002[78] (Efficacy and safety) 2	9 centers; Japan	Nov 2004; Completed Dec 2005; 24/20	Efficacy, safety, and dose-response	Open-label, dose-titration	Tolvaptan Tablet PO 15 mg QD 30 mg QD 60 mg QD	24/18/15	9 days (titration with 3-day administration of each dose)	M (82.4%) F (17.6%); 57 (44-69) years; Japanese (100.0%)	Hospitalized patients with peripheral edema or ascites secondary to liver disease	The rate of improvement in ascites and peripheral edema (on evaluation at final dose)

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156-06-005[79] (Efficacy and safety) 2	Multicenter; Japan	June 2007; Completed; Jul 2008; 104/100	Efficacy and safety	Randomized, double-blind, placebo-controlled, parallel group	Tolvaptan Tablet PO 7.5 mg QD 15 mg QD 30 mg QD Placebo QD	26/25/20 25/25/24 26/25/21 27/26/23	7 days	Placebo: M (65.4%) F (34.6%) Tolvaptan: M (72.0%) F (28.0%) Placebo: 63.5 (41-79) years Tolvaptan: 64.0 (39-80) years Japanese (100%)	Liver cirrhosis patients with ascites despite having received treatment with conventional diuretics	Change from baseline in body weight
156-08-001[80] (Efficacy and safety) 3	Multicenter; Japan	Feb 2010; Completed Aug 2011; 164/160	Efficacy and safety	Randomized, double-blind, placebo-controlled, parallel group	Tolvaptan Tablet PO 7.5 mg QD, Placebo QD	84/82/74 80/80/70	7 days	Placebo: M (61.3%) F (38.8%) Tolvaptan: M (63.4%) F (36.6%) Placebo: 66.4 (46-78) years Tolvaptan: 66.3 (31-80) years Asian (Japanese) (100.0%)	Liver cirrhosis patients with ascites despite having received treatment with conventional diuretics	Change from baseline in body weight

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156-08-002[81] (Safety, efficacy, PK, and PD) 3	Multicenter; Japan	Jan 2010; Completed Dec 2010; 51/50	Safety, efficacy, PK, and PD	Open-label	Tolvaptan Tablet PO 7.5 mg QD, or increased to 15 mg QD	7.5 mg for 7 days: 51/51/46 Continued 7.5 mg for 14 days: 30/30/28 Increased to 15 mg QD after Day 8: 13/13/11	14 days maximum	Continued 7.5 mg for 14 days: M (70.0%) F (30.0%) Increased to 15 mg QD after Day 8: M (69.2%) F (30.8%) Continued 7.5 mg for 14 days: 63.9 (45-77) years Increased to 15 mg QD after Day 8: 61.0 (40-75) years Asian (Japanese) (100.0%)	Liver cirrhosis patients with ascites despite having received treatment with conventional diuretics	AEs, vital signs, clinical laboratory tests, and ECGs
156-08-804-01[82] (Efficacy and Safety) 2	Multicenter; 21 centers; China	Mar 2009, Completed; Feb 2010 184/180;	Efficacy and safety	Randomized, double-blind, placebo-controlled	Tolvaptan tablet PO 15 mg QD 30 mg QD Placebo QD	58/57/50 63/63/57 63/61/50	4 or 7 days	M (75.7%) F (24.3%) 50.4 (25-75) years Asian (Chinese) (100.0%)	Patients with cirrhosis and ascites after failure of conventional diurectics	Change from baseline in body weight after 7 days

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156-08-805-01[83] (Safety and eficacy) 3	Multicenter; China	Sept 2010; Completed Jan 2012; 535/525	Safety and efficacy	Randomized, double-blind, placebo-controlled, parallel-group	Tolvaptan Tablet PO 7.5 mg QD 15 mg QD Placebo QD	154/154/139 305/305/271 76/76/64	7 days	Tolvaptan 7.5 mg: M (71.2%) F (28.8%) 53.8 (22-75) years Tolvaptan 15 mg: M (71.4%) F (28.6%) 54.2 (24-75) years Placebo: M (71.1%) F (28.9%) 54.4 (23-75) years Chinese (100%)	Patients with cirrhosis and ascites despite routine diuretic therapy	Change from baseline in body weight after 7 days

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156-09-004[84] (PK/PD) 3	Multicenter; Japan	May 2010; Completed Jul 2011; 40/40	Pharmacody-namics, pharmaco-kinetics, efficacy and safety	Randomized, double-blind, parallel group	Tolvaptan Tablet PO 3.75 mg QD 7.5 mg QD	 19/19/16 21/21/17	7 days	3.75 mg QD: M (75.0%) F (25.0%) 7.5 mg QD: M (65.0%) F (35.0%) 3.75 mg QD: 67.7 (44-80) years 7.5 mg QD: 63.6 (47-78) years Asian (Japanese) (100.0%)	Liver cirrhosis patients with ascites despite having received treatment with conventional diuretics	Daily urine volume, serum electrolyte concentration, PK of tolvaptan and metabolites
156-09-806-01[85] (PK/PD) 1	Zeng Minde, MD, China	Mar 2009 Completed; Jun 2009; 11/12	PK in Chinese patients with hepato-cirrhosis	Open-label, multiple dose	Tolvaptan Tablet PO 15 mg QD	11/11/10	7 days	M (81.8%), F (18.2%) 55.4 (46-68) years Chinese (100.0%)	Child-Pugh Class B (score 7-9) hepatic impairment	PK/PD safety

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156-04-001[86] (Safety, PK/PD) 2	Tomoko Hasunuma, MD, PhD; Japan	Dec 2004; Completed May 2005; 19/18	Safety, PK, and PD	Randomized, open-label trial	Tolvaptan Tablet PO Group I: 15 mg single dose, 30 mg single dose, 15 mg BID Group II: 15 mg single dose, 30 mg single dose, 30 mg QD	Group I: 9/9/9 Group II: 9/9/9	Group I: Single ascending 15- and 30-mg doses, 15 mg BID for 5 days; treatments separated by a 1-3 week washout Group II: Single ascending 15-and 30-mg doses, 30 mg QD for 5 days, treatments separated by a 1-3 week washout	M (50.0%) F (50.0%); 39.3 (21-59) years Asian (Japanese) (100.0%)	ADPKD	Urine osmolality
156-04-248[87] (PK/PD) 2	Thomas Marbury, MD; United States	Oct 2004; Completed Oct 2004; 11/9-21	Single-dose safety, tolerability, PK and PD	Randomized, double-blind, placebo-controlled, ascending dose	Tolvaptan Tablet PO Ascending doses: 15 mg 30 mg 60 mg 120 mg Placebo	8/8/8 3/3/3	Single ascending doses of tolvaptan or matching placebo separated by 3-day washout	M (36.4%) F (63.6%); 37 (22-47) years; Caucasian (90.9%) Other (9.1%)	ADPKD	Tolvaptan PK parameters; urine osmolality

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156-04-249[88] (PK/PD) 2	Thomas Marbury, MD; United States	Nov 2004; Completed Mar 2005; 37/18-48	Safety, PK and PD of multiple doses and regimens	Randomized, double-blind, in-patient, parallel arm	Tolvaptan Tablet PO 15 mg BID 30 mg AM + placebo PM 30 mg AM + 15 mg PM 30 mg BID	9/9/9 9/9/9 9/9/9 10/10/10	5 days	M (21.6%) F (78.4%); 42 (25-58) years; Caucasian (94.6%) Black (2.7%) Other (2.7%)	ADPKD	Tolvaptan PK parameters; urine osmolality
156-06-260[89] (PK/PD) 1	Vincente Torres, MD; United States	Mar 2007; Completed Feb 2010; 20/24 to 36	Effect of multiple doses on renal function	Open-label, multiple dose	Tolvaptan Tablet PO QD 45/15 mg split dose (AM/PM)	20/20/20	8 days	M (50.0%) F (50.0%) 47.8 (29-60) years Caucasian: (100.0%)	Subjects with ADPKD with varying degrees of renal function	Glomerular filtration rate, renal blood flow, renal plasma flow, filtration fraction
156-09-282[90] (PK/PD) 1	2 centers; United States	Mar 2010; Completed; Dec 2010 37/36	Effects of degree of renal impairment on PK and PD of tolvaptan (60 mg)	Open-label, single-dose	Tolvaptan Tablet PO 60 mg	37/37/37	Single dose	M (67.6%) F (32.4%) 62.2 (28-79) years Caucasian (91.9%) Black (8.1%)	Subjects with varying degrees of renal function	PK/PD parameters,
156-09-284[91] (Efficacy, safety, PK/PD) 2a	Single-center; Netherlands	Oct 2010; Completed Nov 2011; 29/36	Effect of maximally tolerated doses of tolvaptan at steady state on renal function	Open-label, multiple dose	Tolvaptan Tablet PO QD 45/15 mg 60/30 mg 90/30 mg split dose (AM/PM) (titrated)	29/29/27	21 days	M (51.7%) F (48.3%) 46.0 (25-69) years Caucasian (96.6%) Other (3.4%)	ADPKD, including those with renal impairment	Glomerular filtration rate, effective renal plasma flow, filtration fraction

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156-09-285[92] (PK/PD) 2	Multicenter; United States	Nov 2010; Completed Jun 2011; 25/24	Compare PK, PD, and tolerability of multiple doses of tolvaptan administered as either IR tablets or MR capsules	Parallel-group, randomized, double-blind, placebo-masked, multiple dose, 3-period crossover for each of 2 separate groups	Tolvaptan IR Tablet and MR Capsule, PO (and matching placebo tablet and capsule) Group 1: 90/30 mg IR, 120 mg MR QD; and either 20 mg MR QD, or 20 mg MR BID, or 60 mg MR QD Group 2: 20 mg MR QD 20 mg MR BID 60 mg MR QD	Total: 25/25/25 20 mg MR: 17/17/17 20 + 20 mg MR: 17/17/17 60 mg MR: 17/17/17 120 mg MR: 12/12/12 90 + 30 mg IR: 12/12/12	21 days (7 days for each regimen)	M (56.0%) F (44.0%) 38.0 (21-50) years Caucasian (100.0%)	ADPKD	PK/PD
156-04-250[93] (Long-term safety) 2	Multicenter; United States	Dec 2005; Completed; Jun 2010 46/30 to 47	Safety, tolerability, and efficacy of split-dose regimens ranging from 30-120 mg/day	Open-label, split-dose regimen with titration followed by randomization to fixed dose	Tolvaptan Tablet PO QD Titration: 15/15 mg 30/15 mg 45/15 mg 60/30 mg 90/30 mg split dose (AM/PM) Fixed Dose: 45/15 mg or 60/30 mg split dose (AM/PM)	Fixed dose through Month 36: 22/22/18 24/24/21 Extension: 17/17/17 18/18/18	Dose titration for up to 2 months followed by up to 36 months long-term treatment, with an optional 12-month extension	M (26.1%) F (73.9%) 41.7 (24-59) years Caucasian (97.8%) Black (2.2%)	ADPKD subjects who previously participated in Trial 156-04-248 or 156-04-249	AEs, vital signs, clinical laboratory tests, ECGs, and physical examinations

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156-04-251[94] (Long-term efficacy and safety) 3	Multicenter; International	Mar 2007; Completed Jan 2012; 1445/1200 to 1500	Long-term efficacy and safety	Randomized, double-blind, placebo-controlled, parallel-arm	Tolvaptan Tablet PO QD 60-120 mg QD given as: 45/15 mg 60/30 mg 90/30 mg split dose (AM/PM) Placebo BID	961/961/740 484/483/417	Up to 36 months	M (51.6%) F (48.4%) 38.7 (18-51) years Caucasian (84.3%) Asian (12.7) Hispanic (1.5%) Black (1.3%) Other (0.2%)	ADPKD	Rate of total renal (both kidneys) volume change (%) for tolvaptan (combining all doses) relative to placebo
156-05-002[95] (Long-term safety) 2	Multicenter; Japan	June 2006; Completed; Mar 2010 17/18	Safety and efficacy	Open-label, long-term safety; Extension of 156-04-001	Tolvaptan Tablet PO 15 mg BID	17/17/12	Up to 36 months long-term treatment	M (47.1%) F (52.9%); 41.8 (26-61) years Asian (Japanese) (100.0%)	ADPKD subjects who previously participated in Trial 156-04-001	AEs, vital signs, clinical laboratory tests, ECGs, and physical examinations
156-08-271[96] (Safety and efficacy) 3b	Multicenter; International	May 2010; Ongoing; up to 1500	To demonstrate whether tolvaptan modified ADPKD progression	Open-label, extension	Tolvaptan Tablet PO QD 45/15 mg 60/30 mg 90/30 mg split dose (AM/PM)	NA	24 months (minimum)	NA	ADPKD subjects who had completed a Phase 1, 2, or 3 tolvaptan trial	Changes from baseline (from Trial 156-04-251) in total kidney volume and renal function

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156-09-003[97] (Safety and Efficacy) 3/4	Multicenter; Japan	Dec 2009; Completed Jul 2014; 13/15	Safety and efficacy	Open-label, long-term safety; Extension of 156-05-002	Tolvaptan Tablet PO QD 15/15 mg 45/15 mg 60/30 mg 90/30 mg split dose (AM/PM)	13/13/9	Until approval for the treatment of ADPKD in Japan	Not provided	ADPKD subjects who previously participated in Trial 156-05-002	Safety: AEs, vital signs, clinical laboratory tests, body weight, plasma AVP concentra-tion, and ECGs; Efficacy: total kidney volume, eGFR, renal function tests
156-09-290[98] (Safety and Efficacy) 2	Multicenter; United States	Nov 2011; Completed;[a] Jul 2013; 177/180	Compare efficacy, tolerability, and safety of MR and IR formulations of tolvaptan	Randomized, placebo-controlled, double-blind, placebo-masked, parallel-group	Tolvaptan Tablet PO QD 60/30 mg split dose (AM/PM) Tolvaptan MR Capsule PO 50 mg QD 80 mg QD Placebo (matching placebo tablet and capsule)	44/44/42 45/45/42 45/44/40 43/42/39	8 weeks	M (52.5%) F (47.5%) 34.0 (18-50) years Caucasian (89.8%) Black (3.4%) Asian (3.4%) Other (2.8%) American Indian or Alaska native (0.6%)	ADPKD subjects with eGFR > 45 mL/ min/1.73 m^2	Percent change from baseline in TKV at Week 3

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156-10-003[99] (Safety and efficacy) 3/4	Multicenter; Japan	Oct 2010; Ongoing; up to 150 planned	Long-term safety and efficacy	Open-label, extension	Tolvaptan Tablet PO QD 45/15 mg, 60/30 mg 90/30 mg split dose (AM/PM)	NA	Until approximately 5 months after manufacturing and distribution approval is granted in Japan	NA	ADPKD subjects in Japan who had participated in Trial 156-04-251	Adverse events, clinical laboratory tests, plasma AVP concentra-tion, vital signs, body weight, ECG, combined renal volume, renal function, urine albumin
156-13-210[100] 3b	Multicenter: International	Jul 2014; Ongoing; up to 1300 planned	Safety and efficacy	Randomized-withdrawal, placebo-controlled, double-blind, parallel-group	Tolvaptan Tablet PO QD 30/15 mg 45/15 mg 60/30 mg 90/30 mg split dose (AM/PM)	NA	12 months	NA	ADPKD	Treatment difference in the change of eGFR from pre-treatent baseline to post-treatment follow-up
156-13-211[101] 3b	Multicenter; International	Oct 2014; Ongoing; approximately 2500 planned	Long-term safety	Open-label extension	Tolvaptan Tablet PO QD 15/15 mg, 30/15 mg 45/15 mg 60/30 mg 90/30 mg split dose (AM/PM)	NA	Until the last subject from Trial 156-13-210 completes 18 months of tolvaptan treatment, or until tolvaptan becomes available through routine prescription, compassionate use or patient-named program	NA	ADPKD subjects who had completed Trial 156-13-210, Trial 156-08-271 or completed, discontinued or interruped treatment in a prior tolvaptan trial	No formal endpoints. Adverse events, hepatic monitoring, vital signs, clinical laboratory assessments

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156-12-001[102] (Efficacy, PK/PD, and safety) 2	Multicenter; Japan	Nov 2012; Completed Nov 2013; 43/40	Efficacy, PK, PD, and safety of short-term administration of tolvaptan to increase urine volume in patients with volume overload associated with cancer and to determine initial and maintenance doses	Open-label, dose-escalation, dose-finding	Tolvaptan Tablet PO QD 3.75 mg 7.5 mg 15 mg 30 mg	69/43/35	Up to 11 days	M (40.0%) F (60.0%) 65.3 (44-80) Asian (Japanese) (100.0%)	Patients with volume overload associated with cancer	Changes from baseline in body weight, ascites, abdominal circumfer-ence; improvement, resolution, and exacerbation rates of ascites and lower limb edema; clinical symptoms of ascites, resolution and exacerbation rate of pleural effusion, QOL

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156-12-002[103] (Efficacy, PK/PD, and safety) 2	Multicenter; Japan	Aug 2013; Completed Jan 2014; 20/20	Efficacy, PK, PD, and safety of tolvaptan by dose escalation and repeated administration at the fixed dose at which urine volume is increased	Open-label, dose-escalation, dose-finding	Tolvaptan Tablet PO QD 7.5 mg 15 mg 30 mg 60 mg	22/20/7	Dose escalation for up to 8 days; washout period of at least 14 days; repeat administration for 5 days at fixed dose	M (60%) F (40%) 65.1 (31-79) Asian (100%)	Patients with chronic renal failure who are undergoing peritoneal dialysis	Change and percent change in daily urine volume from baseline, change and percent change in body weight from baseline, cardiothoracic ratio and severity of pulmonary congestion (chest x-ray), and lower limb edema

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156-12-007[104] (Efficacy, PK/PD, and safety) 2	Multicenter Japan	Jul 2013; Completed Oct 2013; 23/20	Safety, PK, PD, and efficacy of tolvaptan in patients with chronic renal failure undergoing hemodialysis or hemo-diafiltration	Open-label, dose-escalation, dose-finding	Tolvaptan Tablet PO QD 7.5 mg 15 mg 30 mg 60 mg Dose-titration: administration followed by 6-day intervals between dose steps until determining the fixed dose, followed by ≥ 7 days of confirmation period Intermittent Administra-tion: an intermittent 4-day administration at the fixed dose with the preceding 8 days without administration	26/23/16	Up to 8 days Dose-titration: up to 4 days Intermittent Administration: Up to 4 days	M (65.2%) F (34.8%) 60.4 (29-76) Asian (100%)	Patients with chronic renal failure who are undergoing hemo-dialysis or hemodiafiltration	Change and percent change in daily urine volume, percent change in interdialytic weight gain, total volume of fluid removed by dialysis per week, frequency of achievement of dry weight by dialysis, psychological burden due to fluid intake restriction, Kidney Disease Quality of Life Short Form™ (KDQOL-SF, Version 1.3), Frequency of medical treatment for drop in BP during dialysis,

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156-13-003[105] 2	Multicenter Japan	Feb 2015; Ongoing 120 planned	Safety and efficacy of tolvaptan in patients with chronic renal failure undergoing hemodialysis or hemo-diafiltration	Placebo-controlled, double-bind, randomized, parallel-group	Tolvaptan Tablet PO QD 15 mg 30 mg Placebo	NA	Up to 24 weeks	NA	Patients with chronic renal failure who are undergoing hemo-dialysis or hemodiafiltration	Change in daily urine volume, interdialytic weight gain, total volume of fluid removed per week by dialysis

ADPKD = autosomal dominant polycystic kidney disease; AE = adverse event; $A_{e,0-24h}$ = amount of drug excreted in the urine from time zero to 24 hours; AUC = area under the concentration-time curve; AUC_{0-24h} = area under the concentration-time curve from time zero to 24 hours; AUC_{∞} = Area under the concentration-time curve from time zero to infinity; AUC_{τ} = area under the concentration-time curve during a dosage interval (τ) at steady state; AVP = arginine vasopressin; BA = bioavailability; BE = bioequivalence; BID = twice daily; BP = blood pressure; CHF = congestive heart failure; C_{max} = maximum plasma concentration; $C_{ss,max}$ = maximum steady-state drug concentration in the plasma during a dosage interval; $C_{ss,min}$ = minimum steady-state drug concentration in the plasma during a dosage interval; CV = cardiovascular; CYP = cytochrome P450; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; F = female; FDA = Food and Drug Administration; HCTZ = hydrochlorothiazide; HF = heart failure; IR = immediate-release; IV = intravenous; M = male; MR = modified-release; MTD = maximum tolerated dose; NA = not applicable; PD = pharmacodynamic; PK = pharmacokinetic; PO = oral; QD = daily; QOL = quality of life; QTc = corrected QT interval; SDT = slow-disintegration tablet; SIAD = syndrome of inappropriate antidiuresis; SIADH = syndrome of inappropriate secretion of antidiuretic hormone; TKV = total kidney volume; US = United States; vs = versus.

[a] Trial is completed with final data analyses pending. For Trial 156-09-290, safety data are included in all pooled exposure and AE summary presentations reported in this update. For Trial 156-09-101, safety data are presented as ‘ongoing’.

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Appendix 2, List of Treatment-emergent Adverse Events in Tolvaptan-treated Subjects by MedDRA System Organ Class and Preferred Term, Regardless of Causal Relationship to Investigational Medicinal Product

System Organ Class	MedDRA Preferred Term
Blood and lymphatic system disorders	Agranulocytosis, anaemia, anaemia macrocytic, anaemia megaloblastic, coagulopathy, deficiency anaemia, disseminated intravascular coagulation, eosinophilia, haemoconcentration, haemolytic anaemia, haemorrhagic anaemia, heparin-induced thrombocytopenia, hypercoagulation, hyperprothrombinaemia, hypersplenism, hypochromasia, hypochromic anaemia, hypoprothrombinaemia, hypothrombinaemia, iron deficiency anaemia, leukocytosis, leukopenia, lymph node pain, lymphadenopathy, lymphocytosis, macrocytosis, microcytic anaemia, monocytosis, nephrogenic anaemia, neutropenia, neutrophilia, normochromic normocytic anaemia, pancytopenia, platelet dysfunction, polycythaemia, retroperitoneal lymphadenopathy, spleen disorder, splenic granuloma, splenic vein thrombosis, splenomegaly, thrombocytopenia, thrombocytosis
Cardiac disorders	Accelerated idioventricular rhythm, acute coronary syndrome, acute myocardial infarction, angina pectoris, angina unstable, aortic valve incompetence, arrhythmia, arrhythmia supraventricular, arteriosclerosis coronary artery, atrial fibrillation, atrial flutter, atrial tachycardia, atrial thrombosis, atrioventricular block, atrioventricular block complete, atrioventricular block first degree, atrioventricular block second degree, atrioventricular dissociation, bradyarrhythmia, bradycardia, bundle branch block, bundle branch block left, bundle branch block right, cardiac aneurysm, cardiac arrest, cardiac asthma, cardiac discomfort, cardiac disorder, cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, cardiac failure high output, cardiac flutter, cardiac hypertrophy, cardiac tamponade, cardiac valve disease, cardiac ventricular thrombosis, cardio-respiratory arrest, cardiogenic shock, cardiomegaly, cardiomyopathy, cardiopulmonary failure, cardiorenal syndrome, cardiovascular insufficiency, conduction disorder, congestive cardiomyopathy, coronary artery disease, coronary artery occlusion, coronary artery stenosis, cyanosis, extrasystoles, hepatojugular reflux, intracardiac thrombus, ischaemic cardiomyopathy, left atrial dilatation, left ventricular dysfunction, left ventricular failure, left ventricular hypertrophy, low cardiac output syndrome, mitral valve disease, mitral valve incompetence, mitral valve prolapse, mitral valve stenosis, myocardial fibrosis, myocardial infarction, myocardial ischaemia, nodal rhythm, palpitations, pericardial effusion, pericardial rub, pericarditis, pneumopericardium, pulmonary valve incompetence, pulseless electrical activity, rhythm idioventricular, right ventricular failure, sick sinus syndrome, sinus arrest, sinus arrhythmia, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, supraventricular tachycardia, systolic dysfunction, tachyarrhythmia, tachycardia, tricuspid valve incompetence, trifascicular block, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation, ventricular flutter, ventricular tachycardia, wolff-parkinson-white syndrome
Congenital, familial and genetic disorders	Arteriovenous malformation, buried penis syndrome, congenital musculoskeletal anomaly, congenital syphilitic osteochondritis, dermoid cyst, ichthyosis, kidney duplex, myocardial bridging, phimosis, polycystic liver disease, pyloric stenosis, renal hypoplasia, spine malformation
Ear and labyrinth disorders	Cerumen impaction, deafness, deafness neurosensory, ear canal erythema, ear congestion, ear discomfort, ear haemorrhage, ear pain, eustachian tube disorder, hearing impaired, hypoacusis, middle ear effusion, middle ear inflammation, motion sickness, tinnitus, tympanic membrane hyperaemia, tympanic membrane perforation, vertigo, vertigo positional
Endocrine disorders	Adrenal insufficiency, androgen deficiency, autoimmune thyroiditis, Basedow's disease, cushingoid, diabetes insipidus, endocrine disorder, euthyroid sick syndrome, goitre, hyperaldosteronism, hyperparathyroidism, hyperparathyroidism primary, hyperparathyroidism secondary, hyperthyroidism, hypoparathyroidism secondary, hypothyroidism, oestrogen deficiency, thyroid disorder, thyroiditis
Eye disorders	Abnormal sensation in eye, accommodation disorder, angle closure glaucoma, aphakia, arcus lipoides, arteriosclerotic retinopathy, asthenopia, astigmatism, blepharitis, blepharospasm, cataract, cataract nuclear, chalazion, chorioretinopathy,

System Organ Class	MedDRA Preferred Term
	colour blindness acquired, conjunctival deposit, conjunctival discolouration, conjunctival disorder, conjunctival haemorrhage, conjunctival hyperaemia, conjunctival pallor, conjunctivitis allergic, corneal scar, diabetic retinal oedema, diabetic retinopathy, diplopia, dry eye, erythema of eyelid, exophthalmos, eye disorder, eye haemorrhage, eye inflammation, eye irritation, eye oedema, eye pain, eye pruritus, eye swelling, eyelid margin crusting, eyelid oedema, eyelid ptosis, eyelid skin dryness, eyelids pruritus, glaucoma, hypermetropia, iritis, keratitis, lacrimation increased, macular degeneration, maculopathy, meibomianitis, mydriasis, myopia, ocular hyperaemia, ocular icterus, ocular vascular disorder, ophthalmoplegia, periorbital oedema, photophobia, photopsia, presbyopia, pterygium, pupillary disorder, pupils unequal, retinal detachment, retinal vascular disorder, retinal vein occlusion, retinopathy, retinopathy hypertensive, scleral haemorrhage, scleritis, ulcerative keratitis, vision blurred, visual acuity reduced, visual impairment, vitreous degeneration, vitreous detachment, vitreous floaters, vitreous haemorrhage, vitreous opacities
Gastrointestinal disorders	Abdominal adhesions, abdominal discomfort, abdominal distension, abdominal hernia, abdominal mass, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal rigidity, abdominal strangulated hernia, abdominal symptom, abdominal tenderness, abdominal wall haematoma, abdominal wall haemorrhage, anal erosion, anal fissure, anal fistula, anal haemorrhage, anal pruritus, aphthous stomatitis, apical granuloma, ascites, Barrett's oesophagus, bowel movement irregularity, breath odour, chapped lips, cheilitis, colitis, colitis ischaemic, colitis ulcerative, constipation, Crohn's disease, dental alveolar anomaly, dental caries, diabetic gastroparesis, diarrhoea, diverticular perforation, diverticulum, diverticulum intestinal, diverticulum intestinal haemorrhagic, dry mouth, duodenal polyp, duodenal ulcer, duodenal ulcer perforation, duodenitis, dyschezia, dyspepsia, dysphagia, enteritis, enterocolitis, epigastric discomfort, epiploic appendagitis, erosive duodenitis, erosive oesophagitis, eructation, faecal incontinence, faecaloma, faeces discoloured, faeces hard, faeces soft, femoral hernia, flatulence, food poisoning, frequent bowel movements, gastric antral vascular ectasia, gastric disorder, gastric haemorrhage, gastric mucosal lesion, gastric polyps, gastric ulcer, gastric ulcer haemorrhage, gastric varices, gastritis, gastritis atrophic, gastritis erosive, gastritis haemorrhagic, gastroduodenitis, gastrointestinal angiodysplasia haemorrhagic, gastrointestinal disorder, gastrointestinal haemorrhage, gastrointestinal hypermotility, gastrointestinal inflammation, gastrointestinal motility disorder, gastrointestinal pain, gastrointestinal sounds abnormal, gastrointestinal telangiectasia, gastrooesophageal reflux disease, gingival bleeding, gingival pain, gingival recession, gingival swelling, glossitis, glossodynia, haematemesis, haematochezia, haemorrhoidal haemorrhage, haemorrhoids, hiatus hernia, hyperchlorhydria, hypoaesthesia oral, ileus, inguinal hernia, inguinal hernia, obstructive, internal hernia, intestinal haemorrhage, intestinal infarction, intestinal ischaemia, intestinal obstruction, intestinal ulcer, intra-abdominal haemorrhage, irritable bowel syndrome, large intestinal haemorrhage, large intestinal obstruction, large intestine polyp, lip dry, lip exfoliation, lip haemorrhage, lip pain, lip swelling, loose tooth, lower gastrointestinal haemorrhage, mallory-weiss syndrome, malocclusion, melaena, melanosis coli, mouth haemorrhage, mouth ulceration, nausea, odynophagia, oesophageal stenosis, oesophageal ulcer, oesophageal varices haemorrhage, oesophagitis, oral discomfort, oral disorder, oral lichen planus, oral mucosal blistering, oral mucosal erythema, oral pain, pancreatic calcification, pancreatic cyst, pancreatic disorder, pancreatic mass, pancreatitis, pancreatitis acute, pancreatitis chronic, paraesthesia oral, peptic ulcer, periodontal disease, plicated tongue, portal hypertensive gastropathy, proctalgia, radicular cyst, rectal haemorrhage, rectal polyp, rectal prolapse, reflux gastritis, regurgitation, retching, retroperitoneal haemorrhage, salivary gland disorder, salivary gland pain, salivary hypersecretion, sensitivity of teeth, small intestinal obstruction, stomatitis, tongue coated, tongue discolouration, tongue disorder, tongue dry, tongue exfoliation, tongue haemorrhage, tooth disorder, tooth impacted, toothache, umbilical hernia, umbilical hernia perforation, umbilical hernia, obstructive, upper gastrointestinal haemorrhage, varices oesophageal, volvulus, vomiting

System Organ Class	MedDRA Preferred Term
General disorders and administration site conditions	Adverse drug reaction, application site burn, application site dermatitis, application site erythema, application site irritation, application site rash, asthenia, axillary pain, cardiac death, catheter site discharge, catheter site erythema, catheter site haematoma, catheter site haemorrhage, catheter site inflammation, catheter site pain, catheter site phlebitis, catheter site related reaction, catheter site swelling, chest discomfort, chest pain, chills, crepitations, cyst, death, device dislocation, device failure, device malfunction, device occlusion, discomfort, early satiety, effusion, energy increased, exercise tolerance decreased, extravasation, face oedema, facial pain, fat tissue increased, fatigue, feeling abnormal, feeling cold, feeling drunk, feeling hot, feeling jittery, foaming at mouth, gait disturbance, general physical health deterioration, general symptom, generalised oedema, granuloma, hangover, hernia, hernia obstructive, hunger, hyperthermia, hypothermia, impaired healing, implant site extravasation, implant site haematoma, implant site haemorrhage, implant site inflammation, implant site irritation, implant site oedema, implant site pain, implant site reaction, implant site swelling, inflammation, influenza like illness, infusion site bruising, infusion site erythema, infusion site extravasation, infusion site irritation, infusion site pain, infusion site phlebitis, infusion site swelling, injection site bruising, injection site erosion, injection site haemorrhage, injection site pain, injection site swelling, ischaemic ulcer, local swelling, localised oedema, malaise, mass, medical device complication, mucosal dryness, multi-organ failure, nodule, non-cardiac chest pain, obstruction, oedema, oedema due to hepatic disease, oedema peripheral, pacemaker generated arrhythmia, pain, product taste abnormal, puncture site haemorrhage, puncture site pain, pyrexia, sensation of foreign body, sensation of pressure, sluggishness, sudden cardiac death, sudden death, suprapubic pain, swelling, temperature intolerance, temperature regulation disorder, thirst, thirst decreased, thrombosis in device, ulcer, ulcer haemorrhage, unevaluable event, vessel puncture site bruise, vessel puncture site haematoma, vessel puncture site haemorrhage, vessel puncture site inflammation, vessel puncture site pain, vessel puncture site pruritus, xerosis
Hepatobiliary disorders	Bile duct stone, biliary cirrhosis primary, biliary colic, biliary dyskinesia, cardiac cirrhosis, cholangitis, cholecystitis, cholecystitis acute, cholecystitis chronic, cholelithiasis, cholestasis, chronic hepatic failure, chronic hepatitis, cirrhosis alcoholic, drug-induced liver injury, gallbladder disorder, gallbladder pain, gallbladder polyp, granulomatous liver disease, hepatic cirrhosis, hepatic congestion, hepatic cyst, hepatic cyst ruptured, hepatic failure, hepatic fibrosis, hepatic function abnormal, hepatic lesion, hepatic necrosis, hepatic pain, hepatic steatosis, hepatitis, hepatitis acute, hepatitis toxic, hepatocellular injury, hepatomegaly, hepatorenal failure, hepatorenal syndrome, hepatosplenomegaly, hyperbilirubinaemia, ischaemic hepatitis, jaundice, jaundice cholestatic, liver disorder, liver injury, liver tenderness, portal hypertension, portal vein thrombosis
Immune system disorders	Allergic oedema, allergy to arthropod bite, allergy to arthropod sting, anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, drug hypersensitivity, food allergy, house dust allergy, hypersensitivity, iodine allergy, multiple allergies, seasonal allergy
Infections and infestations	Abdominal abscess, abdominal infection, abdominal sepsis, abscess, abscess limb, acarodermatitis, acute sinusitis, acute tonsillitis, adenoiditis, alveolar osteitis, amoebiasis, anal fungal infection, anal infection, appendicitis, arthritis bacterial, arthritis infective, aspergillus infection, asymptomatic bacteriuria, atypical pneumonia, bacteraemia, bacterial infection, bacterial rhinitis, bacterial sepsis, bacterial vaginosis, bacteriuria, Bartholin's abscess, biliary sepsis, biliary tract infection, body tinea, bronchiolitis, bronchitis, bronchitis viral, bronchopneumonia, bursitis infective, candida infection, carbuncle, catheter site cellulitis, catheter site infection, cellulitis, cervicitis, chlamydial infection, clostridium colitis, clostridium difficile colitis, clostridium difficile infection, conjunctivitis, corneal abscess, corneal infection, cystitis, cytomegalovirus infection, cytomegalovirus viraemia, device related infection, device related sepsis, diarrhoea infectious, diverticulitis, ear infection, ear lobe infection, empyema, endocarditis, enteritis infectious, enterococcal bacteraemia, enterococcal infection, enterococcal sepsis, enterocolitis viral, epididymitis, erysipelas, erythema migrans, escherichia sepsis, eye infection, eyelid infection, folliculitis, fungal infection, fungal oesophagitis, fungal peritonitis, fungal skin infection, furuncle, gangrene, gastric infection, gastroenteritis, gastroenteritis norovirus,

System Organ Class	MedDRA Preferred Term
	gastroenteritis viral, gastrointestinal bacterial infection, gastrointestinal fungal infection, gastrointestinal infection, gastrointestinal viral infection, genital herpes, genitourinary tract infection, giardiasis, gingival abscess, gingivitis, helicobacter gastritis, helicobacter infection, hepatic cyst infection, hepatitis A, hepatitis B, hepatitis C, herpes simplex, herpes virus infection, herpes zoster, HIV infection, hordeolum, impetigo, implant site infection, incision site cellulitis, incision site infection, infected bites, infected cyst, infected skin ulcer, infection, infectious colitis, infectious mononucleosis, infective glossitis, influenza, infusion site abscess, kidney infection, klebsiella infection, klebsiella sepsis, labyrinthitis, laryngitis, liver abscess, lobar pneumonia, localised infection, lower respiratory tract infection, lung abscess, lung infection, lyme disease, lymphangitis, malaria, mucosal infection, mycobacterium avium complex infection, mycoplasma infection, nail bed infection, nasopharyngitis, nematodiasis, nosocomial infection, oesophageal candidiasis, omphalitis, onchocerciasis, onychomycosis, oral bacterial infection, oral candidiasis, oral fungal infection, oral herpes, oropharyngeal candidiasis, osteomyelitis, otitis externa, otitis media, otitis media acute, papilloma viral infection, paronychia, parotitis, perineal abscess, periodontitis, peritonitis, peritonitis bacterial, peritonsillar abscess, peritonsillitis, pertussis, pharyngitis, pharyngitis streptococcal, pneumonia, pneumonia klebsiella, pneumonia mycoplasmal, pneumonia staphylococcal, pneumonia viral, post procedural infection, postoperative wound infection, prostate infection, pseudomembranous colitis, pseudomonal sepsis, pseudomonas bronchitis, pseudomonas infection, pulmonary tuberculosis, purulence, pyelonephritis, pyelonephritis chronic, rash pustular, renal cyst infection, respiratory tract infection, respiratory tract infection viral, rhinitis, salmonellosis, salpingo-oophoritis, scrotal abscess, sepsis, sepsis syndrome, septic shock, sialoadenitis, sinusitis, sinusitis fungal, skin bacterial infection, skin candida, skin infection, soft tissue infection, staphylococcal bacteraemia, staphylococcal infection, staphylococcal pharyngitis, staphylococcal sepsis, staphylococcal skin infection, stitch abscess, streptococcal infection, streptococcal sepsis, strongyloidiasis, subcutaneous abscess, syphilis, tinea cruris, tinea infection, tinea pedis, tinea versicolour, tonsillitis, tooth abscess, tooth infection, tracheitis, tracheobronchitis, trichomoniasis, tuberculosis, tuberculosis of central nervous system, tuberculous pleurisy, upper respiratory tract infection, urethritis, urinary tract infection, urinary tract infection enterococcal, urinary tract infection fungal, urinary tract infection staphylococcal, urogenital infection bacterial, urogenital infection fungal, urosepsis, vaginal infection, vestibular neuronitis, viral infection, viral rhinitis, viral tracheitis, viral upper respiratory tract infection, vulvovaginal candidiasis, vulvovaginal mycotic infection, wound infection, wound sepsis
Injury, poisoning and procedural complications	Abdominal injury, accidental exposure to product, accidental overdose, anaemia postoperative, anastomotic stenosis, animal bite, ankle fracture, arteriovenous fistula site haemorrhage, arteriovenous fistula thrombosis, arthropod bite, arthropod sting, avulsion fracture, back injury, barotrauma, bite, bone contusion, burns first degree, bursa injury, cartilage injury, cervical vertebral fracture, chemical injury, chest injury, chillblains, clavicle fracture, colon injury, compression fracture, concussion, contusion, corneal abrasion, craniocerebral injury, epicondylitis, eschar, excoriation, extradural haematoma, eye contusion, eye injury, eye penetration, face injury, facial bones fracture, fall, femur fracture, foot fracture, foreign body in eye, fracture, fractured sacrum, genital injury, gingival injury, hand fracture, head injury, heat exhaustion, heat stroke, hip fracture, humerus fracture, iliotibial band syndrome, incision site erythema, incision site oedema, incision site pain, incisional hernia, induced abortion haemorrhage, injury, joint dislocation, joint injury, laceration, ligament injury, ligament rupture, ligament sprain, limb injury, lip injury, lower limb fracture, lumbar vertebral fracture, meniscus injury, multiple fractures, muscle rupture, muscle strain, nail avulsion, neck injury, overdose, patella fracture, pelvic fracture, periorbital contusion, periorbital haematoma, pocket erosion, post procedural complication, post procedural fistula, post procedural haematuria, post procedural haemorrhage, post procedural oedema, post-traumatic pain, postoperative fever, postoperative thrombosis, postoperative wound complication, procedural haemorrhage,procedural hypotension, procedural nausea, procedural pain, procedural vomiting, pubis fracture, radius fracture, rib fracture, road traffic accident,

System Organ Class	MedDRA Preferred Term
	scapula fracture,scar, scratch, scrotal haematoma, seroma, shunt stenosis, skeletal injury, soft tissue injury, spinal compression fracture, spinal fracture, splenic injury, stab wound, stress fracture, subcutaneous haematoma, subdural haematoma, sunburn, superficial injury of eye, tendon injury, tendon rupture, thermal burn, thoracic vertebral fracture, tibia fracture, tooth fracture, tooth injury, toxicity to various agents, traumatic haematoma, traumatic intracranial haemorrhage, ulna fracture, ulnar nerve injury, upper limb fracture, urethral injury, vaccination complication, vascular graft occlusion, wound, wound complication, wound dehiscence, wound haemorrhage, wound secretion, wrist fracture
Investigations	Abdominal bruit, activated partial thromboplastin time prolonged, alanine aminotransferase abnormal, alanine aminotransferase increased, ammonia increased, anticoagulation drug level below therapeutic, antiphospholipid antibodies positive, aortic bruit, arterial bruit, aspartate aminotransferase abnormal, aspartate aminotransferase increased, aspiration bronchial, bacterial test positive, band neutrophil count increased, basophil count increased, bile output, bile output increased, bilirubin conjugated increased, bilirubin urine, bleeding time prolonged, blood albumin abnormal, blood albumin decreased, blood albumin increased, blood aldosterone increased, blood alkaline phosphatase decreased, blood alkaline phosphatase increased, blood antidiuretic hormone increased, blood bicarbonate decreased, blood bilirubin abnormal, blood bilirubin increased, blood bilirubin unconjugated increased, blood calcium decreased, blood calcium increased, blood chloride decreased, blood chloride increased, blood cholesterol abnormal,blood cholesterol decreased, blood cholesterol increased, blood count abnormal, blood creatine increased, blood creatine phosphokinase decreased, blood creatine phosphokinase increased, blood creatinine abnormal, blood creatinine increased, blood culture positive, blood electrolytes abnormal, blood glucose abnormal, blood glucose decreased, blood glucose fluctuation, blood glucose increased, blood iron decreased, blood lactate dehydrogenase abnormal, blood lactate dehydrogenase increased, blood magnesium decreased, blood magnesium increased, blood osmolarity decreased, blood osmolarity increased, blood parathyroid hormone, blood parathyroid hormone increased, blood phosphorus decreased, blood phosphorus increased, blood potassium decreased, blood potassium increased, blood pressure decreased, blood pressure diastolic increased, blood pressure increased, blood pressure systolic increased, blood prolactin increased, blood sodium decreased, blood sodium increased, blood testosterone decreased, blood thyroid stimulating hormone increased, blood triglycerides abnormal, blood triglycerides increased, blood urea increased, blood uric acid abnormal, blood uric acid decreased, blood uric acid increased, blood urine present, body temperature increased, brain natriuretic peptide increased, breath sounds, breath sounds abnormal, c-reactive protein increased, carbon monoxide diffusing capacity decreased, cardiac murmur, cardiac output decreased, cardioactive drug level decreased, cardioactive drug level increased, cardiolipin antibody positive, carotid bruit, catheterisation cardiac, central venous pressure increased, clostridium test positive, coagulation time prolonged, creatine urine decreased, creatinine renal clearance decreased, creatinine renal clearance increased, crystal urine present, culture urine positive, cystatin c increased, ejection fraction decreased, electrocardiogram abnormal, electrocardiogram PR prolongation, electrocardiogram qrs complex prolonged, electrocardiogram QT interval, electrocardiogram QT prolonged, electrocardiogram repolarisation abnormality, electrocardiogram ST segment abnormal, electrocardiogram ST segment depression, electrocardiogram ST-T change, electrocardiogram ST-T segment abnormal, electrocardiogram ST-T segment depression, electrocardiogram T wave abnormal, electrocardiogram T wave amplitude decreased, electrocardiogram T wave inversion, electrocardiogram T wave peaked, eosinophil count decreased, eosinophil count increased, escherichia test positive, fluid wave test, fungal test positive, gamma-glutamyltransferase abnormal, gamma-glutamyltransferase increased, glucose urine, glucose urine present, haematocrit decreased, haematocrit increased, haemoglobin decreased, haemoglobin increased, heart rate decreased, heart rate increased, heart rate irregular, heart sounds abnormal, hepatic enzyme abnormal, hepatic enzyme increased, high density lipoprotein decreased, high density lipoprotein increased, human papilloma virus test positive,

System Organ Class	MedDRA Preferred Term
	iliac bruit, inflammatory marker increased, international normalised ratio, international normalised ratio decreased, international normalised ratio increased, intraocular pressure increased, kidney palpable, laboratory test abnormal, left ventricular end-diastolic pressure increased, lipase increased, lipids increased, liver function test abnormal, liver palpable subcostal, lymphocyte count decreased, lymphocyte morphology abnormal, lymphocyte percentage decreased, lymphocyte percentage increased, mean cell haemoglobin concentration decreased, mean cell volume decreased, mean cell volume increased, monoclonal immunoglobulin present, monocyte count increased, monocyte percentage increased, myoglobin blood increased, n-terminal prohormone brain natriuretic peptide increased, neurological examination abnormal, neutrophil count decreased, neutrophil count increased, neutrophil percentage decreased, neutrophil percentage increased, occult blood, occult blood positive, oxygen saturation decreased, pedal pulse decreased, peripheral pulse decreased, ph urine abnormal, ph urine decreased, platelet count abnormal, platelet count decreased, platelet count increased, procollagen type i c-terminal propeptide increased, prostatic specific antigen increased, protein induced by vitamin k absence or antagonist ii increased, protein total, protein total abnormal, protein total decreased, protein total increased, protein urine present, prothrombin time abnormal, prothrombin time prolonged, prothrombin time shortened, pulse absent, qrs axis abnormal, quality of life decreased, red blood cell count decreased, red blood cell count increased, red blood cell sedimentation rate increased, red blood cells urine positive, renal function test abnormal, renin increased, residual urine volume increased, respiratory rate increased, serratia test positive, serum ferritin decreased, serum ferritin increased, skin turgor decreased, specific gravity urine decreased, staphylococcus test positive, thyroid function test abnormal, total bile acids increased, total lung capacity decreased, transaminases increased, troponin increased, troponin t increased, ultrasound ovary abnormal, urinary casts, urinary casts present, urinary sediment abnormal, urine analysis abnormal, urine bilirubin increased, urine ketone body, urine osmolarity decreased, urine osmolarity increased, urine output decreased, urine output increased, urine sodium decreased, urobilinogen urine, urobilinogen urine increased, venous pressure increased, venous pressure jugular increased, volume blood decreased, waist circumference increased, weight decreased, weight increased, white blood cell count abnormal, white blood cell count decreased, white blood cell count increased, white blood cells urine positive
Metabolism and nutrition disorders	Abnormal loss of weight, acidosis, acidosis hyperchloraemic, alkalosis, alkalosis hypochloraemic, appetite disorder, cachexia, calcium deficiency, central obesity, decreased appetite, dehydration, diabetes mellitus, diabetes mellitus inadequate control, diabetic complication, diabetic ketoacidosis, dyslipidaemia, electrolyte imbalance, enzyme abnormality, failure to thrive, fluid overload, fluid retention, food craving, food intolerance, fructose intolerance, glucose tolerance impaired, gout, hyperammonaemia, hypercalcaemia, hyperchloraemia, hypercholesterolaemia, hypercreatininaemia, hyperglycaemia, hyperkalaemia, hyperlipidaemia, hypermagnesaemia, hypernatraemia, hyperosmolar state, hyperphagia, hyperphosphataemia, hyperproteinaemia, hypertriglyceridaemia, hyperuricaemia, hypervolaemia, hypoalbuminaemia, hypocalcaemia, hypochloraemia, hypoglycaemia, hypokalaemia, hypomagnesaemia, hyponatraemia, hypophagia, hypophosphataemia, hypoproteinaemia, hypovolaemia, increased appetite, iron deficiency, lactic acidosis, lactose intolerance, lipomatosis, magnesium deficiency, malnutrition, metabolic acidosis, metabolic alkalosis, obesity, overweight, polydipsia, salt craving, type 1 diabetes mellitus, type 2 diabetes mellitus, vitamin B12 deficiency, vitamin D deficiency, weight fluctuation
Musculoskeletal and connective tissue disorders	Ankylosing spondylitis, arthralgia, arthritis, arthritis reactive, arthropathy, back pain, bone formation increased, bone pain, bursa calcification, bursitis, cartilage hypertrophy, cervical spinal stenosis, chondrocalcinosis pyrophosphate, coccydynia, compartment syndrome, costochondritis, crystal arthropathy, exostosis, exostosis of jaw, fasciitis, fibromyalgia, fistula, flank pain, foot deformity, gouty arthritis, gouty tophus, groin pain, haemarthrosis, hypercreatinaemia, intervertebral disc degeneration, intervertebral disc disorder, intervertebral disc protrusion, joint contracture, joint effusion, joint range of motion decreased, joint swelling, joint warmth,

System Organ Class	MedDRA Preferred Term
	kyphosis, ligament pain, limb asymmetry, limb discomfort, lumbar spinal stenosis, mixed connective tissue disease, mobility decreased, muscle contracture, muscle fatigue, muscle haemorrhage, muscle rigidity, muscle spasms, muscle swelling, muscle tightness, muscle twitching, muscular weakness, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, myofascial pain syndrome, myositis, neck mass, neck pain, osteitis, osteoarthritis, osteoarthropathy, osteochondrosis, osteonecrosis, osteopenia, osteoporosis, osteosis, pain in extremity, pain in jaw, patellofemoral pain syndrome, pathological fracture, periarthritis, plantar fasciitis, polyarthritis, polymyalgia rheumatica, polymyositis, pubic pain, rhabdomyolysis, rheumatic disorder, rheumatoid arthritis, rotator cuff syndrome, sacroiliitis, scoliosis, sensation of heaviness, soft tissue necrosis, spinal column stenosis, spinal disorder, spinal osteoarthritis, spinal pain, spondylolisthesis, synovial cyst, temporomandibular joint syndrome, tendon disorder, tendon pain, tendonitis, tenosynovitis, tenosynovitis stenosans, torticollis, trigger finger, trismus, upper extremity mass
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Abdominal neoplasm, acrochordon, adenocarcinoma, adrenal neoplasm, aesthesioneuroblastoma, basal cell carcinoma, benign breast neoplasm, benign mesothelioma, benign neoplasm of thyroid gland, bile duct cancer, bladder cancer, breast cancer, breast cancer metastatic, breast neoplasm, bronchial neoplasm, cancer pain, cervix carcinoma stage 0, cholangiocarcinoma, chronic myeloid leukaemia, colon adenoma, colon cancer, gastric cancer, glomus jugulare tumour, haemangioma, haemangioma of liver, hepatic cancer, hepatic neoplasm, hepatocellular carcinoma, invasive ductal breast carcinoma, Kaposi's sarcoma, keratoacanthoma, large intestine benign neoplasm, lipoma, lung neoplasm, lung neoplasm malignant, lymphoma, malignant melanoma, malignant melanoma in situ, mantle cell lymphoma, melanocytic naevus, meningioma, metastases to bone, metastases to central nervous system, metastases to liver, metastasis, metastatic malignant melanoma, metastatic neoplasm, myelodysplastic syndrome, myelofibrosis, myeloid leukaemia, neoplasm, neoplasm skin, neuroma, non-Hodgkin's lymphoma, oesophageal carcinoma, pancreatic carcinoma, pancreatic neoplasm, pituitary tumour benign, prostate cancer, prostate cancer recurrent, prostatic adenoma, rectal adenoma, renal cell carcinoma, renal neoplasm, salivary gland adenoma, seborrhoeic keratosis, skin cancer, skin papilloma, small cell carcinoma, small cell lung cancer, squamous cell carcinoma, squamous cell carcinoma of lung, sweat gland tumour, testicular neoplasm, thyroid neoplasm, ureteric cancer, uterine cancer, uterine leiomyoma

System Organ Class	MedDRA Preferred Term
Nervous system disorders	Ageusia, altered state of consciousness, amnesia, aphasia, aphonia, arachnoid cyst, areflexia, asterixis, ataxia, balance disorder, brain hypoxia, brain oedema, burning sensation, carotid arteriosclerosis, carotid artery aneurysm, carotid artery occlusion, carotid artery stenosis, carpal tunnel syndrome, cauda equina syndrome, cerebral artery embolism, cerebral atrophy, cerebral cyst, cerebral haemorrhage, cerebral hypoperfusion, cerebral infarction, cerebral ischaemia, cerebral microangiopathy, cerebrovascular accident, cerebrovascular disorder, cerebrovascular insufficiency, cluster headache, cognitive disorder, cogwheel rigidity, coma, convulsion, coordination abnormal, dementia, dementia Alzheimer's type, demyelinating polyneuropathy, depressed level of consciousness, diabetic neuropathy, diplegia, disturbance in attention, dizziness, dizziness exertional, dizziness postural, dysaesthesia, dysarthria, dysgeusia, dyskinesia, embolic stroke, encephalopathy, epilepsy, essential tremor, extrapyramidal disorder, glossopharyngeal neuralgia, haemorrhage intracranial, haemorrhagic stroke, head discomfort, headache, hemiparesis, hepatic encephalopathy, hydrocephalus, hyperaesthesia, hypergeusia, hyperreflexia, hypertonia, hypoaesthesia, hypogeusia, hypoglycaemic coma, hypokinesia, hyporeflexia, hypotonia, hypoxic-ischaemic encephalopathy, intention tremor, intercostal neuralgia, intracranial aneurysm, ischaemic cerebral infarction, ischaemic neuropathy, ischaemic stroke, lacunar infarction, lethargy, loss of consciousness, lumbar radiculopathy, memory impairment, mental impairment, metabolic encephalopathy, migraine, migraine with aura, monoplegia, movement disorder, muscle contractions involuntary, myoclonus, narcolepsy, nerve compression, nerve root compression, neuralgia, neurological symptom, neuropathy peripheral, nystagmus, orthostatic intolerance, paraesthesia, Parkinson's disease, parkinsonism, parosmia, periventricular leukomalacia, petit mal epilepsy, phantom pain, pneumocephalus, polyneuropathy, polyneuropathy alcoholic, poor quality sleep, presyncope, psychomotor hyperactivity, radiculitis, radiculitis lumbosacral, radiculopathy, resting tremor, restless legs syndrome, sciatica, sedation, sensory disturbance, sensory loss, sinus headache, slow response to stimuli, somnolence, speech disorder, subarachnoid haemorrhage, syncope, tension headache, tongue biting, transient ischaemic attack, tremor, trigeminal neuralgia, tunnel vision, unresponsive to stimuli, vascular dementia, vascular encephalopathy, vertebral artery dissection, vertebrobasilar insufficiency, viith nerve paralysis, visual field defect, vocal cord paralysis
Pregnancy, puerperium, perinatal conditions	Abortion spontaneous, cephalhaematoma
Psychiatric disorders	Abnormal dreams, adjustment disorder with depressed mood, affect lability, aggression, agitation, alcoholism, anxiety, anxiety disorder, attention deficit/hyperactivity disorder, autism spectrum disorder, belligerence, bipolar disorder, bradyphrenia, bulimia nervosa, burnout syndrome, claustrophobia, confusional state, delirium, delusion, dependence, depressed mood, depression, depressive symptom, disorientation, dysphoria, dyssomnia, eating disorder, emotional distress, hallucination, hallucination, visual, hyposomnia, initial insomnia, insomnia, irritability, libido decreased, libido disorder, loss of libido, major depression, mental disorder, mental status changes, middle insomnia, mood altered, mood swings, nervousness, neurosis, nicotine dependence, nightmare, panic attack, panic disorder, panic reaction, paranoia, persecutory delusion, psychotic disorder, restlessness, schizophrenia, sleep disorder, somnambulism, stress, suicidal ideation, suicide attempt
Renal and urinary disorders	Acute prerenal failure, albuminuria, anuria, azotaemia, bladder dilatation, bladder discomfort, bladder disorder, bladder dysfunction, bladder irritation, bladder mass, bladder neck sclerosis, bladder pain, bladder prolapse, bladder spasm, calculus bladder, calculus ureteric, calculus urinary, chromaturia, cystitis noninfective, diabetic nephropathy, dysuria, enuresis, glomerulosclerosis, glycosuria, haematuria, hydronephrosis, hypertonic bladder, hypotonic urinary bladder, incontinence, kidney enlargement, leukocyturia, micturition disorder, micturition urgency, nephrolithiasis, nephropathy, nephropathy toxic, nephroptosis, nephrosclerosis, nephrotic syndrome, neurogenic bladder, nocturia, obstructive uropathy, oliguria, pollakiuria, polyuria, prerenal failure, proteinuria,

System Organ Class	MedDRA Preferred Term
	pyelocaliectasis, pyuria, renal artery occlusion, renal artery stenosis, renal colic, renal cyst, renal cyst haemorrhage, renal cyst ruptured, renal failure, renal failure acute, renal failure chronic, renal impairment, renal infarct, renal mass, renal pain, renal tubular necrosis, strangury, terminal dribbling, tubulointerstitial nephritis, urethral disorder, urethral haemorrhage, urethral pain, urethral stenosis, urethritis noninfective, urge incontinence, urinary hesitation, urinary incontinence, urinary retention, urinary tract disorder, urine abnormality, urine flow decrease
Reproductive system and breast disorder	Adnexa uteri pain, adnexal torsion, amenorrhoea, atrophic vulvovaginitis, benign prostatic hyperplasia, breast cyst, breast enlargement, breast hyperplasia, breast mass, breast pain, breast tenderness, cervical dysplasia, cervical polyp, coital bleeding, cystocele, dysfunctional uterine bleeding, dysmenorrhoea, dyspareunia, ejaculation disorder, endometriosis, erectile dysfunction, galactorrhoea, genital discomfort, genital haemorrhage, genital pain, genital paraesthesia, gynaecomastia, haematospermia, haemorrhagic ovarian cyst, hypomenorrhoea, menometrorrhagia, menopausal symptoms, menorrhagia, menstrual disorder, menstruation delayed, menstruation irregular, metrorrhagia, nipple pain, oedema genital, ovarian cyst, ovarian cyst ruptured, ovulation pain, pelvic discomfort, pelvic pain, pelvic prolapse, penile discharge, penile necrosis, penile oedema, penile pain, penis disorder, perineal erythema, perineal pain, Peyronie's disease, postmenopausal haemorrhage, premenstrual syndrome, prostatic disorder, prostatism, prostatitis, prostatomegaly, scrotal haematocoele, scrotal irritation, scrotal oedema, scrotal pain, scrotal swelling, seminal vesicular cyst, sexual dysfunction, testicular cyst, testicular mass, testicular oedema, testicular pain, testicular swelling, uterine cervical squamous metaplasia, uterine disorder, uterine haemorrhage, uterine prolapse, uterovaginal prolapse, vaginal cyst, vaginal discharge, vaginal erosion, vaginal haemorrhage, vaginal mucosal blistering, vaginal prolapse, varicocele, vulvovaginal discomfort, vulvovaginal dryness
Respiratory, thoracic and mediastinal disorders	Acute interstitial pneumonitis, acute pulmonary oedema, acute respiratory distress syndrome, acute respiratory failure, allergic sinusitis, anoxia, apnoea, asphyxia, aspiration, asthma, asthmatic crisis, atelectasis, bronchial disorder, bronchial obstruction, bronchiectasis, bronchitis chronic, bronchopleural fistula, bronchopulmonary disease, bronchospasm, bronchostenosis, cheyne-stokes respiration, choking, choking sensation, chronic obstructive pulmonary disease, cough, diaphragmatic disorder, dry throat, dysphonia, dyspnoea, dyspnoea at rest, dyspnoea exertional, dyspnoea paroxysmal nocturnal, emphysema, epistaxis, haemoptysis, haemothorax, hiccups, hydrothorax, hyperventilation, hypoventilation, hypoxia, idiopathic pulmonary fibrosis, increased bronchial secretion, increased upper airway secretion, interstitial lung disease, laryngeal cyst, laryngeal discomfort, laryngeal inflammation, laryngeal oedema, lung disorder, lung infiltration, mediastinal haemorrhage, nasal congestion, nasal disorder, nasal dryness, nasal mucosal discolouration, nasal obstruction, nasal polyps, nasal septum deviation, nasal ulcer, obstructive airways disorder, oropharyngeal discomfort, oropharyngeal pain, orthopnoea, paranasal sinus hypersecretion, pharyngeal erythema, pharyngeal inflammation, pleural effusion, pleural fibrosis, pleural rub, pleurisy, pleuritic pain, pneumonia aspiration, pneumonitis, pneumothorax, pneumothorax spontaneous, productive cough, prolonged expiration, pulmonary congestion, pulmonary embolism, pulmonary fibrosis, pulmonary granuloma, pulmonary haemorrhage, pulmonary hypertension, pulmonary mass, pulmonary oedema, pulmonary sarcoidosis, pulmonary vascular disorder, rales, reflux laryngitis, respiration abnormal, respiratory acidosis, respiratory arrest, respiratory depression, respiratory disorder, respiratory distress, respiratory failure, respiratory tract congestion, restrictive pulmonary disease, rhinalgia, rhinitis allergic, rhinorrhoea, rhonchi, sinus congestion, sinus disorder, sleep apnoea syndrome, sneezing, snoring, sputum discoloured, sputum increased, tachypnoea, throat irritation, throat tightness, tonsillar hypertrophy, tonsillar inflammation, tonsillolith, tracheal fistula, tracheal stenosis, tracheomalacia, upper respiratory tract congestion, upper respiratory tract inflammation, upper-airway cough syndrome, vasomotor rhinitis, vocal cord inflammation, wheezing

System Organ Class	MedDRA Preferred Term
Skin and subcutaneous tissue disorders	Acanthosis nigricans, acne, actinic keratosis, alopecia, androgenetic alopecia, angioedema, blister, blood blister, campbell de morgan spots, chloasma, cold sweat, cutis laxa, decubitus ulcer, dermal cyst, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis contact, dermatitis exfoliative, dermatitis herpetiformis, dermatosis, diabetic bullosis, diabetic dermopathy, diabetic foot, diabetic ulcer, drug eruption, dry skin, dyshidrotic eczema, ecchymosis, eczema, eczema asteatotic, erythema, erythema multiforme, excessive skin, facial wasting, haemorrhage subcutaneous, hair growth abnormal, hangnail, henoch-schonlein purpura, hidradenitis, hyperhidrosis, hyperkeratosis, hypohidrosis, ingrowing nail, intertrigo, lentigo, livedo reticularis, macule, mechanical urticaria, miliaria, nail disorder, neurodermatitis, night sweats, onychoclasis, pain of skin, palmar-plantar erythrodysaesthesia syndrome, papule, peau d'orange, petechiae, photosensitivity reaction, pigmentation disorder, pityriasis rosea, prurigo, pruritus, pruritus generalised, psoriasis, purpura, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rosacea, scab, sebaceous gland disorder, sebaceous hyperplasia, seborrhoeic dermatitis, senile pruritus, skin depigmentation, skin discolouration, skin disorder, skin erosion, skin exfoliation, skin fissures, skin haemorrhage, skin hyperpigmentation, skin irritation, skin lesion, skin mass, skin oedema, skin plaque, skin ulcer, spider naevus, stasis dermatitis, subcutaneous emphysema, swelling face, telangiectasia, urticaria, urticaria cholinergic, urticaria chronic, vitiligo, xeroderma
Social circumstances	Family stress, menopause, physical assault, stress at work, tanning
Surgical and medical procedures	Astringent therapy, cardioversion, dental care, diphtheria immunisation, drug therapy, laparotomy, liver transplant, rapid correction of hyponatraemia, toe amputation, tooth extraction, transfusion, umbilical hernia repair, vasectomy, vitamin supplementation
Vascular disorders	Angiopathy, aortic aneurysm, aortic arteriosclerosis, aortic dilatation, aortic embolus, aortic stenosis, aortic thrombosis, arterial disorder, arterial insufficiency, arterial occlusive disease, arteriosclerosis, arteriovenous fistula, arteritis, axillary vein thrombosis, bleeding varicose vein, blood pressure inadequately controlled, circulatory collapse, deep vein thrombosis, diabetic macroangiopathy, diabetic vascular disorder, diastolic hypertension, embolism, embolism arterial, extremity necrosis, femoral artery occlusion, flushing, haematoma, haemodynamic instability, haemorrhage, haemorrhagic infarction, hot flush, hyperaemia, hypertension, hypertensive crisis, hypotension, hypovolaemic shock, iliac artery occlusion, intermittent claudication, intra-abdominal haematoma, ischaemia, jugular vein distension, jugular vein thrombosis, labile blood pressure, lymphocele, lymphoedema, lymphorrhoea, macroangiopathy, microangiopathy, orthostatic hypotension, pallor, pelvic venous thrombosis, peripheral arterial occlusive disease, peripheral artery thrombosis, peripheral coldness, peripheral embolism, peripheral ischaemia, peripheral vascular disorder, phlebitis, phlebitis superficial, poor peripheral circulation, Raynaud's phenomenon, shock haemorrhagic, steal syndrome, subclavian vein thrombosis, temporal arteritis, thrombophlebitis, thrombophlebitis superficial, thrombosed varicose vein, thrombosis, varicose ulceration, varicose vein, vascular calcification, vascular insufficiency, vascular occlusion, vasculitis, vasculitis necrotising, vasodilatation, vasospasm, vein disorder, vena cava thrombosis, venous insufficiency, venous occlusion, venous thrombosis, venous thrombosis limb

ADPKD = autosomal dominant polycystic kidney disease; MedDRA = Medical Dictionary for Regulatory Activities; UK = United Kingdom; US = United States.

Trials: 156-95-301, 156-95-302, 156-95-303, 156-95-304, 156-95-305, 156-96-301, and 156-03-242 (healthy subjects phase 1 UK); 156-96-205, 156-97-202, 156-98-201, 156-98-202, 156-98-210, 156-01-223, 156-01-225, 156-01-229, 156-01-233, 156-01-234, 156-03-239, 156-03-240, 156-03-245, 156-05-252, 156-05-253, 156-05-254, 156-05-256, 156-07-262, 156-07-263, 156-08-269, 156-08-270, 156-11-295, and 156-12-202 (healthy subjects phase 1 US); 156-01-226 (healthy subjects phase 1 US and Argentina); 156-00-001, 156-00-002, 156-00-003, 156-05-001, 156-05-003, 156-05-004, 156-07-002, 156-10-004, and 156-10-006 and 156-14-004 (healthy subjects phase 1 Japan); 156-06-801-01, 156-11-807-01, 156-11-808-01 (healthy subjects phase 1 China); 156-KOA-0801 (healthy subjects Korea); 156-09-806-01 (hepatocirrhosis phase 1 China); 156-09-282 (renal impairment phase 1 US); 156-96-201,

156-96-203, 156-97-204, 156-02-235, 156-03-238, 156-03-244, 156-04-246, 156-07-802-01, 156-08-275 (phase 2/3 hyponatremia); 156-KOB-1101i (phase 4 hyponatremia); 156-97-251, 156-97-252, 156-98-213, 156-00-220, 156-00-221, 156-00-222, 156-01-231, 156-01-232, 156-03-236, and 156-04-247 (phase 2/3 heart failure); 156-04-001, 156-04-248, 156-04-249, 156-04-250, 156-04-251, 156-05-002, 156-06-260, 156-09-284, 156-09-285, and 156-09-290 (phase 2/3 ADPKD); 156-03-001, 156-06-002, 156-06-004, and 156-06-006 (phase 2/3 cardiac edema Japan); 156-12-809-01 (phase 3 cardiac edema China); 156-10-005 (phase 4 cardiac edema Japan); 156-03-002, 156-06-005, 156-08-001, 156-08-002, 156-08-804-01, 156-08-805-01, and 156-09-004 (phase 2/3 hepatic edema Japan/China), 156-12-001 (carcinomatous edema, phase 2 Japan), 156-12-002, 156-12-007 (chronic renal failure, phase 2 Japan) and 156-TWA-1101i (cardiac edema, phase 3 Taiwan).

Note: Trials 156-94-001 (N = 25) and 156-94-002 (N = 6) are not included because safety data were unavailable for inclusion in the pooled safety database; however, safety data from these trials are representative of the data in the pooled database. Also not included are data for ongoing trials.

Note: Events are coded using MedDRA version 17.0.

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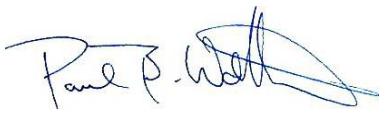
Appendix 3, Safety Report May 2014

Watkins Tolvaptan Liver Safety Report Update

Updated review of the liver safety database for tolvaptan in the treatment of Autosomal Dominant Polycystic Kidney Disease: An addendum to the October 28, 2012 report

Prepared by:



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University of North Carolina - Chapel Hill

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May 8, 2014

Watkins Tolvaptan Liver Safety Report Update

I. Background

I prepared a written report, dated October 28, 2012, regarding the liver safety of tolvatpan in the treatment of Autosomal Dominant Polycystic Kidney Disease (ADPKD). The conclusions in the report were based on the liver safety database as of March 31, 2012. This report was reviewed and approved by the additional three hepatologists involved in causality assessment of the tolvaptan cases - Drs. Kaplowitz, Lewis and Alpers. All blinded clinical trials had been completed as of March 31, 2012 and all patients receiving tolvaptan since that time have been doing so in open label trials.

In this report, I summarize the liver safety data that has accumulated since the time of the last report with the goal of determining whether, based on these data, there is reason to change the conclusions regarding the liver safety of tolvaptan expressed in the October 28, 2012 report.

II. Conclusions of the October 28, 2012 report

As of the data capture cutoff date for the October 2012 report (31 March 2012), there were no patients in the database who had developed liver failure attributed to tolvaptan treatment and all liver injuries attributed to tolvaptan appeared to be reversible. There were however three cases in the liver safety database determined to be Hy's Law Cases. It was therefore concluded that in patients with ADPKD, tolvaptan has the potential to cause acute liver failure. Based on the estimate that 10% of Hy's Law Cases will experience liver failure and the estimate that about 900 subjects in the database had been treated with tolvaptan for at least 14 months, the risk of liver failure was estimated be about 1:3000 patients chronically treated with Tolvaptan for ADPKD.

A "signature" clinical presentation was identified from the liver safety database and it had the following characteristics:

1). Hepatocellular injury with "R value" > 5.0

2). Characteristic onset between 3 and 14 months on treatment. (This "window of susceptibility" was later extended to 18 after discussions between myself and the company).

3). Progressive rise in serum ALT/AST for several weeks after stopping treatment with tolvaptan followed by a return of these clinical chemistries to baseline over one to several months.

III. Data Analyzed for this report

The data capture cut off for this report is 28 February, 2014. The selection criteria for cases submitted to the hepatologists for adjudication remained unchanged since the February, 2012 data capture for the October 2012 report, except that the criteria “total Bilirubin >2x ULN” was not employed. This change was prompted by discussions among the hepatology experts who agreed that a patient with an elevated serum bilirubin in the absence of meeting the other selection criteria was not a safety concern. The makeup of the external hepatology panel involved in the adjudications, the process of adjudication, and the causality grading systems used were unchanged from those described in the October, 2012 report. The protocol driven frequency of liver chemistry monitoring was increased from every 6 months to every 3 months in June 2011 and further increased to monthly for the first 18 months of treatment in November 2012 for the open-label roll-over study 156-08-271. Also added at the same time as the implementation of the monthly monitoring were recommendations for following up abnormal liver chemistries and for interrupting or terminating treatment as listed in Appendix A.

IV. Data analysis

The patient exposure to tolvaptan as of the data cut off 28 February,2014 is shown in table 1 below. Since the February 2012 data capture, the total number of patients treated with tolvaptan for at least 18 months rose by 437, from 838 to 1275.

Table 1. Extent of Exposure to Tolvaptan: All ADPKD Studies as of February 28, 2014

	TOTAL TOLVAPTAN (N=1588)			
	LAST DOSE		CUMULATIVE[1]	
DURATION OF EXPOSURE	n	(%)	n	(%)
1 DAY	5	(0.3)	1588	(100.0)
1 WEEK	24	(1.5)	1583	(99.7)
2 WEEKS	28	(1.8)	1559	(98.2)
3 WEEKS	22	(1.4)	1531	(96.4)
6 MONTHS	141	(8.9)	1509	(95.0)
12 MONTHS	93	(5.9)	1368	(86.1)
18 MONTHS	80	(5.0)	1275	(80.3)
24 MONTHS	96	(6.0)	1195	(75.3)
30 MONTHS	137	(8.6)	1099	(69.2)
36 MONTHS	174	(11.0)	962	(60.6)
42 MONTHS	111	(7.0)	788	(49.6)
48 MONTHS	21	(1.3)	677	(42.6)
54 MONTHS	24	(1.5)	656	(41.3)
60 MONTHS	84	(5.3)	632	(39.8)
66 MONTHS	243	(15.3)	548	(34.5)
> 66 MONTHS	305	(19.2)	305	(19.2)

The incidence of ALT elevations > 3 X ULN over time in the open label extension is shown in appendix B. Most of the subjects completing the 251 blinded trial entered the open label trial. Six hundred and forty subjects (640) had received tolvaptan in the 251 trial before entering the open label trial. In this group, the incidence of initial elevations in serum ALT was low and similar to the rate observed among placebo treated subjects in the 251 trial. There were 363 subjects who had received placebo prior to entering the open label trial and the incidence of initial ALT elevations in this group appears to be somewhat higher than had been observed among subjects receiving tolvaptan for the first time in the 251 trial. None of the subjects receiving tolvaptan for the first time in the open label experienced first ALT elevations > 3 X ULN after 400 days of treatment.

Twenty five cases were referred to the hepatology experts for adjudication since the March 31, 2012 data cut off for the October 28, 2012 report. Fifteen patients had received tolvaptan and 10 had received placebo during the double-blind phase prior to entering the open label extension phase. The consensus causality assessments by the hepatologists, as well as the patients' course after the event, are summarized in the

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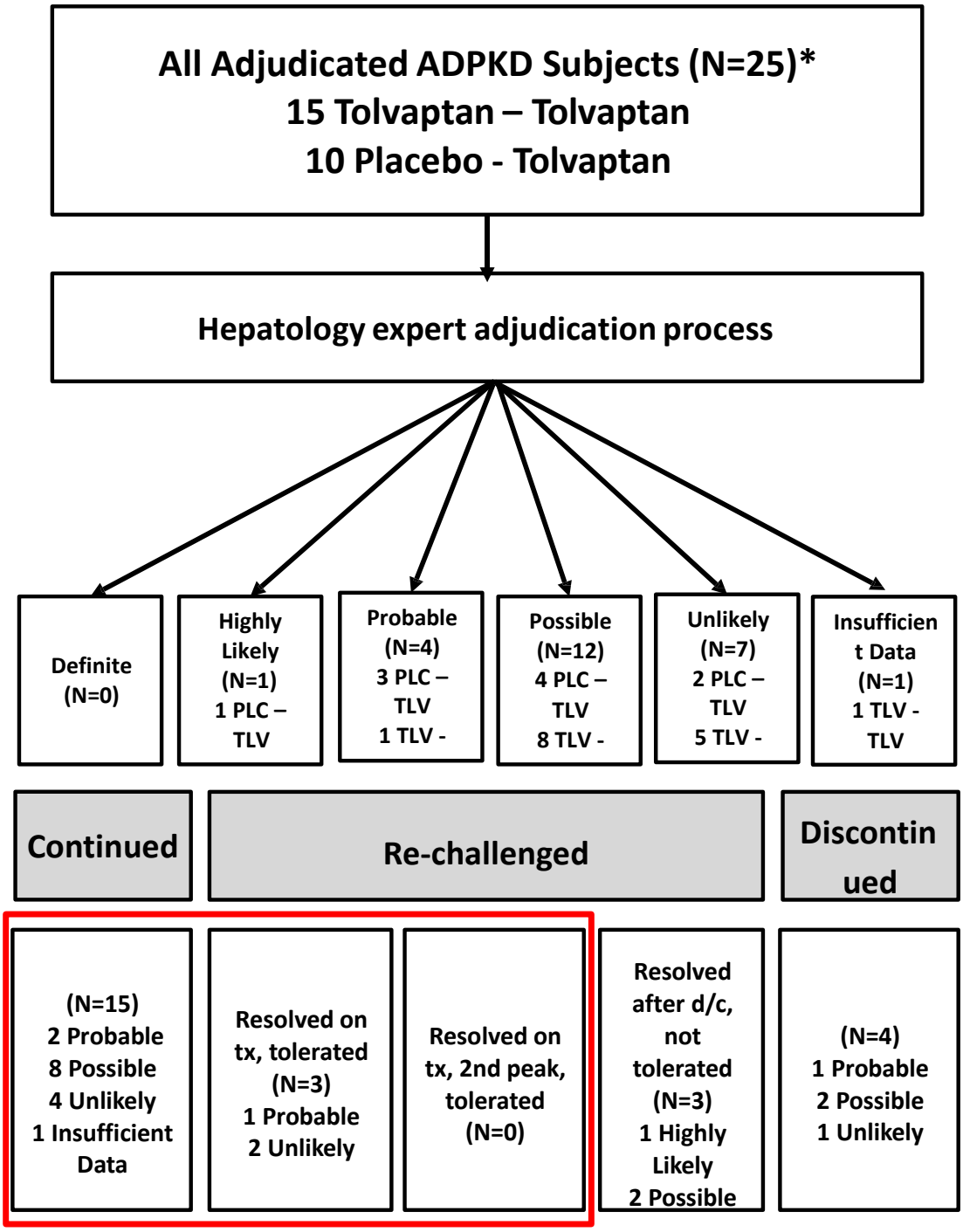
table below. It can be seen that most of these patients were able to continue to be treated with tolvaptan (the red box).



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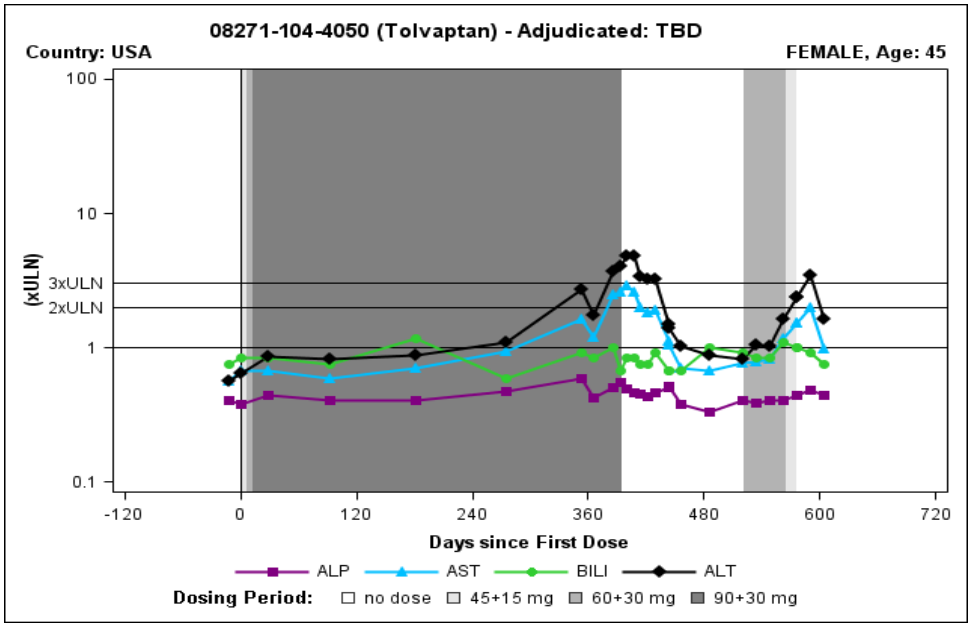
Five patients were judged by the hepatologist panel to have at least probably experienced liver injury due to tolvaptan (4 probable and 1 highly likely). Four of these patients had received placebo during the blinded clinical trial and received tolvaptan for the first time when they entered the open label trial. Only one patient (a “probable” case - Subject 138-9162, study 156-08-271) had received tolvaptan treatment in a blinded clinical trial. This patient’s blinded treatment was in a small trial 290 which only required study drug treatment for 2 months (only 134 subjects received tolvaptan in this trial), This patient had received only two months of tolvaptan treatment before entering the open label extension trial. None of these 5 patients experienced liver failure or would be considered a Hy’s Law Case. Each recovered from the event.
Below is a summary of each of these 5 cases:

Subject: 104-4050, study 156-08-271

46 year old woman who after about 1 year of treatment with tolvaptan experienced a modest (~5-fold) rise in serum ALT and AST which resolved upon discontinuation of tolvaptan. She was rechallenged with tolvaptan and had a prompt recurrence signifying a positive rechallenge. There was limited evaluation reported, but the data available was sufficient to assess this modest liver injury as “highly likely” to be the result of tolvaptan treatment.



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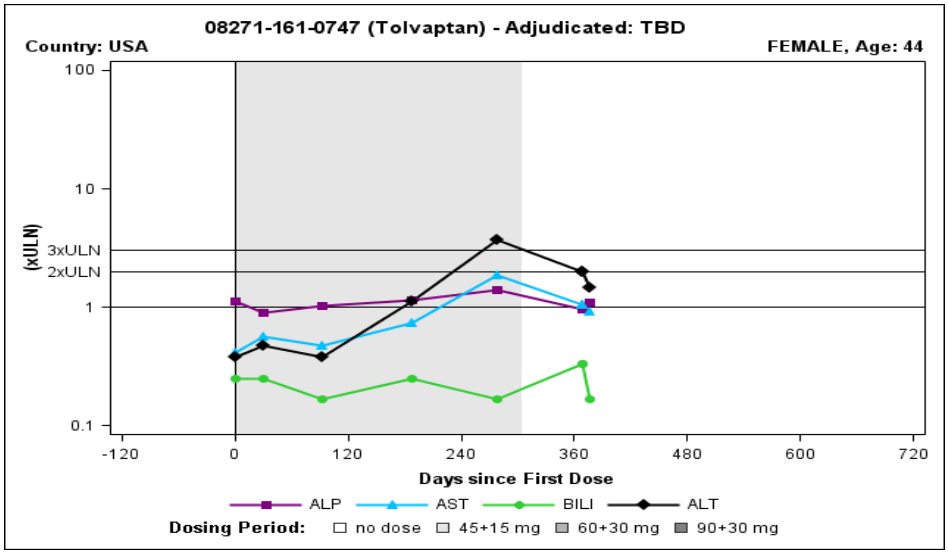
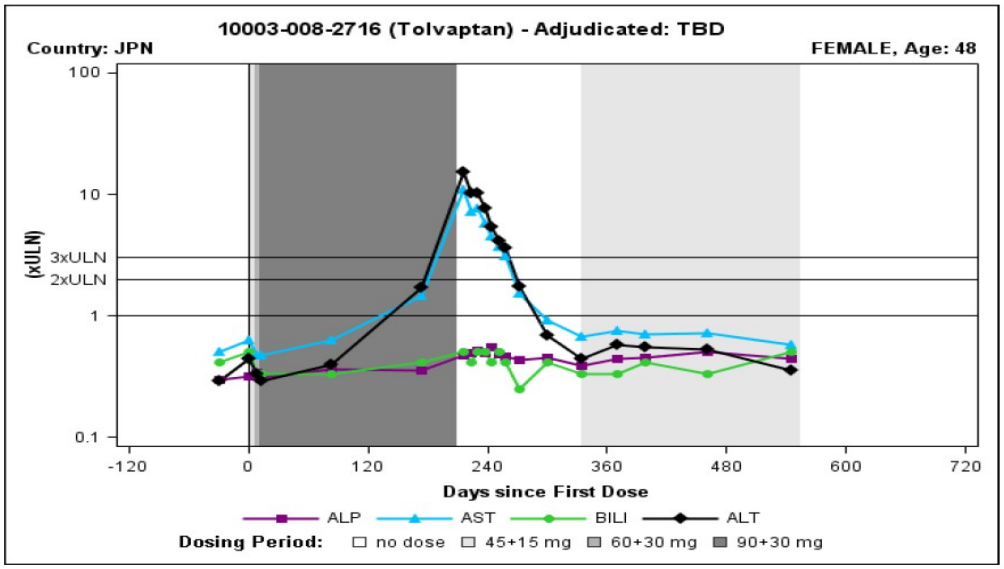
Subject 161-0747, study 156-08-271

45 year old woman who at about 10 months of treatment with tolvaptan in the open label study experienced a mild rise in serum ALT and AST to about 4 X ULN. Although this event did not meet hepatic trigger criteria for adjudication of >5 x ULN it was reported as a serious adverse event and therefore met the criteria for adjudication. These values returned to normal with discontinuation of treatment. There was no formal evaluation for other causes evident, but the timing and positive dechallenge was considered sufficient for a causality assessment of “probable”.



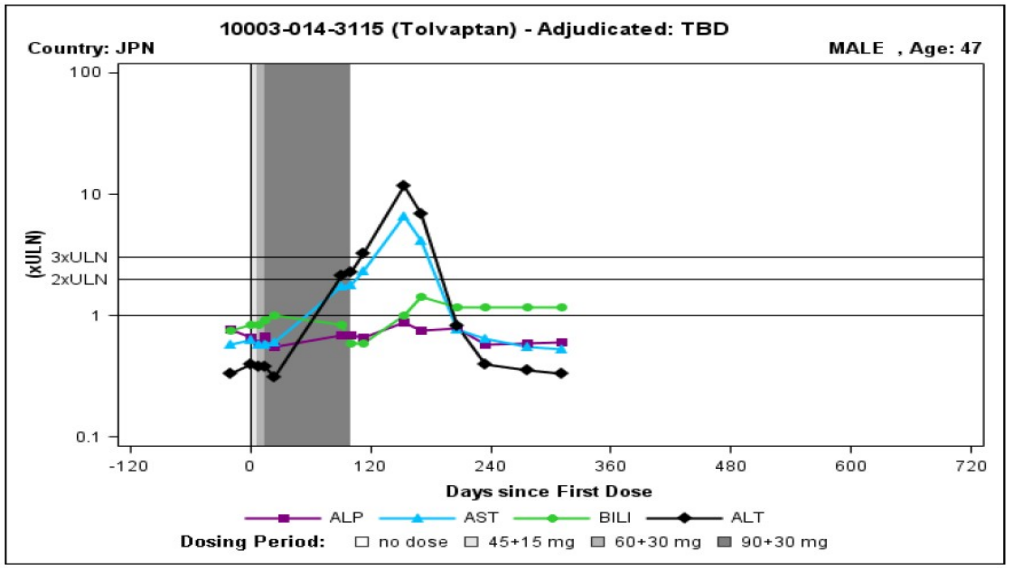
Subject 008-2716, study 156-10-003

46 year old woman who after 7 months of treatment with tolvaptan experienced a rise in serum ALT and AST which gradually resolved after discontinuation of treatment. There was no evaluation for alternate causes reported and a negative rechallenge at a lower dose. However, the injury resembled the signature clinical presentation of tolvaptan DILI so the hepatologists considered the event as probably the result of tolvaptan treatment.



Subject 014-3115, study 156-10-003

47 year old man who experienced elevations in serum ALT and AST after about 2 months of treatment with tolvaptan. These enzymes continued to rise for about weeks after discontinuing treatment to peak at > 10 X ULN before gradual resolution. This was considered to be consistent with the signature clinical presentation and the event was therefore considered probably related to tolvaptan treatment.



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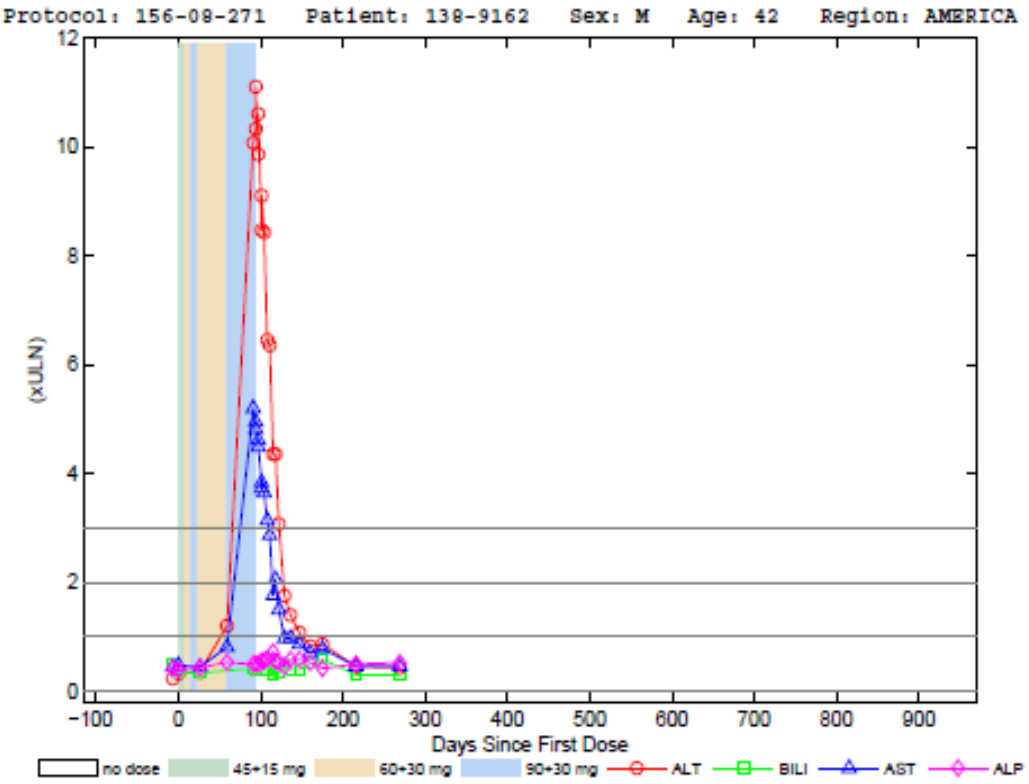
Subject 138-9162, study 156-08-271

42 year old man who after 3 months exposure in open label experienced elevations in serum ALT and AST to 444 IU and 178 IU respectively. Tolvaptan treatment was discontinued and there was resolution of the enzyme elevations over the next 2 months. Acute viral hepatitis screens were reported to be negative but the data are not provided and hepatitis E testing is not mentioned. After unblinding, it was discovered that this patient had received tolvaptan for just two months in a blinded clinical trial prior to entering the open label study. The total duration of exposure prior to the onset of injury was therefore about 5 months. Although the rapid fall in transaminases after discontinuing treatment is not typical for tolvptan DILI, this case was judged as probably related to tolvaptan treatment given timing, positive dechallenge, and lack of alternate etiologies.



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V. Discussion:

As of March 2014, 1275 patients had received tolvaptan through the estimated “window of susceptibility” of 18 months. There have been no new Hy’s Law cases, currently 3, or about 1:400 patients treated for at least 18 months. Assuming 10% of Hy’s Law cases will progress to acute liver failure, the estimate of incidence of acute liver failure in ADPKD patients chronically receiving treated with tolvaptan would therefore be about 1 in 4,000 ADPKD patients receiving chronic tolvaptan treatment. This estimate of risk is somewhat less the 1:3,000 arrived at in the prior October 2012 report. Whereas it is reassuring that no new Hy’s Law Cases have emerged, the number of additional patients treated through 18 months is not sufficient to assure a reduced risk of acute liver failure. Likewise, too few of patients have been treated under the risk management strategy that went into effect in November 2012 to assess the effectiveness of this strategy. It is of note that Subjects 161-0747 and 014-3115 discussed above appear to have discontinued treatment as a result of the risk management strategy and may have otherwise continued treatment It is not possible to know what would have happened had the drug been continued for an additional 4 month monitoring interval after the first abnormality was detected.

It should also be noted that each of the 5 cases with liver injuries assessed as probably or highly likely due to tolvaptan fit the signature pattern as defined in the October 2012 report. As shown in Appendix B, the risk of ALT elevations exceeding 3 X ULN is very low after 18 months and may approach the background incidence in this patient population. There was a trend for increased incidence of ALT elevations > 3 X ULN in those who received tolvaptan for the first time in the open label trial relative to those that received tolvaptan in the 251 double blind trial. This likely reflects the increased frequency of monitoring employed and supports other data that indicate most modest elevations in serum ALT due to tolvaptan will resolve with uninterrupted treatment. It is likely that a small number of transient and benign elevations occurred but were missed with the 4 monthly monitoring schedule employed for most of the 251 trial.

Watkins Tolvaptan Liver Safety Report Update

VI. Summary

The liver safety data that has accumu,lated from the tolvaptan clinical trials between the data cut off for my last report (March 31, 2012) and this report (February 28, 2014) is reassuring in that no new Hy's Law Cases have occurred. However, the new data is not sufficient to support a lower risk of acute liver failure due to tolvaptan treatment or to assess the efficacy of the current risk management strategy.

VII. Review of this report by Kaplowitz, Lewis, and Alpers –

Drs. Kaplowitz, Lewis and Alpers have reviewed this report and have approved its content and conclusions.

Confirm an increase of serum ALT or AST to >3x ULN by repeat testing (of ALT, AST, ALP, and BT) within 48 to 72 hours, ie, do not wait a week or two, because levels can change rapidly and might become normal, leading to false conclusions.

Evaluate relevant symptom data and history of concurrent diseases and also concomitant medications including nonprescription medications, herbal, and dietary supplements, alcohol use, recreational drug use, and special diets.

Follow subjects closely if:

- ALT or AST becomes >3x ULN (for subjects with a normal baseline value, elevations <3x ULN are common and nonspecific)
- ALT or AST becomes >2x ULN (for subjects with an elevated baseline value).

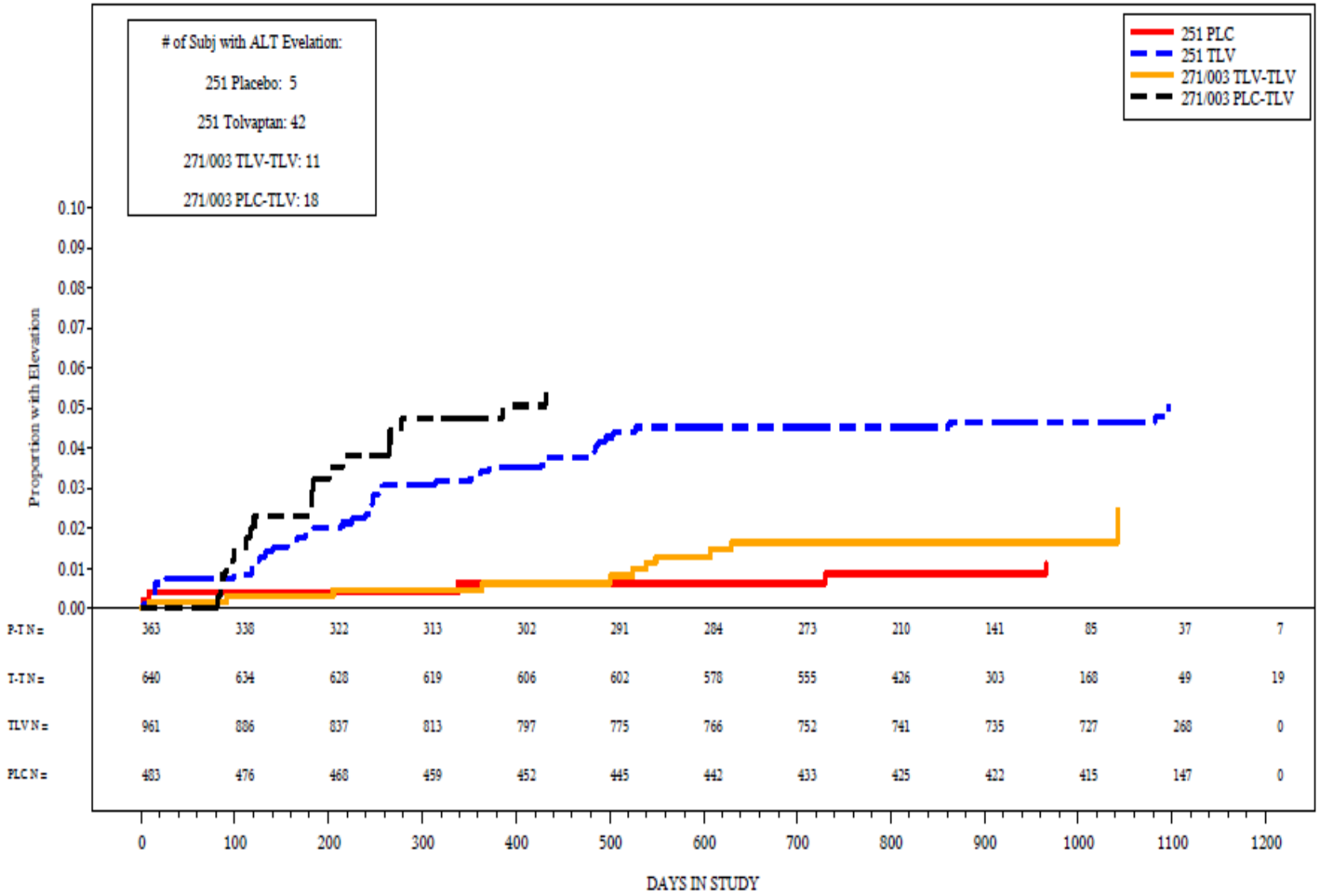
Follow up with repeat LFTs 2 to 3 times per week (decrease to once per week if abnormalities stabilize or IMP has been interrupted and subject is asymptomatic) and perform other tests of liver function, as appropriate (e.g., INR).

Consider interruption of IMP in the following contexts (automatic interruption of IMP upon finding an ALT or AST elevation of >3x ULN may be unnecessary, i.e., transient rises and falls of ALT or AST are common):

- ALT or AST becomes >8x ULN (no rechallenge)
- ALT or AST becomes >5x ULN for more than 2 weeks (no rechallenge)
- ALT or AST becomes >3x ULN and BT is >2x ULN or INR is >1.5
- ALT or AST becomes >3x ULN with appearance of worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia

Follow until resolution and consider IMP reinitiation (rechallenge) if appropriate.

Appendix B: Kaplan-Meier curves of time to first elevation in serum ALT > 3 X ULN – Included are Study 251 subjects both in the double blind phase and those who entered the open label extension. Lines were terminated when the last patient in the cohort experienced ALT>3XULN for the first time



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Appendix 4, Samsca Summary of Product Characteristics

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Samsca 15 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 15 mg tolvaptan.

Excipient with known effect:
Each tablet contains approximately 35 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet
Blue, triangular, shallow-convex, debossed with “OTSUKA” and “15” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Due to the need for a dose titration phase with close monitoring of serum sodium and volume status (see section 4.4), treatment with Samsca should be initiated in hospital.

Posology
Treatment with tolvaptan should be initiated at a dose of 15 mg once daily. The dose may be increased to a maximum of 60 mg once daily as tolerated to achieve the desired level of serum sodium. During titration, patients should be monitored for serum sodium and volume status (see section 4.4). In case of inadequate improvement in serum sodium levels, other treatment options should be considered, either in place of or in addition to tolvaptan. Use of tolvaptan in combination with other options may increase the risk of overly rapid correction of serum sodium (see sections 4.4 and 4.5). For patients with an appropriate increase in serum sodium, the underlying disease and serum sodium levels should be monitored at regular intervals to evaluate further need of tolvaptan treatment. In the setting of hyponatraemia, the treatment duration is determined by the underlying disease and its treatment. Tolvaptan treatment is expected to last until the underlying disease is adequately treated or until such time that hyponatraemia is no longer a clinical issue.
Samsca should not be taken with grapefruit juice (see section 4.5).

Patients with renal impairment
Tolvaptan is contraindicated in anuric patients (see section 4.3).
Tolvaptan has not been studied in patients with severe renal failure. The efficacy and safety in this population is not well established.
Based on the data available, no dose adjustment is required in those with mild to moderate renal impairment.

Patients with hepatic impairment
No information is available in patients with severe hepatic impairment (Child-Pugh class C). In these patients dosing should be managed cautiously and electrolytes and volume status should be monitored (see section 4.4).No dose adjustment is needed in patients with mild or moderate hepatic impairment (Child-Pugh classes A and B).

Elderly population
No dose adjustment is needed in elderly patients.

Paediatric population
The safety and efficacy of tolvaptan in children and adolescents under the age of 18 years have not yet been established. Samsca is not recommended in the paediatric age group.

Method of administration
For oral use.
Administration preferably in the morning, without regard to meals. Tablets should be swallowed without chewing with a glass of water.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Anuria
- Volume depletion
- Hypovolaemic hyponatraemia
- Hypernatraemia
- Patients who cannot perceive thirst
- Pregnancy (see section 4.6)
- Breastfeeding (see section 4.6)

4.4 Special warnings and precautions for use

Urgent need to raise serum sodium acutely
Tolvaptan has not been studied in a setting of urgent need to raise serum sodium acutely. For such patients, alternative treatment should be considered.

Access to water
Tolvaptan may cause adverse reactions related to water loss such as thirst, dry mouth and dehydration (see section 4.8). Therefore, patients should have access to water and be able to drink sufficient amounts of water. If fluid restricted patients are treated with tolvaptan, extra caution should be exercised to ensure that patients do not become overly dehydrated.

Dehydration
Volume status should be monitored in patients taking tolvaptan because treatment with tolvaptan may result in severe dehydration, which constitutes a risk factor for renal dysfunction. If dehydration becomes evident, take appropriate action which may include the need to interrupt or reduce the dose of tolvaptan and increase fluid intake.

Urinary outflow obstruction
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.

Fluid and electrolyte balance
Fluid and electrolyte status should be monitored in all patients and particularly in those with renal and hepatic impairment. Administration of tolvaptan may cause too rapid increases in serum sodium (≥ 12 mmol/l per 24 hours, please see below); therefore, monitoring of serum sodium in all patients should start no later than 4-6 hours after treatment initiation. During the first 1-2 days and until the tolvaptan dose is stabilised serum sodium and volume status should be monitored at least every 6 hours.

Too rapid correction of serum sodium
Patients with very low baseline serum sodium concentrations may be at greater risk for too rapid correction of serum sodium.
Too rapid correction of hyponatraemia (increase ≥ 12 mmol/l/24 hours) can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma or death. Therefore after initiation of treatment, patients should be closely monitored for serum sodium and volume status (see above).
In order to minimise the risk of too rapid correction of hyponatraemia the increase of serum sodium should be less than 10-12 mmol/l/24 hours and less than 18 mmol/l/48 hours. Therefore, more precautionary limits apply during the early treatment phase.
If sodium correction exceeds 6 mmol/l during the first 6 hours of administration or 8 mmol/l during the first 6-12 hours, respectively, the possibility that serum sodium correction may be overly rapid should be considered. These patients should be monitored more frequently regarding their serum sodium and administration of hypotonic fluid is recommended. In case serum sodium increases ≥ 12 mmol/l within 24 hours or ≥ 18 mmol/l within 48 hours, tolvaptan treatment is to be interrupted or discontinued followed by administration of hypotonic fluid.
In patients at higher risk of demyelination syndromes, for example those with hypoxia, alcoholism or malnutrition, the appropriate rate of sodium correction may be lower than that in patients without risk factors; these patients should be very carefully managed.

Patients who received other treatment for hyponatraemia or medicinal products which increase serum sodium concentration (see section 4.5) prior to initiation of treatment with Samsca should be managed very cautiously. These patients may be at higher risk for developing rapid correction of serum sodium during the first 1-2 days of treatment due to potential additive effects.
Co-administration of Samsca with other treatments for hyponatraemia, and medications that increase serum sodium concentration, is not recommended during initial treatment or for other patients with very low baseline serum sodium concentrations (see section 4.5).

Diabetes mellitus
Diabetic patients with an elevated glucose concentration (e.g. in excess of 300 mg/dl) may present with pseudohyponatraemia. This condition should be excluded prior and during treatment with tolvaptan.
Tolvaptan may cause hyperglycaemia (see section 4.8). Therefore, diabetic patients treated with tolvaptan should be managed cautiously. In particular this applies to patients with inadequately controlled type II diabetes.

Hepatotoxicity
Drug induced liver injury has been observed in clinical trials investigating a different potential indication (autosomal dominant polycystic kidney disease) with long-term use of tolvaptan at higher doses than for the approved indication (see section 4.8).
In these clinical trials, clinically significant increases (greater than 3 x Upper Limit of Normal) in serum alanine aminotransferase (ALT), along with clinically significant increases (greater than 2 x Upper Limit of Normal) in serum total bilirubin were observed in 3 patients treated with tolvaptan. In addition, an increased incidence of significant elevations of ALT was observed in patients treated with tolvaptan [4.4% (42/958)] compared to those receiving placebo [1.0% (5/484)]. Elevation (>3xULN) of serum aspartate aminotransferase (AST) was observed in 3.1% (30/958) of patients on tolvaptan and 0.8% (4/484) patients on placebo. Most of the liver enzyme abnormalities were observed during the first 18 months of treatment. The elevations gradually improved after

discontinuation of tolvaptan. These findings may suggest that tolvaptan has the potential to cause irreversible and potentially fatal liver injury.

Liver function tests should be promptly performed in patients taking tolvaptan who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. If liver injury is suspected, tolvaptan should be promptly discontinued, appropriate treatment should be instituted, and investigations should be performed to determine the probable cause. Tolvaptan should not be re-initiated in patients unless the cause for the observed liver injury is definitively established to be unrelated to treatment with tolvaptan.

Anaphylaxis
In post-marketing experience, anaphylaxis (including anaphylactic shock and generalised rash) has been reported very rarely following administration of Samsca. Patients should be carefully monitored during treatment. If an anaphylactic reaction or other serious allergic reactions occur, administration of Samsca should be discontinued immediately and appropriate therapy initiated.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Co-administration with other treatments for hyponatraemia and medicinal products that increase serum sodium concentration
There is no experience from controlled clinical trials with concomitant use of Samsca and other treatments for hyponatraemia such as hypertonic saline, oral sodium formulations, and medicinal products that increase serum sodium concentration. Medicinal products with high sodium content such as effervescent analgesic preparations and certain sodium containing treatments for dyspepsia may also increase serum sodium concentration. Concomitant use of Samsca with other treatments for hyponatraemia or other medicinal products that increase serum sodium concentration may result in a higher risk for developing rapid correction of serum sodium (see section 4.4) and is therefore not recommended during initial treatment or for other patients with very low baseline serum sodium concentrations where rapid correction may represent a risk for osmotic demyelination (see section 4.4).

CYP3A4 inhibitors
Tolvaptan plasma concentrations have been increased by up to 5.4-fold area under time-concentration curve (AUC) after the administration of strong CYP3A4 inhibitors. Caution should be exercised in co-administering CYP3A4 inhibitors (e.g. ketoconazole, macrolide antibiotics, diltiazem) with tolvaptan (see section 4.4).
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CYP3A4 substrates
In healthy subjects, tolvaptan, a CYP3A4 substrate, had no effect on the plasma concentrations of some other CYP3A4 substrates (e.g. warfarin or amiodarone). Tolvaptan increased plasma levels of lovastatin by 1.3 to 1.5-fold. Even though this increase has no clinical relevance, it indicates tolvaptan can potentially increase exposure to CYP3A4 substrates.

Diuretics
While there does not appear to be a synergistic or additive effect of concomitant use of tolvaptan with loop and thiazide diuretics, each class of agent has the potential to lead to severe dehydration, which constitutes a risk factor for renal dysfunction. If dehydration or renal dysfunction becomes evident, take appropriate action which may include the need to interrupt or reduce doses of tolvaptan and/or diuretics, increase fluid intake, evaluate and address other potential causes of renal dysfunction or dehydration.

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 [AUC_{τ}]) when co administered with multiple once daily 60 mg doses of tolvaptan. Patients receiving digoxin should therefore be evaluated for excessive digoxin effects when treated with tolvaptan.

Co-administration with vasopressin analogues
In addition to its renal aquaretic effect, tolvaptan is capable of blocking vascular vasopressin V2 receptors involved in the release of coagulation factors (e.g., von Willebrand factor) from endothelial cells. Therefore, the effect of vasopressin analogues such as desmopressin may be attenuated in patients using such analogues to prevent or control bleeding when co-administered with tolvaptan.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of tolvaptan in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.
Samsca must not be used during pregnancy (see section 4.3).

Women of childbearing potential
Women of childbearing potential should use adequate contraceptive measures during tolvaptan use.

Breastfeeding
It is unknown whether tolvaptan is excreted in human breast milk. Studies in rats have shown excretion of tolvaptan in breast milk.
The potential risk for humans is unknown. Samsca is contraindicated during breastfeeding (see section 4.3).

Fertility
Two fertility studies in rats showed effects on the parental generation (decreased food consumption and body weight gain, salivation), but tolvaptan did not affect reproductive performance in males and there were no effects on the foetuses. In females, abnormal oestrus cycles were seen in both studies. The no observed adverse effect level (NOAEL) for effects on reproduction in females (100 mg/kg/day) was about 16-times the maximum human recommended dose on a mg/m^2 basis.

4.7 Effects on ability to drive and use machines

Samsca has no or negligible influence on the ability to drive or use machines. However, when driving vehicles or using machines it should be taken into account that occasionally dizziness, asthenia or syncope may occur.

4.8 Undesirable effects

Summary of the safety profile
The adverse reaction profile of tolvaptan is based on a clinical trials database of 3294 tolvaptan-treated patients and is consistent with the pharmacology of the active substance. The pharmacodynamically predictable and most commonly reported adverse reactions are thirst, dry mouth and pollakiuria occurring in approximately 18%, 9% and 6% of patients.

Tabulated list of adverse reactions
The frequencies of the adverse reactions correspond with very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	**Frequency**			
	Very common	Common	Uncommon	Not known
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Nervous system disorders			dysgeusia	
Vascular disorders		orthostatic hypotension		
Gastrointestinal disorders	nausea	constipation, dry mouth		
Skin and subcutaneous tissue disorders		ecchymosis, pruritus		
Renal and urinary disorders		pollakiuria, polyuria	renal impairment	
General disorders and administration site conditions	thirst	asthenia, pyrexia		
Investigations		increased blood creatinine		
Surgical and medical procedures		rapid correction of hyponatraemia, sometimes leading to neurological symptoms		

In clinical trials investigating other indications the following undesirable effects have been observed:
Common: alanine aminotransferase increased (see section 4.4), aspartate aminotransferase increased (see section 4.4), hypernatraemia, hypoglycaemia, hyperuricaemia, syncope, dizziness, headache, malaise, diarrhoea, blood urine present.
Uncommon: bilirubin increased (see section 4.4), pruritic rash.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Single doses up to 480 mg and multiple doses up to 300 mg per day for 5 days have been well tolerated in clinical trials in healthy volunteers.

The oral median lethal dose (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.

A profuse and prolonged aquaresis (free water clearance) is anticipated. Adequate fluid intake must be maintained.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diuretics, vasopressin antagonists, ATC code C03XA01

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 tolvaptan 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 tolvaptan 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.

Hyponatraemia
In 2 pivotal, double-blind, placebo-controlled, clinical trials, a total of 424 patients with euvolaemic or hypervolaemic hyponatraemia (serum sodium <135 mEq/l) due to a variety of underlying causes (heart failure [HF], liver cirrhosis, SIADH and others) were treated for 30 days with tolvaptan (n=216) or placebo (n=208) at an initial dose of 15 mg/day. The dose could be increased to 30 and 60 mg/day depending on response using a 3 day titration scheme. The mean serum sodium concentration at trial entry was 129 mEq/l (range 114 - 136).

The primary endpoint for these trials was the average daily AUC for change in serum sodium from baseline to Day 4 and baseline to Day 30. Tolvaptan was superior to placebo ($p<0.0001$) for both periods in both studies. This effect was seen in all patients, the severe (serum sodium: < 130 mEq/l) and mild (serum sodium: 130 - < 135 mEq/l) subsets and for all disease aetiology subsets (e.g. HF, cirrhosis, SIADH/other). At 7 days after discontinuing treatment, sodium values decreased to levels of placebo treated patients.

Following 3 days of treatment, the pooled analysis of the two trials revealed five-fold more tolvaptan than placebo patients achieved normalisation of serum sodium concentrations (49% vs. 11%). This effect continued as on Day 30, when more tolvaptan than placebo patients still had normal concentrations (60% vs. 27%). These responses were seen in patients independent of the underlying disease. The results of self-assessed health status using the SF-12 Health Survey for the mental scores showed statistically significant and clinically relevant improvements for tolvaptan treatment compared to placebo.

Data on the long-term safety and efficacy of tolvaptan were assessed for up to 106 weeks in a clinical trial in patients (any aetiology) who had previously completed one of the pivotal hyponatraemia trials. A total of 111 patients started tolvaptan treatment in an open-label, extension trial, regardless of their previous randomisation. Improvements in serum sodium levels were observed as early as the first day after dosing and continued for on-treatment assessments up to Week 106. When treatment was discontinued, serum sodium concentrations decreased to approximately baseline values, despite the reinstatement of standard care therapy.

Clinical data from trials in other patient populations
EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan) was a long-term outcome, double-blind, controlled clinical trial in patients hospitalised with worsening HF and signs and symptoms of volume overload. In the long-term outcome trial, a total of 2072 patients received 30 mg tolvaptan with standard of care (SC) and 2061 received placebo with SC. The primary objective of the study was to compare the effects of tolvaptan + SC with placebo + SC on the time to all-cause mortality and on the time to first occurrence of cardiovascular (CV) mortality or hospitalisation for HF. Tolvaptan treatment had no statistically significant favourable or unfavourable effects on overall survival or the combined endpoint of CV mortality or HF hospitalisation, and did not provide convincing evidence for clinically relevant benefit.

The European Medicines Agency has deferred the obligation to submit the results of studies with Samsca in one or more subsets of the paediatric population in treatment of dilutional hyponatraemia (see section 4.2 for information on paediatric use).

5.2 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. The terminal elimination half-life is about 8 hours and steady-state concentrations of tolvaptan are obtained after the first dose. Tolvaptan binds reversibly (98%) to plasma proteins.

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%).

Linearity
Tolvaptan has linear pharmacokinetics for doses of 15 to 60 mg.

Pharmacokinetics in special populations
Clearance of tolvaptan is not significantly affected by age.

The effect of mildly or moderately impaired hepatic function (Child-Pugh classes A and B) on the pharmacokinetics of tolvaptan was investigated in 87 patients with liver disease of various origins. No

clinically significant changes have been seen in clearance for doses ranging from 5 to 60 mg. Very limited information is available in patients with severe hepatic impairment (Child-Pugh class C).

In a population pharmacokinetic analysis in patients with hepatic edema, AUC of tolvaptan in severely (Child-Pugh class C) and mildly or moderately (Child-Pugh classes A and B) hepatic impaired patients were 3.1 and 2.3 times higher than that in healthy subjects.

In an analysis on population pharmacokinetics for patients with heart failure, tolvaptan concentrations of patients with mildly (creatinine clearance [C_{cr}] 50 to 80 ml/min) or moderately (C_{cr} 20 to 50 ml/min) impaired renal function were not significantly different to tolvaptan concentrations in patients with normal renal function (C_{cr} 80 to 150 ml/min). The efficacy and safety of tolvaptan in those with a creatinine clearance <10 ml/min has not been evaluated and is therefore unknown.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenic potential.
Teratogenicity was noted in rabbits given 1000 mg/kg/day (15 times the exposure from the recommended human dose on an AUC basis). No teratogenic effects were seen in rabbits at 300 mg/kg/day (about 2.5 to 5.3 times the exposure in humans at the recommended dose, based on AUC).
In a peri- and post-natal study in rats, delayed ossification and reduced pup bodyweight were seen at the high dose of 1000 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Hydroxypropylcellulose
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose
Indigo carmine (E 132) aluminium lake

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

10 x 1 tablets in PVC/aluminium perforated unit dose blister.
30 x 1 tablets in PVC/aluminium perforated unit dose blister.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Europe Ltd
Gallions, Wexham Springs
Framewood Road
Wexham, SL3 6PJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/539/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03/08/2009
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Samsca 30 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 30 mg tolvaptan.

Excipient with known effect:
Each tablet contains approximately 70 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet
Blue, round, shallow-convex, debossed with “OTSUKA” and “30” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Due to the need for a dose titration phase with close monitoring of serum sodium and volume status (see section 4.4), treatment with Samsca should be initiated in hospital.

Posology
Treatment with tolvaptan should be initiated at a dose of 15 mg once daily. The dose may be increased to a maximum of 60 mg once daily as tolerated to achieve the desired level of serum sodium. During titration, patients should be monitored for serum sodium and volume status (see section 4.4). In case of inadequate improvement in serum sodium levels, other treatment options should be considered, either in place of or in addition to tolvaptan. Use of tolvaptan in combination with other options may increase the risk of overly rapid correction of serum sodium (see sections 4.4 and 4.5). For patients with an appropriate increase in serum sodium, the underlying disease and serum sodium levels should be monitored at regular intervals to evaluate further need of tolvaptan treatment. In the setting of hyponatraemia, the treatment duration is determined by the underlying disease and its treatment. Tolvaptan treatment is expected to last until the underlying disease is adequately treated or until such time that hyponatraemia is no longer a clinical issue.
Samsca should not be taken with grapefruit juice (see section 4.5).

Patients with renal impairment
Tolvaptan is contraindicated in anuric patients (see section 4.3).
Tolvaptan has not been studied in patients with severe renal failure. The efficacy and safety in this population is not well established.
Based on the data available, no dose adjustment is required in those with mild to moderate renal impairment.

Patients with hepatic impairment
No information is available in patients with severe hepatic impairment (Child-Pugh class C). In these patients dosing should be managed cautiously and electrolytes and volume status should be monitored (see section 4.4).No dose adjustment is needed in patients with mild or moderate hepatic impairment (Child-Pugh classes A and B).

Elderly population
No dose adjustment is needed in elderly patients.

Paediatric population
The safety and efficacy of tolvaptan in children and adolescents under the age of 18 years have not yet been established. Samsca is not recommended in the paediatric age group.

Method of administration
For oral use.
Administration preferably in the morning, without regard to meals. Tablets should be swallowed without chewing with a glass of water.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Anuria
- Volume depletion
- Hypovolaemic hyponatraemia
- Hypernatraemia
- Patients who cannot perceive thirst
- Pregnancy (see section 4.6)
- Breastfeeding (see section 4.6)

4.4 Special warnings and precautions for use

Urgent need to raise serum sodium acutely
Tolvaptan has not been studied in a setting of urgent need to raise serum sodium acutely. For such patients, alternative treatment should be considered.

Access to water
Tolvaptan may cause adverse reactions related to water loss such as thirst, dry mouth and dehydration (see section 4.8). Therefore, patients should have access to water and be able to drink sufficient amounts of water. If fluid restricted patients are treated with tolvaptan, extra caution should be exercised to ensure that patients do not become overly dehydrated.

Dehydration
Volume status should be monitored in patients taking tolvaptan because treatment with tolvaptan may result in severe dehydration which constitutes a risk factor for renal dysfunction. If dehydration becomes evident, take appropriate action which may include the need to interrupt or reduce the dose of tolvaptan and increase fluid intake.

Urinary outflow obstruction
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.

Fluid and electrolyte balance
Fluid and electrolyte status should be monitored in all patients and particularly in those with renal and hepatic impairment. Administration of tolvaptan may cause too rapid increases in serum sodium (≥ 12 mmol/l per 24 hours, please see below); therefore, monitoring of serum sodium in all patients should start no later than 4-6 hours after treatment initiation. During the first 1-2 days and until the tolvaptan dose is stabilised serum sodium and volume status should be monitored at least every 6 hours.

Too rapid correction of serum sodium
Patients with very low baseline serum sodium concentrations may be at greater risk for too rapid correction of serum sodium.
Too rapid correction of hyponatraemia (increase ≥ 12 mmol/l/24 hours) can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma or death. Therefore after initiation of treatment, patients should be closely monitored for serum sodium and volume status (see above).
In order to minimise the risk of too rapid correction of hyponatraemia the increase of serum sodium should be less than 10-12 mmol/l/24 hours and less than 18 mmol/l/48 hours. Therefore, more precautionary limits apply during the early treatment phase.
If sodium correction exceeds 6 mmol/l during the first 6 hours of administration or 8 mmol/l during the first 6-12 hours, respectively, the possibility that serum sodium correction may be overly rapid should be considered. These patients should be monitored more frequently regarding their serum sodium and administration of hypotonic fluid is recommended. In case serum sodium increases ≥ 12 mmol/l within 24 hours or ≥ 18 mmol/l within 48 hours, tolvaptan treatment is to be interrupted or discontinued followed by administration of hypotonic fluid.
In patients at higher risk of demyelination syndromes, for example those with hypoxia, alcoholism or malnutrition, the appropriate rate of sodium correction may be lower than that in patients without risk factors; these patients should be very carefully managed.

Patients who received other treatment for hyponatraemia or medicinal products which increase serum sodium concentration (see section 4.5) prior to initiation of treatment with Samsca should be managed very cautiously. These patients may be at higher risk for developing rapid correction of serum sodium during the first 1-2 days of treatment due to potential additive effects.
Co-administration of Samsca with other treatments for hyponatraemia, and medications that increase serum sodium concentration, is not recommended during initial treatment or for other patients with very low baseline serum sodium concentrations (see section 4.5).

Diabetes mellitus
Diabetic patients with an elevated glucose concentration (e.g. in excess of 300 mg/dl) may present with pseudohyponatraemia. This condition should be excluded prior and during treatment with tolvaptan.
Tolvaptan may cause hyperglycaemia (see section 4.8). Therefore, diabetic patients treated with tolvaptan should be managed cautiously. In particular this applies to patients with inadequately controlled type II diabetes.

Hepatotoxicity
Drug induced liver injury has been observed in clinical trials investigating a different potential indication (autosomal dominant polycystic kidney disease) with long-term use of tolvaptan at higher doses than for the approved indication (see section 4.8).
In these clinical trials, clinically significant increases (greater than 3 x Upper Limit of Normal) in serum alanine aminotransferase (ALT), along with clinically significant increases (greater than 2 x Upper Limit of Normal) in serum total bilirubin were observed in 3 patients treated with tolvaptan. In addition, an increased incidence of significant elevations of ALT was observed in patients treated with tolvaptan [4.4% (42/958)] compared to those receiving placebo [1.0% (5/484)]. Elevation (>3xULN) of serum aspartate aminotransferase (AST) was observed in 3.1% (30/958) of patients on tolvaptan and 0.8% (4/484) patients on placebo. Most of the liver enzyme abnormalities were observed during the first 18 months of treatment. The elevations gradually improved after

discontinuation of tolvaptan. These findings may suggest that tolvaptan has the potential to cause irreversible and potentially fatal liver injury.

Liver function tests should be promptly performed in patients taking tolvaptan who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. If liver injury is suspected, tolvaptan should be promptly discontinued, appropriate treatment should be instituted, and investigations should be performed to determine the probable cause. Tolvaptan should not be re-initiated in patients unless the cause for the observed liver injury is definitively established to be unrelated to treatment with tolvaptan.

Anaphylaxis
In post-marketing experience, anaphylaxis (including anaphylactic shock and generalised rash) has been reported very rarely following administration of Samsca. Patients should be carefully monitored during treatment. If an anaphylactic reaction or other serious allergic reactions occur, administration of Samsca should be discontinued immediately and appropriate therapy initiated.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Co-administration with other treatments for hyponatraemia and medicinal products that increase serum sodium concentration
There is no experience from controlled clinical trials with concomitant use of Samsca and other treatments for hyponatraemia such as hypertonic saline, oral sodium formulations, and medicinal products that increase serum sodium concentration. Medicinal products with high sodium content such as effervescent analgesic preparations and certain sodium containing treatments for dyspepsia may also increase serum sodium concentration. Concomitant use of Samsca with other treatments for hyponatraemia or other medicinal products that increase serum sodium concentration may result in a higher risk for developing rapid correction of serum sodium (see section 4.4) and is therefore not recommended during initial treatment or for other patients with very low baseline serum sodium concentrations where rapid correction may represent a risk for osmotic demyelination (see section 4.4).

CYP3A4 inhibitors
Tolvaptan plasma concentrations have been increased by up to 5.4-fold area under time-concentration curve (AUC) after the administration of strong CYP3A4 inhibitors. Caution should be exercised in co-administering CYP3A4 inhibitors (e.g. ketoconazole, macrolide antibiotics, diltiazem) with tolvaptan (see section 4.4).
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Women of childbearing potential
Women of childbearing potential should use adequate contraceptive measures during tolvaptan use.

Breastfeeding
It is unknown whether tolvaptan is excreted in human breast milk. Studies in rats have shown excretion of tolvaptan in breast milk.
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Fertility
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Gastrointestinal disorders	nausea	constipation, dry mouth		
Skin and subcutaneous tissue disorders		ecchymosis, pruritus		
Renal and urinary disorders		pollakiuria, polyuria	renal impairment	
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Oral administration of 15 to 120 mg doses of tolvaptan 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.

Hyponatraemia
In 2 pivotal, double-blind, placebo-controlled, clinical trials, a total of 424 patients with euvolaemic or hypervolaemic hyponatraemia (serum sodium <135 mEq/l) due to a variety of underlying causes (heart failure [HF], liver cirrhosis, SIADH and others) were treated for 30 days with tolvaptan (n=216) or placebo (n=208) at an initial dose of 15 mg/day. The dose could be increased to 30 and 60 mg/day depending on response using a 3 day titration scheme. The mean serum sodium concentration at trial entry was 129 mEq/l (range 114 - 136).

The primary endpoint for these trials was the average daily AUC for change in serum sodium from baseline to Day 4 and baseline to Day 30. Tolvaptan was superior to placebo ($p<0.0001$) for both periods in both studies. This effect was seen in all patients, the severe (serum sodium: < 130 mEq/l) and mild (serum sodium: 130 - < 135 mEq/l) subsets and for all disease aetiology subsets (e.g. HF, cirrhosis, SIADH/other). At 7 days after discontinuing treatment, sodium values decreased to levels of placebo treated patients.

Following 3 days of treatment, the pooled analysis of the two trials revealed five-fold more tolvaptan than placebo patients achieved normalisation of serum sodium concentrations (49% vs. 11%). This effect continued as on Day 30, when more tolvaptan than placebo patients still had normal concentrations (60% vs. 27%). These responses were seen in patients independent of the underlying disease. The results of self-assessed health status using the SF-12 Health Survey for the mental scores showed statistically significant and clinically relevant improvements for tolvaptan treatment compared to placebo.

Data on the long-term safety and efficacy of tolvaptan were assessed for up to 106 weeks in a clinical trial in patients (any aetiology) who had previously completed one of the pivotal hyponatraemia trials. A total of 111 patients started tolvaptan treatment in an open-label, extension trial, regardless of their previous randomisation. Improvements in serum sodium levels were observed as early as the first day after dosing and continued for on-treatment assessments up to Week 106. When treatment was discontinued, serum sodium concentrations decreased to approximately baseline values, despite the reinstatement of standard care therapy.

Clinical data from trials in other patient populations
EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan) was a long-term outcome, double-blind, controlled clinical trial in patients hospitalised with worsening HF and signs and symptoms of volume overload. In the long-term outcome trial, a total of 2072 patients received 30 mg tolvaptan with standard of care (SC) and 2061 received placebo with SC. The primary objective of the study was to compare the effects of tolvaptan + SC with placebo + SC on the time to all-cause mortality and on the time to first occurrence of cardiovascular (CV) mortality or hospitalisation for HF. Tolvaptan treatment had no statistically significant favourable or unfavourable effects on overall survival or the combined endpoint of CV mortality or HF hospitalisation, and did not provide convincing evidence for clinically relevant benefit.

The European Medicines Agency has deferred the obligation to submit the results of studies with Samsca in one or more subsets of the paediatric population in treatment of dilutional hyponatraemia (see section 4.2 for information on paediatric use).

5.2 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. The terminal elimination half-life is about 8 hours and steady-state concentrations of tolvaptan are obtained after the first dose. Tolvaptan binds reversibly (98%) to plasma proteins.

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%).

Linearity
Tolvaptan has linear pharmacokinetics for doses of 15 to 60 mg.

Pharmacokinetics in special populations
Clearance of tolvaptan is not significantly affected by age.

The effect of mildly or moderately impaired hepatic function (Child-Pugh classes A and B) on the pharmacokinetics of tolvaptan was investigated in 87 patients with liver disease of various origins. No

clinically significant changes have been seen in clearance for doses ranging from 5 to 60 mg. Very limited information is available in patients with severe hepatic impairment (Child-Pugh class C). In a population pharmacokinetic analysis in patients with hepatic edema, AUC of tolvaptan in severely (Child-Pugh class C) and mildly or moderately (Child-Pugh classes A and B) hepatic impaired patients were 3.1 and 2.3 times higher than that in healthy subjects.

In an analysis on population pharmacokinetics for patients with heart failure, tolvaptan concentrations of patients with mildly (creatinine clearance [C_{cr}] 50 to 80 ml/min) or moderately (C_{cr} 20 to 50 ml/min) impaired renal function were not significantly different to tolvaptan concentrations in patients with normal renal function (C_{cr} 80 to 150 ml/min). The efficacy and safety of tolvaptan in those with a creatinine clearance <10 ml/min has not been evaluated and is therefore unknown.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenic potential.
Teratogenicity was noted in rabbits given 1000 mg/kg/day (15 times the exposure from the recommended human dose on an AUC basis). No teratogenic effects were seen in rabbits at 300 mg/kg/day (about 2.5 to 5.3 times the exposure in humans at the recommended dose, based on AUC).
In a peri- and post-natal study in rats, delayed ossification and reduced pup bodyweight were seen at the high dose of 1000 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Hydroxypropylcellulose
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose
Indigo carmine (E 132) aluminium lake

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

10 x 1 tablets in PVC/aluminium perforated unit dose blister.
30 x 1 tablets in PVC/aluminium perforated unit dose blister.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Europe Ltd
Gallions, Wexham Springs
Framewood Road
Wexham, SL3 6PJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/539/003-004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03/08/2009
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

AndersonBrecon (UK) Ltd.
Wye Valley Business Park
Brecon Road
Hay-on-Wye
Hereford, HR3 5PG
United Kingdom

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Samsca 15 mg tablets
tolvaptan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 15 mg tolvaptan.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 tablets
30 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Europe Ltd.
Gallions, Wexham Springs
Framewood Road
Wexham, SL3 6PJ
UK

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/539/001 10 tablets
EU/1/09/539/002 30 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Samsca 15 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Samsca 15 mg tablets
tolvaptan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Otsuka

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Samsca 30 mg tablets
tolvaptan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 30 mg tolvaptan.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 tablets
30 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Europe Ltd.
Gallions, Wexham Springs
Framewood Road
Wexham, SL3 6PJ
UK

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/539/003 10 tablets
EU/1/09/539/004 30 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Samsca 30 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Samsca 30 mg tablets
tolvaptan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Otsuka

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Samsca 15 mg tablets
Samsca 30 mg tablets
tolvaptan

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

In this leaflet:

1. What Samsca is and what it is used for

Samsca, which contains the active substance tolvaptan, belongs to a group of medicines called vasopressin antagonists. Vasopression is a hormone that helps prevent the loss of water from the body by reducing urine output. Antagonist means that it prevents vasopressin having its effect on water retention. This leads to a reduction in the amount of water in the body by increasing urine production and as a result it increases the level or concentration of sodium in your blood.

Samsca is used to treat low serum sodium levels in adults. You have been prescribed Samsca because you have a lowered sodium level in your blood as a result of a disease called “syndrome of inappropriate antidiuretic hormone secretion” (SIADH) where the kidneys retain too much water. This disease causes an inappropriate production of the hormone vasopressin which has caused the sodium levels in your blood to get too low (hyponatraemia). That can lead to difficulties in concentration and memory, or in keeping your balance.

2. What you need to know before you take Samsca

<u>Do not</u> take Samsca

- if you are allergic to tolvaptan or any of the other ingredients of this medicine (listed in section 6)
- if your kidneys do not work (no urine production)
- if you have a condition which increases the salt in your blood (“hypernatraemia”)
- if you have a condition which is associated with a very low blood volume
- if you do not realise when you are thirsty
- if you are pregnant
- if you are breastfeeding.

Warnings and precautions

Talk to your doctor or pharmacist before taking Samsca:

- if you cannot drink enough water or if you are fluid restricted
- if you have difficulties in urination or have an enlarged prostate
- if you suffer from liver disease
- if you have diabetes.

Drinking enough water
Samsca causes water loss because it increases your urine production. This water loss may result in side effects such as dry mouth and thirst or even more severe side effects like kidney problems (see section 4). It is therefore important that you have access to water and that you are able to drink sufficient amounts when you feel thirsty.

Children and adolescents
Samsca is not suitable for children and adolescents (under age 18).

Other medicines and Samsca

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Products containing ketoconazole (against fungal infections), macrolide antibiotics, or diltiazem (treatment for high blood pressure and chest pain) may increase the effects of Samsca. Samsca may increase the effect of digoxin (used for treatment of irregularities of heart beat and heart failure). Barbiturates (used to treat epilepsy/seizures and some sleep disorders) or rifampicin (against tuberculosis) may decrease the effects of Samsca.

Other products which increase the salt in your blood or which contain large amounts of salt may increase the effects of Samsca. Medicines which also increase your urine production (diuretics) may further increase the risk of water loss related side effects (see “Drinking enough water” above). Therefore, please tell your doctor about all medicines you are receiving or have recently received, including medicines obtained without a prescription.

Samsca may reduce the effect of desmopressin (used to increase blood clotting factors).

It may still be alright for you to take these medicines and Samsca together. Your doctor will be able to decide what is suitable for you.

Samsca with food and drink

- Avoid drinking grapefruit juice when taking Samsca.

Pregnancy and breastfeeding

Pregnant women **must not** take this medicine.
Breastfeeding women **must not** take this medicine.

Women of childbearing potential should use adequate contraceptive measures during use of this medicine.

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

Samsca is unlikely to adversely affect your ability to drive a car or to operate machinery. However, you may occasionally feel dizzy or weak or you may faint for a short period.

Samsca contains lactose.
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Samsca

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

- Treatment with Samsca will be initiated in hospital
- For treatment of your low sodium (hyponatraemia), the dose can be from 15 mg to 60 mg once a day. Your doctor will start with a dose of 15 mg and may then increase it to a maximum of 60 mg to achieve the desired level of serum sodium. To monitor the effects of Samsca your doctor will do regular blood tests.
- Swallow the tablet without chewing, with a glass of water.
- Take the tablets once a day preferably in the morning with or without food.

If you take more Samsca than you should

If you have taken more tablets than your prescribed dose, **drink plenty of water and contact your doctor or your local hospital immediately**. Remember to take the medicine pack with you so that it is clear what you have taken.

If you forget to take Samsca

If you forget to take your medicine you should take the dose as soon as you remember on the same day. If you do not take your tablet on one day, take your normal dose on the next day. **DO NOT** take a double dose to make up for a forgotten dose.

If you stop taking Samsca

If you stop taking Samsca this may lead to reoccurrence of your low sodium. Therefore, you should only stop taking Samsca if you notice side effects requiring urgent medical attention (see section 4) or if your doctor tells you to.

If you have further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you notice any of the following side effects, you may need urgent medical attention. Stop taking Samsca and immediately contact a doctor or go to the nearest hospital if you:

- find it difficult to urinate
- find a swelling of the face, lips or tongue, itching, generalised rash, or severe wheezing or breathlessness (symptoms of an allergic reaction).

Consult your doctor if symptoms of fatigue, loss of appetite, right upper abdominal discomfort, dark urine or jaundice (yellowing of skin or eyes) occur.

Other side effects

Very common (may affect more than 1 in 10 people)
- thirst
- nausea

Common (may affect up to 1 in 10 people)
- raised levels of liver enzymes in the blood
- dry mouth
- excessive drinking of water
- increased need to urinate, or to urinate more frequently
- water loss
- tiredness, general weakness
- decreased appetite
- constipation
- dizziness
- low blood pressure when standing up
- fainting
- patchy bleeding in the skin
- itching
- fever
- high levels of sodium, potassium, creatinine, uric acid and blood sugar
- rapid rise in level of sodium
- decrease in level of blood sugar
- headache
- general feeling of being unwell
- diarrhoea
- blood in urine

Uncommon (may affect up to 1 in 100 people)
- increase of bilirubin in the blood
- kidney problems
- sense of taste altered
- itchy rash

Not known
Other side effects have occurred in a very small number of people but their exact frequency is unknown.
- allergic reactions (see above)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Samsca

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the blister after EXP. The expiry date refers to the last day of that month.

Store in the original package in order to protect from light and moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Samsca contains

The active substance is tolvaptan.
Each Samsca 15 mg tablet contains 15 mg tolvaptan.
Each Samsca 30 mg tablet contains 30 mg tolvaptan.

The other ingredients are lactose monohydrate, maize starch, microcrystalline cellulose, hydroxypropylcellulose, magnesium stearate, indigo carmine (E 132) aluminium lake.

What Samsca looks like and contents of the pack

Samsca 15 mg is a blue, triangular, convex tablet, with “OTSUKA” and “15” on one side.
Samsca 30 mg is a blue, round, convex tablet, with “OTSUKA” and “30” on one side.

Your medicine is supplied in perforated unit dose blisters of 10 x 1 tablets. One pack with 10 Samsca tablets contains one blister of 10 tablets and one pack with 30 Samsca tablets contains three blisters of 10 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Otsuka Pharmaceutical Europe Ltd
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Framewood Road
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United Kingdom

Manufacturer

AndersonBrecon (UK) Ltd.
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United Kingdom

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This leaflet was last revised in {MM/YYYY}**.**

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Otsuka Pharmaceutical Development & Commercialization, Inc.
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