26 February 2015
EMA/154879/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Jinarc

International non-proprietary name: tolvaptan

Procedure No. EMEA/H/C/002788/0000

Note

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

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List of abbreviations

ADPKD	Autosomal dominant polycystic kidney disease
ARPKD	Autosomal recessive polycystic kidney disease
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under the curve
AVP	Arginine vasopressin
b.d	Twice daily
BMI	Body mass index
BP	Blood pressure
cAMP	Cyclic adenosine monophosphate
CI	Confidence interval
CKD	Chronic kidney disease
CL/F	Oral clearance
Cmax	Maximum plasma concentration
COMP	Committee for orphan medicinal products
CrCL	Creatinine clearance
CRISP	Consortium for Radiologic Imaging Studies in Polycystic Kidney Disease
CT	Computed tomography
CV	Coefficient of variability
CYP3A/3A4	Cytochrome P450 3A enzyme
ECG	Electrocardiogram
EOT	End of treatment
eCrCLCG	Creatinine clearance estimated by Cockcroft-Gault equation
eGFR	Estimated glomerular filtration rate
eGFR-EPI	Estimated glomerular filtration rate, using the Kidney Disease Epidemiology Collaboration formula
eGFR-MDRD	Estimated glomerular filtration rate, using the Modification Of Diet In Renal Disease formula
ESRD	End stage renal failure
ET	Early termination
F	Bioavailability
FDA	Food And Drug Administration (USA)
GFR	Glomerular filtration rate
GI	Gastrointestinal
GMP	Good manufacturing practice
HR	Hazard ratio
HTN	Hypertension
htTKV	Height-corrected total kidney volume
ICH	International Committee For Harmonisation
IMP	Investigational medicinal product
IOP	Intraocular pressure
ITT	Intention to treat
KDIGO	Kidney Disease Improving Global Outcomes group
Ki	Inhibition constant
LOCF	Last observation carried forward
MAA	Marketing authorisation application
MCP-1	Monocyte chemotactic protein-1
mGFR	Measured glomerular filtration rate
MHRD	Maximum human recommended dose
MMRM	Mixed-effect model repeated measure

mOsm/kg	Milliosmole per kilogram
MRI	Magnetic resonance imaging
n	Number
ND	Not determined
PASS	Post authorisation safety study
PD	Pharmacodynamic
P-gp	P-glycoprotein
PK	Pharmacokinetic
PKD	Polycystic kidney disease
PKD1, PKD2	Polycystin 1, 2
q.d	Once daily
QT	QT interval
QTc	Corrected QT interval
Rac	Accumulation ratio
RHD	Recommended human dose
RMP	Risk management plan
RPF	Renal plasma flow
SAP	Statistical analysis plan
SD	Standard deviation
SMQ	Standardised medical query
SmPC	Summary of product characteristics
ss	Steady state
t1/2	Half-life
TEAE	Treatment emergent adverse event
TKV	Total kidney volume
Tmax	Time of maximum concentration
ULN	Upper limit of normal
UTI	Urinary tract infection
V1a, V1b, V2	Vasopressin receptor subtypes

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Otsuka Pharmaceutical Europe Ltd submitted on 29 November 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Jinarc, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004 .
The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 December 2013.

Jinarc was designated as an orphan medicinal product EU/3/13/1175 on 5 August 2013. Jinarc was designated as an orphan medicinal product in the following indication: Treatment of autosomal dominant polycystic kidney disease.

Following the CHMP positive opinion and at the time of the review of the orphan designation by the Committee on Orphan Medicinal Products (COMP), this product was withdrawn from the Community Register of designated orphan medicinal products on 26.03.2015 on request of the sponsor.

The applicant applied for the following indication:

Jinarc is indicated to slow the progression of kidney disease in patients with autosomal dominant polycystic kidney disease (ADPKD).
Jinarc is indicated in adults.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that tolvaptan was considered to be a known active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

This application is submitted as a multiple of Samsca authorised on 03 August 2009 in accordance with Article 82.1 of Regulation (EC) No 726/2004.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0221/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request for consideration

Additional Data/Market exclusivity

The applicant requested consideration of one year data/market exclusivity in regards of its application for a new indication in accordance with Article 14(11) of Regulation (EC) 726/2004.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 18 November 2005. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status

A Marketing Authorisation has been granted in the EU for Samca (tolvaptan) on 03 August 2009 for the treatment of adult patients with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion.

A new application for tolvaptan in the treatment of ADPKD was filed in the following countries: United States of America, Japan.

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

1.2. Manufacturers

Manufacturers responsible for batch release

AndersonBrecon (UK) Limited
Units 2-7, Wye Valley Business Park,
Brecon Road
Hay-on-Wye, Hereford, Herefordshire
HR3 5PG
United Kingdom

Almac Pharma Services Ltd
Almac House,
20 Seagoe Industrial State
Craigavon
BT63 5QD
United Kingdom

1.3. Steps taken for the assessment of the product

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

Rapporteur: Greg Markey

Co-Rapporteur: Daniela Melchiorri

PRAC Rapporteur: Julie Williams

PRAC Co-Rapporteur: Carmela Macchiarulo

- The application was received by the EMA on 29 November 2013.
- The procedure started on 26 December 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 March 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 16 March 2014.
- The PRAC RMP Advice and assessment overview was adopted by PRAC on 10 April 2014 .
- During the meeting on 25 April 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 28 April 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18

September 2014.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 27 October 2014.
- The PRAC RMP Advice and assessment overview was adopted by PRAC on 6 November 2014.
- During the CHMP meeting on 20 November 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 23 January 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 2 February 2015.
- The PRAC RMP Advice and assessment overview was adopted by PRAC on 12 February 2015.
- During the meeting on 26 February 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Jinarc.
- The CHMP adopted a report on the novelty of the indication/significant clinical benefit for Jinarc in comparison with existing therapies.

2. Scientific discussion

2.1. Introduction

Problem statement

Disease background

Autosomal dominant polycystic kidney disease (ADPKD, previously known as adult polycystic kidney disease) is a hereditary disorder characterized by cyst formation and enlargement in the kidney and other organs. ADPKD is the most common genetic condition to affect the kidneys.

Autosomal dominant polycystic kidney disease demonstrates considerable phenotypic variability. The number, distribution, and growth rate of cysts determine the timing and severity of related clinical outcomes. Some patients experience renal failure soon after the condition is diagnosed, others have a mild disease course throughout life. Clinical features, commonly pain in the abdomen, flank or back, usually begin in the third to fourth decade of life, but cysts may be detectable much earlier in life as an incidental finding or during screening of affected families. Other symptoms include urinary tract infections, haematuria, and pain. ADPKD is characterised by progressive hypertension and renal impairment. Up to 50% of patients with ADPKD require renal replacement therapy by 60 years of age, and around 10% of end-stage renal disease (ESRD) patients treated with haemodialysis in Europe were initially diagnosed and treated for ADPKD.

ADKPD has been granted orphan medicinal product status pursuant to Regulation (EC) No 141/2000 for the treatment of autosomal dominant polycystic kidney disease.

ADPKD results from loss-of-function mutations in either of 2 genes (PKD1 and PKD2) encoding respectively transmembrane polycystin proteins PC1 (polycystin 1) and PC2 (polycystin 2). These gene defects disrupt the normal differentiated phenotype of the renal tubular epithelium. The mutations lead to increases in intracellular adenosine cyclic 3', 5'-monophosphate (cAMP) resulting in increased cellular proliferation and cyst formation. Cyst growth displaces and destroys normal kidney tissue, leading to decreased number and function of nephrons. The cyst initially fills with fluid from the glomerular filtrate, but even if the cyst becomes isolated from the tubular system it continues to grow as the epithelial wall proliferates and there is transepithelial secretion of water into the lumen.

ADPKD shows a focal expression, which is thought to be due to random mutations of the protective normal allele.

The commonest genotype is ADPKD type 1, accounting for around 90% of patients, followed by ADPKD type 2. Respectively these affect relate to genes coding PKD1 and PKD2. These variants appear to differ primarily in the number of visible renal cysts formed at any given age. The mean time to ESRD for patients with ADPKD1 is 53 years, whilst the mean age for patients with ADPKD2 is 74 years. As ADPKD is inherited in an autosomal dominant manner, each child of an affected individual has a 50% chance of inheriting the mutation. About 95% of individuals with ADPKD have an affected parent and about 5% have a *de novo* mutation. Homozygous mutations in either PKD1 or PKD2 are not seen, as these are thought to be incompatible with live birth, except for rare cases where there is incomplete penetrance.

Current treatment of ADPKD

There is a clear unmet need for an effective therapy in APKD. No medication is specifically licensed to slow the progression of kidney disease in these patients. Current drug therapy is focused on the treatment of symptoms and complications, such as hypertension, pain and infection. As renal function progressively worsens, patients who progress to end-stage renal disease will require dialysis or renal transplantation if clinically appropriate. Other treatments include cyst decompression with cyst aspiration and sclerosis, laparoscopic or surgical cyst fenestration, and renal denervation. In cases of portal hypertension due to polycystic liver or hepatomegaly with unresectable areas, liver transplantation may be necessary.

Other research

A number of other vasopressin antagonists are in development. Additional specific renoprotective approaches studied include somatostatin analogues, statins, ACE inhibitors and angiotensin receptor blockers.

About the product

AVP (arginine vasopressin) is a neuropeptide hormone, synthesized in the brain by the hypothalamus and released into the bloodstream by the posterior pituitary gland. Secretion of this hormone is regulated by baroreceptors and osmoreceptors, and is affected by other medications, central nervous system disorders, infections, cardiopulmonary diseases, and endocrinopathies. Three receptor subtypes for AVP have been identified in man: V1a, V1b and V2.

AVP is actively involved in the regulation of water and solute excretion by the kidney, as well as blood pressure control. A decrease in blood pressure or increase in plasma osmolality leads to a marked increase in blood AVP concentrations, causing vasoconstriction (via V1a receptors) and water reabsorption in the kidneys (via V2 receptors). This potent effect on water reabsorption is reflected in the alternative name for AVP of “antidiuretic hormone” (ADH). When the hormone is completely absent or unable to activate the antidiuretic receptors, diuresis and water needs are enhanced about tenfold.

Tolvaptan (previous company internal name OPC-41061) is a non-peptide vasopressin antagonist that specifically blocks the binding of AVP at the V2 receptors of the distal nephron. Tolvaptan affinity for the human V2-receptor is 1.8 times that of native AVP. Tolvaptan has a single chiral centre and can exist as two enantiomers, which are equipotent at the V2 receptor (see figure 1).

Mechanism of action in ADPKD

Tolvaptan specifically blocks the binding of pituitary arginine vasopressin (AVP) at the V2 receptors of the distal nephron. Tolvaptan affinity for the human V2-receptor is 1.8 times that of native AVP.

It is thought to act selectively on the cells from which ADPKD cysts arise. Stimulation of the V2 receptor in the distal nephron elevates intracellular cAMP levels, which is linked to reduced cell proliferation and a decrease of fluid excretion into cysts.

Successful treatment of disease progression in ADPKD is presumed to require early, chronic and constant inhibition of the V2 receptor, as this was required to produce decreased rates of kidney growth in animal models.

Claimed therapeutic indication

The initially proposed indication for Jinarc was as follows:

Jinarc is indicated to slow the progression of kidney disease in patients with autosomal dominant polycystic kidney disease (ADPKD). Jinarc is indicated in adults.

Approved therapeutic indication

Jinarc is indicated to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease (see Section 5.1).

Proposed posology

The proposed dose is to be titrated and given twice daily in unequal doses – referred to by the applicant as “split dosing”.

The proposed initial dosage for Jinarc is 60 mg tolvaptan per day as a split-dose regimen - 45 mg taken upon waking and 15 mg taken 8 hours later. This initial dose is proposed to be titrated upward to a split-dose regimen of 60 mg + 30 mg, and then to a target regimen of 90 mg + 30 mg, if tolerated, with at least weekly intervals between titrations. Accordingly, these correspond to total daily tolvaptan doses of 60, 90, or 120 mg.

Type of Application and aspects on development

This is an application in accordance with article 8 (3) of Directive 2001/83/EC as amended, for approval of Jinarc through the centralised procedure.

The designated orphan indication is “Treatment of autosomal dominant polycystic kidney disease”. An application for accelerated approval pursuant to Article 14 (9) of Regulation (EC) No 726/2004 was submitted previously, but not granted due to the complexity of the dossier requiring detailed evaluation.

No other medication is licensed in the EU to slow the progression of kidney disease in ADPKD. An indication in ADPKD was approved in Japan in March 2014

Tolvaptan tablets 15 and 30 mg have a separate MA (Samsca, EU/1/09/539/001-004, licenced on 03 August 2009 for the treatment of adult patients with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion. The maximum daily dose in this indication is 60 mg per day. Clinical pharmacology trials relevant for the Jinarc MAA include single dose (15-480 mg) and multiple dose (up to 30 mg daily) healthy volunteer studies, drug interaction studies and a QT study. Tolvaptan has been investigated clinically in Japan since 1994, in Europe and the US since 1996. Whilst the target population, dose and treatment duration for the ADPKD indication are different, the Samsca programme and subsequent post-marketing data offer some supporting safety information. Tolvaptan has also been studied in heart failure patients; however this indication was not accepted by CHMP in 2009. The safety dataset for the Samsca MAA consisted of 3294 subjects treated with any dose of tolvaptan, and 817 subjects treated with tolvaptan in placebo-controlled trials for 1 year or more.

Scientific Advice

Advice was sought from CHMP on 18/11/5 (EMEA/386179/2005). Key questions included the need for data in varying degrees of renal impairment, dose selection for the pivotal trial, the choice of primary efficacy endpoint, the acceptability of 1 pivotal trial, and the supportive value of safety data from other study programmes. In general the advice has been followed for the development program.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as tablets containing 15 mg or 30 mg or 45 mg or 60mg or 90 mg of tolvaptan as active substance.

Other ingredients are: lactose (as monohydrate), maize starch, hydroxypropylcellulose, magnesium stearate,microcrystalline cellulose, Indigo carmine (E 132) aluminium lake.

The product is available in PVC/aluminium foil blister.

2.2.2. Active Substance

General information

The chemical name of tolvaptan is (±)-4'-[(7-chloro-2,3,4,5-tetrahydro-5-hydroxy-1*H*-1-benzazepin-1-yl) carbonyl]-*o*-tolu-*m*-toluidide and it has the following structure:

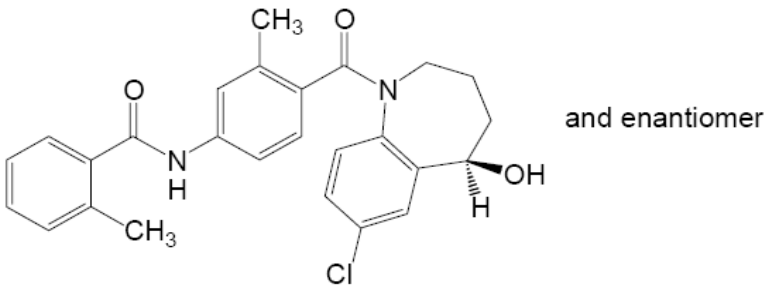


Figure 1: Structure of tolvaptan

The structure of tolvaptan was elucidated by means of elemental analysis, UV absorption spectroscopy, IR spectroscopy, ^{1}H NMR spectroscopy, ^{13}C NMR spectroscopy and mass spectrometry.

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

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

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

Manufacture, characterisation and process controls

Tolvaptan is synthesized in 3 main steps using well defined starting materials with acceptable specifications.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Specification

The active substance specification includes tests for: description, identity (IR, UV and HPLC), melting point, heavy metals (USP), related substances (HPLC), residual solvents (GC), loss on drying (USP), residue on ignition (Ph. Eur.), assay (HPLC), specific optical rotation (Ph. Eur.), microbial limit (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis data (including 11 production size batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on 3 commercial-scale batches of active substance from one of the proposed manufacturing sites stored in the intended commercial package for 60 months under long term conditions at 30ºC / 65% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

The following parameters were tested*:* description, identification (IR and HPLC), melting point, impurities (HPLC), assay (HPLC) and loss on drying. The analytical methods used were the same as for release and were stability indicating.

Photostability testing following the ICH guideline Q1B was performed on one batch. Results on stress conditions: 60 ºC in closed amber glass bottle and 25ºC / 90% RH in open dish during 3 months were also provided on one batch.

The result of photostability study indicates that the active substance is stable to light. The data from the open dish studies and elevated temperature study (60 ºC) demonstrate the stability of the drug substance to heat and humidity.

The stability results indicate that the drug substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Tolvaptan tablets have been developed as immediate-release uncoated tablets of 15 mg, 30 mg, 45 mg, 60 mg and 90 mg strengths. The immediate release formulation of tolvaptan 15 mg and 30 mg tablets is the same approved in 2009 in MAA as Samsca (EMA/H/C/980) for the treatment of hyponatremia. The 15 mg and 30 mg strengths are dose proportional with regard to the active

substance and excipients. The 45 mg and 90 mg strengths of tablets were designed to be quantitatively proportional with the 60-mg tablets.

Given that tolvaptan is practically insoluble in water and shows no pH dependence of solubility, studies were focused on dissolution enhancement.

All excipients are well-known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

A number of formulations were used during development and a series of bioavailability studies have been presented to summarise the clinical/formulation development and to compare the bioequivalence (BE) of those formulations used in Phase I/II/III studies. With the exception of the colourant, the 30 mg tablet used in phase II & III studies is the same as the commercial formulation. The 15 mg tablet is dose proportional to the 30 mg tablet and *in vitro* dissolution data are comparable. The 60 mg tablet was demonstrated to be bioequivalent to the 15 mg and 30 mg tablet strengths and in addition, bioequivalence was confirmed between 30 mg and 90 mg tablets. Since the 45 mg and 90 mg tablets are quantitatively proportional, and comparison of dissolution profiles demonstrated the dissolution equivalency of 45 mg and 90 mg tablets, a bio-waiver can be applied for 45 mg strength.

Information on the development of the dissolution method and selection of the dissolution media was provided. The discriminatory power of the dissolution method has been demonstrated.

The capability of conversion to crystalline form from amorphous tolvaptan is a critical point of pharmaceutical development and pharmaceutical process because a solid state transition can significantly affect dissolution and bioavailability; this is controlled during manufacture by X-ray diffraction. The *in vitro* dissolution method included in the specification is used as a quality control and also as an indirect method of evaluating any crystallisation of the active substance. The data provided suggest that no amorphous crystalline conversion occurs during manufacture or storage.

During development two wet-granulation methods (fluid bed granulation and high-shear granulation) and a semi direct compression method were compared. The effect of high humidity and temperature on the stability of amorphous form in tablets was evaluated. No significant differences were observed in dissolution profiles of the tablets manufactured by each method, demonstrating that the exposure of tolvaptan powder to high humidity and high temperature has little impact on the stability of the tolvaptan powder. Fluid bed granulation was identified to be suitable for the granulation. Apart from the change from fine granules (sachet formulation) to tablet dosage there have been no significant changes to the manufacturing process except for the increase of batch scale. The same granules and the same manufacturing process for 15 mg and 30 mg tablets are used. The same granules for 60 mg tablets are used for 45 and 90 mg tablets. Manufacturing processes for the 45 and 90 mg tablets are the same as those for 60 mg tablets except for tableting step where the appropriate tooling for each tablet strength is used.

The primary packaging is PVC/aluminium foil blister. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of two main steps: preparation of tolvaptan powder, and subsequent granulation and tablets compression. The manufacturing process does not involve novel processes but several steps are considered as critical to ensure the solubility and hence, the bioavailability of the active substance: granulation/drying, lubrication/final blending and compression. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated on minimum three pilot scale batches of each strength. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

The manufacturing process of the 45, 60 and 90 mg tablets will be validated at the proposed commercial production scale according to an appropriate validation scheme provided prior to product launch.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description, identification (HPLC), impurities/degradation products (HPLC), uniformity of dosage units (HPLC), dissolution, assay HPLC and microbial limits (Ph.Eur.).

In-house analytical methods have been developed and are described in detail; all methods have been fully validated.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Batch analysis results are provided for three pilot scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of three batches of finished product for each strength that are at least pilot scale batches stored under long term conditions for up to 48 months (15, 30 and 60 mg)/24 month (45, 90 mg) at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested according to release specifications. The primary stability protocols also include tests for friability, disintegration, water content, hardness, and microbial limit.

In addition, one batch of each strength as well as loose tablets were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results indicate that increases in one oxidative degradation product were observed for the 15mg, 30mg 60mg tablets stored in open petri dish. No similar increase was observed for the 45mg and 90mg tablets however for 90-mg strength, a slight change of appearance from blue to greenish blue was observed under open dish study. Photostability results also demonstrate that the product packaged in the PVC/aluminium foil blister is not light sensitive.

Additional stress stability studies were performed. The data from the elevated temperature study (50°C) demonstrate the stability of tablets to heat. In the data from the open dish studies at high humidity, moisture increase and decrease in hardness were observed. For tablet stored in PVC/aluminium blisters a slight increase in moisture content is observed but all other parameters remained unaffected. The data from the cycling studies (-15 °C to +40 °C /75% RH / one cycle) indicate that the product is not affected by temperature excursions.

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

Additionally, stability study was conducted on tolvaptan powder intermediate and on bulk tablet. The data support the proposed holding times.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

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

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

None

2.3. Non-clinical aspects

2.3.1. Introduction

Tolvaptan (also referred to as OPC-41061 or OPC-156), a V2-receptor (V2R) antagonist, was approved in Europe for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (MA EU/1/09/539/001-004). For the current MAA, Otsuka is seeking approval for tolvaptan for the treatment of autosomal dominant polycystic kidney disease (ADPKD). The non-clinical testing for tolvaptan is supported in part on the non-clinical results from previous non-clinical studies conducted to support the approved indication for clinically significant hypervolemic and euvolemic hyponatremia.

Arginine vasopressin (AVP) is a neuropeptide hormone synthesised in the hypothalamus and the axons extend into the posterior pituitary where the hormone is released into the blood stream. Central nervous system (CNS) disorders, infections, cardiopulmonary diseases, endocrinopathies and other disease conditions may affect the secretion of AVP.

Increases in plasma osmolality or a decrease in blood pressure can also lead to a marked increase in blood AVP concentrations. AVP can cause vasoconstriction via V1a-receptors and promote water reabsorption in the kidneys via V2R, both of which are G-protein-coupled transmembrane receptors. The V2R are primarily responsible for the antidiuretic effect of AVP.

PKD is an inherited renal disease that exhibits profound morphological disorganisation that is exemplified by abnormal cellular proliferation and apoptosis of immature epithelial cells, accumulation of fluid within the cysts, abnormal cell/cell-matrix interactions and cilia function.[1,2] In the human population, the most clinically significant type of PKD is inherited as an autosomal dominant trait (ADPKD). Approximately 85% of ADPKD is caused by a mutation in the PKD1 gene and 15% by mutation in the PKD2 gene. Although less common but still clinically significant is autosomal

recessive PKD (ARPKD). ARPKD is associated with a mutation in the polycystic kidney and hepatic disease-1 (PKHD1) gene.[3,4] Cystic enlargement is mediated by increased and persistent epithelial cell proliferation due to the mitogenic action associated with cyclic adenosine monophosphate (cAMP) as well as active secretion of fluid into the lumen mediated by apically located cystic fibrosis transmembrane conductance regulator (CFTR) chloride channels.[5] Inhibition of V2R reduces renal cAMP levels that lead to an inhibition of cyst formation and kidney enlargement.[6,7] In several studies, vasopressin V2R antagonists have demonstrated efficacy in PKD by decreasing intracellular levels of cAMP which reportedly plays a major role in cyst formation by promoting transepithelial fluid secretion and stimulating cyst-derived cell proliferation.[6,8,9]

2.3.2. Pharmacology

Primary pharmacodynamic studies

Primary Pharmacodynamics

Test Article: Tolvaptan

Organ Systems Evaluated	Species/ Strain	Method of Admin.	Doses (mg/kg) or	Gender/ No. per Group	Noteworthy Findings	GLP Compliance	Report No.
Effect of OPC-41061 on AVP- induced cell proliferation	ADPKD cells NHK cells	In vitro	0.001 - 100 nM	Cells obtained from 8 ADPKD patients and 2 patients with normal human kidneys (NHK)	ADPKD cells: OPC-41061 inhibited AVP-induced cell proliferation (IC_{50} ~ 0.01-0.1 nM), cAMP accumulation (IC_{50} ~ 0.1-1 nM), P-ERK expression (IC_{50} ~ 0.01-0.1 nM). No effect on calcium levels was observed. NHK cells: OPC-41061 inhibited AVP-induced cAMP accumulation (IC_{50} ~ 0.1-1 nM). No other effects in NHK cells observed.	No	019680
Effects of OPC-41061in WS25/-Pkd2 mice	Mice/ $Pkd2^{WS25/-}$	Oral (diet)	0, 0.01, 0.03 and 0.1% in diet	M and F/ 9 to 12/ group/ gender	Administration of OPC-41061 to mice between 4 and 16 weeks of age (12 weeks of administration) exerted a protective effect on the development of PKD, as reflected by significantly lower kidney weights, fibrosis volumes, mitotic and apoptotic indices, and plasma BUN concentrations.	No	017968
Effect of OPC-41061 in pcy mice	Mice/ pcy Mice/ CD1 (Normal Controls)	Oral (diet)	0, 0.01, 0.03 and 0.1% in diet	M and F/ 10/ group/ gender	No effects observed in CD1 mice. In pcy mice treated for either 15 weeks (15 weeks of age at initiation) or 26 weeks (4 weeks of age at initiation), OPC-41061 inhibited renal cyst enlargement (PKD disease progression), reducing apoptosis and improved renal function.	No	018373
Effects of OPC-41061 in pcy mice	Mice/pcy	Oral (diet)	0, 0.01, 0.03, 0.1 and 0.3% in diet	M/ 14/ group	Mice were treated for 10 weeks (5 weeks of age at initiation). A dose-related decrease in kidney weight (% body weight) was observed with a maximum effect seen at 0.1%. A decreasing trend	No	028257

Primary Pharmacodynamics

Test Article: Tolvaptan

Organ Systems Evaluated	Species/ Strain	Method of Admin.	Doses (mg/kg) or Concentration	Gender/ No. per Group	Noteworthy Findings	GLP Compliance	Report No.

	Mice/ DBA/2 (Normal Controls)			Normal Control M/5	observed for kidney cyst volume, kidney fibrosis volume and mitotic index with a significant reduction observed at 0.1 or 0.3%. A dose-related aquaretic effect was observed with a maximum effect seen at 0.1%. A significant dose-related decrease in urinary NGAL was observed. Significantly decreased kidney cAMP content was observed compared to pcy controls. Because of the decreased in kidney cAMP, kidney ERK activity and kidney aquaporin-2 mRNA level were significantly decreased. A dose-related increase in serum concentrations of tolvaptan was observed.		
Serum concentrations of OPC-41061 in pcy mice	Mice/pcy	Oral (diet)	0.01 and 0.1% in diet	M and F 12/ group (3/sex/time point)	Mice were treated for 2 weeks (7 weeks of age at initiation). Serum levels of OPC-41061 were determined at 7 days and three times (morning, evening, midnight) on Day 14. OPC-41061 serum concentrations increased with dietary concentration. The highest concentrations were observed on Day 14 at the midnight blood sample collection with comparable levels observed at the morning collection. At 0.01% in male and female pcy mice at 14 days (morning collection) were 16.5 and 10.0 ng/mL, respectively. At 0.1% in male and female pcy mice 14 days (morning collection) were 177.9 and 169.8 ng/mL, respectively. There was no clear difference between male and female mice.	No	028160
Effects of OPC-41061 in pcy mice	Mice/pcy Mice/	Oral (diet)	0 and 0.1% in diet	M/ 15/ group Normal	Mice were treated for 24 weeks (5 weeks of age at initiation). Survival was lower in the pcy controls (~40%) compared to normal controls (~90%) and OPC-41061-treated mice (~80%). In control pcy mice, left kidney volume progressively increased	No	028192

Primary Pharmacodynamics

Test Article: Tolvaptan

Organ Systems Evaluated	Species/ Strain	Method of Admin.	Doses (mg/kg) or Concentration	Gender/ No. per Group	Noteworthy Findings	GLP Compliance	Report No.
	DBA/2Jcl (Normal Controls)			Control M/9	from 4weeks of age to 20 weeks of age, subsequently, left kidney volume was maintained constant to the end of study (29weeks of age); by the end of the study (20 weeks of age) the maximal left kidney volume was 702 mm^3 in OPC-41061- treated pcy mice compared to 354 mm^3 in normal controls and 1113 mm^3 in pcy control mice. Increased urine volume and decreased urine osmolality were observed during the study in the OPC-41061-treated mice. OPC-41061 significantly decreased urine albumin excretion compared to pcy controls. BUN tended to increase in pcy control and OPC-41061-treated mice during the study, compared to normal mice. Urinary AVP levels in pcy control mice and OPC-41061-treated mice were generally similar throughout the study, and the levels were higher than normal control mice. Plasma electrolytes and osmolality were similar for pcy control mice and OPC-41061-treated mice.		
Effects of OPC-41061 in PCK rats	Rat/ PCK	Oral (diet)	0, 0.01, 0.03 and 0.1% of diet	M and F 10/group/ gender	OPC-41061 lowered renal cAMP and exerted a protective effect on the development of PKD as reflected by significantly lower kidney weights, cyst and fibrosis volumes, and mitotic and apoptotic indices.	No	016916
Effects of OPC-41061 in PCK rats	Rat/ PCK Rat/Sprague Dawley (Controls)	Oral (gavage)	PCK rat: 10 mg/kg once daily and 10 mg/kg twice daily for 8 weeks	Male/10	OPC-41061 was administered at a dose of 10 mg/kg once daily (QD) or twice daily (BID) by gavage. Suppressive effects of OPC-41061 against the progression of PKD were not observed when OPC-41061 was administered orally at 10 mg/kg QD or BID in male PCK rats.	No	017738

ADPKD - autosomal dominant polycystic kidney disease; AVP - vasopressin; BUN - blood urea nitrogen; cAMP - 3’,5’-cyclic adenosine monophosphate; Cl - chloride; PKD - polycystic kidney disease; ERK - extracellular signal-regulated kinase; Na - sodium; NGAL - neutrophil gelatinase-associated lipocalin;

NHK - normal human kidney; OPC-41061 - tolvaptan; P-ERK - phosphorylated extracellular signal-regulated kinase; SD - Sprague Dawley.

In the PCK rat, an animal model of ARPKD, oral administration of tolvaptan resulted in a decrease in kidney levels of cAMP and a reduction in cyst volume and cyst fibrosis. Increases in urine volume and water intake and decreased urinary osmolality also were evident and are consistent with the established pharmacological action of tolvaptan. Slight changes in BUN, creatinine, and sodium levels were observed in the treated rats, although the changes were not considered to be biologically meaningful.

In the mouse models for ADPKD (Pkd2WS25/-, pcy and cpk) similar results are observed as with the PCK rat. Decreases in kidney weights, cyst volume, and fibrotic volume were observed in the pcy mouse and the Pkd2WS25/- mouse treated with tolvaptan via the diet. With prolonged treatment of the pcy mouse with tolvaptan for 26 weeks, decreases in BUN were observed in both males and females. Decreases in BUN were also observed in Pkd2WS25/- mice treated with tolvaptan for 12 weeks. Similarly, prolonged treatment of pcy mice with tolvaptan for 25 weeks resulted in a significant decline in kidney volume compared to untreated control pcy mice. In male pcy mice, tolvaptan at 0.01% to 0.3% in the diet resulted in a dose dependent decreased kidney weight, cyst volume, fibrotic volume and mitotic index. Tolvaptan also showed a dose-dependent aquaretic action at the same dose range. Maximum renal-protective effect and aquaretic effect were observed at 0.1%. Furthermore, consistent with the reduced kidney volume, a dose-related reduction in kidney cAMP content and ERK activity were observed in pcy mice compared to controls. Serum levels of tolvaptan were determined in the pcy mice treated via the diet for 2 weeks. Serum levels of tolvaptan increased with dietary concentration, and the levels tended to be higher at midnight. These data demonstrate exposure to tolvaptan in the pcy mouse at pharmacologically active doses.

In vitro studies examined cell proliferation in normal human kidney cells (NHK) and cells obtained from ADPKD patients. The addition of AVP to NHK cultures resulted in an inhibition of cell proliferation. Addition of AVP to ADPKD cultures resulted in increased proliferation with a corresponding increase in cAMP. This series of in vitro experiments show that tolvaptan inhibits the cellular proliferation response in human ADPKD cyst epithelial cells at concentrations that can be achieved in the plasma of ADPKD patients. It appears cAMP plays a key role in cellular proliferation through AVP that activates G-proteins. Activation of the kinase pathway in turn stimulates the expression of P-BRAF and P-ERK, leading to initiation of the cell cycle, leading to an increase in cell division. Tolvaptan modulates the increase in cell division, and therefore cyst formation in ADPKD, by inhibiting the accumulation of cAMP, and interferes with the mitogenic action of AVP. Tolvaptan also inhibited AVP-induced chloride secretion and decreased in vitro cyst growth of ADPKD cells.

Secondary pharmacodynamic studies

Secondary Pharmacodynamics							
							Test Article: Tolvaptan
Type of Study	**Species/ Strain**	**Method of Administration.**	**Doses (mg/kg)**	**Gender/ No. per Group**	**Noteworthy Findings**	**GLP Compliance**	**Report No.**
Cardiovascular and renal function	Dog/Beagle	Intravenous	OPC-41061: 0.3 mg/kg (1 min injection) hANP: 0.3 or 1.0 µg/kg/min	M/5	OPC-41061 and hANP caused aquaretic and natriuretic effects when administered alone. In combination, OPC-41061 and hANP had an additive effect on diuresis and an additive reduction in pulmonary capillary wedge pressure without affecting other cardiovascular or renal hemodynamic parameters.	No	027439
Effects of OPC-41061 on vascular permeability induced by histamine	Rats/ Sprague Dawley	Oral (gavage)	OPC-41061: 0, 1, 3, 10 Furosemide: 30	M/8	Pretreatment with OPC-41061 or furosemide significantly decreased EB leakage area 1-hour after histamine injection (10 µg) into the dorsal skin. The inhibition rate[a] was 11.9, 18.9, and 36.7% for OPC-41061-treated rats at 1, 3, and 10 mg/kg, respectively, and 39.4% for rats treated with furosemide.	No	022600

Secondary Pharmacodynamics

Test Article: Tolvaptan

Type of Study	Species/ Strain	Method of Administration.	Doses (mg/kg)	Gender/ No. per Group	Noteworthy Findings	GLP Compliance	Report No.
Effect of OPC-41061 on paw-edema induced by carrageenan	Rats/ Sprague Dawley	Oral (gavage)	OPC-41061: 0, 1, 3, 10 Furosemide: 30	M/8	Pretreatment with OPC-41061 dose-dependently suppressed the carrageenan-induced increase in paw-volume with a significant suppression at 10 mg/kg. Furosemide also significantly suppressed the increase in paw- volume. The anti-edematous effect of OPC-41061 at 10 mg/kg was similar to that of furosemide at 30 mg/kg.	No	022601
Effect of OPC-41061 on ascites induced by DMNA	Rats/Wistar	Oral (gavage)	OPC-41061: 0, 1, 3 Furosemide: 30	M/8	Single oral administration of OPC-41061 resulted in decreased body weight and a reduction in abdominal circumference, a marker of DMNA-induced ascites. The serum concentrations were 45.29 and 437.4 ng/mL at 1 and 3 mg/kg, respectively, at 2 hours postdose.	No	020656
Effect of DM-4107, a metabolite of OPC-41061, on cloned human oxytocin receptors	Human oxytocin receptor-expressing HeLa cells	in vitro	DM-4107 0.1 □M	n = 4	DM-4107 did not inhibit he binding of oxytocin to human oxytocin receptor	No	021228

DMNA - dimethylnitrosamine; EB - Evans Blue; hANP - human atrial natriuretic peptide; OPC-41061 = OPC-156 = tolvaptan.

a The inhibition rate of EB leakage was determined as the ratio of leakage area from drug treated animals to the leakage area of the control.

Secondary pharmacodynamic studies included animal models of cirrhosis and oedema. Tolvaptan improved the appearance of oedema and ascites. These effects are considered consistent with the increase in free water clearance observed with tolvaptan.

Safety pharmacology programme

A core battery of safety pharmacology studies as indicated in CPMP/ICH/539/00 Note for Guidance was conducted for the application related to the tolvaptan indication in adult patients with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH).
The main results are following described from the AR adopted by the CHMP. Those studies conducted after publication of the guidance were carried out in compliance with GLP.

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

Cardiovascular effects were studied in vivo and in vitro. In anaesthetised dogs, heart rate and respiration rate increased and blood pressure decreased at 10 mg/kg intravenously, but these parameters were unaffected in conscious dogs following oral doses up to 1000 mg/kg, at which dose the serum Cmax for tolvaptan was 2.83 µg/ml. T-wave amplitude of the EGC decreased at this dose, and following a 10 mg/kg intravenous dose in anaesthetised animals. In vitro studies in guinea pig papillary muscle and CHO-K1 cells stably transfected with the hERG channel showed tolvaptan had no effect on action potential parameters or hERG current at concentrations up to 3x10-5M and 2x10-6M, respectively. There were no effects on gastrointestinal motility in vivo or in vitro at clinically relevant concentrations.

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

Pharmacodynamic drug interactions

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

2.3.3. Pharmacokinetics

3 supplemental studies regarding preparation of radiolabeled tolvaptan, stability and analytical validation for tolvaptan, and 1 additional tissue distribution study were completed.

Study report ref. 023793 Stability test of OPC-41061 and its metabolites DM-4103, and DM-4107 in rat serum using LC-ESI-MS/MS

Long-term stability of OPC-41061 and its metabolites DM-4103 and DM-4107 in the rat serum were determined. [1] The data revealed that OPC-41061 and two metabolites in the rat serum were stable for at least 6 weeks when stored at -15°C or below. OPC-41061 and its metabolites DM-4103 and DM-4107 in the stock solution were stable for at least 9 weeks when stored at 10°C or below under protection from light.

Study report ref. 023613 Validation of assay method for OPC-41061 in mouse serum using LC-ESI-MS/MS

A supplemental study on analytical validation for determining OPC-41061 in the mouse serum by LC-ESI-MS/MS[2] (new assay conditions using a new system) was also included. The calibration curve of OPC-41061 ranged from 5 to 500 ng/mL. The LLOQ for OPC-41061 in the serum samples was 5 ng/mL. The intra-day and inter-day precisions were within 4.0% and 2.9% of the coefficient of

variation (CV) for the analyte in the serum samples. The intra-day accuracies were 97.1% to 101.5% and the inter-day accuracies were 98.1% to 100.9%, respectively. OPC-41061 in the processed samples stored at 10°C was stable for 48 hours.

In the tissue distribution study (see below), the serum concentration of radioactivity was determined following single oral administration of ^{14}C-OPC-41061 suspension at 30 mg/kg to the fasted male Long-Evens rats. The C_{max} and AUC∞ were 8.384 μg eq/mL and 162.0 μg eq·h/mL, and t_{max} and t1/2 were 2.0 and 54.94 hours, respectively.

Study report ref. 021883 Tissue distribution of radioactivity following single oral administration of ^{14}C-OPC-41061 at 30 mg/kg to Male Long-Evans Rats

The radioactivity concentrations in the tissues were determined following a single oral administration of ^{14}C-OPC-41061 suspension at 30 mg/kg to the fasted male Long-Evans rats for the purpose of investigating the tissue distribution of radioactivity in the pigmented rats.

The radioactivity concentrations in the tissues were determined following single oral administration of ^{14}C-OPC-41061 suspension at 30 mg/kg to the fasted male Long-Evans rats. [3] In the melanin-containing tissues (eyeball and pigmented skin), the radioactivity concentrations were lower than those in the serum, the ratios of the tissues to the serum were 0.045 to 0.228 at all time-points. The radioactivity concentration in the pigmented skin was similar to that in the non-pigmented skin. The radioactivity concentrations in the liver, brown fat, blood, kidney, fat and muscle were similar to or less than that of the serum. The radioactivity in all tissues decreased gradually. In the serum, the C_{max}, t_{max}, $t_{1/2}$, AUC_t, AUC_∞, Cl/F and Vz/F were 8.384 μg eq/mL, 2.0 hours, 54.94 hours, 150.7 μg eq·h/mL, 162.0 μg eq·h/mL , 185.2 mL/h/kg and 14680 mL/kg, respectively.

2.3.4. Toxicology

Single dose toxicity

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

Repeat dose toxicity

Please refer to toxicokinetic chapter below.

Genotoxicity

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

Carcinogenicity

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

Reproduction Toxicity

Teratogenicity was noted in rabbits given 1000 mg/kg/day (7.5 times the exposure from the 120 mg/day human dose on an AUC basis). No teratogenic effects were seen in rabbits at 300 mg/kg/day (about 1.25 to 2.65 times the exposure in humans at the 120 mg/day 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.

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 8-times the maximum human recommended dose of 120 mg/day on a mg/m^2 basis.

Toxicokinetic data

Tolvaptan is extensively metabolised in humans with unchanged drug accounting for <3% of the administered dose. The major human metabolite of tolvaptan is DM-4103, and accounts for approximately 50% of the plasma radioactivity with administration of radiolabeled tolvaptan.[14] Therefore, the safety margin of exposure for DM-4103 was determined at the highest dose for toxicity studies. The AUC for DM-4103 in humans was estimated from plasma concentrations for ADPKD patients treated with tolvaptan for about 3 years at the MHRD (90+30 mg).[15]

Table 5 – Safety margins relating to tolvaptan for ADPKD patients treated with tolvaptan

Table 2.4.5.3-1 Margin of Exposure for ADPKD Patients Treated with Tolvaptan

Study	26 Weeks[a]		52 Weeks[b]		Embryofetal Development[c]		104 Weeks[d]				Human[e]
Species	Rat		Dog		Rat	Rabbit	Rat		Mouse		
Gender	Male	Female	Male	Female			Male	Female	Male	Female	
	NOAEL						High Dose				
Dose (mg/kg/day)	1000	100	100	100	100	300	1000	1000	60	100	120 mg (90 + 30)
AUC (ng·h/mL)	12,716	20,700	31,451	42,346	28,671	8117	12,716	33,449	2859.5	4331.7	6570
Ratio (Animal/ Human)	1.9	3.2	4.8	6.4	4.4	1.2	1.9	5.1	0.4	0.7	-

Source: Otsuka Report No. 013774 (26-week rat), Otsuka Report No. 012707 (52-week dog), Otsuka Report No. 013227 (rat embryofetal development; TK Otsuka Report No. 012903), Otsuka Report No. 013174 (rabbit embryofetal development; TK Otsuka Report No. 012779), Otsuka Report No. 014253 (2-year rat; TK Otsuka Report No. 013774) and Otsuka Report No. 014252 (2-year mouse).

[a]AUC values determined at Week 4

[b]AUC values determined at Week 52.

[c]AUC values for rats determined at Gestation Day 17. For rabbits, AUC values determined at Gestation Day 18.

[d]As no carcinogenic response was observed in these studies, the high dose from the rat and mouse study is given. TK parameters were determined at 4 weeks.

[e]From clinical trial 156-09-285. Patients were treated for 21 days with pharmacokinetic parameters determined on day 7. The split dose (30+90 mg) of 120 mg represents the MRHD.

Table 6 – Safety margins relating to DM-4103 for ADPKD patients treated with tolvaptan

Table 2.4.5.3-2 Margin of Exposure for DM-4103 in ADPKD Patients Treated with Tolvaptan									
Study	26 Weeks[a]		52 Weeks[b]		104 Weeks[c]				Human[d]
Species	Rat		Dog		Rat		Mouse		
Gender	Male	Female	Male	Female	Male	Female	Male	Female	
Dose (mg/kg/day)[e]	1000	1000	1000	1000	1000	1000	60	100	120 mg (90 + 30)
AUC (ng·h/mL)	581,170	169,460[f]	16,190	34,562	581, 170	169,460[f]	6067	72,921	180,000
Ratio (Animal/ Human)	3.2	0.9	0.09	0.2	3.2	0.9	0.03	0.4	-

Source: Otsuka Report No. 013774 (26-week rat), Otsuka Report No. 011976 (52-week dog), Otsuka Report No. 014253 (2-year rat; TK Otsuka Report No. 013774) and Otsuka Report No. 014252 (2-year mouse).

[a]AUC values determined at Week 4.

[b]AUC values determined at Week 52.

[c]As no carcinogenic response was observed in these studies, the high dose from the rat and mouse study is given. TK parameters were determined at 4 weeks.

[d]CSR156-04-251. Patients were treated for about 3 years; the MHRD is 120 mg. The AUC is estimated from average of male (6500 ng/mL) and female (8500 ng/mL) concentrations times 24 hours (7500 * 24 =180,000 ng/mL·h). The plasma values for DM-4103 were estimated from Figure PKF-2 of CSR 156-04-251.

[e]Maximum dose used in toxicology studies.

[f]$AUC_{0\text{-}6h}$.

In spite of the low safety margins associated with some studies, no notable toxicity was observed in a single dose subcutaneous toxicity study.[16] In this study, rats were treated with subcutaneous doses up to 500 mg/kg. No changes were noted in body weight or food consumption. Bloody urine and scabs/alopecia at the injection site were observed in several treated and control animals that was attributed to the vehicle (dimethyl sulfoxide).

At necropsy, a white substance was noted in the subcutis at the injection site of all animals given DM-4103. The amount of the material appeared to be increased in a dose-related manner. These results suggested that the serum concentration of DM-4103 was positively correlated with the amount of absorption at the injection site.

Exposure to DM-4103 (AUC0-24h) was higher in animals given 100 mg/kg (743 µg h/mL) than in animals given 500 mg/kg (319 µg h/mL). In a separate study, the serum concentration of DM-4103 at 4 hours after subcutaneous administration was higher at 100 mg/kg compared to 500 mg/kg.[17]

Overall, these data suggest that DM-4103 has low toxicity at exposures that are greater than expected with repeated dosing in patients. Therefore, DM-4103 appears to be adequately characterised in toxicity studies with tolvaptan.

Local Tolerance

N/A

Other toxicity studies

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

2.3.5. Ecotoxicity / environmental risk assessment

Table 1. Summary of main study results

Substance (INN / Invented Name):					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …	3.95			Potential PBT (Y/N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	3.95			not B
	BCF	16			not B
Persistence	DT50 or ready biodegradability	Not ready biodegradable			P
Toxicity	NOEC or CMR	0.2 mg/L			not T
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.36	µg/L			> 0.01 threshold (Y/N)
Other concerns (e.g. chemical class)					(Y/N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106 or …	K_{oc} = 1534-3284			List all values
Ready Biodegradability Test	OECD 301	Not ready biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ =6.9-7.4 $DT_{50,\ sediment}$ =125-217 $DT_{50,\ whole\ system}$ =135-318 % shifting to sediment =90			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	0.2	mg/ L	*P. subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	1	mg/ L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	1	mg/ L	*Daphnia magna*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC15	1000	mg/ L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCFlipid	16	L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$			for all 4 soils
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/ kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/ kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/ kg	
Collembola, Reproduction Test	ISO 11267	NOEC		mg/ kg	
Sediment dwelling organism		NOEC	200	mg/ kg	*C. riparius*

An ERA for tolvaptan describing a predicted environmental concentration of 0.3 µg/L was already submitted with the initial approved MAA for Samsca. The applicant has provided the updated ERA documentation, including a study on sediment dwelling organisms.

In order to support further the environmental risk assessment the identification of the transformation product M1 occurring in a water sediment study is needed. Generation of this data take approximately 12 months and exceed the time of the procedure.

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of Tolvaptan to the environment.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points to be addressed: To identify the transformation product M1 occurring in a water sediment study.

2.3.6. Discussion on non-clinical aspects

The non-clinical testing for tolvaptan for human ADPKD is supported based on the results from previous non-clinical studies conducted to support the Samsca indication for clinically significant hypervolemic and euvolemic hyponatremia (MA EU/1/09/539/001-004).

Taken together, the pharmacodynamic data demonstrate that tolvaptan reduced the total kidney volume in rat and mouse models of PKD based on reductions of kidney weights and reduced cyst formation. Furthermore, with the reduced kidney levels of cAMP, the data indicate that tolvaptan is acting as an inhibitor of the V2R.

A few additional pharmacokinetic studies have been performed. The findings from the tissue distribution study in Long Evans rats indicated that in melanin-containing tissues (eyeball and pigmented skin), the radioactivity concentrations were lower than those in the serum, the ratios of these tissues to the serum were 0.045 to 0.228 at all time-points. The radioactivity in the pigmented skin was similar to that in the non-pigmented skin. The radioactivity concentrations in the liver, brown fat, blood, kidney, fat and muscle were similar to or less than that of the serum. The radioactivity in all tissues decreased gradually.

The toxicity of tolvaptan in animals was characterised in a non-clinical program of single and repeat dose oral studies in mice, rats, and dogs, a battery of genotoxicity studies, carcinogenicity studies in rodents, reproductive and developmental toxicity studies in 2 species, mechanistic studies, ocular and dermal irritation studies in rabbits, an antigenicity study in guinea pigs, an immunotoxicity study in rats, and phototoxicity studies.

Tolvaptan is extensively metabolised in humans with unchanged drug accounting for <3% of the administered dose. The major human metabolite of tolvaptan is DM-4103, and accounts for approximately 50% of the plasma radioactivity with administration of radiolabeled tolvaptan. Therefore, the margin of exposure for DM-4103 was determined at the highest dose for toxicity studies. The AUC for DM-4103 in humans was estimated from plasma concentrations for ADPKD patients treated with tolvaptan for about 3 years at the MHRD (90+30 mg).

Safety margins for tolvaptan and the main metabolite were generally equal to or exceeded human exposure at the recommended human dose (RHD) for general toxicity, toxicity to reproduction and development and/or carcinogenicity. The safety margins in male and female rats are 1.9 and 3.2-fold respectively, relative to the exposure in humans at the maximum recommended human dose for PKD (120 mg; AUC24h 6570 ng·h/mL in the 26 week rat toxicity study). The no adverse effect level in the 1 year dog toxicity study resulted in a safety margin in males and females of 4.8 fold and 6.4 fold, respectively, relative to the exposure in humans at the maximum recommended human dose for PKD (120 mg; AUC24h 6570 ng·h/mL. The safety margin for carcinogenicity in rodents relative to the exposure in humans at the maximum recommended human dose for PKD (120 mg; AUC24h 6570

ng·h/mL) is 1.9- and 5.1-fold in male and female rats and <1 in mice. A justification relating to the low exposures seen in mice compared to human exposure at the RHD has been provided for tolvaptan and DM-4103. The results from repeat dose studies in mice indicated that the mouse was a more sensitive rodent species for the toxicity of tolvaptan than rats. In the 2-year rodent bioassays there were no neoplastic or non-neoplastic pathological changes up to the maximum tolerated dose in mice and at exposures of tolvaptan and DM-4103 comparable or higher (0.9- to 5.1-fold) than those at the MRHD. Neither tolvaptan nor DM-4103 was genotoxic and thus overall, these data suggest that tolvaptan was not carcinogenic.

Given that the mechanism of the teratogenic effects in rabbits has not been elucidated and the safety margin for tolvaptan in rats is reduced further in the current application, it is agreed that tolvaptan should remain contraindicated during pregnancy and lactation and in line with the Samsca labelling.

Exposure margins relating to reproductive toxicity have been recalculated based on the newly proposed posology and reflected in the SmPC. Overall; tolvaptan is unlikely to pose serious safety concerns for chronic oral administration to patients at the daily recommended human dose of 120mg.

2.3.7. Conclusion on the non-clinical aspects

The applicant has provided primary and secondary pharmacology studies in support of the new indication. Further stability and validation PK studies have been provided. Recalculation of the safety margins in the preclinical species has been conducted based on the higher dose of 120mg compared to the previous approved dose. There was no carcinogenic signal in the initial bioassays conducted in rodents and tolvaptan is not genotoxic. Tolvaptan is contraindicated during pregnancy and lactation due to safety margins and lack of mechanistic information.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 1: Summary of Clinical Pharmacology studies

Protocol / Country	Trial Objective Trial Design	Population No. Subjects (Male/Fe-male) Age Range	Treatment	Treatment Group, n	Tolvaptan Pharmacokinetic Parameters Mean (Standard Deviation)				
					Cmax (ng/mL)	tmax[b] (h)	AUC (ng·h/mL), duration	t1/2 (h)	CL/F (mL/min/kg)
156-KOA-0801 KOR	Safety, tolerability, PK and PD following single oral doses Randomized, double-blind, placebo-controlled sequentially-dosed, parallel groups	Healthy Korean Men 46 (46M/0F) 20-41 years	Tolvaptan Single Dose 15 mg	Men (6)	103 (39.5)	1.75 (1.50-3.02)	467 (178), 0-∞	2.76 (1.09)	38.7 (21.2) L/h
			Tolvaptan Single Dose 30 mg	Men (24)	190 (45.5)	2.00 (1.00-4.03)	1281 (432), 0-∞	4.74 (1.85)	25.8 (8.02) L/h
			Tolvaptan Single Dose 60 mg	Men (6)	247 (65.8)	2.00 (1.50-4.00)	1911 (642), 0-∞	5.24 (1.84)	35.6 (15.8) L/h
156-04-001 JPN	Safety, PK/PD of tolvaptan following different dosage regimens Randomized, double-blind, parallel group, multiple dose and regimen study	Japanese Subjects with ADPKD 18 (9M/9F) 21-59 years	Tolvaptan Single Dose 15 mg	Men/ Women (18)	181.12 (50.39)	1.00 (1.0-2.0)	833.08 (305.46), 0-∞	4.18 (1.36)	6.103 (3.519)
			Tolvaptan Single Dose 30 mg	Men/ Women (18)	372.59 (149.65)	1.00 (1.0-3.0)	1964.81 (1026.42), 0-∞	4.57 (1.07)	5.621 (3.461)
			Tolvaptan Day 1 15 mg am/15 mg pm	Men/ Women (9)	202.58 (91.30)	1.00 (1.0-2.0)	1510.82 (722.52), 0-24h	ND	ND
			Tolvaptan Day 1 30 mg QD am	Men/ Women (9)	339.01 (77.55)	1.00 (1.0-1.0)	1532.37 (671.76), 0-24h	ND	ND
			Tolvaptan Day 5 15 mg am/15 mg pm	Men/ Women (9)	205.09 (71.63)	1.00 (1.0-9.0)	1460.20 (524.57), 0-24h	4.36 (0.77)	ND
			Tolvaptan Day 5 30 mg QD am	Men/ Women (9)	359.19 (139.59)	1.00 (1.0- 2.0)	1665.31 (875.23), 0-24h	5.00 (1.47)	6.159 (3.433)

Protocol/ Country	Trial Objective Trial Design	Population No. Subjects (Male/Fe-male) Age Range	Treatment	Treatment Group, n	Tolvaptan Pharmacokinetic Parameters Mean (Standard Deviation)				
					Cmax (ng/mL)	tmax[b] (h)	AUC (ng·h/mL), duration	t1/2 (h)	CL/F (mL/min/kg)
156-04-248 US	Safety, PK and PD of single ascending doses of tolvaptan Randomized (8:3) double-blind, placebo-controlled, sequential administration of single doses, 72-hour washout	ADPKD Subjects 11 (4M/7F) 22-47 years	Tolvaptan Single 15 mg Dose, Day 1	Men/ Women (8)	146 (35.4)	1.00 (1.00-2.00)	880 (318), 0-∞	4.5 (2.7)	3.78 (1.69)
			Tolvaptan Single 30 mg Dose, Day 4	Men/ Women (8)	263 (74.5)	1.00 (1.00-2.00)	1430 (615), 0-∞	4.3 (1.3)	6.03 (2.30)
			Tolvaptan Single 60 mg Dose, Day 7	Men/ Women (8)	481 (177)	1.50 (1.00-3.00)	4150 (1140), 0-∞	5.1 (1.0)	3.99 (1.93)
			Tolvaptan Single 120 mg Dose, Day 10	Men/ Women (8)	917 (237)	1.50 (1.00-3.00)	7740 (3100), 0-∞	5.6 (2.0)	4.45 (2.66)
156-04-249 US	Safety, PK/PD of tolvaptan following different dosage regimens Randomized, double-blind, parallel group, multiple dose and regimen study	ADPKD Subjects 37 (8M/29F) 25-58 years	Tolvaptan Day 1 15 mg am/15 mg pm	Men/ Women (9)	201 (88.5)	8.97 (1.00-11.00)	1650 (774), 0-24h	ND	ND
			Tolvaptan Day 1 30 mg am/0 mg pm	Men/ Women (9)	312 (205)	2.00 (1.00-4.00)	1950 (1490), 0-24h	ND	ND
			Tolvaptan Day 1 30 mg am/15 mg pm	Men/ Women (9)	262 (55.1)	1.00 (1.00-10.00)	2270 (1650), 0-24h	ND	ND
			Tolvaptan Day 1 30 mg am/30 mg pm	Men/ Women (10)	335 (135)	2.00 (1.00-10.00)	2900 (1340), 0-24h	ND	ND
			Tolvaptan Day 5 15 mg am/15 mg pm	Men/ Women (9)	190 (60.5)	2.04 (1.42-5.42)	1890 (1070), 0-24h	6.2 (3.3)	ND

Protocol / Country	Trial Objective Trial Design	Population No. Subjects (Male/Fe-male) Age Range	Treatment	Treatment Group, n	Tolvaptan Pharmacokinetic Parameters Mean (Standard Deviation)				
					Cmax (ng/mL)	tmax[b] (h)	AUC (ng·h/mL), duration	t1/2 (h)	CL/F (mL/min/kg)
			Tolvaptan Day 5 30 mg am/0 mg pm	Men/ Women (9)	330 (230)	1.98 (0.98- 2.98)	2140 (1620), 0-24h	4.3 (1.2)	5.38 (4.88)
			Tolvaptan Day 5 30 mg am/15 mg pm	Men/ Women (9)	269 (69.2)	0.98 (0.97-9.95)	2770 (2020), 0-24h	6.4 (3.7)	ND
			Tolvaptan Day 5 30 mg am/30 mg pm	Men/ Women (10)	295 (122)	5.47 (0.93-12.02)	2990 (1640), 0-24h	4.7 (1.8)	ND
156-06-260 US	Effect of multiple doses of tolvaptan on renal function Open-label, 7 days, administration as 45 mg am/15 mg pm, 45 mg before renal function test on Day 8	Patients with ADPKD and eCrCLCG ≥60 mL/min Patients with ADPKD and hypertension treated with ACE/ARBs and eCrCLCG of ≥60, 45 to <60 and 30 to <45 mL/min 20 (10M/10F) 29-60 years	Tolvaptan Day 8 45 mg am	Men/ Women eCrCLCG ≥60 mL/min, no hyper-tension (5)	270 (52.4)	2.67 (1.12-4.33)	635 (72.8), 0-3.5h	ND	ND
				Men/ Women eCrCLCG ≥60 mL/min, with hyper-tension (3)	303 (144)	2.13 (1.03-2.80)	845 (486)), 0-3.5h	ND	ND
				Men/ Women eCrCLCG 45 to <60 mL/min, hyper-tension (4)	412 (132)	2.89 (2.38-3.18)	971 (283)), 0-3.5h	ND	ND
				Men/ Women eCrCLCG 30 to <45 mL/min, hyper-tension (2)	377 (ND)	2.38 (2.30-2.45)	961 (ND)), 0-3.5h	ND	ND

Protocol / Country	Trial Objective Trial Design	Population No. Subjects (Male/Fe-male) Age Range	Treatment	Treatment Group, n	Tolvaptan Pharmacokinetic Parameters Mean (Standard Deviation)				
					Cmax (ng/mL)	tmax[b] (h)	AUC (ng·h/mL), duration	t1/2 (h)	CL/F (mL/min/kg)
156-07-262 US ONLY TABLET DATA PROVIDED	Relative bioavailability of immediate release (IR) tablets to modified release (MR) formulations Effect of Food on MR formulations Open-label, randomized, incomplete-block	Healthy Subjects 18 (11M/7F) 24-45 years	Tolvaptan 45 mg am /15 mg pm	Men/ Women (18)	414 (96.3)	2.00 (1.00-10.00)	4840 (1510), 0-∞	7.6 (1.9)	ND
156-09-282 US	PK/PD of tolvaptan in subjects with varying degrees of renal function Single dose, open-label, parallel-group with matched subjects	Subjects with measured 24-hour CrCL values of >60, 30 to 60 and <30 mL/min 37 (25M/12F) 28-79 years	Tolvaptan Single Dose 60 mg	Men/ Women CrCL<30 mL/min (12)	535 (183)	3.50 (2.00-6.00)	7360 (3580), 0-∞	9.1 (2.8)	2.65 (2.40)
			Tolvaptan Single Dose 60 mg	Men/ Women CrCL30 to 60 mL/min (12)	621 (241)	3.00 (2.00-4.00)	6980 (3360), 0-∞	9.2 (3.3)	2.37 (0.80)

Protocol / Country	Trial Objective Trial Design	Population No. Subjects (Male/Fe-male) Age Range	Treatment	Treatment Group, n	Tolvaptan Pharmacokinetic Parameters Mean (Standard Deviation)				
					Cmax (ng/mL)	tmax[b] (h)	AUC (ng·h/mL), duration	t1/2 (h)	CL/F (mL/min/kg)
			Tolvaptan Single Dose 60 mg	Men/ Women CrCL>60 mL/min (12)	417 (150)	2.00 (1.00-4.00)	3890 (1910), 0-∞	10.1 (8.3)	4.55 (2.58)
156-09-284 NLD	Safety and effect of a maximum tolerated dose of tolvaptan on renal function Open-label, multiple dose administration for 21 days, titration of 7 days as 45 mg am/15 mg pm, 7 days as 60 mg am/30 mg pm, 7 days as 90 mg am/30 mg pm	Patients with ADPKD and eGFRMDRD ≥60, 30 to 60 and <30 mL/min/ 1.73 m2 Patients with hyper-tension treated with ACE/ARBs 29 (15M/14F) 25-69 years	Tolvaptan Day 21 90 mg am	Men/ Women eGFRMDRD ≥60 mL/min/ 1.73 m2 (9)	828 (297)	2.00 (1.00-3.00)	2850 (774), 0-5h	ND	ND
				Men/ Women eGFRMDRD 30 to 60 mL/min/ 1.73 m2 (9)	591 (235)	2.00 (1.00-3.00)	2140 (863), 0-5h	ND	ND
				Men/ Women eGFRMDRD <30 mL/min/ 1.73 m2 (9)	840 (355)	2.00 (1.00-5.00)	3100 (1060), 0-5h	ND	ND

Protocol/ Country	Trial Objective Trial Design	Population No. Subjects (Male/Fe-male) Age Range	Treatment	Treatment Group, n	Tolvaptan Pharmacokinetic Parameters Mean (Standard Deviation)				
					Cmax (ng/mL)	tmax[b] (h)	AUC (ng·h/mL), duration	t1/2 (h)	CL/F (mL/min/kg)
156-09-285 US ONLY TABLET DATA PROVIDED	PK/PD and tolerability of tolvaptan as immediate release (IR) tablets compared to modified release (MR) capsule formulations Parallel-group, randomized, double-blind, placebo-masked, multiple dose trial	Patients with ADPKD and eGFRMDRD >60 mL/min/ 1.73 m2 12 (5M/7F) 32-49 years	Tolvaptan Day 7 90 mg am /30 mg pm	Men/ Women (12)	716 (344)	2.00 (1.00-9.00)	6570 (3230), 0-24h	ND	ND

[a]Number analyzed reflects actual numbers of subjects for C_{max} and t_{max}.
[b]Median (minimum-maximum).

Table 2: Pivotal and supportive efficacy studies in ADPKD patients

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjects by arm entered/ completed	Duration	Gender Median Age	Diagnosis Incl. criteria	Primary Endpoint
156-04-251	129 sites with at least 1 randomised subject. Americas, Japan, Europe,	**Pivotal efficacy study** Phase III, Double-blind, Placebo-contro	Tolvaptan daily oral split-dose (titrated) 45/15 mg 60/30 mg 90/30 mg	Long-term efficacy and safety	Tolvaptan: 961/740	3 years	M - 746 F-699F 39 years (range 18-51)	ADPKD [c] 18 to 50 years of age eCrCLCG ≥ 60 mL/min	Rate of TKV change for tolvaptan relative to placebo

	Australia	lled, Parallel-arm	Placebo split-dose		Placebo: 484/417			TKV ≥ 750 mL	
156-04-250	11 centres in US	Phase II, open-label	2 month titration phase: 15/15 mg 30/15 mg 45/15 mg 60/30 mg 90/30 mg Followed by random assignment to: 45/15 or 60/30 mg	Safety TKV	Titration – 46/46 Fixed dose through Month 36 @ 45/15 mg: 22/18 Fixed dose through Month 36 @ 60/30 mg: 24/21 Optional extension: 45/15 mg:17/17 60/30 mg: 18/18	3 years Optional 1 year extension	M – 12 F – 34 42 years (range 24-59)	ADPKD [a] Subjects enrolled from prior studies 248 and 249	Long-term safety
156-05-002	10 sites in Japan	Phase II, open-label extension	15 mg b.d	Safety TKV	17/12	3 years	M – 8 F – 9 43 years (range 26-61)	ADPKD patients [b] completing dose-finding trial (156-04-001).	Long-term safety

Notes:

a) ADPKD diagnosed by 1994 Ravine criteria/based on previous diagnosis

b) ADPKD diagnostic criteria as established by the Japanese Progressive Renal Disturbance Study Team (unpublished, detailed in the study report)

See section 3.3 for study ADPKD diagnostic criteria

2.4.2. Pharmacokinetics

In vitro clinical pharmacology studies included plasma protein binding studies and studies with liver microsome preparations/P-gp.

The healthy subject PK/PD clinical trials included single dose studies ranging from 5 to 480 mg (including studies 156-98-210, 156-98-229, 156-98-001 and 156-98-003). Multiple dose data were also obtained from healthy subjects (study 146-00-003, 156-95-305, 156-03-245), the highest dose being 300 mg once daily for 5 days administered in the QT study (156-03-245). A mass balance study was also performed (156-97-202).

Drug-drug interaction trials in healthy subjects assessed the effects of CYP3A4 inducers and inhibitors, plus the effect of tolvaptan on sensitive CYP3A4 and P-gp substrates. Additional interaction studies were performed with warfarin, diuretics and amiodarone.

ADPKD program – healthy volunteer studies

For the ADPKD program there were 3 clinical pharmacology trials in healthy volunteers. The most important is study 156-11-295, which looked at bioequivalence of the 90 mg formulation and the food effect at this dose. Study 156-KOA-0801 was a single dose study in Korean subjects. Study 156-07-262 is mentioned for completeness; however this was predominantly for a modified release formulation not relevant to this application.

ADPKD program – patient studies

There were 6 clinical pharmacology trials specifically in ADPKD subjects.

Single dose PK/PD: studies 156-04-248 and 156-04-01

Multiple dose PK/PD: 156-04-249 and 156-09-285

Renal impairment studies: 156-06-260, 156-09-284

In study 156-09-285, only data with the immediate release tablet are relevant.

There was an additional study in patients with varying degrees of renal function (156-09-282) which did not enrol any ADPKD patients.

Absorption

Tolvaptan drug substance is practically insoluble in water (0.00005 w/v% at 25°C) and the solubility is pH independent. However the potential for low absorption due to poor solubility has been addressed by the pharmaceutical development of the tablets. After oral administration, tolvaptan tablets were shown to be rapidly absorbed in healthy volunteers with peak plasma concentrations occurring about 2 hours after dosing. Absolute BA was determined by the oral/i.v. ratio of dose-normalised AUC0-∞ after oral administration of 30 mg tolvaptan as tablet and i.v. administration of 1 mg (1 h infusion). The absolute bioavailability of tolvaptan was 56%, with a range of 42-80% (study 156-05-254). Following single oral doses of ≥ 300 mg, peak plasma concentrations appeared to plateau, possibly due to saturation of absorption.

Bioequivalence

The previously authorised Samsca product is only available in 15 and 30 mg strengths to meet the approved hyponatraemia posology, although in the Samsca development program, relative bioavailability was also established between 15, 30 and 60mg tablets (study 156-01-233)

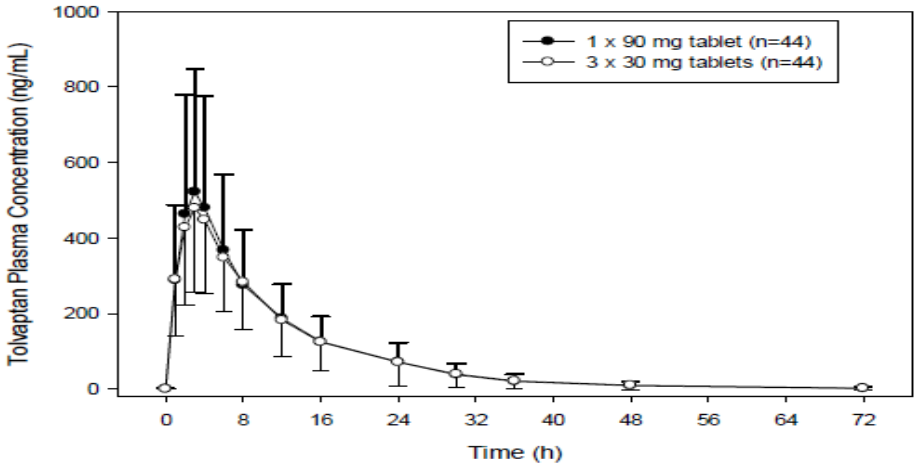
45 and 90 mg tablets have been newly developed for the proposed ADPKD MAA. A new bioequivalence study was conducted with the 90 mg tablet (Study 156-11-295, part 1). This was an open-label, 2-period, randomized, crossover trial. Forty-four healthy subjects were enrolled and completed the trial. On Days 1 and 5, subjects were given tolvaptan as either 3 x 30 mg tablets or 1

x 90 mg tablet in a randomized, crossover fashion. All doses were given fasted. Serial blood samples were taken for 72 hours postdose.

Table 3: Bioequivalence Study 156-11-295: summary of PK parameters

Treatments (Dose, Dosage Form, Route) Lot #	Population No. Subjects (Male/Female) Age Range	Tolvaptan Pharmacokinetic Parameters Mean (SD)				Comparison Geometric Mean Ratio (90% CI)	
		C_{max} (ng/mL)	t_{max} (h)	AUC_{∞} (ng·h/mL)	$t_{1/2,z}$ (h)	C_{max}	AUC
3 x 30 mg tablet oral 0K81TB1SW	44 (20/24) Healthy subjects 19-45 y	538 (215)	3.00 (1.00-8.00)	6150 (2850)	10.8 (6.9)	**1 x 90 /3 x 30** 1.002 (0.931-1.078)	**1 x 90 /3 x 30** 0.978 0.922-1.037
90 mg tablet oral 11F82A090A		560 (323)	3.00 1.00-6.00)	6090 (3110)	8.9 (4.3)		

Figure 2: Bioequivalence Study 156-11-295: 3 x 30 mg tablets vs. 1 x 90 mg Tablet



45 and 90 mg tablets have been newly developed for the proposed ADPKD MAA. A single 90 mg tablet with the proposed commercial formulation was dose strength equivalent to three 30 mg tablets (approved formulation per the Samsca MAA) for Cmax and AUC0-72 based on the standard bioequivalence criteria.

The biowaiver request for the 45mg tablet strength is accepted. It is quantitatively proportional to the 90mg and 60mg strengths, is qualitatively the same and is manufactured at the same sites using the same methods. Tolvaptan has linear pharmacokinetics for single doses of 15 to 90 mg.

Influence of food

Co-administration with food had no significant or clinically relevant food effect on plasma concentrations, with both the 30 and 60 mg tablet (studies 156-00-002, 156-00-242)

The bioequivalence study noted above had 2 extra arms to evaluate food effect with the 90 mg tablet. This was a randomized, open-label, crossover comparison in 14 subjects and showed that the geometric mean ratios and 90% CI for the fed to fasted comparison met the bioequivalence criteria for AUCt and AUCinf, but not Cmax. The t1/2 is also shorter in the fed state.

Table 4: Study 156-11-295: summary of PK parameters

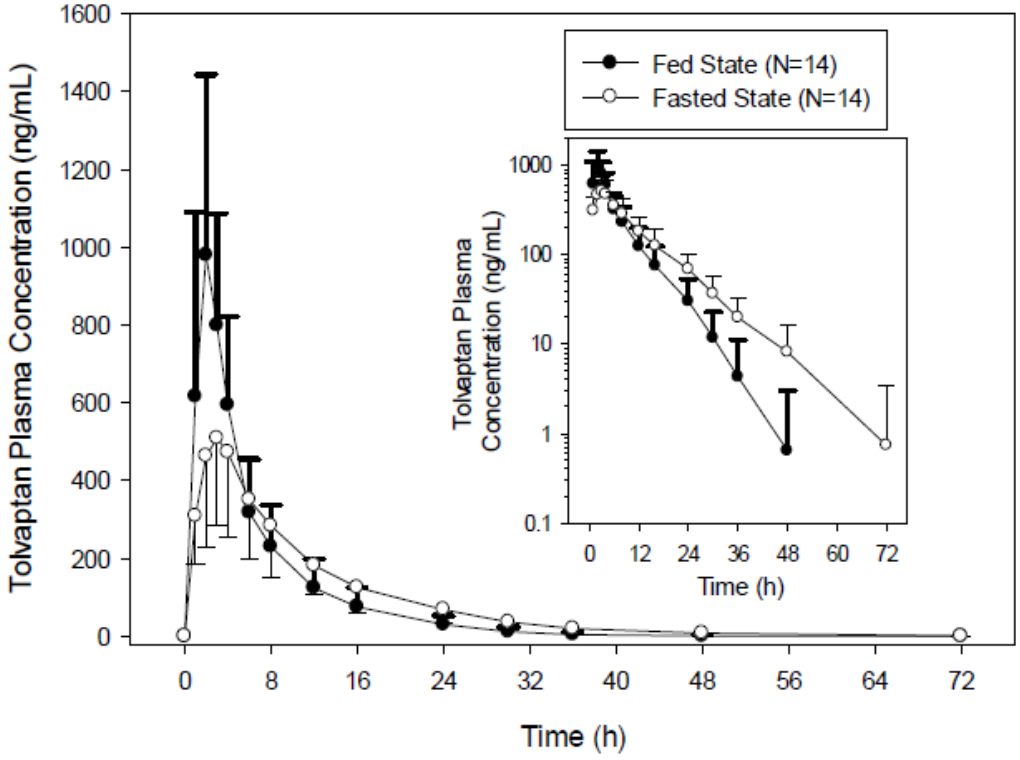
Parameter	Statistic	Fasted (N = 14)	Fed (N = 14)
C_{max} (ng/mL)	Mean (SD) Geo Mean	539 (243) 496	1050 (443) 972
t_{max} (h)	Median (Range)	2.00 (1.00-4.00)	2.00 (1.00-3.00)
AUC_t (ng·h/mL)	Mean (SD) Geo Mean	5970 (2440) 5480	5850 (2730) 5310
AUC_∞ (ng·h/mL)	Mean (SD) Geo Mean	6110 (2450) 5640	6210 (2630)[a] 5780
$t_{1/2,z}$ (h)	Mean (SD)	9.8 (4.8)	5.4 (1.2)[a]
CL/F (mL/min/kg)	Mean (SD)	3.69 (1.75)	3.54 (1.21)[a]

Geo Mean = geometric mean.
[a]n = 13.

Comparison		C_{max} (N = 14)	AUC_t (N = 14)	AUC_∞ (N = 14)
1 × 90 mg tolvaptan Fed (T) versus 1 × 90 mg tolvaptan Fasted (R)	Ratio	1.960	0.968	0.948
	90% CI	1.726-2.226[a]	0.912-1.026	0.894-1.005

R = reference; T = test.
[a]Not equivalent, 90% CI outside the interval of 0.80-1.25.

Figure 3: Study 156-11-295: mean plasma concentrations (inset: semi-log plot)



A conventional design high fat meal as defined in FDA guidelines was used in this study to assess the food effect at 90 mg, the highest proposed dose for Jinarc. A high-fat meal increased absorption and Cmax values of tolvaptan; this was not seen with previous food interaction studies at the 30 and 60 mg dose. Following single doses of 30, 60 and 90 mg the mean fold changes in Cmax were respectively around 1.1, 1.4 and 2. The implication is that as dissolution and/or saturation limitations increase with dose, food has a greater impact on facilitating absorption. The report notes that in the single ascending dose trials, tolvaptan doses from 60 to 480 mg produced similar mean urine volumes for the first 12 hours postdose as plasma concentrations in this interval produced a maximal rate of urine output. Therefore, the increased tolvaptan concentrations observed in the fed state would not be expected to have any additional effect on urine output in the first 6 hours postdose when compared to the fasted state.

Distribution

Tolvaptan is around 98% bound to plasma proteins. In plasma, it was bound mainly to serum albumin and α1−acid glycoprotein. The extent of binding to plasma proteins is not significantly altered in patients with liver disease. Binding is reversible.

There was no effect from digoxin, diazepam or warfarin on the binding of tolvaptan. Various other agents including furosemide, spironolactone, propranolol, disopyramide, lidocaine and warfarin did not alter plasma protein binding of tolvaptan or metabolites or vice versa.

The apparent volume of distribution was around 3 L/kg. Preclinical tissue distribution studies showed radioactivity mainly distributed to liver, GI tract and kidney. Transfer of radioactivity across the placenta and into breast milk was also observed.

Otsuka report No 8223216 also establishes no clinically significant difference in plasma protein binding in patients with renal impairment, based on pooled human plasma samples from normal subjects and from renally impaired patients (taken from clinical study 156-09-282)

Elimination

Tolvaptan is a CYP3A4 and P-gp substrate, metabolized in the gut wall and liver. Renal clearance of unchanged tolvaptan is negligible. In porcine kidney epithelial cells, tolvaptan was also shown to be both a substrate and inhibitor of the P-gp efflux transporter.

A mass-balance study in healthy volunteers 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 (study 156-97-202). In healthy subjects the terminal elimination half-life is about 8 hours (SD 4.9) with no or minimal accumulation of tolvaptan following multiple administration, and a clearance of approximately 4 mL/min/kg.

The pharmacokinetic properties of tolvaptan are stereospecific, with a steady-state ratio of the S-(-) to the R-(+) enantiomer of about 3. However, both enantiomers were found to be equally potent at the V2 receptor in *in vitro* binding studies.

There are 7 main metabolites. The predominant metabolite, with >50% of the total dose using the mass balance approach was DM-4103. The terminal elimination half-life of DM-4103 is around 183 hours and after multiple dosing it shows accumulation by day 28. DM-4103 and other main metabolites have previously been shown to be pharmacologically inactive.

Dose proportionality and time dependencies

Cmax increases linearly with dose from 30-300 mg and a plateau is noted at doses >300mg. The AUC also increased linearly up to the maximum single dose studied of 480 mg (study 156-01-229). Data from healthy subjects showed no or minimal accumulation of tolvaptan following multiple administration.

The maximum dose given long-term in patients was 60 mg in the separate hyponatraemia development program. The potential for accumulation of tolvaptan and the main metabolite in ADPKD patients is covered below.

Special populations

Intra-and inter-individual variability

The intersubject variability for Cmax, AUC and CL/F was similar for healthy subjects and subjects with ADPKD and relatively intact renal function, with percent coefficients of variation (% CV) ranging from 20 to 75%; values in the range of 35-50% were the most frequently observed.

For 28 healthy subjects, intrasubject variation for Cmax, AUC and CL/F was about 21% for tolvaptan given as single oral 60 to 240 mg doses. For 9 subjects with ADPKD and relatively intact renal function, the intrasubject variations for Cmax and AUC0-24h were 15.3 and 26.6%, respectively, for tolvaptan given as a single 30 mg dose.

Pharmacokinetics in target population

Single dose PK

Study 156-04-248 was a double-blind, randomised, placebo-controlled, ascending single dose trial in 11 (8 active/3 placebo) subjects with ADPKD. Subjects had to meet the 1994 Ravine criteria for diagnosis of ADPKD and have relatively intact renal function (i.e., serum creatinine value of ≤ 1.4 mg/dL for men or ≤ 1.2 mg/dL for women). Subjects of either gender with a serum creatinine above 1.8 mg/dL were excluded. Each single dose was separated by 3 days.

Study 156-04-01 done in Japan was a randomised, parallel-group trial in ADPKD patients (9 subjects per group) with sequential administration of single doses of 15 mg and 30 mg. Subjects had to meet somewhat different ADPKD diagnostic criteria but the criteria for renal function were similar.

Table 5: Study 156-04-248. Summary of PK results

Mean (SD) Plasma Pharmacokinetic Parameters for Tolvaptan Following Single Ascending Doses of Tolvaptan (72 h Apart) to 8 Subjects With ADPKD

Parameter	TLV 15 mg (Day 1)	TLV 30 mg (Day 4)	TLV 60 mg (Day 7)	TLV 120 mg (Day 10)
C_{max} (ng/mL)	146 (35.4)	263 (74.5)	481 (177)	917 (237)
t_{max} (h)[a]	1.00 (1.00-2.00)	1.00 (1.00-2.00)	1.50 (1.00-3.00)	1.50 (1.00-3.00)
AUC_t (ng·h/mL)	686 (258)	1520 (698)	3280 (1400)	6900 (2790)
AUC_∞ (ng·h/mL)	880 (318)[b]	1430 (615)[c]	4150 (1140)[d]	7740 (3100)[d]
$t_{1/2,z}$ (h)	4.5 (2.7)[b]	4.3 (1.3)[c]	5.1 (1.0)[d]	5.6 (2.0)[d]
CL/F (mL/min/kg)	3.78 (1.69)[b]	6.03 (2.30)[c]	3.99 (1.93)[d]	4.45 (2.66)[d]

Figure 4: Study 156-04-248. Semi-log plot of mean plasma concentration vs. time by dose, ADPKD patients

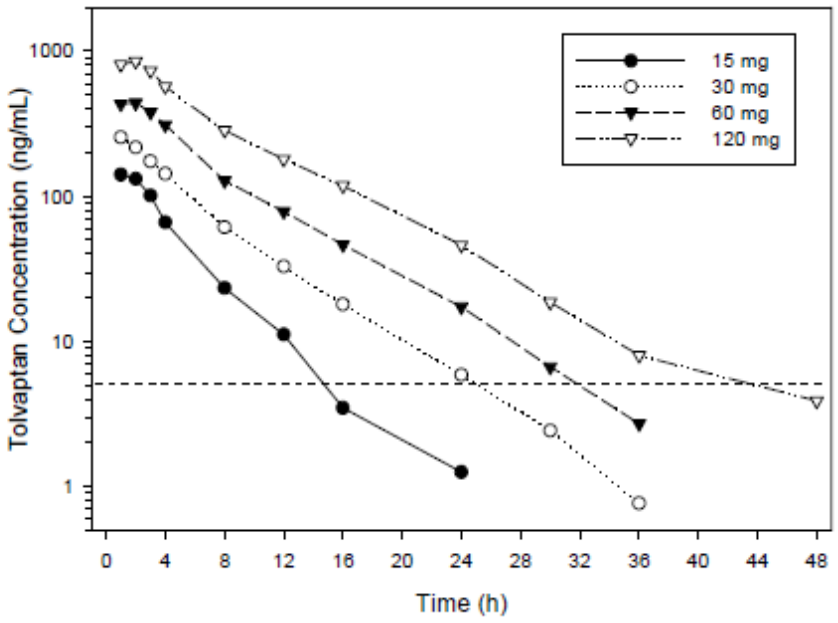


Table 6: Study 156-04-01. Summary of PK results

Table 8.3-1 Plasma Pharmacokinetic Parameters of OPC-41061 Following Single Oral Administration

		Single 15-mg dose			Single 30-mg dose		
Parameter	(Unit)	n	Mean	SD	n	Mean	SD
C_{max}	(ng/mL)	18	181.12	50.39	18	374.59	149.65
AUC_{24h}	(ng·h/mL)	18	815.73	290.43	18	1913.10	965.81
AUC_t	(ng·h/mL)	18	816.71	303.29	18	1941.24	1019.29
AUC_∞	(ng·h/mL)	18	833.08	305.46	18	1964.81	1026.42
t_{max}	(h)	18	1.33	0.49	18	1.39	0.61
$t_{1/2z}$	(h)	18	4.18	1.36	18	4.57	1.07
λ_z	(h^{-1})	18	0.18732	0.07292	18	0.16286	0.05148
CL/F	(mL/min)	18	349.73	152.31	18	318.61	147.93
CL/F/BW	(mL/min/kg)	18	6.103	3.519	18	5.621	3.461
V_z/F	(L)	18	113.86	30.43	18	119.73	52.55
$V_z/F/BW$	(L/kg)	18	1.920	0.662	18	2.063	1.031
AUC %Extrap	(%)	18	2.14	0.74	18	1.36	0.58

The new data can be compared to existing single dose healthy volunteer data as follows:

Table 7: Comparison of single dose PK in target population to healthy volunteer data

Mean (SD) [n] of Tolvaptan Pharmacokinetic Parameters Following A Single Dose of Tolvaptan in Fasted Healthy Subjects and ADPKD Subjects					
Dose	**Subjects**	**C_{max} (ng / mL)**	**AUC_∞ (ng·h / mL)**	**$AUC_{0\text{-}24h}$ (ng·h / mL)**	**CL / F (mL / min / kg)**
15 mg	ADPKD	146 ± 35.4 [8]	880 ± 318 [4]	—	3.78 ± 1.69 [4]
	ADPKD	181.12 ± 50.39 [18]	833.08 ± 305.46 [18]	—	6.103 ± 3.519 [18]
30 mg	Healthy	235 ± 90 [133]	1620 ± 710 [81]	1660 ± 693 [97]	5.00 ± 2.04 [81]
	ADPKD	289 ± 155 [17]	1430 ± 615 [8]	1950 ± 1490 [9]	6.03 ± 2.30 [8]
	ADPKD	372.59 ± 149.65 [18]	1964.81 ± 1026.42 [18]	1913.10 ± 965.81 [18]	5.621 ± 3.461 [18]
60 mg	Healthy	396 ± 136 [135]	3630 ±1650 [119]	—	4.64 ± 2.24 [119]
	ADPKD	481 ± 177 [8]	4150 ± 1140 [8]	—	3.99 ± 1.93 [8]
120 mg	Healthy	564 ± 124 [6]	5800 ± 1640 [6]	—	4.51 ± 0.96 [6]
	ADPKD	917 ± 237 [8]	7740 ± 3100 [8]	—	4.45 ± 2.66 [8]

AUCinf values are less than AUC 0-24, because the most appropriate data from different trials has been combined. For single oral doses ranging from 15 to 120 mg, the increase in tolvaptan plasma concentrations with increasing dose was approximately dose proportional. Single dose PK parameters in ADPKD patients were similar to previous healthy volunteer data, across the proposed dose range in ADPKD.

Multiple dose PK

Study 156-04-249 was a randomised, placebo-controlled parallel group multiple dose trial in 37 subjects with AKPKD (inclusion criteria as per US study 156-04-248). Four dose regimens of 5 days duration were tested. Subjects were randomized to 1 of four treatments:

15 mg a.m. +15 mg p.m. (n=9)
30 mg a.m. +15 mg p.m. (n=9)
30 mg a.m. +30 mg p.m. (n=9)
30 mg a.m. + placebo p.m. (n=10)

The first dose was given at approximately 9 in the morning, the second dose 8 hours later. PK assessments were performed for 24 hours after the first dose on day 1, and for 48 hours after the first dose on day 5. These are summarized below:

Figure 5: Study 156-04-249: Mean plasma tolvaptan concentrations following multiple oral doses of tolvaptan for 5 days to subjects with ADPKD

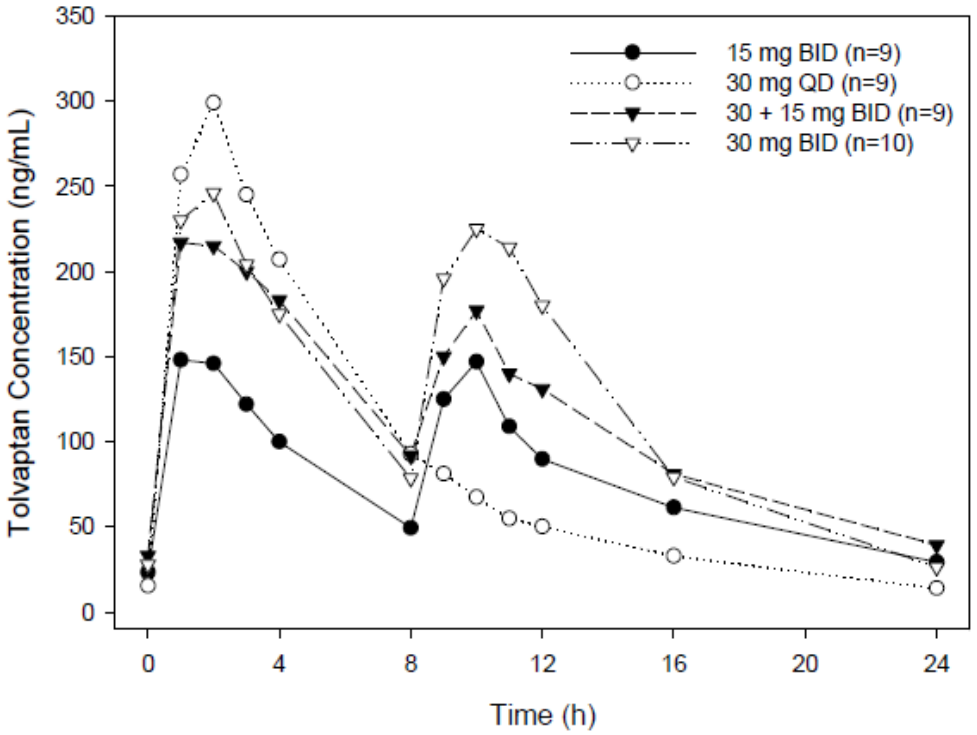


Table 8: Study 156-04-249: Summary of PK parameters following multiple oral doses of tolvaptan for 5 days to subjects with ADPKD

Parameter	TLV 15 mg BID (N = 9)	TLV 30 mg QD (N = 9)	TLV 30 + 15 mg BID (N = 9)	TLV 30 mg BID (N = 10)
C_{max} / $C_{ss,max}$ (ng/mL)	190 (60.5)	330 (230)	269 (69.2)	295 (122)
t_{max} (h)[a]	9.00 (0.95-9.98)	1.98 (0.98-2.98)	0.98 (0.97-9.95)	5.47 (0.93-12.02)
AUC_{0-24h} / AUC_{τ} (ng·h/mL)	1890 (1070)	2140 (1620)	2770 (2020)	2990 (1640)
$t_{1/2,z}$ (h)	6.2 (3.3)	4.3 (1.2)[b]	6.4 (3.7)[c]	4.7 (1.8)[d]
CL_{ss}/F (mL/min/kg)	ND	5.38 (4.88)	ND	ND
$R_{ac}(C_{max})$	1.04 (0.45)	1.03 (0.18)	1.04 (0.26)	0.91 (0.22)
$R_{ac}(AUC)$	1.16 (0.38)	1.09 (0.22)	1.21 (0.24)	1.02 (0.13)

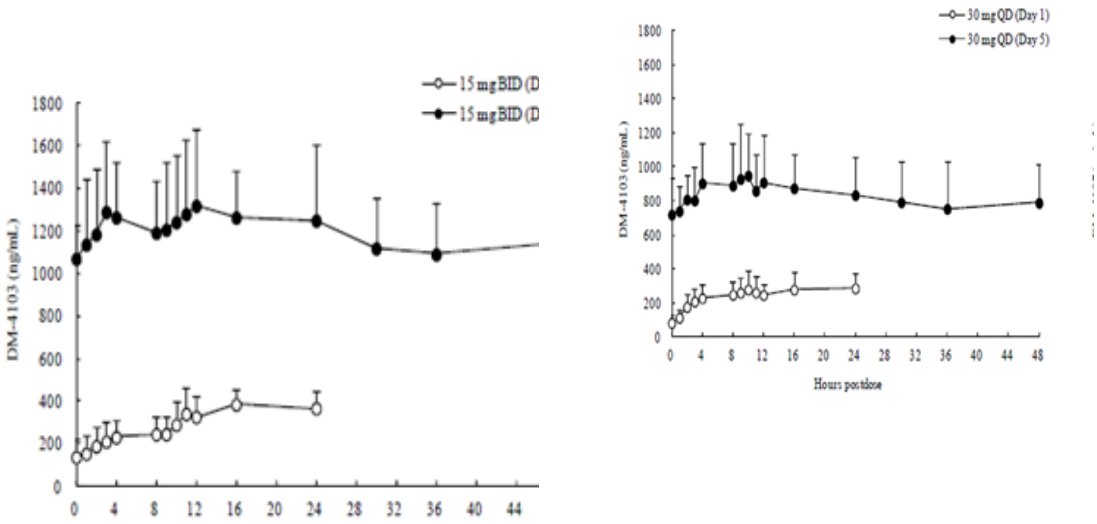
Cmax and AUC were less than dose-proportional between 15 mg b.d and 30 mg b.d; however plasma concentrations following 30 mg in the morning were also around 20% higher compared with healthy subjects. No dose dependence in tolvaptan PK parameters was observed. Accumulation of tolvaptan following multiple oral doses ranging from 30 to 60 mg/day was minimal. This study analysed the major metabolite DM-4103, although this was not presented fully. From the individual data, a similar level of DM-4103 accumulation to the study 156-4-001 (see below) is however apparent

The Japanese study 156-04-001 already mentioned above included a second part which compared 5 days of a split-dose regimen of 15 mg twice daily to 30 mg once daily in the morning. These data are presented below.

Table 9. Study 156-04-001: Summary of PK parameters following multiple oral doses of tolvaptan for 5 days in ADPKD patients

Period III			15 mg BID			30 mg QD		
Trial day	Parameter	(Unit)	n	Mean	SD	n	Mean	SD
Day 1	C_{max}	(ng/mL)	9	202.58	91.30	9	339.01	77.55
	AUC_{24h}	(ng·h/mL)	9	1510.82	722.52	9	1532.37	671.76
	t_{max}	(h)	9	1.11	0.33	9	1.00	0.00
	C_{24h}	(ng/mL)	9	7.51	4.08	9	5.18	6.26
Day 3	C_{24h}	(ng/mL)	9	6.84	3.23	9	5.08	6.94
Day 4	C_{24h}	(ng/mL)	9	6.89	2.36	9	5.43	6.18
Day 5	C_{max}	(ng/mL)	9	205.09	71.63	9	359.19	139.59
	AUC_{24h}	(ng·h/mL)	9	1460.20	524.57	9	1665.31	875.23
	t_{max}	(h)	9	2.78	3.53	9	1.11	0.33
	$t_{1/2,z}$	(h)	9	4.36	0.77	9	5.00	1.47
	λ_z	(h^{-1})	9	0.16429	0.03171	9	0.15237	0.05412
	CL/F	(mL/min)	9	392.49	165.31	9	370.84	160.69
	CL/F/BW	(mL/min/kg)	9	7.520	4.096	9	6.159	3.433
	V_z/F	(L)	9	142.51	48.01	9	144.01	40.71
	V_z/F/BW	(L/kg)	9	2.684	1.102	9	2.311	0.801
	C_{24h}	(ng/mL)	9	7.53	3.47	9	5.99	6.42
	$R_{5,ac}(AUC_{24h})$		9	1.021	0.199	9	1.072	0.228
	$R_{5,ac}(C_{max})$		9	1.070	0.184	9	1.044	0.240
	$R_{5,ac}(C_{24h})$		9	1.083	0.479	9	1.125	0.505

Figure 6: Study 156-04-001: Timecourses of Plasma Concentrations of DM-4103 Following Repeated Oral Administration in ADPKD patients - Comparison Between day 1 and day 5



The main metabolite DM-4103 was eliminated from the plasma very slowly and accumulated with repeated dosing. Following 5 days of dosing the mean accumulation ratio was 4.253 for AUC 0-24. A lesser degree of accumulation was seen with metabolite DM 4107, however the plasma concentrations were around 10 fold lower than DM 4103

The new multiple dose data in patients can be compared to existing healthy volunteer data as follows:

Table 10: Mean (SD) [n] of Tolvaptan pharmacokinetic parameters following oral multiple once daily or split-dose oral doses in healthy subjects and ADPKD Subjects

Dosage Regimen	T_{max} (h)	AUC_{0-24h} (ng·h/mL)	$t_{1/2,z}$ (h)	CLss/F (mL/min/kg)	$R_{ac}(C_{max})$	R_{ac}(AUC)
Healthy Subjects						
30 mg QD	2.00 (1.00-4.00) [41]	1800 ± 730 [28]	—	4.84 (2.18) [28]	1.14 ± 0.31 [41]	1.16 ± 0.22 [21]
ADPKD Subjects						
30 mg QD_{AM} USA	1.98 (0.98-2.98) [9]	2140 ± 1620 [9]	4.3 ± 1.2 [8]	5.38 ± 4.88 [9]	1.03 ± 0.18 [9]	1.09 ± 0.21 [9]
30 mg QD_{AM}	1.00 (1.0- 2.0) [9]	1665.31 ± 875.23 [9]	5.00 ± (1.47) [9]	6.159 ± 3.433 [9]	1.044 ± 0.240 [9]	1.072 ± 0.228 [9]
15/15 mg split-dose	2.04 (1.42-5.42) [9]	1890 ± 1070 [9]	6.2 ± (3.3) [9]	—	1.04 ± 0.45 [9]	1.16 ± 0.38 [9]
15/15 mg split-dose	1.00 (1.0-9.0) [9]	1460.20 ± 524.57 [9]	4.36 ± (0.77) [9]	—	1.070 ± 0.184 [9]	1.021 ± 0.199 [9]
30/15 mg split-dose	0.98 (0.97-9.95) [9]	2770 ± 2020 [9]	6.4 ± (3.7) [5]	—	1.04 ± 0.26 [9]	1.21 ± 0.24 [9]
30/30 mg split-dose	5.47 (0.93-12.02) [10]	2990 ± 1640 [10]	4.7 ± (1.8) [9]	—	0.91 ± 0.22 [10]	1.02 ± 0.13 [10]
90/30 mg split-dose	2.00 (1.00-9.00) [12]	6570 ± 3230 [12]	—	—	—	—

PK parameters following multiple dosing were comparable between healthy subjects and ADPKD patients, although subjects in the PK studies had relatively intact renal function, so the specific renal impairment studies should be referred to. The new data as a whole shows minimal accumulation of tolvaptan following multiple dosing, across the proposed dose regimens. Significant accumulation is seen for the main metabolite DM-4103.

Impaired renal function

Study 156-09-282 explored the effect of a single oral 60 mg dose in subjects with varying degrees of renal impairment. Values for tolvaptan mean Cmax and AUC∞ were about 1.3 and 1.9-fold higher for subjects with creatinine clearance (CrCL) < 30 mL/min when compared to subjects with CrCL > 60 mL/min. Subjects with ADPKD were eligible for this study, however none were recruited.

The next 2 studies were with multiple doses, done specifically in ADPKD patients. Study 156-06-260 assessed PK parameters on day 8 of dosing with the 45/15 split dose regime, whilst study 156-09-284 assessed PK on day 21 of dosing, the dose being titrated to the 90/30 mg dose regime (26/27 patients successfully titrated to this dose). The renal function subgroups were slightly different as shown in the tables below.

Table 11: Study 156-06-260: Day 8 PK parameters, 45/15 dose regime, following the 45 mg a.m. dose

Parameter	eGFR ≥ 60, NBP (n = 5)	eGFR ≥ 60, HBP (n = 3)	eGFR 45 to < 60 (n = 4)	eGFR 30 to < 45 (n = 2)
C_{max} (ng/mL)	270 (52.4)	303 (144)	412 (132)	377 (ND)
t_{max} (h)[a]	2.67 (1.12-4.33)	2.13 (1.03-2.80)	2.89 (2.38-3.18)	2.38 (2.30-2.45)
$AUC_{0-3.5h}$ (ng·h/mL)	635 (72.8)[b]	845 (486)	971 (283)	961 (ND)

Table 12: Study 156-06-284: Day 21 PK parameters on day 21, titration to 90/30 mg regime, following the 90 mg dose

Parameter	$eGFR_{MDRD}$ > 60 mL/min/1.73 m^2 (N = 8)	$eGFR_{MDRD}$ 30 to 60 mL/min/1.73 m^2 (N = 9)	$eGFR_{MDRD}$ < 30 mL/min/1.73 m^2 (N = 9)
C_{max} (ng/mL)	828 (297)	591 (235)	840 (355)
t_{max} (h)[a]	2.00 (1.00-3.00)	2.00 (1.00-3.00)	2.00 (1.00-5.00)
AUC_{0-5h} (ng·h/mL)	2850 (774)	2140 (863)	3100 (1060)

Impaired hepatic function

Based on 87 patients, no clinically significant changes were seen in clearance for doses ranging from 5 to 60 mg, in subjects with mildly or moderately impaired hepatic function (Child-Pugh classes A and B). Very limited information was available in patients with severe hepatic impairment (Child-Pugh class C). Plasma protein binding is not significantly affected by hepatic disease.

In a population pharmacokinetic analysis in patients with hepatic edema, AUCs of tolvaptan in severely and mildly or moderately hepatically impaired patients were 3.1 and 2.3 times higher than that in healthy subjects.

The data include an ascending multiple dose trial in 36 subjects with hyponatraemia secondary to liver disease (Child-Pugh score 6-12, median 10, i.e. mostly class A or B) who received doses ranging from 5 to 60 mg doses, each administered once daily for 13 days, with 5 or 6 subjects per dose (Trial 156-96-203). In this study, after 13 days (13 subjects remaining) Cmax and AUC increased proportionally to dose, and tolvaptan concentrations accumulated 1.7- to 1.8-fold. Clearance following a single dose was about half that of healthy subjects. Following multiple dosing (comparing at 30 mg once daily) clearance was about a third that of healthy subjects. The numbers per subset would have been too small to subdivide this analysis by baseline severity of liver disease.

Age, race, gender and weight

The clearance of tolvaptan is not significantly affected by age or gender following single dosing and 7 days of dosing at 60 mg per day. (Study 156-98-202, in 51 healthy subjects). The effect of weight was estimated in a population PK analysis, which found that tolvaptan oral clearance slightly increased with weight, while apparent volume of distribution was proportional to weight. Study 156-03-242 compared the PK of tolvaptan in Caucasian and Japanese subjects following oral administration in the fasted state, after a high-fat meal and a Japanese standard meal. Tolvaptan mean Cmax and AUC values were slightly higher (+10-30 %) in Japanese subjects with respect to Caucasian subjects, both under fating and fed conditions. The difference was however thought to be due to differences in body weight between the 2 populations, since mean CL/F values adjusted for body weight (mL/min/kg) were very similar.

In ADPKD subjects, single doses were compared in Japanese (Trial 156-04-001) and US (primarily Caucasian, Trial 156-04-248 and 156-04-249) subjects and gave similar results.

There are no existing or new data in children, and the proposed indication is restricted to adults.

Additional information from the ADPKD program is available from the population PK report 156-11-296.

Covariate analysis revealed the following effects:

- A reduction of CL/F when CYP3A4 inhibitors were co-administered and with increased BMI values
- An increase of CL/F with increased eGFRCKD-EPI values
- A reduction of apparent central volume in subjects enrolled in Japanese sites and with increased age
- A higher absorption rate constant in females than in males

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 eGFRCKD-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%. Females appear to have a faster absorption, with Ka 50% greater than that for males. Other covariate effects had a less significant impact. Inter individual variability in PK parameters was within the expected range for such a large population: 43% in CL/F, 34% in Vc/F and 67% in Ka. A visual predictive check showed acceptable model predictive performance across all dose regimens.

Pharmacokinetic interaction studies

No new *in vitro* or *in-vivo* pharmacokinetic interaction studies have been done in the ADPKD program. The proposed dose reduction in ADPKD patients taking strong CYP 3A4 inhibitors is based on modelling, as detailed below.

The table below summarises PK interaction studies, these also include PD interaction studies.

Table 13: Summary of *in vivo* interaction studies

Study	Interacting agent	Subjects (n)	Tolvaptan dose	Ratio of mean values Effect on Tolv		Ratio of mean values Effect on Drug	
				Cmax	AUC	Cmax	AUC
156-96-205	Furosemide 80mg	HV (=6)	30mg	1.18	1.24		
	Hctz 100mg	HV (=6)	30 mg	0.91	1.13		
156-98-201	Ketoconazole 200mg	HV (24;14M)	30mg	**3.48**	**5.40**		
156-01-233	Lovastatin 80mg	HV (30; 23M)	60mg	1.20	1.19		
156-01-234	Digoxin 0.25 x 8 days	HV (14; 9M)	60mg	1.10	1.02		
	Digoxin 0.25 x 12 days	HV (14; 9M)	60mg	1.07	1.02		
156-03-239	Rifampicin 600mg x 8 d	HV (15 (9M)	240mg on day 6	0.17	0.13		
156-03-240	Grapefruit juice 240ml	HV (20; 15M)	60mg	**1.88**	**1.73**		
156-96-205	Furosemide 80mg	HV (6)	30mg			0.90	0.91
156-96-205	Hctz 100mg	HV (6)	30mg			1.08	1.10
156-01-223	Lovastatin 80mg	HV (15;9M)	60mg			1.36	1.33
	Lovastatin 80mg	HV (15;9M)	90mg			1.34	1.38
156-01-226	Amiodarone 200mg	Pts (22;11M)	30mg	1.00	1.01		
	Amiodarone 200		90 mg	1.03	0.96		
						Desethylamiodarone	
	Amiodarone 200	Pts (22;11M)	30mg			1.00	1.01
			90mg			0.99	0.98
156-01-234	Digoxin ss 0.25mg	HV(14; 9M)	60 mg QD x5			**1.30**	**1.18**

The strong CYP 3A4 inhibitor ketoconazole caused a 5-fold increase in tolvaptan AUC, a 3-fold increase in Cmax, and a 50% increase in half-life. Grapefruit juice increased tolvaptan Cmax by 86% and AUC by 56%, without affecting the elimination half-life (consistent with CYP 3A4 inhibition primarily in the gut wall)

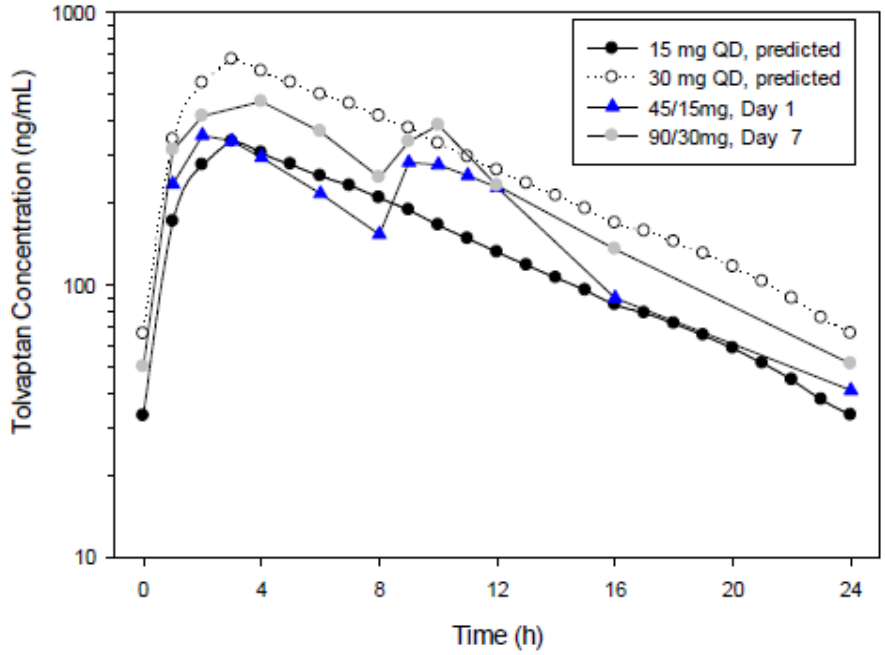
Conversely, the strong CYP inducer rifampicin decreased tolvaptan Cmax and AUCt by 83% and 87% respectively. The effect of CYP3A4 inhibition or induction on the PK parameters varied among metabolites because some of them are also metabolised by CYP3A4. The major metabolite DM-4103 was not found to have the potential for interaction at steady-state concentrations.

Steady state digoxin (P-gp substrate) concentrations were increased, with a 1.3-fold increase in Cmax and a 1.2-fold increase in AUC, when co administered with multiple once daily 60 mg doses of tolvaptan.

No relevant interaction was noted between tolvaptan and statins, amiodarone, or warfarin.

In patients taking strong CYP3A inhibitors, Jinarc is proposed to be administered once daily in doses of 15 mg or 30 mg. Based on previous interaction data, individual subject tolvaptan concentration-nominal time profiles were used to estimate steady state concentrations following regimens of 15 mg or 30 mg once daily, if given with a strong CYP 3A inhibitor. This was compared with data from trial 156-07-262 (45/15 mg regimen) and trial 156-09-285 (90/30 mg regimen). The results of this predictive exercise are shown below.

Figure 7: Median tolvaptan plasma concentrations from superposition predictions for tolvaptan dosed with ketoconazole compared to clinical trial data



Tolvaptan is a CYP 3A4 substrate and also a substrate for P-GP. Data on interactions secondary to other inhibitors and inducers have been added in the SmPC, along with other relevant warnings (see also discussion on safety).

Pharmacokinetics using human biomaterials

For studies using human biomaterials see non clinical part of the report

2.4.3. Pharmacodynamics

Mechanism of action

Stimulation of V2 receptors in the kidney increases intracellular levels of the key "second messenger" molecule, cyclic adenosine monophosphate (cAMP). This activates cAMP-dependent protein kinases that phosphorylate their downstream targets. Stimulation of V2 receptors causes vesicles within the renal epithelial cells containing aquaporin 2 to fuse with the plasma membrane. Aquaporin 2 then forms a transmembrane channel which selectively reabsorbs water from the urine. Other roles of the V2 receptor identified in the kidney are an increase in permeability to urea, stimulation of potassium secretion, and stimulation of sodium reabsorption.

In an animal model of ADPKD, endogenous AVP is elevated; there is elevated renal cAMP, increased accumulation of fluid into cysts and epithelial cell growth. In this model and in preclinical models for similar conditions, tolvaptan delayed development of renal cysts. The preclinical work has been supported by *in vitro* studies using cultures of mural epithelial cells derived from human ADPKD cysts. These cells generated increased amounts of cAMP in response to AVP, which promoted cell

proliferation and electrolyte secretion[1]. Increased fluid secretion into cysts is due to AVP-induced transepithelial secretion of chloride. Human ADPKD patients also have elevated plasma AVP concentrations or exaggerated response of AVP to sodium challenge, compared to normal individuals.[2]

To summarise, tolvaptan is thought to act selectively on the cells from which ADPKD cysts arise. Stimulation of the V2 receptor in the distal nephron elevates intracellular cAMP levels, which is linked to reduced cell proliferation and a decrease of fluid excretion into cysts.

Primary and Secondary pharmacology

There were 6 clinical pharmacology trials in ADPKD subjects which included PD endpoints following single or multiple dosing, the same studies already discussed in the PK section above. The PD endpoints selected for short term clinical trials were based on the observed physiological changes shown to occur in animal data:

- Urine osmolality
- Urine volume/excretion rate
- Free water clearance
- Fluid balance
- Body weight
- Serum or plasma sodium, osmolality, potassium, creatinine, cystatin C, uric acid, urea nitrogen, AVP, AVP-neurophysin, copeptin, renin activity, renin concentration, aldosterone, albumin, cAMP, ionized calcium, intact parathyroid hormone
- Urinary concentrations and excretion of albumin, cAMP, aquaporin 2, sodium, potassium, creatinine, urea nitrogen, uric acid, and aldosterone
- Urine albumin/creatinine and cAMP/creatinine ratios
- Glomerular filtration rate , renal plasma flow , renal blood flow , filtration fraction
- Urinary clearance of creatinine, urea nitrogen, uric acid, sodium and potassium and fractional clearances of free water, urea nitrogen, uric acid, sodium and potassium to creatinine clearance
- Total kidney volume (TKV)
- Mean arterial blood pressure

Primary pharmacology

Inhibition of AVP at the V2 receptor leading to increased renal excretion of water (aquaresis) is the primary pharmacological effect of tolvaptan, and is the mechanism proposed to decrease cAMP and cystogenesis in ADPKD. The aquaretic effect can be easily monitored by measuring urine osmolality. The applicant hypothesizes that suppression of urine osmolality to less than 300 mOsm/kg(hypotonic urine) may decrease secretion of fluid into cysts. Limited dose-response data on total kidney volume is also available from pilot study 156-04-250.

Urine osmolality

In addition to determining the average urine osmolality for each urine collection interval, a spot urine sample obtained prior to the first morning dose tested if suppression were continued through the night. These values were summarized in a number of ways:

- Mean urine osmolality in the spot sample
- Percent of subjects with spot urine osmolality < 300 mOsm/kg
- Duration urine osmolality remained <300 mOsm/kg

[1] Belibi FA *et al*, Reif G, Wallace DP, Yamaguchi T, Olsen L, Li H, Helmkamp GM, Grantham JJ. Cyclic AMP promotes growth and secretion in human polycystic kidney epithelial cells. Kidney International 2004;66: 964-973

[2] Michalski A, Grzeszczak W. The influence of hypervolemia on electrolytes level and hormones regulating volemia in patients with autosomal dominant polycystic kidney disease (ADPKD). Pol. Arch. Med. Wewn 1996;96:329-343

- Area under the urine osmolality curve

In the AUC0-24h, a value <7200 mOsm·h/kg would indicate the average urine osmolality was <300 mOsm/kg.

Single dose data in ADPKD patients: study 156-04-248

In 8 ADPKD subjects with relatively intact renal function given ascending single doses of tolvaptan (as outlined in the PK section above) the number of subjects that had urine osmolality < 300 mOsm/kg for at least 28 hours was 1, 4, 4, and 8 for the 15, 30, 60, and 120 mg doses, respectively. Mean urine osmolality AUC0-28h values for the same doses were 6615, 5313, 4663 and 3251 mOsm·h/kg respectively, and respective average urine osmolality values were 236, 189, 166 and 116 mOsm/kg. Suppression of urine osmolality at 60 mg in this group of subjects was similar to that in healthy subjects (Study 156-09-282)

"Split-dose" regimen in ADPKD patients: Study 156-04-249, 156-04-001, 156-09-285 and 156-04-250

Based on healthy subject data, a 60 mg daily dose as a "split-dose" regimen (45 mg and 15 mg) appeared to provide better suppression of urine osmolality than a single 60 mg dose (study 156-07-262). This was explored in ADPKD patients.

In ADPKD subjects with relatively intact renal function administered tolvaptan in split-dose regimens of 30 to 60 mg/day for 5 days (study 156-04-249), a dose regimen of tolvaptan 15/15 mg was more effective than 30 mg once daily in reducing urine osmolality AUC0-28h, as mean (SD) values were 4871 (1672) and 6322 (3060) mOsm·h/kg respectively. The dosing regimen of 30/15 mg was equally effective as 15/15 mg regimen. The 30/30 mg regimen gave a mean (SD) AUC0-28h of 4216 (1863) mOsm·h/kg.

As tolvaptan daily dose increased, the mean duration of time that urine osmolality remained <300 mOsm/kg also increased; in the 48-hour period after dosing on Day 5, mean values were 34.2, 25.3, 31.5, and 39.6 hours for the 15/15 mg, 30 mg once daily, 30/15 mg and 30/30 mg dose regimens, respectively The number of subjects with mean urine osmolalities of <300 mOsm/kg for 24 hours on Day 5 was 8/9, 4/9, 7/9, and 9/10 for the four regimens, respectively.

In groups of 9 Japanese subjects with ADPKD and relatively intact renal function (Trial 156-04-001), mean (SD) urine osmolality AUC0-28h on Day 5 for tolvaptan 15/15 mg and 30 mg once daily regimens were 4592.4 (1961.7) and 8332.4 (2175.2) mOsm·h/kg, respectively, and the mean duration of suppression <300 mOsm/kg was 25.3 (5.3) and 16.4 (7.9) hours respectively. When compared to US subjects in trial 156-04-249, discussed above, mean AUC0-28h values for the 15/15 mg regimen were similar but the 30 mg once daily regimen was much less effective. The mean duration of suppression <300 mOsm/kg was about 9 hours shorter for Japanese subjects for both regimens.

In US subjects with ADPKD (eGFRMDRD>60 mL/min/1.73 m^2) administered the 90/30 mg split-dose regimen for 7 days, the mean urine osmolality AUC0-24h was 3226.9 (555.3) mOsm·h/kg (for an average concentration of 134 mOsm/kg). All subjects had urine osmolality in each collection interval maintained below 300 mOsm/kg and 11/12 subjects had urine osmolality <300 mOsm/kg at 23.5 hours postdose. These results were obtained while subjects were in an in-clinic setting, with defined schedules for meals, sleeping and PK/PD assessments.

Similar results were seen in the outpatient setting of the open-label trial 156-04-250, which included subjects previously enrolled in Trial 156-04-248 and Trial 156-04-249. During the titration period of this trial, subjects self-administered tolvaptan in an out-patient setting and collected spot urine samples prior to the first dose, prior to the second dose and prior to bedtime, according to their own schedules, on the day prior to their clinic visit. Mean urine osmolality values for spot urine samples taken prior to the first dose, prior to the second dose and prior to bedtime during weeks 1 through 4 of the titration period are presented in the table below.

Table 16: Study 156-04-250: Mean (SD) Urine Osmolality (mOsm/kg) Following Split-dose Regimens of Tolvaptan in ADPKD Subjects

Time of Day	Week of Treatment and Dose					
	Day 0	Week 1	Week 2	Week 3	Week 4	
	Baseline n=45	30/15 mg n=45	45/15 mg n=43	60/30 mg n=43	45/15 mg n=14	90/30 mg n=27
Before First Dose	467 (227)	276 (143)	264 (104)	239 (122)	300 (99)	174 (98)
Before Second Dose	455 (237)	191 (108)	154 (66)	140 (70)	175 (85)	136 (58)
Before Bedtime	438 (207)	170 (106)	163 (75)	136 (110)	206 (109)	108 (28)

The percentage of subjects with urine osmolality > 300 mOsm/kg in this study is presented in the next table.
As tolvaptan doses increased, urine osmolality prior to the second dose and prior to bedtime were most easily suppressed.

Table 17: Study 156-04-250. Percent of Subjects with Urine Osmolality greater Than 300 mOsm/kg Following Split-dose Regimens of Tolvaptan in ADPKD Subjects

Time of Day	Week of Treatment and Dose					
	Day 0	Week 1	Week 2	Week 3	Week 4	
	Baseline n=45	30/15 mg n=45	45/15 mg n=43	60/30 mg n=43	45/15 mg n=14	90/30 mg n=27
Prior to First Dose	76	36	30	23	58	15
Prior to Second Dose	67	16	2.3	2.3	7.1	0
Prior to Bedtime	62	8.9	7.0	2.3	8.3	0

Following the 60/30 mg regimen, 23% of subjects had urine osmolality >300 mOsm/kg at prior to first dose and of the 27 subjects that up- titrated up to the 90/30 mg regimen, 15% were still not maximally suppressed prior to first dose.

PD effect according to degree of renal impairment: Study 156-06-284

The most relevant data in renal impairment are from study 248, in which subjects were titrated to a maximum dose of 90/30mg. The baseline data shows (as expected) that patients with severe renal impairment were less able to form concentrated urine, given a reduction in functional nephrons and thus a reduction in V2 receptor density. Consequently, although an effect is still seen, there is less of a response to tolvaptan as renal impairment progresses.

Table 18: Study156-06-284: Mean Urine Concentrations (24-hour Collection) after 3 Weeks of Tolvaptan Treatment

Osmolality (mOsm/kg)			
Baseline	506.22 (142.59)	299.00 (91.97)	291.68 (67.69)
Final Treatment	153.42 (51.54)	136.76 (23.34)	158.88 (26.98)
Change from Baseline	−352.8 (130.52)[a]	−162.2 (95.08)[a]	−132.8 (51.30)[a,c]

Secondary Pharmacology

Many of the other pharmacological effects studied relate to aquaresis. These include urine volume, body weight, effect on serum electrolytes and urine sodium excretion, and effect on plasma AVP concentrations. Whilst these are important in SIADH, in the treatment of ADPKD patients without hyponatraemia or oedema any pronounced effect on sodium or fluid balance could be undesirable.

Reductions in GFR due to tolvaptan were observed in some subjects in the assessment of the Samsca MAA, and clearly this is highly relevant to the ADPKD indication. GFR was assessed in detail in the 2 of the PD studies, along with renal plasma flow, renal blood flow and filtration fraction. Various other markers were studied, including urinary cAMP and aquaporin 2 as exploratory markers of action, and urine albumin excretion. A QT study was also submitted (156-03-245).

Urine volume

In healthy subjects, urine excretion rate was increased at tolvaptan concentrations as low as 25-40 ng/mL, these concentrations were achieved within approximately 20 minutes after a 45 mg dose of tolvaptan. A maximal urine excretion rate of 3-5 times greater than baseline was observed at plasma concentrations above100 ng/mL. Marked elevations of tolvaptan plasma concentrations produced a sustained effect, but not a greater magnitude of response.

Single dose data in ADPKD patients: study 156-04-248

In US ADPKD subjects with relatively intact renal function, changes in urine volumes and excretion rates were similar to those previously observed in healthy subjects. For example, mean 24-hour urine volumes of 8209 and 10126 mL were seen following single 60 and 120 mg doses, respectively. Also, the rate of offset of effect for the above doses was similar for ADPKD and healthy subjects as urine excretion rates had returned to baseline by the 24-28 hour collection interval for both groups.

Split-dose regimen in ADPKD patients: Study 156-04-249, 156-04-001, 156-09-285 and 156-04-250

ADPKD subjects with relatively intact renal function showed a reduction in daily urine volume following multiple doses. For subjects given 30 mg once daily or split-dose regimens ranging from 15/15 mg to 30/30 mg, 24-hour urine output on Day 5 was about 20% less than observed on Day 1. In clinical pharmacology trials with ADPKD and relatively intact renal function maintained on a 60/30 mg (1 subject in 284 trial) or 90/30 mg dose regimen for at least 7 days, mean (SD) 24-hour urine volumes were 7464 (2103) mL and 6532 (2036) mL

Effect according to degree of renal impairment: Study 156-06-284

As renal function declines, the volume of urine produced for a given dose of tolvaptan declines; following a 90/30 mg split-dose regimen, mean (SD) 24-hour urine volumes for subjects with ADPKD and $eGFR_{MDRD}$ 30 to 60 and <30 mL/min/1.73 m^2 were 6233 (1307) mL and 5024 (1767) mL, respectively (table). Taking into account the variability seen, the differences between the 2 groups with the most pronounced renal impairment are not well defined.

Table 19: Study156-06-284: Change in 24 hour urine volume after 3 weeks of tolvaptan treatment (patients titrated to 90/30 mg regime)

Parameter	$eGFR_{MDRD}$ > 60 mL/min/1.73 m^2 (N = 9)	$eGFR_{MDRD}$ 30 to 60 mL/min/1.73 m^2 (N = 9)	$eGFR_{MDRD}$ < 30 mL/min/1.73 m^2 (N = 9)
24-hour Collection (mL)			
Baseline	1981.7 (552.8)	2959.4 (789.9)	2809.4 (857.7)
Final Treatment	6532.8 (2036.9)	6233.9 (1307.1)	5024.4 (1767.5)
Change from Baseline	4551.1 (1792.7)[a,b]	3274.4 (1293.3)[a]	2215.0 (1142.0)[a,c]

Acute effect on renal function

The acute effect of tolvaptan on GFR was formally assessed in both done specifically in ADPKD patients with varying degrees of renal impairment, studies 156-06-260 and 156-09-284.

Measured GFR (mGFR, based on iothalamate clearance) values at baseline ranged from 30.4 to 159.2 mL/min and 18.0 to 148.4 mL/min respectively, in the two trials. Results from the two trials were comparable. Modest (approximately 6-10%) but statistically significant, reductions in mean mGFR were seen in subjects with well preserved (mGFR MDRD> 60 mL/min) and moderately impaired (30-60 mL/min) renal function, and a decrease of 2.1% was seen in subjects with poor renal function (< 30 mL/min)

The results from the larger study 156-06-284 are shown in the table below.

Table 20: Study156-06-284: Change in mGFR after 3 weeks of tolvaptan treatment and at 3 weeks post-treatment (patients titrated to 90/30 mg regime)

Parameter	$eGFR_{MDRD}$ > 60 mL/min/1.73 m^2 (N = 9)	$eGFR_{MDRD}$ 30 to 60 mL/min/1.73 m^2 (N = 9)	$eGFR_{MDRD}$ < 30 mL/min/1.73 m^2 (N = 9)
mGFR (mL/min)			
Baseline	112.3 (20.3)	66.3 (20.3)	29.3 (10.6)
Final Treatment	104.3 (22.7)	60.1 (16.6)	28.6 (10.0)
Change from Baseline	−8.0 (9.1)[a]	−6.2 (6.2)[a,b]	−0.7 (1.5)[c]
Percent Change	−7.4 (8.7)	−8.4 (6.8)[a]	−2.1 (5.5)
Post Treatment	112.3 (23.1)	64.8 (18.1)	26.9 (9.3)
Change from Baseline	0.1 (4.9)	−1.5 (4.0)	−1.2 (3.0)
Percent Change	−0.3 (4.8)	−1.4 (5.2)	−2.6 (12.4)

The mGFR results were comparable irrespective of duration of tolvaptan exposure (8 days compared with 2 days) suggesting that changes in response to tolvaptan administration occur within days after the start of dosing. At 21 days post-treatment, although most mean change from baseline GFR values were negative; they were not significantly different from baseline. The percent change from baseline in renal plasma flow (RPF), as measured by clearance of hippuran, decreased as baseline GFR decreased and was highly correlated with the percent change in mGFR. As this was the case, filtration fraction (mGFR/RPF) was minimally affected.

Mean creatinine and uric acid clearances were decreased about 12-16% and 20-25%, respectively, and the percent decreases were independent of baseline renal function. Tolvaptan administered as 60+30 mg or 90+30 mg regimens had a small negative effect on urea nitrogen clearance. There was no effect on sodium or potassium clearance at any level of renal impairment

Other endpoints

In line with the small reduction in GFR, tolvaptan treatment initially increases serum or plasma creatinine and cystatin C (a further marker of renal function), as well as increasing uric acid levels. There is also a small increase in AVP, mirrored in AVP-neurophysin, and copeptin concentrations. For parameters where post-treatment concentrations were measured, concentrations returned to baseline after discontinuation of tolvaptan. Tolvaptan-induced increases in plasma sodium and osmolality are related to the aquaretic action of tolvaptan and the subsequent production of urinary free water.

In the ascending dose tolerance trial in subjects with ADPKD (156-04-248) in which single doses of tolvaptan 15-120 mg were given, serum sodium concentrations exhibited dose-related increases with a maximal mean increase of around 5 mmol/L at 12 h for the 120-mg dose.

Tolvaptan treatment did not meaningfully change urea nitrogen, potassium, albumin, aldosterone, renin, cAMP, calcium, or parathyroid hormone concentrations. Following multiple doses, tolvaptan treatment did not have a clinically significant effect on albumin, sodium, osmoles, potassium, urea nitrogen or aldosterone urinary excretion or the albumin/creatinine ratio.

Urinary excretion of cAMP and unglycosylated aquaporin 2 decreased following multiple doses of 30 to 60 mg/day to subjects with ADPKD. These results are consistent with the proposed mechanism of action.

Changes in urine creatinine and uric acid excretion were consistent with changes observed in clearance; however the clearance of uric acid was reduced to a proportionally greater extent. This is consistent with an effect of tolvaptan reducing distal reabsorption of sodium and sodium dependent uric acid reabsorption.

In a thorough QT study (study 156-03-245) 172 subjects in 4 groups (43 subjects per arm) participated; 30 or 300mg tolvaptan, placebo and 400 mg moxifloxacin were administered for 5 consecutive days. Independent reviewers blinded to each subject's treatment read the digital ECGs manually. There was no significant change from baseline in mean QTc on day 5 following multiple doses of either 30 or 300 mg dose of tolvaptan. In contrast, moxifloxacin increased mean QTc by 8.20 msec (95% CI 5.89 to 10.50 msec). The plot of change in QTcI (from time matched baseline values) against drug concentration had a positive slope only for moxifloxacin. In a *post hoc* analysis, the largest time matched difference in QTc on day 5 was seen with moxifloxacin with an increase of 15.78msec (95% CI upper limit 19.35) at 2hours post dose, while that for tolvaptan was 2.68msec (Upper limit 6.75 msec) at 300mg dose.

Relationship between plasma concentration and effect

The key PD endpoint of change in urine osmolality, which is a measure of AVP suppression, showed a dose-response as discussed above, however due to due to the variability in PK parameters and the effect of covariates such as GFR, body mass index, gender, and of use of CYP3A4 inhibitors, analysis of clinical responses by modal dose was not definitive for exposure-response. The PK/ PD model (report 156-11-296) therefore derived individual estimates of tolvaptan exposure for subsequent PK/PD analyses. There was no clear exposure response for the clinical endpoints tested. However, change in urine osmolality was correlated with tolvaptan exposure using Cmin,ss for individual subjects. Reductions in urine osmolality were also positively correlated with reductions in the rate of increase in total kidney volume, and subjects with greater suppression of urine osmolality were also less likely to experience an ADPKD clinical progression event.

Use of the highest proposed dose, 90+30 mg, is supported by the urine osmolality PK/PD model and considering the Cmin and AUC at steady state. The Cmin,ss corresponding to 50% of the maximum effect was 43 ng/mL, around the expected Cmin,ss values with the 45+15 mg split-dose regimen (geometric mean of 38 ng/mL). The Cmin,ss geometric mean value at the 90+30 mg split-dose regimen was 81 ng/mL, corresponding to 70.9% of the maximum effect. Likewise, the AUCss corresponding to 50% of the maximum effect was situated between the expected AUCss values obtained with the split-dose regimens of 45+15 mg (geometric mean of 3.7 µg·mL-1·h) and 60+30 mg (geometric mean of 5.5 µg·mL-1·h). The AUCss geometric mean value for the 90+30 mg split-dose regimen was 7.5 µg·mL-1·h, corresponding to 88% of the maximum effect.

Pharmacodynamic interactions with other medicinal products or substances

No additional formal PD interactions are submitted for the Jinarc MAA.

Interaction with diuretics

The PK and PD interactions between tolvaptan and furosemide or hydrochlorothiazide (HCTZ) were determined in a single-centre, randomised, open-label, parallel-arm, 3- period crossover study in healthy male volunteers (study 156-96-205). Twelve subjects were enrolled, with six subjects assigned to each of the two treatment arms: Arm 1 involved 30 mg tolvaptan/80 mg furosemide. Arm 2 involved 30 mg tolvaptan/100 mg HCTZ. Doses were separated by a 48-hour washout. No clinically significant changes were noted in the PK profiles of tolvaptan and furosemide, or tolvaptan and HCTZ, when co-administered. Free water clearance, 24- hour urine volume, plasma Na+ and AVP concentrations, and plasma osmolality were higher, while urine osmolality was lower, when tolvaptan was administered either alone, or in combination with furosemide or HCTZ, compared with furosemide or HCTZ administered alone. At 24 hours post-dose, plasma renin activity was increased following furosemide or HCTZ administered alone or with tolvaptan; it was unchanged following tolvaptan alone. Tolvaptan did not significantly affect the natriuretic activity of furosemide or HCTZ. Furosemide and HCTZ did not significantly affect the aquaretic activity of tolvaptan. An increase in free water clearance and urine volume were higher, but urine osmolality lower. Free water clearance was increased following tolvaptan administration alone and in combination with either furosemide or

hydrochlorothiazide. Co-administration with furosemide or HCTZ did not change the effect of tolvaptan.

No significant PD interaction was seen in this study. However, subsequent to the grant of the MAA for Samsca, a signal was identified for the risk of more severe dehydration when tolvaptan is given with a diuretic, leading to renal dysfunction this is also reflected in the Jinarc SmPC in sections 4.4, 4.5 and 4.8.

Other PD interactions

In addition to its 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 reduced in patients using such analogues (used to prevent or control bleeding) when co-administered with tolvaptan. This was added to the Samsca product information by variation following a case report. The Jinarc SmPC reflects general statements on medications which can interact with tolvaptan. These include diuretics, vasopressin analogues, and therapies which raise or lower serum sodium concentration.

Genetic differences in PD response

Approximately 85-90% of patients with ADPKD have an abnormality on the short arm of chromosome 16, coding for PKD1 (polycystin 1) and giving rise to ADPKD type 1. A second defect, termed ADPKD type 2 (dysfunction of polycystin 2, ADPKD type 2), is responsible for 10-15% of cases and is found on the long arm of chromosome 4. A third genotype may exist, but no genomic locus is assigned.

The two variants of ADPKD appear to differ primarily in the relative number of visible renal cysts formed at any given age. The mean age of ESRD for patients with ADPKD1 is 53 years, whilst the mean age of ESRD for patients with ADPKD2 is 74 years. ADPKD genotype was not assessed in any of the submitted studies.

2.4.4. Discussion on clinical pharmacology

Basic PK profile

Standard pharmacokinetic parameters following single and multiple dose administration have been described. This includes multiple dose data in ADPKD patients with the proposed split dose regimens. The analytical methods used in the Jinarc development program have been validated satisfactorily. The PK studies including the population PK report are also acceptable in design and methods of analysis.

Tolvaptan is a lipophilic molecule with poor aqueous solubility. Whilst the formulation allows rapid absorption and reasonable bioavailability, dissolution and/or saturation limitations probably explain both the Cmax plateau at very high doses and the effect of food on absorption.

Tolvaptan is extensively bound to plasma proteins, as reflected in the low volume of distribution. Tolvaptan is a CYP3A4 and P-gp substrate. It is extensively metabolized; the terminal elimination half-life is about 8 hours.

Jinarc shows dose proportionality within the therapeutic dose range. Cmax increases linearly with dose from 30-300 mg and a plateau is noted at doses >300mg. The AUC also increased linearly up to the maximum single dose studied of 480 mg.

Data from healthy subjects and patients showed minimal accumulation of tolvaptan following multiple administration.

The applicant evaluated food effect with the 90 mg tablet within a bioequivalence study. A high-fat meal increased absorption and Cmax values of tolvaptan, an effect which was not seen with previous food interaction studies at the 30 and 60 mg dose. Given the PK/PD relationship and the lack of significant tolerability issues related to peak drug level for tolvaptan, the observed food effect for

Cmax is of doubtful clinical significance but to minimise the unnecessary risk of increasing the maximal exposure the morning dose should be taken under fasted conditions as outlined in the SmPC.

Notes on main metabolite

The main metabolite DM-4103 is eliminated from the plasma more slowly than the parent and therefore accumulates with repeated dosing. Following 5 days of dosing the mean accumulation ratio was 4.253 for AUC 0-24h. A lesser degree of accumulation was seen with metabolite DM 4107, however its plasma concentrations were around 10-fold lower than DM 4103. In patients with renal impairment, the mean half-life for DM-4103 was considerably longer (308 hours) for subjects with eGFRMDRD < 30 compared to subjects with lesser degrees of renal impairment.

Whilst this metabolite has previously been noted as having no pharmacological activity, given the higher doses proposed for Jinarc compared to the separate Samsca MAA, the potential for long term use and target population of patients with renal impairment, the applicant has provided information on its pharmacological activity, including any effect on CYPs or drug transporters, following the exposure levels anticipated in a "worst case" scenario. The data provided by the applicant showed that there is no separate trial which includes multiple dose metabolite PK data in ADPKD patients receiving the highest proposed dose regime. The applicant however notes that 7.5 µg/mL (15.7 µM) is the average concentration in the pivotal 156-04-251 trial, from steady state sampling at 12, 24 and 36 months. The response also provides reassurance that the pharmacological activity at the V2 receptor is associated with tolvaptan and not DM-4103. Regarding other receptors, non-clinical pharmacology studies indicated low potential for the metabolite to have any pharmacological activity. The highest concentration tested across all receptors was 4.5 µg/mL, but the human plasma albumin concentration would be about 10 times higher than those used in the above assays, reducing the free concentration.

Preclinical studies did not show hepatotoxicity after 6 and 9 months in non-clinical species given the parent and exposed to the main metabolite, although these data are now superseded by the clinical data.

In clinical trial subjects adjudicated for hepatic toxicity events, DM-4103 concentrations were highly variable and were not higher when compared with other subjects. Despite this and the presumption that hepatic toxicity with Jinarc is idiosyncratic rather than dose related, the role of DM-4103 cannot however be ruled out in the absence of a confirmed alternative mechanism, the limited number of serious hepatotoxicity cases, and the lack of long-term in vivo toxicity studies involving DM-4103. The planned post authorisation safety study will give more insight into the hepatic safety of Jinarc (as described in the RMP).

Bioequivalence data

The submitted bioequivalence data support the expanded range of strengths required for the proposed dose regime in ADPKD.

Renal impairment

The proposed SmPC states that dose adjustment is not required in patients with renal impairment. As the risk of hepatic damage in patients with severely reduced renal function (i.e. eGFR < 20) may be increased these patients will need to be carefully monitored for hepatic toxicity as outlined in the SmPC. Given the lack of renal clearance for the active molecule, no relationship between renal function and exposure is expected on this basis; however in general terms, the disease state of renal impairment can impair hepatic metabolism indirectly, affect the elimination of metabolites, or change weight and volume of distribution. Renal impairment may also affect the level of plasma proteins, however plasma protein binding of tolvaptan was previously determined to be unaffected by renal function.

The previously available data from the Samsca MAA was limited. Therefore 3 studies in ADPKD patients with varying degrees of renal impairment have been submitted. Overall there is no significant correlation between tolvaptan and baseline renal function, although the numbers are relatively small and there is considerable intersubject variability within each subset. A population PK analysis however revealed a reduction of clearance with worsening renal function, with a decrease in eGFRCKD-EPI resulting in a 32% reduction in CL/F. No clinical trials in subjects with a creatinine clearance <10 mL/min or in patients undergoing dialysis have been conducted. There is also no clinical rationale for the use of tolvaptan in ADPKD patients with end-stage renal failure and the SmPC states that the treatment should be discontinued if the stage of renal insufficiency progresses to CKD stage 5.

Pharmacodynamic data discussed later show reduced effectiveness with worsening renal function and further data on efficacy in later stages of ADKPD is to be provided within a post authorisation efficacy study as outlined in Annex II and RMP (see efficacy discussion and Benefit Risk section of this report)

Hepatic impairment

No new formal PK data in hepatic impairment are presented for the ADPKD indication; the dosing recommendations are basically derived from the previous Samsca development program. The effect of hepatic impairment on PK may differ by the cause of liver disease, so even the limited existing data such as in patients with hepatic oedema secondary to CHF might not directly extrapolate. However, in a population pharmacokinetic analysis in patients with hepatic oedema, AUC of tolvaptan in severely and mildly/moderately impaired patients was respectively 3.1 and 2.3 times higher than that in healthy subjects. Clearly, there may be concomitant liver disease in ADPKD patients due to other reasons, but cystic involvement of the liver (polycystic liver disease) is common in AKPD, especially in female patients. Significant hepatic impairment due to massive cystic involvement is uncommon; however acute hepatic impairment can result from infection, haemorrhage, rupture or torsion of single cysts. Rarely, ADPKD patients may have additional congenital defects. Overall, PK data are limited in patients with hepatic impairment, especially in patients with severe impairment whose benefit risk is to be carefully evaluated and monitored by the treating doctor as outlined in the smPC.

Other special populations

Clearance of tolvaptan is not affected by gender or race to a clinically significant extent. A population PK analysis revealed a reduction of clearance with increased BMI values (as dose is not weight-based) and increased age. There is increased absorption in females, the reasons of this are not clear. There are no available data in children. and tolvaptan is indicated in adults only.

Interactions

Steady state digoxin concentrations were increased (1.3-fold for Cmax, 1.2 fold for AUCt) and patients receiving digoxin should be evaluated for excessive digoxin effects when treated with Jinarc as outlined in the SmPC. Also, tolvaptan increased plasma levels of lovastatin by 1.3 to 1.5-fold. This indicates that tolvaptan can potentially increase exposure to CYP3A4 and P-gp substrates. Interactions secondary to other inhibitors and inducers have been added in the SmPC.

The applicant has provided further clarification on the expected concentrations of tolvaptan in the intestine following the highest proposed dose, and the expected free concentration at the liver and kidney, where MDR1 efflux transporters are also found. Although the plasma concentrations calculated at only 40 fold are not above the 50 fold IC50 recommended in the CHMP interaction study guideline, the Ki would be expected to be lower, therefore it is agreed that the effect is likely to be due to inhibition in the intestine and is likely to be similar at the higher dose. For cytochrome P450s, all IC50's are reported as greater than 50 µM with the exception of 2C8/9 which is reported as 38.9 µM. Therefore any effects on CYP 3A4 are likely to be in the intestine only and a similar argument would apply with effects at the higher dose likely to be similar. For CYP1A1/2, CYP2C8/9, CYP2C19, CYP2D6,

CYP2E1, and CYP3A4, a human liver microsome study suggests little potential for interaction for the DM-4103 metabolite.

The SmPC has been amended to advise caution with sensitive P-gp substrates such as digoxin which is acceptable for marketing authorisation. An in vitro P-glycoprotein (P-gp) study with DM-4103 is on-going and results will be submitted as described in the RMP.

Studies with tolvaptan and DM-4103 to assess the potential inhibition of other drug transporters (BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, BSEP, MATE1, and MATE2-K) show potential for interaction. For marketing authorisation adequate cautionary statements on the use with substrates for OAT3, OATP1B1 and 1B3A have been added to the SmPC and the risk is considered balanced. As interactions at BCRP in the gut and OCT 1 in the liver are relatively rare they are handled with cautionary statements in the SmPC.

However clinical studies are recommended to look at interactions with OAT3, OATP1B1 and 1B3 substrates, unless clinical PK or safety data can be provided or further justification that these studies can be waived based on new modelling and analysis of existing data.

The proposed SmPC recommends that concomitant administration of Jinarc with potent CYP 3A inducers are to be avoided. For patients taking moderate CYP3A inhibitors, twice daily split dose regimen are applied but in reduced doses by half which is acceptable.

The applicant has committed in the RMP to conduct a new drug-drug interaction trial using fluconazole as a moderate CYP3A4 inhibitor, and is also recommended to provide further analysis and modelling data regarding more frequent co-administration of CYP 3A4 inhibitors than the existing ketoconazole study, as well as administration of CYP 3A4 inhibitors with a shorter or longer half-life. The SmPC contains appropriate cautionary statements to balance the risk for authorisation.

Pharmacodynamics

Based on the background research, preclinical and *in-vitro* data presented by the applicant, an effect in ADPKD is definitely plausible and the endpoints chosen for initial studies were appropriate to assess the pharmacology in ADPKD patients.Inhibition of AVP at the V2 receptor leading to increased renal excretion of water (aquaresis) is already a well-established effect of tolvaptan from the Samsca program, and inhibition of the V2 receptor is also the mechanism proposed to reduce cyst progression in ADPKD.

The aquaretic effect can be easily monitored by measuring urine osmolality, which is a marker for AVP level and a practical tool to optimise the clinical benefit of tolvaptan therapy in ADPKD patients. There is a clear ceiling effect for aquaresis. A maximal urine excretion rate of 3-5 times greater than baseline was observed at tolvaptan concentrations >100 ng/mL. Marked elevations of tolvaptan plasma concentrations produced a sustained, but not a greater magnitude of response.

The applicant hypothesizes that suppression of urine osmolality to less than 300 mOsm/kg (hypotonic urine) decreases secretion of fluid into cysts. Given this and the need, based on preclinical work, to maintain a constant effect, the applicant has explored modified release formulations, but instead proposes a “split-dose” dosing regimen – twice daily doses separated by 8 hours with the main dose being given in the morning. This is proposed to maintain constant inhibition of the V2 receptor, whilst hopefully avoiding excessive diuresis at night which would cause disruptive nocturia for the patient.

At the proposed split-dose regimens of 45+15 mg to 90+30 mg daily, tolvaptan clearly blocks AVP at the V2 receptor, increasing urine output and suppressing urine osmolality in ADPKD subjects. The 45/15 mg dose was the lowest at which >90% of subjects had urine osmolality values below 300 mOsm/kg before the pre-second dose and pre- bedtime samples, indicating that urine osmolality would be suppressed for at least 16 hours per day. A 60/30 mg regimen may be suitable for many subjects, with the 90/30 mg regimen providing additional inhibition in others. Complete suppression could not be achieved at any of the dose regimens, as the top dose is limited by tolerability.

Other than urine osmolality, due to the variability in PK parameters and the effect of covariates such as GFR, body mass index, gender, and of use of CYP3A4 inhibitors, analysis of clinical responses by modal dose was not definitive for exposure-response. However, change in urine osmolality was correlated with tolvaptan exposure using Cmin,ss and AUCss for individual subjects.

Pilot data suggested a dose-response for total kidney volume in study 250; this is referred to in the efficacy section of this report.

Pharmacodynamic effect in renal impairment

The baseline data shows (as expected) that patients with severe renal impairment were less able to form concentrated urine, given a reduction in functional nephrons and thus a reduction in V2 receptor density. Consequently, although an effect is still seen, there is less of a response to tolvaptan as renal impairment progresses. There is a short-term and reversible haemodynamic effect when tolvaptan is initiated, as discussed below. This effect decreases as renal function declines, but there are limited data in patients with more severe renal impairment.

Secondary pharmacodynamic effects

Whilst the therapeutic rationale in ADPKD is to slow the rate of renal progression, tolvaptan at dose regimens of 45+15 mg to 90+30 mg, initially decreases GFR by around 6 to 10%. These changes occur rapidly and are reversible after the end of tolvaptan treatment. The potential causes are discussed in the submitted reference by Irazabal *et al* 2011.[3] The authors speculate that this is probably not explained by the small relative contraction of plasma volume, or via direct haemodynamic effects of elevated vasopressin on V1a receptors in the renal vasculature. It is hypothesised that the effect could be due to reduced pressure within the glomerulus due to a direct effect of AVP, or due to some hemodynamic changes involving tubuloglomerular feedback that occur in response to the decrease in urine osmolality. If this is the case, if the offset of tolvaptan's action on urine osmolality after discontinuation of treatment is rapid and it would be expected that the decreases observed in eGFR would be quickly reversible as well.

Tolvaptan-induced increases in plasma sodium and osmolality are related to the aquaretic action of tolvaptan and the subsequent production of urinary free water. Overall in ADPKD patients, sodium concentrations exhibited dose-related increases (from a generally normal baseline value) with a maximal mean increase of around 5 mmol/L at 12 h for the 120 mg dose.

In line with the small initial reduction in GFR, tolvaptan treatment initially increases serum or plasma creatinine and cystatin C (a further marker of renal function), as well as increasing uric acid levels. There is also a small increase in AVP, mirrored in AVP-neurophysin, and copeptin concentrations. For parameters where post-treatment concentrations were measured, concentrations returned to baseline after discontinuation of tolvaptan. Tolvaptan treatment did not meaningfully change urea nitrogen, potassium, albumin, aldosterone, renin, calcium, or parathyroid hormone concentrations. Following multiple doses, tolvaptan treatment did not have a clinically significant effect on albumin, sodium, osmoles, potassium, urea nitrogen or aldosterone urinary excretion or the albumin/creatinine ratio. Urinary excretion of cAMP and unglycosylated aquaporin 2 were decreased following multiple doses of 30 to 60 mg/day to subjects with ADPKD. These results are consistent with the proposed mechanism of action.

Changes in urine creatinine excretion and uric acid excretion were consistent with changes observed in clearance; however the clearance of uric acid was reduced to a proportionally greater extent. This is consistent with tolvaptan reducing distal reabsorption of sodium and sodium dependent uric acid reabsorption. Hyperuricamia is an identified risk of tolvaptan treatment and a common adverse event as labelled in the SmPC.

[3] Short-term effects of tolvaptan on renal function and volume in patients with autosomal dominant polycystic kidney disease. Irazabal MV *et al*. Kidney International (2011) 80, 295–301

A thorough QT study did not indicate the potential for QT interval prolongation.

V2R is now known to be expressed in many extrarenal tissues, including vascular and pulmonary endothelial cells, the inner ear, parathyroid, nonkeratinized squamous epithelia, exocrine pancreas, salivary glands, smooth muscle, breast cells, and Leydig cells. There is also evidence to suggest that the V2R is expressed at low levels in the brain. It is accepted that activation of the V2 receptor in vascular endothelium increases the circulating levels of coagulation factor VIII, VWF, and tissue plasminogen activator. However, the relevance and function of V2Rs in other cell types is not determined and no adverse events are signaled for related off-target effects w.

Pharmacodynamic interactions

As anticipated from the properties of tolvaptan, there are potential pharmacodynamic interactions between tolvaptan and diuretics, when co-administered with medicinal products that affect serum sodium concentration, and vasopressin analogues such as desmopressin. The applicant has not considered possible PD interactions such as hypotension, orthostatic hypotension, and dizziness due to the combination of tolvaptan with diuretics or non-diuretic anti-hypertensive drugs, and the pivotal study did not measure standing blood pressure. Therefore the prescriber is made aware in the SmPC on the lack of specific data about standing blood pressure and the possibility of hypotension which is acceptable.

2.4.5. Conclusions on clinical pharmacology

Pharmacokinetics

Adequate studies to characterise tolvaptan PK and support the proposed posology in ADPKD patients have been performed in the ADPKD development program. Missing areas regarding interaction potential as discussed above are followed up within the RMP and are balanced with appropriate warning statements in the SmPC

Pharmacodynamics

The primary and secondary pharmacodynamic properties of tolvaptan in ADPKD are adequately described. The entirety of available pharmacodynamic data indicates that tolvaptan is promising in the proposed target population of APKD to reduce the progression of disease, within the doses studied.

At the proposed split-dose regimens of 45+15 mg to 90+30 mg daily, tolvaptan blocks AVP at the V2 receptor, increasing urine output and suppressing urine osmolality in ADPKD subjects. The 45/15 mg dose was the lowest at which >90% of subjects had urine osmolality values below 300 mOsm/kg for at least 16 hours per day. In terms of the pharmacodynamic principle the split dosage can be considered adequately justified.

2.5. Clinical efficacy

2.5.1. Dose response studies

The initial dosage of tolvaptan in ADPKD is 60 mg per day as a split-dose regimen of 45+15 mg (45 mg taken upon waking and 15 mg taken 8 hours later). The initial dose is to be titrated upward to a split-dose regimen of 90 mg per day (60+30 mg) then to a target split-dose regimen of 120 mg per day (90+30 mg) if tolerated, with at least weekly intervals between titrations. Patients may down-titrate to lower doses based on tolerability.

Based on animal models of ADPKD, the aim of dose escalation was to block the activity of AVP at the renal V2 receptor as completely and constantly as possible, whilst maintaining adequate fluid balance and achieving acceptable tolerability. The hypothesis is that maximal efficacy depends on AVP being

maximally inhibited for the entire day and night. Urine osmolality was used as a marker of AVP inhibition.

Single daily doses in ADPKD subjects did not adequately suppress urine osmolality over a 24 hour period. Twice daily regimens with unequal doses (the main dose given in the morning) were tested with the goal of prolonging tolvaptan action throughout the night without increasing night-time urine excretion so much that nocturia would be a significant problem.

The titration data for the open-label 156-04-250 trial provide the basis for the doses selected in the pivotal trial. During the titration period, as tolvaptan doses increased, urine osmolality prior to the second dose and prior to bedtime were most easily suppressed. The urine osmolality data from this study are discussed in the PD section above. The 45/15 mg dose was the lowest dose at which >90% of subjects had urine osmolality values below 300 mOsm/kg before pre-second dose and pre- bedtime samples, indicating that urine osmolality would be suppressed for at least 16 hours per day. A 60/30 mg regimen may be suitable for many subjects, with the 90/30 mg regimen providing additional inhibition in others. Complete suppression could not be achieved at any of the dose regimens; the top dose is limited as only 46% of subjects (21/46) tolerated the 90/30 mg dose.

The results from study 250, whilst preliminary and only compared to historical controls, also suggested that tolvaptan may favourably impact the rate of kidney growth in subjects with ADPKD, with a dose response between the group randomised to 3 years of the 45+15 mg regime, compared to the 60+30 mg group. The deterioration in this measure in the gap between the end of the fixed dose period and the extension period appeared to confirm the suggestion from the preclinical model that continuous treatment with tolvaptan is important.

2.5.2. Main study

156-04-251

A Phase 3, Multi-center, 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

Methods

Study Participants

The study involved 135 centres, with 129 centres enrolling patients. The centres were in North and South America, Europe, Australia and Japan.

Inclusion criteria

Subjects aged 18 to 50 years with early, progressive ADPKD

At least 50% preserved renal function (estimated creatinine clearance by Cockcroft-Gault formula [eCrCLCG] ≥ 60 mL/min

Kidney size consistent with rapid cystic growth (≥ 750 mL by MRI)

Diagnosis of ADPKD required:

In those with a family history of ADPKD: 3 cysts in each kidney if by ultrasound, 5 cysts in each kidney if by CT/MRI

If there was no family history: 10 cysts (by any radiologic method) in each kidney and exclusion of other cystic kidney diseases

Exclusion criteria

Subjects who, in the opinion of the trial investigator and/or sponsor, presented a safety risk

Subjects who were unlikely to adequately comply with the trial's procedures

Subjects having contraindications to MRI assessments, or factors which would interfere with their interpretation

Subjects who were taking medications or had concomitant illnesses likely to confound endpoint assessments

Subjects taking other experimental (non-marketed) therapies or taking approved therapies for the purpose of affecting PKD cysts, or those taking or with a history of taking tolvaptan

Treatments

The trial began with a screening period for baseline evaluation, and proceeded to a treatment period which included an initial titration phase of up to 3 weeks, followed by a long-term maintenance phase up to 36 months, and 2 follow up visits after discontinuation of tolvaptan. Eligible subjects were randomised to receive either tolvaptan or matched placebo in a 2:1 ratio. 3 split-dose regimens of tolvaptan were selected as per the proposed posology. Subjects began treatment with the 45/15 mg split dose regime and on the day following each 1-week safety assessment, doses were titrated to the next higher dose treatment group until either a level of intolerability or the highest dose was reached. Subjects were to maintain the highest tolerated dose for 3 years, but could titrate up or down as clinical circumstances warranted. If subjects could not tolerate the lowest effective dose of 45/15 mg, they were withdrawn from the trial. Drug interruptions were allowed as needed for intervening illness, with resumption of therapy either at the highest tolerated dose or at lower doses with titration as tolerated. The first of the daily doses was given in the morning on waking, with the second smaller dose given around 9 hours later, regardless of meals.

Objectives

The primary objective was to evaluate the long-term efficacy of tolvaptan in ADPKD through rate of TKV change (%) for tolvaptan compared with placebo subjects.

Other objectives of the trial were to evaluate the following:

Long-term efficacy of tolvaptan using individual clinical markers of ADPKD progression
Long-term safety of tolvaptan through standard clinical measures
Pharmacokinetic, pharmacodynamic and exploratory parameters for effects of tolvaptan in ADPKD

Outcomes/endpoints

The primary endpoint was the rate of change in kidney volume from baseline relative to placebo. The volume was added for both kidneys and then normalised as a percentage. As tolvaptan was individually titrated, data from all tolvaptan doses was combined. Total kidney volume was assessed by MRI.

Total kidney volume was selected as the primary endpoint for a number of reasons:

- The lack of information linking other endpoints (renal pain, haematuria, hypertension) with the anticipated effect of tolvaptan on renal growth
- Endpoints related to onset of end-stage renal disease (for example, time to reach CKD stage 3, doubling of serum creatinine, renal replacement therapy, all-cause mortality) would require more subjects and a longer duration of study than reasonably possible in this rare disease
- The slower progression of GFR, its variability and the confounding of compensatory hyperfiltration in early stages of disease
- Literature evidence to support TKV as a marker of disease progression in ADPKD

The primary analysis was based on observed cases (completers)

The key secondary composite efficacy endpoint was the time to multiple investigator reported ADPKD clinical progression events for tolvaptan (combining all doses) relative to placebo while on treatment, including:

- Onset or progression of HTN (BP measurement, need for HTN treatment)

- Severe renal pain requiring medical intervention
- Worsening albuminuria (by change in category)
- Worsening renal function (25% decrease in reciprocal of serum creatinine from steady-state postdose baseline value)

Other secondary efficacy endpoints were:

1) Rate of renal function change from steady-state postdose baseline value (end of titration to last on-drug trial visit) based on the reciprocal of serum creatinine

2) For subjects who were non-hypertensive at baseline, change from baseline for resting mean arterial pressure at scheduled clinic visits up to the point of exposure to antihypertensive therapy for any reason

3) Change from baseline in renal pain as assessed by a 0 to 10 pain scale as average AUC, between baseline and the last trial visit or the last visit prior to initiating medical (e.g. narcotics, tricyclic antidepressants) or surgical therapy for pain.

4) For subjects who were non-hypertensive at baseline, time to progress to:

Systolic BP > 129 mmHg and/or diastolic BP > 84 mmHg
Systolic BP > 139 mmHg and/or diastolic BP > 89 mmHg
Need for antihypertensive therapy

5) For subjects who were taking antihypertensive therapy at baseline, percentage with clinically sustained decreases of BP leading to a sustained reduction in antihypertensive therapy compared with baseline (while taking study drug) at visit on Months 12, 24, and 36 for hypertensive subjects

Pharmacokinetic/pharmacodynamic and safety endpoints (see later section) were also taken. Urine samples were collected to evaluate trough osmolality and MCP-1 (monocyte chemotactic protein-1, a marker of renal injury). Blood samples were collected to evaluate the plasma concentrations of tolvaptan and metabolites (DM-4103 and DM-4107) in sparse samples, as well as plasma concentrations of cystatin C and uric acid.

Sample size

The original sample size calculation was based on the CRISP (see outline above) and HALT [4] studies. A 7% and 5.6% (or 20% reduction) kidney growth rates per year was assumed in placebo and tolvaptan treated groups respectively. It was further assumed (in $\log_{10}$ scale) that the total noise standard deviation and the standard deviation of the slope across subjects were respectively about 0.017 and 0.0184, which were provided or derived from the information provided by the HALT PKD website. Using the sample size calculation formula for longitudinal trials provided by J. Lefante, with 85% power and 2:1 randomization, the sample size was calculated at 504. After an assumption of 20% withdrawal rate for the trial, about 600 subjects could be enrolled to the trial. By doubling this number, the applicant hoped to effectively attain a power equivalent to two independent studies. The sample size needed for the key secondary composite endpoint was unknown at the planning stage of the protocol since there was no reliable information on its likely event rate. Blinded sample size re-calculation was pre-specified in the protocol. This re-calculation was conducted on 20/10/08 when 1000 subjects had been enrolled, and suggested that a total sample size of 1400 would be appropriate. At this point a 20% reduction in the key secondary composite endpoint was anticipated.

Randomisation

After trial eligibility was determined, subjects were centrally randomised in each region independently (Americas, Japan, Europe, others)

Subjects were stratified into 3 groups, permuting to 8 strata:

- Hypertensive or not; eCrCL < 80 or ≥ 80 mL/min; TKV < 1000 or ≥ 1000 mL
- Indicators of eCrCL status (eCrCL < 80, 80-120, or > 120 mL/min)

[4] HALT PKD: A Clinical Research Study to HALT Progression of Polycystic Kidney Disease. Available from: www.niddk.nih.gov/fund/divisions/kuh/kdcsi/haltpkd.pdf.

- Extreme TKV enlargement (< 1500 or ≥ 1500 mL)

Blinding (masking)

The study was double-blind, patient treatment allocation was implemented by an interactive voice recognition system. Bioanalytical personnel were also blinded to treatment. No interim efficacy analyses were performed.

Statistical methods

Data sets

The primary analysis was based on observed cases. The intent-to-treat (ITT) dataset was defined as a dataset including data from all subjects who were randomized. There were subsets of this based on whether the subject was hypertensive or not at baseline. For each of these there was an observed cases (OC) dataset and a time-to-event dataset associated with it.

The OC dataset consisted of only data points obtained from those subjects who were evaluated at the Baseline visit, post-baseline visits during the double-blind treatment period of the trial, and the End of Trial/early termination (ET) visit, so that no imputation was made for missing data. The double-blind treatment period was defined as the period starting from the first dosing day to 14 days after the last dose of IMP. The time-to-event dataset consisted of all randomised subjects with all events occurring during the double-blind treatment period of the trial.

Trial completers were defined as subjects who were evaluated for the primary efficacy endpoint, key secondary composite endpoint, and PKD Outcomes at the last scheduled visit (Month 36) during the treatment period. If a subject who was randomized and taking IMP discontinued the use of the IMP, telephone contact for PKD Outcomes data was conducted at the normally scheduled trial visits to Month 36, Follow-up Visit 1, and Follow-up Visit 2, if the subject agreed to be followed. The PKD Outcomes data from telephone contact were not used in the primary analysis but were utilized in an exploratory ITT analysis. Events of ADPKD clinical progression concurrent with or proximate to a period of IMP interruption were included in the primary analysis of the key secondary composite endpoint.

Analysis

Efficacy analysis was done sequentially; first on the primary endpoint, then the key secondary composite endpoint, and then all other secondary endpoints in the order specified in SAP. The non-composite secondary efficacy endpoints were tested without adjustment for multiplicity. An overall type I error with significance level of 0.05 (two-sided) was to be maintained

Primary efficacy analyses included all subjects who were randomised and had baseline and post baseline observations of TKV (i.e., MRI assessments). Key secondary efficacy analyses included all subjects who were randomised. The TKV primary, key secondary composite, and renal function slope endpoints were subjected to multiple additional sensitivity analyses to evaluate the robustness of these findings and to examine the potential impact of data missing at random (MAR) and data MNAR.

For the purpose of statistical modelling in the primary analysis, time to MRI from randomization was treated as a continuous variable, expressed as years from date of baseline MRI visit to date of MRI visit (date of MRI visit – date of MRI visit at baseline)/365.25, instead of a class variable with values of 0, 1, 2, or 3. Subjects withdrawing from the trial would have an MRI during the ET visit only if the subject's most recent MRI was greater than 6 months prior to withdrawal.

Log_{10} transformation was applied to the TKV data, and they were then analysed by a linear mixed model with terms of treatment, time treatment interaction, covariance baseline as fixed effects, and intercept and time also as random effects. An unconstructed variance covariance matrix was assumed for the random effects of intercept and slope within each subject.

In addition to the primary analysis, a Mixed-Effect Model Repeated Measure (MMRM) analysis was applied to the repeated measures of percent change from baseline in TKV as a sensitivity analysis. Least-squares (LS) mean difference of the 2 treatment groups at Year 3 under the MMRM was used to estimate the treatment effect at Year 3. The MMRM included stratification factors (hypertensive status, kidney volume status and eCrCL status at baseline, and geographic regions), visit, treatment, and treatment visit interaction as class variables and baseline kidney volume and baseline kidney volume visit interaction as covariates. A compound symmetric variance covariance structure was assumed for the repeated measurements within each subject. The observed cases dataset with the same data used in the primary analysis was used in this MMRM analysis.

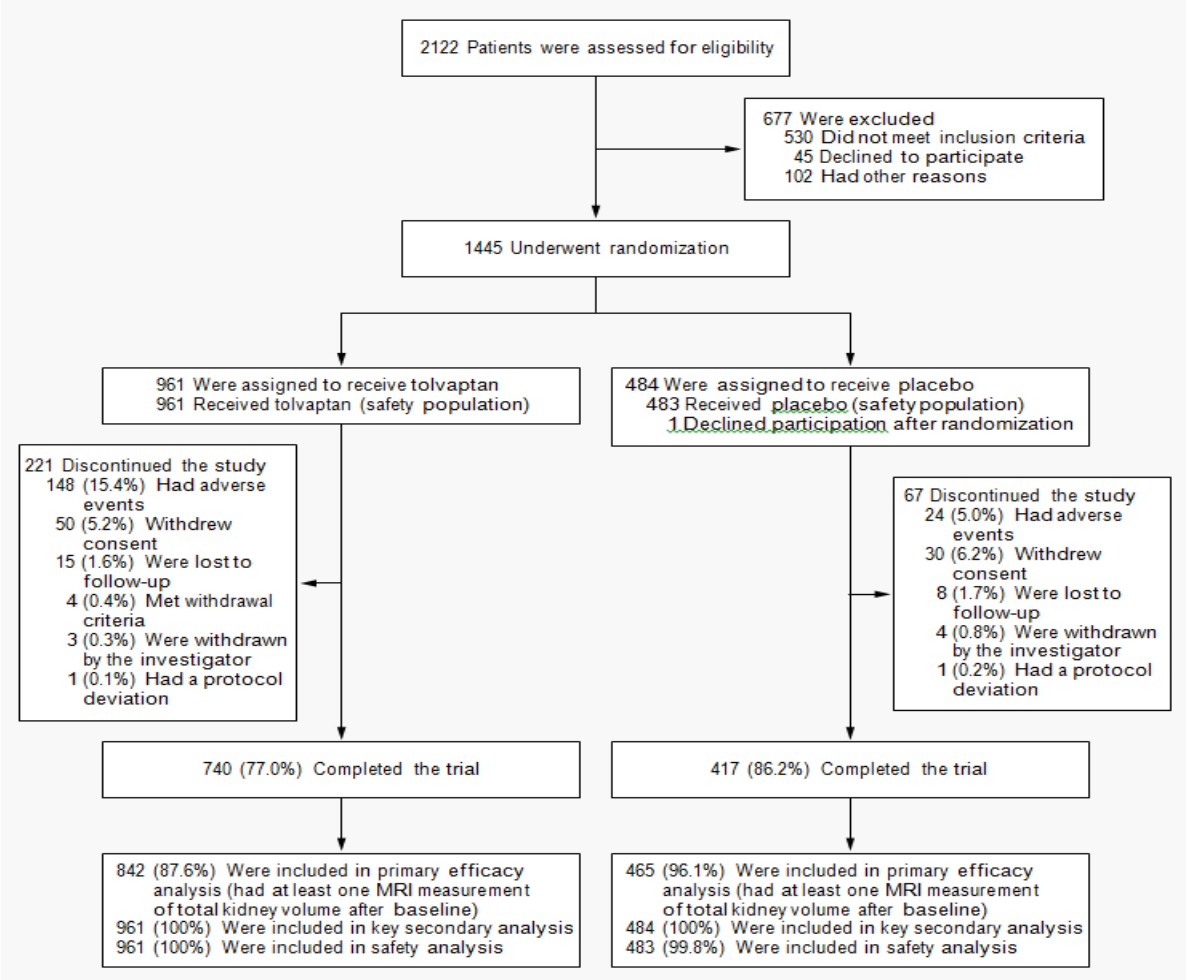
Analysis of time to multiple (recurrent) events using proportional rate and mean model, with only a factor of treatment in the model, was used for the analysis of the key secondary composite endpoint to provide a point estimate of the HR and its p-value. This analysis of rate and mean model is identical to the analysis of the intensity model (Andersen-Gill model) using the sandwich covariance matrix estimate to derive standard errors for the Wald test. An analysis of the time to the first event was designed to be a sensitivity analysis of this composite endpoint.

Handling of missing data

For longitudinal analysis (to determine slope of change), missing data were ignored. For by visit analysis, missing data were imputed by LOCF (LOCF analysis) or censored (observed analysis) or combined with “per protocol” data for strictly exploratory purposes.

Results

Participant flow



Subject disposition and reasons for discontinuation

Number of Subjects	Tolvaptan (N = 961) n (%)	Placebo (N = 484) n (%)	Total (N = 1445) n (%)
Screened	-	-	2122
Randomized	961 (100.0)	484 (100.0)	1445 (100.0)
Treated	961 (100.0)	483 (99.8)	1444 (99.9)
Completed	740 (77.0)[a]	417 (86.2)[b]	1157 (80.1)
Discontinued IMP	221 (23.0)	67 (13.8)	288 (19.9)
Lost to follow-up	15 (1.6)	8 (1.7)	23 (1.6)
AE	148 (15.4)	24 (5.0)	172 (11.9)
Subject met withdrawal criteria	4 (0.4)[c]	0 (0.0)	4 (0.3)
Investigator withdrew subject	3 (0.3)	4 (0.8)	7 (0.5)
Subject withdrew consent	50 (5.2)	30 (6.2)	80 (5.5)
Protocol deviation	1 (0.1)[d]	1 (0.2)[d]	2 (0.1)
Discontinued and followed for PKD Outcomes	102 (10.6)	27 (5.6)	129 (8.9)
Analyzed for primary efficacy[e]	842 (87.6)	465 (96.1)	1307 (90.4)
Analyzed for secondary efficacy[f]	961 (100.0)	484 (100.0)	1445 (100.0)
Analyzed for safety[g]	961 (100.0)	483 (99.8)	1444 (99.9)

Recruitment

The study involved 135 centres, with 129 centres enrolling patients. The centres were in North and South America, Europe, Australia and Japan.

Trial Initiation Date: Jan 2007

First subject randomised: March 2007

First subject randomised: January 2009

Trial Completion Date: January 2012

Conduct of the study

Other than administrative changes, protocol amendments included changes to the screening period, clarified the MRI evaluation (including removing the option of gadolinium contrast) and the addition of more study visits for the Japanese sites following specific regulatory requirements there. All trial sites completed as per the protocol.

The protocol amendments are not considered to have affected the outcome of the studies. No protocol deviations are considered to have significantly affected the integrity of the trial and no significant issues with study conduct are apparent. Adherence was good at around 90% per group.

Baseline data

Approximately half of the subjects were male (746/1445, 51.6%) and the majority of subjects were Caucasian (1218/1445, 84.3%). The mean age of randomized subjects was 38.7 years (range 18 to 51 years)

For the stratification factors, the majority (79.4%) were hypertensive at baseline (approximately 77% of all subjects were receiving hypertensive therapy) 25.7% had creatinine clearance < 80mL/min and 20.6% had a TKV <1000 mL. 53% of subjects had microalbuminuria at baseline, 5% had overt proteinuria.

History of hepatic cysts and haematuria were balanced between treatment groups, overall they were seen in around 60% and 34% of patients respectively. The mean age of ADPKD diagnosis was around 27 years in each group.

Using eGFRCKD-EPI, tolvaptan and placebo subjects were evenly distributed at baseline across KDIGO CKD Stages, mostly stages 1 and 2. With the exception of one subject in the placebo arm, no subjects enrolled in the trial with baseline CKD Stages 4 or 5.

For stage 1, the percentages at baseline were 34.4% in the tolvaptan group, 35.9% for placebo
For stage 2 the percentages at baseline were 48.5% and 46.5% respectively
For stage 3 the percentages at baseline were 17.0% and 17.4% respectively

The following table shows the baseline measures of kidney volume and renal function:

Table 4: Study 156-04-251. Pre-titration Baseline Renal Function and Total Kidney Volume

Parameter	Tolvaptan (N = 961)	Placebo (N = 484)	Total (N = 1445)
1/serum creatinine ([mg/mL]$^{-1}$)			
Number of subjects	958	482	1440
Mean	102.27	104.30	102.95
SD	27.21	33.87	29.61
Median	100.00	100.00	100.00
Minimum	43.7	35.5	35.5
Maximum	263.2	500.0	500.0
$eGFR_{CKD-EPI}$ (mL/min/1.73 m^2)			
Number of subjects	958	482	1440
Mean	81.35	82.14	81.61
SD	21.02	22.73	21.60
Median	80.76	80.40	80.74
Minimum	32.3	26.4	26.4
Maximum	132.8	186.7	186.7
TKV (mL)			
Number of subjects	961	483	1444
Mean	1704.8	1667.5	1692.3
SD	921.27	873.11	905.31
Median	1456.7	1468.5	1458.8
Minimum	750.0	751.1	750.0
Maximum	7555.4	6751.1	7555.4
Height-adjusted TKV (mL/m)			
Number of subjects	960	482	1442
Mean	978.56	958.18	971.75
SD	514.84	483.27	504.43
Median	858.70	849.30	857.00
Minimum	394.7	408.7	394.7
Maximum	4317.4	3750.6	4317.4

Numbers analysed

Refer to details of subject disposition above. Of 2122 screened subjects, 1445 were randomised, of whom 1444 received at least 1 dose. A total of 961 subjects received tolvaptan and 483 subjects received placebo.

Of the patients who completed 36 months of treatment with tolvaptan, 404 (55%) took the high dose (a total daily dose of 120 mg), whereas 157 (21%) and 179 (24%) took the middle dose (90 mg) and low dose (60 mg), respectively. Of the patients who completed 36 months of placebo treatment, 348 (83%), 38 (9%), and 32 (8%) took the corresponding sham doses

Outcomes and estimation

Of 2122 screened subjects, 1445 were randomised, of whom 1444 received at least 1 dose. A total of 961 subjects received tolvaptan and 483 subjects received placebo.

Adherence was good and exceeded 90% in 845 of the 961 patients in the tolvaptan group (88%), with an average dose of 95 mg per day, and in 451 of the 483 patients in the placebo group (93%), with an average sham dose of 110 mg per day. Of the patients who completed 36 months of treatment with tolvaptan, 404 (55%) took the high dose (a total daily dose of 120 mg), whereas 157 (21%) and 179 (24%) took the middle dose (90 mg) and low dose (60 mg), respectively. Of the patients who completed 36 months of placebo treatment, 348 (83%), 38 (9%), and 32 (8%) took the corresponding sham doses.

Primary endpoint

Total kidney volume increased by 18.8% in placebo subjects over 3 years but by only half that (9.6%) in tolvaptan subjects. The rate of growth was 2.80% per year for tolvaptan vs. 5.51% per year for placebo, giving a ratio of geometric mean 0.974; 95% CI 0.969 to 0.980; $p < 0.0001$. This corresponded to a difference of −2.71% per year with a 49.2% reduction in growth rate in the tolvaptan group compared with the placebo group.

The effect of treatment with tolvaptan on TKV was greatest in the first year but treatment effects 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 years. The incremental treatment effect for reduction in TKV from the first year to the second year was −1.92% ($p < 0.0001$) and from the second year to the third year was −1.78% ($p = 0.0005$). These results were replicated in sensitivity analyses, including re-analyses to account for differing model assumptions and datasets, potential MRI quality or reading errors, and analyses by study centre and country.

Table 5: Study 156-04-251. Primary endpoint (random effect intercept): total kidney volume rate of growth (%/year), ITT data set, within treatment period

Parameter	Tolvaptan	Placebo
Rate of percent growth per year[a]		
Number of subjects	819	458
Mean	2.777	5.608
Median	2.265	5.585
SD	5.659	5.330
Minimum	−23.129	−20.634
Maximum	64.270	43.948
Estimated slope[b]	0.0280	0.0551
Treatment effect		
Difference (%)	-2.708	
95% CI[c]	-3.269, -2.147	
Slope reduction (%)	49.2	
Ratio of geometric mean[d]	0.974	
95% CI	0.969, 0.980	
p-value[e]	< 0.0001	

Note: Subjects with baseline and postbaseline MRI results are included in the primary efficacy analysis. "Within the treatment period" was defined as the period starting from the first dosing day to 14 days after the last dose of IMP.

[a] Summary statistics were derived by regressing logarithm-transformed kidney volume data against time, then displaying regression-slope exponentials. Time variable used in the regression was equal to (MRI date - baseline MRI date)/365.25.

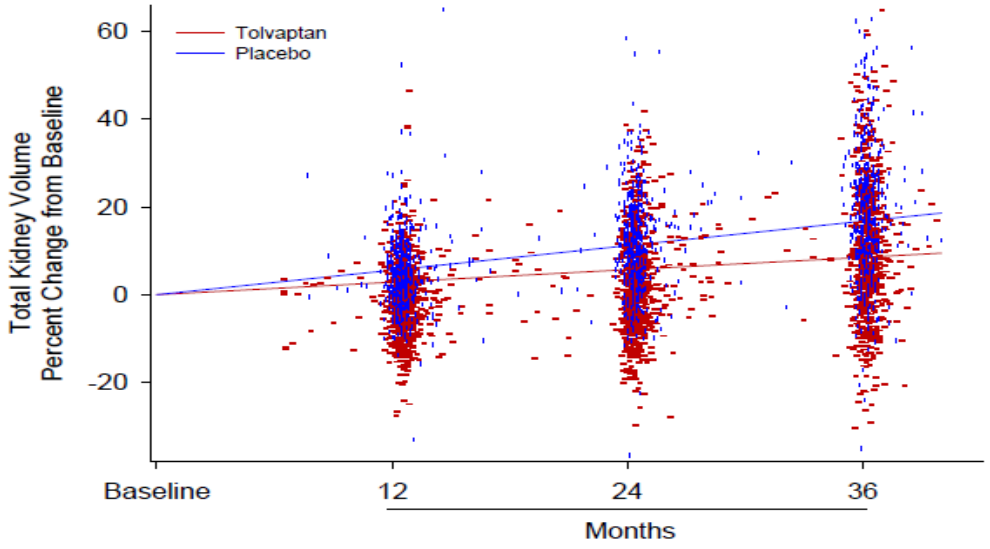
[b] Slope was estimated by subtracting 1 from the geometric mean of annualized growth rate.

[c] Derived from delta method assuming independence between the estimates of the slope between the 2 treatments. Difference in slope produced post-hoc to facilitate clinical interpretation.

[d] An estimate of the ratio of geometric mean of annualized growth rate of tolvaptan and placebo.

[e] Derived from testing the time treatment interaction using linear mixed model in which both intercept and slope are fixed and random effects.

Figure 4: Study 156-04-251. Effect of Tolvaptan on the Rate of TKV Change (Normalized as a percentage)



The above analysis was prospectively defined in the protocol with both intercept and slope as random effects; however, the variance of the random effect intercept was zero, resulting in a non-positive, definite variance-covariance matrix for the random effects. Therefore, a *post-hoc* analysis of the primary endpoint was performed using a linear mixed model in which the intercept was a fixed effect and the slope was fixed and random effect. The results of the revised analysis were consistent with the pre-specified analysis.

A *post-hoc* exploratory analysis of the change from baseline in TKV by modal dose demonstrated a dose response for tolvaptan.

The MMRM sensitivity analysis, which tests year-to-year change, confirmed the results of the primary analysis. Baseline TKV was generally similar for tolvaptan and placebo subjects. Least-squares mean TKV growth at Month 36 for tolvaptan (9.56%) was halved relative to placebo (18.75%), for a treatment group difference of −9.19%. A sensitivity MMRM analysis looking at the absolute change from baseline in TKV in mL produced similar results. The analysis indicated 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. 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, $p < 0.0001$)

Table 6: Study 156-04-251. Sensitivity Analysis: MMRM Analysis of Change from Baseline in TKV (%); ITT, Within Treatment Period

Visit	Treatment Group	Number of Subjects	Mean	Median	SD	Min	Max	LS Mean[a]	Treatment Effect[b]	95% CI	P-value[b]
Total kidney volume (mL)[a]											
Baseline	Tolvaptan	961	1705	1457	921	750	7555	-	-	-	-
	Placebo	483	1668	1469	873	751	6751	-	-	-	-
Total kidney volume, percent change from baseline (%)[a]											
Month 12	Tolvaptan	818	−1.16	−1.47	8.43	−27.69	66.91	−1.65	−6.27	−7.26, −5.28	< 0.0001
	Placebo	457	5.05	4.24	9.35	−33.39	84.91	4.62	-	-	-
Month 24	Tolvaptan	767	3.27	2.29	11.52	−29.72	75.25	2.93	−8.17	−9.50, −6.84	< 0.0001
	Placebo	425	11.49	11.15	11.30	−36.97	72.39	11.10	-	-	-
Month 36	Tolvaptan	698	9.65	7.76	15.38	−30.53	68.76	9.56	−9.19	−11.1, −7.32	< 0.0001
	Placebo	380	18.85	17.18	16.29	−35.46	111.26	18.75	-	-	-

Key secondary endpoint

The key secondary composite efficacy endpoint was the time to multiple investigator reported ADPKD clinical progression events for tolvaptan (combining all doses) relative to placebo while on treatment, including:

Onset or progression of HTN (BP measurement, need for HTN treatment)
Severe renal pain requiring medical intervention
Worsening albuminuria (by category)
Worsening renal function (25% decrease in 1/serum creatinine from steady-state postdose baseline)

This key secondary composite endpoint yielded a hazard ratio (HR) of 0.865 (95% CI 0.775 to 0.965, p = 0.0095) in favour of tolvaptan, a 13.5 % rate reduction.

Figure 5: Cumulative hazard of multiple events of ADPKD progression

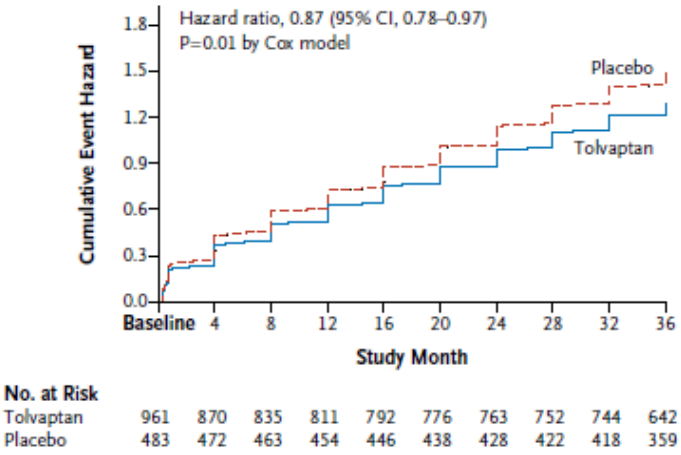
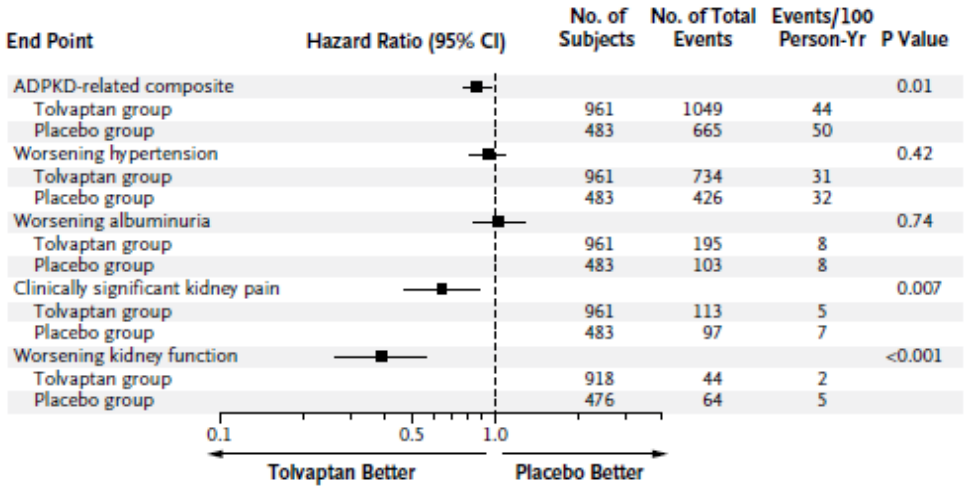


Table 7: Study 156-04-251. Key Secondary Composite Endpoint: Time to Multiple Composite ADPKD Events; ITT, Within Treatment Period

Parameter	Nonadjudicated Composite Events		Adjudicated Composite Events	
	Tolvaptan (N = 961)	Placebo (N = 483)	Tolvaptan (N = 961)	Placebo (N = 483)
Number of events	1049	665	1067	688
Total follow-up years	2387	1329	2387	1329
Events/100 follow-up years	43.94	50.04	44.69	51.77
Mean follow-up years	2.48	2.75	2.48	2.75
HR[a]	0.865		0.852	
95% CI[a]	0.775, 0.965		0.764, 0.951	
p-value[a]	0.0095		0.0044	

Figure 6: Hazard ratios for the secondary end point of ADPKD-related events with tolvaptan as compared with placebo for the secondary composite end point and its component events.



This result was confirmed by similarly significant time to first event and adjudication analyses, as well as multiple other sensitivity analyses (summarised below)

Analyses of time to the first composite ADPKD event (HR 0.826; 95% CI 0.722 to 0.944, p = 0.0051) and the adjudicated time to first composite ADPKD event (HR 0.835, 95% CI 0.729 to 0.955, p = 0.0087) demonstrated fewer ADPKD progression events in the tolvaptan group. These analyses weigh each subject equally by censoring each subject at the time of their first event of clinically significant progression. The analyses confirm that the significance of the key secondary composite endpoint was due to the treatment effects on most of the subjects, instead of a few subjects with multiple events.

More restrictive ITT analyses were conducted using Week 3/EOT as post-titration baseline for event derivation. These analyses were used to exclude the noise associated with trial initiation and the initiation of treatment (e.g., subjects adjusting antihypertensives after discontinuing diuretics). Analyses included the time to multiple events (HR 0.877, 95% CI 0.785 to 0.980, p = 0.0203) and the time to the first composite ADPKD event (HR 0.884, 95% CI 0.770 to 1.014, p = 0.0777); both favoured tolvaptan.

Less restrictive ITT analyses were used to include data collected off treatment up to Month 36. Time to multiple composite ADPKD events analyses used a nonrestricted ITT approach (regardless of treatment period) using either predose baseline (HR 0.874, 95% CI 0.784 to 0.974, p = 0.0147) or Week 3/EOT as baseline (HR 0.889, 95% CI 0.797 to 0.992, p = 0.0354). Both of these analyses maintained statistical significance.

In response to a regulatory request from the US FDA, analyses of the time to multiple composite ADPKD events using a nonrestricted ITT approach, regardless of treatment period, were done to examine the events that occurred before and after SAP finalisation. These favoured tolvaptan in both time periods (before SAP finalization HR 0.925, 95% CI 0.811 to 1.057, p = 0.2522; and after SAP finalisation HR 0.790, 95% CI 0.669 to 0.934, p = 0.0057). While tolvaptan had a numerically favourable effect in both time periods, it became statistically significant in the second time period due to the increasing impact of renal function events, which occurred late in the trial.

In response to a further FDA request to examine the effect of partial missing data on the result of the SAP-defined primary analysis of the key secondary composite endpoint, this was re-done allowing only subjects to contribute to the treatment group denominator at the last visit where an event occurred or where all 4 components were evaluated. This analysis also favoured tolvaptan (HR 0.878, 95% CI 0.787 to 0.979, p = 0.0194)

An exploratory analysis of the key secondary composite endpoint after correction of pain-related baseline covariates from subjects' ADPKD disease history (e.g., renal pain, nephrolithiasis, UTI), maintained the statistical significance of the composite endpoint at a level of p < 0.01 for time to multiple event and time to first event.

Events that signalled a decline in renal function were delayed in both groups until approximately month 12 with the separation of tolvaptan treatment from placebo treatment evident at approximately month 18. The effect of tolvaptan on renal pain was observed early in the treatment period, with increasing separation between the tolvaptan and placebo groups over the remaining 3 years of treatment. Worsening renal function events were correlated with percent change in TKV and TKV slope, whilst renal pain events were not.

Table 8: Study 156-04-251. Time to Multiple Events for Components of the Key Secondary Composite Endpoint; ITT, Within Treatment Period

Parameter	Worsening Renal Function		Worsening Renal Pain		Worsening Hypertension		Worsening Albuminuria	
	Tolvaptan (N = 961)	Placebo (N = 483)	Tolvaptan (N = 961)	Placebo (N = 483)	Tolvaptan (N = 961)	Placebo (N = 483)	Tolvaptan (N = 961)	Placebo (N = 483)
Number of subjects	917	476	961	483	961	483	961	483
Number of events	44	64	113	97	734	426	195	103
Total follow-up years	2378	1323	2387	1329	2387	1329	2387	1329
Events/100 follow-up years	1.85	4.84	4.73	7.30	30.74	32.05	8.17	7.75
Mean follow-up years	2.59	2.78	2.48	2.75	2.48	2.75	2.48	2.75
HR[a]	0.386		0.642		0.942		1.037	
95% CI[a]	0.263, 0.566		0.466, 0.887		0.814, 1.090		0.837, 1.284	
p-value[a]	< 0.0001		0.0071		0.4223		0.7420	

3rd endpoint: Rate of renal function decline

Tolvaptan treatment slowed the estimated rate of renal function decline (reciprocal of serum creatinine) by one-third, observed after the 1 year point. This was confirmed when GFR was estimated by methods other than reciprocal of creatinine, including the CKD-EPI equation.

As seen in some of the earlier studies, tolvaptan treatment was associated with early but transient increases in serum creatinine compared with placebo; this is discussed further in the safety section below.

Table 9: Study 156-04-251. Rate of Change in Renal Function; ITT Subjects With at Least 4-month Follow-up, Excluding Observations Deemed Unreliable by Investigators, Within Treatment Period

Endpoint	Tolvaptan	Placebo
1/serum creatinine ([mg/mL]$^{-1}$)		
Number of subjects	842	464
Mean rate of change per year[a]	−2.555	−3.682
Estimated slope[b]	−2.609	−3.812
Treatment effect[c]	1.203	
95% CI	0.622, 1.783	
p-value[b]	< 0.0001	
$eGFR_{CKD-EPI}$ (mL/min/1.73 m^2)		
Number of subjects	842	464
Mean rate of change per year[a]	−2.680	−3.568
Estimated slope[b]	−2.723	−3.700
Treatment effect[c]	0.977	
95% CI	0.597, 1.357	
p-value[b]	< 0.0001	

As an exploratory analysis, the applicant looked at change in CKD classifications. By the end of the trial, the proportion of placebo subjects with CKD Stage 3 or higher (by eGFRCKD-EPI), signifying a moderate to severe decrease in GFR had more than doubled to approximately 39%. In comparison, in the tolvaptan group, approximately 34% of subjects were classified as having CKD Stage 3 or higher.

Ancillary analyses

Beyond the third endpoint of renal function decline, none of the other planned secondary endpoints yielded clear overall trends. In particular, there was no benefit of tolvaptan on evolution or control of blood pressure compared to placebo, whether subjects were hypertensive or normotensive at baseline, nor a benefit over placebo in change from baseline on the renal pain scale.

In the 13-item composite of complications related to ADPKD progression, tolvaptan reduced the rate of complications by 20.8% in an exploratory analysis. In a further exploratory analysis, treatment with tolvaptan was associated with an improvement in some of the measured clinical outcomes. A smaller proportion of subjects on tolvaptan reported renal pain, nephrolithiasis, haematuria, UTI, and anaemia compared with subjects on placebo.

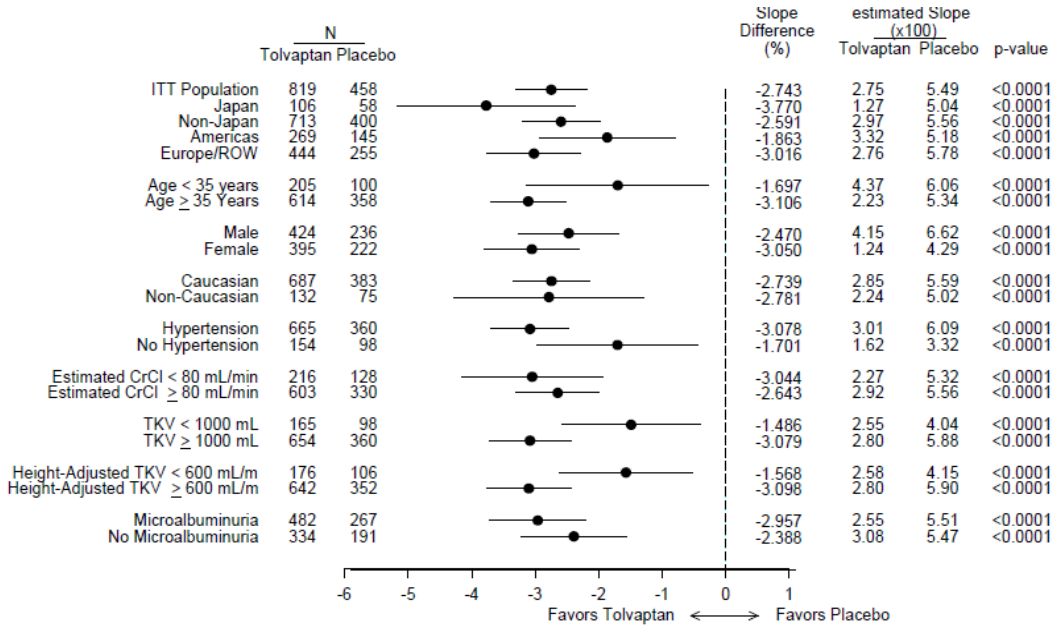
Changes in plasma cystatin C concentrations were consistent with changes in serum creatinine concentrations.

76% to 85% of tolvaptan subjects had trough urine osmolality < 300 mOsm/kg compared with 22% to 24% of placebo subjects, and mean trough urine osmolality was about 250 mOsm/kg lower for tolvaptan compared with placebo subjects. Tolvaptan subjects with the slowest rates of TKV growth or slowest decline in renal function had the greatest mean decreases in urine osmolality.

Subgroup analyses

For the primary endpoint, generally consistent results were seen in all subgroups, including those related to stratification factors, baseline disease severity, adverse prognostic factors, age, gender, and race. Selected factors are shown in the figure below:

Figure 7: Study 156-04-251. Subgroup Analyses of primary efficacy endpoint, TKV Slope Difference



For the secondary and third efficacy endpoints, subgroup analyses produced nominal point estimates that generally favoured tolvaptan.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 2. Summary of Efficacy for trial No. 156-04-251

Title: A Phase 3, Multi-center, 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			
Study identifier	Protocol No. 156-04-251 IND No. 72,975 EudraCT No. 2006-002768-24		
Design	Multi-center, double-bind, placebo-controlled, parallel-arm trial		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		25 Jan 2007 (first signed informed consense) to 23 Jan 2012 (last trial observation) Not applicable Not applicable for 156-04-251. Open label extensions of 156-04-251, with separate protocol nos (156-10-003 [Japan] and 156-08-271 [ROW], are ongoing
Hypothesis	The increase in total kidney volume in subjects with ADPKD treated with tolvaptan is less than in subjects treated with placebo		
Treatments groups	Tolvaptan		Flexible dosing (up to max 90 mg and 30 mg PM), 3 years, N=961
	Placebo		Flexible dosing (up to max 90 mg and 30 mg PM), 3 years, N=484
Endpoints and definitions	Primary endpoint	TKV rate of growth (%/yr)	Rate of renal volume (total, both kidneys) change (normalized as percentage) for tolvaptan (combining all doses) relative to placebo

	Key Secondary endpoint	Time to multiple composite ADPKD events	Time to multiple ADPKD clinical progression events (ie, onset or progression of hypertension (HTN) [blood pressure measurement, need for HTN treatment], severe renal pain [requiring medical intervention], worsening albuminuria [by category], worsening renal function [25% change in reciprocal serum creatinine as a measure of glomerular filtration rate from steady-state post-dose Baseline]) for tolvaptan (combining all doses) relative to placebo while on treatment
	Secondary other: specify endpoint	N.A.	For tolvaptan compared to placebo: 1. Rate of GFR change from post-dose Baseline (End of Titration) to last on-drug trial visit (using 1/serum creatinine as primary measure while Cockcroft-Gault results will be exploratory) 2. For subjects who are non-hypertensive at Baseline, change from Baseline for resting mean arterial pressure (MAP) at scheduled clinic visits up to point of exposure to anti-hypertensive therapy for any reason 3. Change from Baseline in kidney pain as assessed by 1-10 pain scale as average area under the concentration - time curve (AUC) between Baseline and last trial visit or last visit prior to initiating medical (eg, narcotic or tricyclic) or surgical therapy for pain 4. For subjects who are non-hypertensive at Baseline, time to progress to a) high-pre-hypertension (sBP > 129 and/or dBP > 84) or b) hypertension (sBP >139 and/or dBP >89 mm Hg) or c) requiring anti-hypertensive therapy 5. For subjects who are taking anti-hypertensive therapy at Baseline, percentage with clinically sustained decreases of BP leading to a sustained reduction in antihypertensive therapy compared to Baseline (while taking investigational product) at visit Months 12, 24 and 36 for hypertensive subjects
Database lock	12 april 2012		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat (ITT) within treatment period (up to 3 years) Rate of percent growth per year			
Primary Endpoint (Random Effect Intercept): Total Kidney Volume Rate of Growth (%/year), ITT, within Treatment Period	Treatment group	Tolvaptan N=961	Placebo N=483	
	Number of subjects	819	458	
	Rate of percent growth per year, mean	2.777	5.608	
	Median	2.265	5.585	
	SD	5.659	5.330	

Effect estimate per comparison	Primary endpoint	Comparison groups	Tolvaptan vs placebo
		Difference (%)	-2.708
		95% CI	-3.269, -2.147
		P-value Slope reduction (%)	< 0.0001 49.02
	Key Secondary composite endpoint: time to multiple composite ADPKD events-nonadijudicated	Comparison groups	Tolvaptan vs placebo 1049 vs 645 events
		HR	0.865
		95%	0.775, 0.965
		P-value	0.0095
	Key Secondary composite endpoint: time to multiple composite ADPKD events -adijudicated	Comparison groups	Tolvaptan vs placebo 1067 vs 688 events
		HR	0.852
		95%	0.764, 0.951
		P-value	0.0044
Notes	None		

Analysis performed across trials (pooled analyses and meta-analysis)
There was only 1 pivotal trial. Combined data from the 2 open-label studies was used in a case-control study as discussed below.

Clinical studies in special populations
Data on special populations is discussed in the Pharmacology part of this assessment report above

Supportive studies
Supportive evidence of efficacy is available from 2 further studies in ADPKD patients:

A 3-year, open-label extension trial conducted in the US (Trial 156-04-250)
A 3-year, open-label extension trial conducted in Japan (Trial 156-05-002)

A matched-control analysis (study 156-09-283) of the data from 156-04-250 and 156-05-002, with ADPKD natural history data from 2 US National Institutes of Health sponsored studies has also been done.

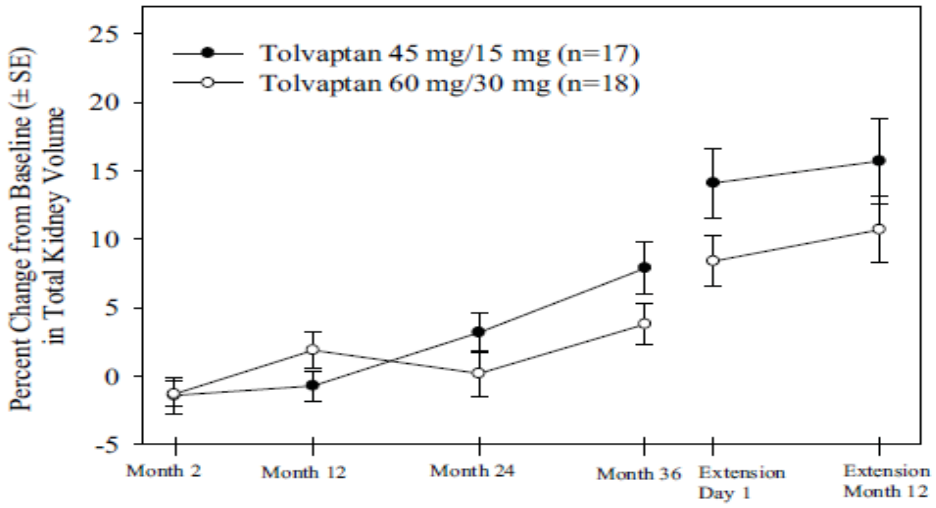
Open-label studies 156-04-250 and 156-05-002

These were preliminary open label studies in a small number of ADPKD patients. Study 156-04-250 was in 46 patients, study 156-05-002 in 17 patients. In these trials, TKV was assessed at 2 or 6 months, then annually up to 3 years after starting treatment. Additionally, the effects of treatment withdrawal on TKV or eGFR were investigated in Trial 156-04-250 during a treatment interruption period, prior to an optional 1-year treatment extension. To confirm long-term outcomes (TKV, eGFR) and the clinical relevance of TKV change, data on the combined 63 ADPKD subjects from these 2 trials were compared with a matched cohort of untreated ADPKD subjects receiving standard of care (analysis designated as Study 156-09-283)

Study 156-04-250 provides the most contributory data of the two open-label studies. Following a 2 month titration phase, ADPKD subjects were randomised to either the 45/15 mg split dose regime or the 60/30 mg regime, and followed this for up to 3 years. These 2 doses were chosen after interim analysis of the titration period. Following this, some patients entered into a 12 month extension, after

an off-drug period of up to 1 year. Total kidney volume by blinded MRI was evaluated as a pilot efficacy measure. The figure below shows the change from baseline in total kidney volume, in those subjects who entered the extension phase. The study excluded patients who at day 1, or extension day 1, had an estimated GFR below 30 mL/min or in whom renal-replacement therapy was anticipated within 1 year of study extension. The mean GFR estimated by the MDRD equation was around 60 mL/min.

Figure 8: Study 156-04-250: Percent change from baseline in TKV by assigned dose regimen



Taking the two open-label trials together, tolvaptan slowed the increase in total kidney volume (1.7% vs. 5.8% per year, P<0.001) and the decline in estimated glomerular filtration rate (GFR; −0.71 vs. −2.1 ml per minute per 1.73 m2 of body-surface area per year, P = 0.01)

Matched-control data: study 156-09-283

Data from the 2 open-label studies was used in a case-control study. The matched-control data were derived from 2 studies: Modification of Diet in Renal Disease (MDRD) and CRISP I (consortium for radiologic imaging studies of polycystic kidney disease) The primary objective was to compare in ADPKD subjects the rate of TKV change, over a 3-year period between tolvaptan-treated subjects and matched-control subjects receiving standard of care. A total of 51 patients receiving tolvaptan and completing studies 156-04-250 and 156-05-002 were included in the primary analysis, with 102 case-matched subjects. Case matching was based on age, TKV, serum creatinine and hypertension status. Subjects missing TKV could be considered for matching for evaluation of GFR and hypertension endpoints. Because of the study designs, for matched-control pairing, the pool of matches was restricted to CRISP subjects for TKV but included both CRISP and MDRD subjects for eGFR.

Table 10: Study 156-09-283. Annualized progression rate in total kidney volume and estimated glomerular filtration rate (MDRD equation) - comparison of open-label tolvaptan data with historical control

Annualized Percent Change in TKV (%/year)[a] CRISP Study Matched by TKV						
Treatment Group	**n**	**Annual Change**	**SD**	**Ratio of Geometric Mean**	**95% CI**	**P-value**
156-04-250/156-05-002	51	1.664	3.534	0.961	0.949, 0.973	<0.0001
Control	102	5.806	4.313			
Annualized Change in eGFR (mL/min/1.73m^2)[b] CRISP and MDRD Study Matched by eGFR MDRD Formula						
Treatment Group	**n**	**Annual Change**	**SD**	**LS Mean Difference**	**95% CI**	**P-value**
156-04-250/156-05-002	51	−0.711	2.238	1.076	0.235, 1.917	0.0122
Control	102	−2.062	3.058			

Additional data from study 156-08-271, open label extension study

At CHMP's request, the applicant has provided a 2 year update from the long-term open-label extension trial 156-08-271, which is on-going. 2 years was the pre-specified time-point for analysis of the efficacy endpoints (corresponding to 5 year's tolvaptan treatment in some patients) but it has now been extended indefinitely. At this point there were 549 patients who had received tolvaptan prior to entry into the open-label study, 309 that had not, very good retention of subjects from corresponding entry figures of 554 and 331. The figure below summarizes eGFR results. Beginning at a pre-treatment baseline for Trial 156-04-251, tolvaptan subjects (blue squares) had a drop in eGFR of approximately 3.38 mL/min/1.73m^2 (difference of estimated treatment effect for tolvaptan versus placebo between pre-treatment Day 1 and End of Titration/Week 3). During the next 3 years of treatment, the slope of decline for these subjects was shallower than for the parallel placebo group (red diamonds) whose eGFR declined linearly to, and beyond, Month 36. At this point the slopes intersect and can be projected to have crossed, had treatment continued. Upon treatment withdrawal, the placebo group's eGFR decline continued, while the tolvaptan group's eGFR recovered by 3.66, 4.02 and 3.52 mL/min/1.73m^2 (differences of the estimated treatment effect for tolvaptan versus placebo between the on-treatment Month 36 visit and post-withdrawal follow-up visits 1 and 2 for Trial 156-04-251 and the pre-treatment baseline for Trial 156-08-271, respectively).

Once all subjects were placed under the same condition of "on tolvaptan treatment" in Trial 156-08-271, both the prior-tolvaptan and prior-placebo groups from Trial 156-04- 251 experienced the same onset of an acute decline in eGFR as seen at the beginning of Trial 156-04-251. The original drop of 3.38 mL/min/1.73m^2, was comparable to the 3.36 and 3.35 mL/min/1.73m^2 declines for prior tolvaptan and prior placebo groups, respectively, during Trial 156-08-271 (differences between LS Mean estimate for baseline and Month 1 visits for Trial 156-08-271). During the 2-years of treatment in Trial 156- 08-271, each group retained a consistently significant treatment difference of between 2 to 3 mL/min/1.73m^2.

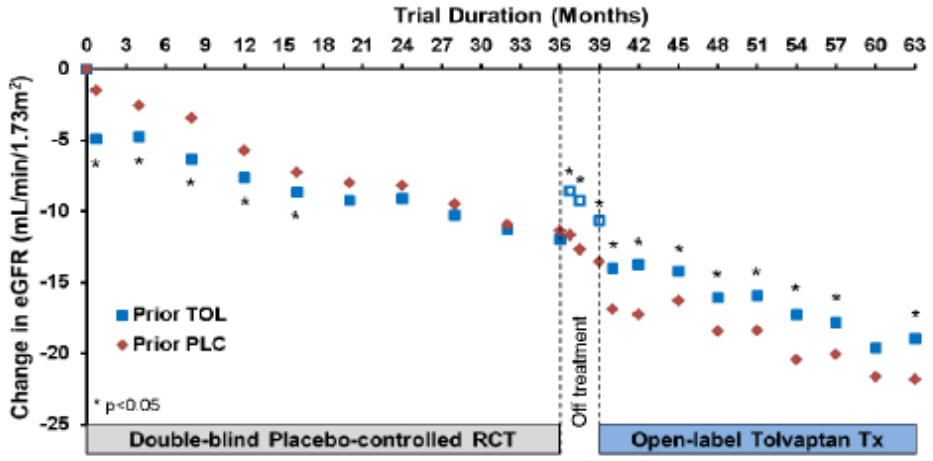


Figure 3.2.3.12-1 **Change from Baseline in Renal Function, Estimated by CKD-EPI Formula, All Visits in Trial 156-04-251 and up to Month 24 in Trial 156-08-271**

Source: Section 5.2.1, Table Q44-1.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical trials

The proposed initial dosage of tolvaptan is 60 mg per day as a split-dose regimen of 45+15 mg (45 mg taken upon waking and 15 mg taken 8 hours later). The initial dose is then titrated upward to a split-dose regimen of 90 mg per day (60+30 mg) then to a target split-dose regimen of 120 mg per day (90+30 mg) if tolerated, with at least weekly intervals between titrations. Patients may down-titrate to lower doses based on tolerability. This was the regimen employed in the pivotal study.

There is no dose-response study that looked at efficacy long-term with all the proposed split-doses. The rarity of the disease and available numbers of patients are taken into account here. The titration data for the open-label 156-04-250 trial can provide the main basis for the doses selected in the pivotal trial. The submitted data from this study and the clinical pharmacology studies provide an adequate basis for the doses selected.

Trial 156-04-251 is the single pivotal phase III trial in ADPKD patients; this was a double-blind, randomised placebo-controlled, parallel arm study. The basic design of the study is sound and the dosing consistent with the proposed posology. The duration of the trial is relatively short given the long evolution of ADPKD, and not able to detect a benefit on clinical endpoints such as time to renal replacement therapy. However, it would hardly be feasible for the main study period to be longer. Further longer-term data will be generated by the open-label extension trial 156-08-271 as described in the RMP.

The inclusion and exclusion criteria were appropriate. The inclusion criteria generated a subject population with a relatively large renal volume consistent with rapid cystic growth, but reasonably preserved renal function. These patients with early but rapidly progressive disease were hoped to benefit from therapy and to have a prognosis for observable changes or outcomes during a 3-year trial. In this respect it is a necessarily “enriched” study population.

The treatment groups were generally well balanced at baseline for demographic factors. Adverse prognostic factors in ADPKD include the ADPKD1 genotype, male gender, presence of sickle cell trait, early age of diagnosis, hypertension, gross haematuria, proteinuria, renal size, increased left ventricular mass, hepatic cysts in women, three or more pregnancies, and urinary tract infections in men. For those factors that were evaluated at baseline, the groups were well balanced. Patients were

not genotyped at baseline, although ADPKD type 1 is the commonest variant (90%) and the mean age of the patients is consistent with this type. It has been added to the SmPC that patients were not genotyped into ADPKD subtypes 1 and 2, and that it is not known whether Jinarc has comparable efficacy in these subgroups.

The diagnostic criteria used for ADPKD were acceptable.

The primary endpoint was the rate of change in kidney volume from baseline for tolvaptan relative to placebo. The volume was added for both kidneys, and normalised as a percentage. As tolvaptan was individually titrated, data from all tolvaptan doses was combined. There was centralised, standardised and blinded assessment of all MRIs. Literature evidence supporting the use of TKV primarily comes from the Consortium for Radiologic Imaging Studies in Polycystic Kidney Disease (CRISP), a cohort of ADPKD patients between the ages of 15 to 45, all of whom had creatinine clearances greater than 70 mL/min. Using standardised MRI renal imaging, these patients were evaluated annually in order to determine reliable measures of disease progression early in ADPKD. Longitudinal data from the CRISP 2 study published in 2012 suggested a correlation between TKV and total cyst volume, and a correlation of height-corrected TKV and GFR, out to 8 years of follow-up. At the 8 year follow-up, 194 out of 441 enrolled (241 originally enrolled in the CRISP 1 study, and 201 re-enrolled) patients were available for assessment. TKV was assessed by standardised serial MRI, GFR by iothalamate clearance. Height corrected TCV (cc/m) was the optimum variable in terms of predicting stage 3 CKD at 8 years from baseline, when compared against serum creatinine, BUN, urine albumin, urinary MCP-1 and age.

The CRISP cohort also confirmed that cystic growth and renal enlargement was significant before any significant impairment of renal function, and that the rate of cyst growth and TKV is continuous in each individual. The mean renal growth rate was found to be 5.3% per year, or about 63.4 mL per year. PKD1 genotypes were associated with larger kidneys compared to PKD2 patients, but with no significant difference in cyst growth rate. To demonstrate the difficulties of instead using GFR as a primary endpoint for the tolvaptan program, the majority of the participants (55.9%) entered the CRISP I study with a GFR > 90 ml/min per 1.73 m^2, and 42.3% continued to maintain this level of renal function by year 8. For ADPKD patients entering the study with GFR of 60-90, the figure was reduced to 27%.

The CRISP cohort has some similarities to the inclusion criteria for the pivotal tolvaptan study. Again, the cohort was at relatively high risk for developing renal insufficiency but had relatively intact renal function upon recruitment. The criteria for enrolment in CRISP required that two-thirds had risk factors for disease progression, including onset of hypertension or gross haematuria before age 35 years, or proteinuria of 300 mg/day. Clearly there are some differences between the population studied in study 156-04-251, and in the measurements and analyses, however overall the applicant has provided a compelling argument for the use of TKV as a primary endpoint. Measures of renal volume are clearly linked to the characteristic progressive development of renal cysts in ADPKD, and correlate with renal function. There is a lack of information on the correlation between renal volume and other clinical endpoints, although a correlation was clinically plausible *a priori*. MRI was done in a standardized and blinded fashion, generally using methodology established in the CRISP program, and a separate validation report is submitted for the pivotal study. Intra-reader variability had a relative error of 0.62%, while inter-reader variability had a relative error of 1.23%. In the clinical trial setting, MRI is the most suitable imaging technique to monitor total kidney volume, to accurately estimate the extent of disease and assess treatment progress. Ultrasound is more suited as a screening tool, and sequential CT scans involve a significant radiation exposure.

It is noted that the total kidney volume endpoint as primary showed lack of a consistent effect in all of the components of the key secondary analysis. Therefore the indication statement was adapted to retardation of cyst growth. Nevertheless it is taken into account that the literature since 2009 more strongly supports the TKV endpoint, with the publication of the CRISP 2 study.

The key secondary endpoint was a composite time to event analysis of defined clinical endpoints relating to hypertension, renal pain, albuminuria and reduction in renal function. These clinical outcomes were considered important in ADPKD, and were anticipated to be influenced by reducing the rate of cyst development. Importantly, all components were subject to independent verification as a sensitivity analysis.

Rate of change in renal function was the third endpoint, based on the reciprocal of serum creatinine. GFR estimates based on serum creatinine alone are not always reliable as a surrogate for renal impairment, however this endpoint does allow comparison to other trials in CKD, and it was supported by standard alternative equations, including the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. A large number of other endpoints looked at the components of the secondary composite endpoints and other PK, PD, safety and clinical outcome measures.

There is no other regulatory precedent for ADPKD interventional trials, but it is clear that the progression of ADPKD is slow, and it is not considered reasonable to expect an analysis based on 50% loss prior to licensing. Increase of 33% in serum creatinine does have significant limitations as an endpoint; however, taking into account the natural history of ADPKD and the practicalities of conducting a study in the limited number of available patients the reasoning behind this choice is understood. A recent paper by the Chronic Kidney Disease Progression Consortium (Coresh *et al* 2014) [5] gives further support for using this endpoint.

Overall, the choice of endpoints is considered acceptable. In particular, it is considered that the primary end point is well supported by clinical arguments and the literature. This takes into account the 3 year study duration, and the fact that harder clinical endpoints such as those related to onset of end-stage renal disease or all-cause mortality would require many more subjects and a longer duration of study than reasonably possible in this rare disease.

Randomisation and blinding procedures were acceptable and there are no indications of significant problems with the study conduct.

Efficacy data – pivotal study

Of 2122 screened subjects, 1445 were randomized, of whom 1444 received at least 1 dose. A total of 961 subjects received tolvaptan and 483 subjects received placebo. Overall, 1157 patients (80.1%) completed the 3-year trial. There is a low loss to follow-up, partly as subjects were regularly followed up by telephone after discontinuation.

The primary efficacy analysis included 1307 of the 1445 patients (90.4%), and the discontinuation rate is much higher (23%) in the tolvaptan group than placebo (13.8%). This difference is due to the difference in the rate of discontinuation due to adverse events (15.4% versus 5%). 12.4% of patients randomised to receive tolvaptan were not included in the primary analysis. In contrast, only 3.9% of placebo patients were excluded from the primary analysis. This is discussed below. The key secondary efficacy analysis included all 1445 (100%), and the key secondary safety analysis included 1444 (99.9%)

Primary endpoint

Total kidney volume increased by 18.8% in placebo subjects over 3 years but by only half that (9.6%) in tolvaptan subjects. The rate of growth was 2.80% per year for tolvaptan, compared to 5.51% per year for placebo-treated patients. The ratio of geometric means was 0.974 (95% confidence interval 0.969 to 0.980; $p < 0.0001$), a difference of −2.71% per year with a 49.2% reduction in growth rate in the tolvaptan group compared with the placebo group. The effect of treatment with tolvaptan on TKV was greatest in the first year but effects of tolvaptan treatment persisted into the second and

[5] Coresh J, Turin TC, Matsushita K, Sang Y, Ballew SH, Appel LJ et al. Decline in Estimated Glomerular Filtration Rate and Subsequent Risk of End-Stage Renal Disease and Mortality. JAMA. Doi:10.1001/jama.2014.6634.

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 years. The rate of progression per year in the placebo group was similar to that expected from historical data and twice that seen in the tolvaptan group.

These results were replicated in multiple sensitivity analyses, including re-analyses to account for differing model assumptions and datasets, potential MRI quality or reading errors, and analyses by study and country. Generally consistent results were seen in all subgroups, including those related to stratification factors, baseline disease severity, adverse prognostic factors, age, gender, and race.

None of the analyses previously provided adequately took into account the differential dropout rate due to adverse events observed in the trial. For the primary endpoint (TKV) and the first two secondary endpoints (composite and eGFR) the applicant performed an analysis of change from baseline to month 36, with a "tipping point" analysis to explore how punitive the imputation of subjects with missing values at month 36 due to withdrawal from the study due to adverse events has to be, before statistical significance of the comparison between treatment groups is lost. For TKV, the p-value does not exceed 0.05 (loss of significance) until 333% of the tolvaptan estimated treatment effect is subtracted from tolvaptan imputed data value. This reduction in treatment effect would equate to TKV growth at Month 36 of 40.25%. For eGFR, the p-value does not exceed 0.05 until 267% of the tolvaptan estimated treatment effect is subtracted from the imputed data - this equates to eGFR decline at Month 36 of 16.19mL/min/1.73m^2, which corresponds to an increase of over 60%. The provided discussion (based on literature) provides reassurance that these penalized imputations are very conservative and highly unlikely.

The Applicant presented sensitivity analyses with BOCF for the primary endpoint TKV and renal function. These results show a statistically significant treatment effect in favour of Tolvaptan at months 12, 24 and 36, with the largest effect (95% CI) of -9.99 (-11.70, -8.26) see at Month 36 for TKV. For renal function, the largest treatment effect (95% CI) of 3.54 (2.43, 4.65) was seen at Month 32

Further analyses of renal function show that treatment effects were significant after exclusion of the possible confounding of dehydration secondary to the aquaretic effects of tolvaptan. Robust evidence of a clinically relevant effect is required, given that there is only one pivotal trial, and as tolvaptan is a new pharmacological principle in ADPKD, with no therapies approved in the proposed indication. Generally however, the study was well designed, well conducted, and based on a plausible hypothesis of action. It is also supported by preclinical, *in vitro* and clinical pharmacology data, with several smaller supporting studies and support for the choice of endpoints in the published literature. The high level of statistical significance, lack of obvious internal bias or concerning centre effects, and support from subgroup analyses are reassuring, and the observed effect size in the primary endpoint is of definite clinical interest.

The study authors note that as all patients were asked to maintain good hydration and avoid thirst, a substantial number of patients in the placebo group reported polyuria and nocturia. Although maintaining hydration helped ensure that the blinding in the study was maintained, the authors speculate whether suppression of vasopressin release in the placebo group may have led to an underestimation of the beneficial effect of tolvaptan. However, increased water intake to suppress vasopressin-mediated cAMP generation is already recommended for patients with ADPKD[6]. It is not known whether an even higher water intake would have reduced the effect size of tolvaptan further, although whether this is tolerable for the patient or appropriate is not clear.

Although there is no suggestion from the data that the tolvaptan and placebo groups are converging, and the decrease in urine osmolality in tolvaptan subjects at month 36 remains comparable to the

[6] Torres VE *et al*. A case for water in the treatment of polycystic kidney disease. Clin J Am Soc Nephrol 2009;4:1140-1150

initial results longer term data efficacy are needed and will be provided within final study report of the long term extension study of the pivotal trial as outlined in the RMP and Annex II.

Key composite secondary endpoint

Overall, there was a statistically significant 13.5 % rate reduction compared to placebo. This was however driven by changes in 2 out of the 4 components of the composite variable. These were the events of renal function decline (based on a 25% decrease in the reciprocal of serum creatinine, an increase in serum creatinine of 33%) and renal pain (severe renal pain requiring medical intervention). No trend for a benefit was seen for the specified hypertension or albuminuria events. The analysis of time to first composite ADPKD event also showed a benefit in favour of tolvaptan.

For the secondary composite endpoint, analyses of time to first event as well as the number of recurrent events per 100 follow-up years have been provided. The applicant presented a tipping point analysis where it is assumed that both groups would follow the Kaplan-Meir curve of time to first event observed in placebo subjects, which correspond to the total of unobserved events in both groups respectively of 50 and 8. With this approach, the applicant concluded that 58 unobserved events would have to be assumed to have occurred in subjects who withdraw from tolvaptan for statistical significance to be lost. Analysis based on this assumption is not conservative.

The applicant presented additional analyses based on estimates imputed by the KM curve of placebo subjects. The tipping point analysis for the time to first event showed that statistical significance is lost when 116% of tolvaptan efficacy is lost.

The HR (95% CI) previously reported for time to recurrent events, based on non-adjudicated events, was 0.865 (0.775, 0.965) corresponding to a total number of recurrent events of 1049 and 665 (original report Table 9.4.1) in the tolvaptan and placebo groups. When missing data are treated as an event, the total number of recurrent events in the tolvaptan and placebo groups are 1262 and 726. The HR (95% CI) when missing values are treated as events is 0.953 (0.861, 1.054)

The time to recurrent events analyses with missing data treated as an event show that statistical significance is lost when 111% of tolvaptan efficacy is lost. This loss of efficacy corresponds to an HR (95% CI) of 0.906 (0.815, 1.006). The corresponding events are 1304 in the Tolvaptan group and 725 in the Placebo group.

The hazard ratio relating to renal function decline was 0.386 (95% CI 0.263 to 0.566) and for renal pain the HR was 0.642 (95% CI 0.466 to 0.887). These correspond to a relative improvement of 61.4% and 35.8% respectively. Analyses of time to first event for these specific endpoints were consistent. The numbers of worsening renal function events are low, but consistent with the relatively intact renal function at study entry, the relatively slow rate of renal function decline in ADPKD, and the length of the study. Events that signaled a decline in renal function were delayed in both groups until around a year, with the separation of tolvaptan treatment from placebo treatment evident at approximately month 18, whilst the effect of tolvaptan on renal pain was observed earlier.

For both the renal worsening and renal pain components, the numbers of events were small as a proportion of the total events for the composite result. The subjective nature of renal pain and the characteristic aquaretic effects of tolvaptan clearly make blinding of this endpoint more difficult, although the main analysis was done on the basis of required interventions for renal pain. Investigator-reported ADPKD clinical progression events for subjects taking tolvaptan relative to subjects on placebo were evaluated by an independent adjudication committee, and aquaretic AEs did not correlate with the reporting of renal pain. Irrespective of any blinding issues, whilst a large total kidney volume has been associated with renal pain in cross-sectional and longitudinal studies and the available data suggest a benefit for tolvaptan, data to show an effect of tolvaptan on renal pain or other clinical manifestations and symptoms of ADPKD are not considered robust at this time. More extensive and longer-term data will be provided within the two PAES.

Tolvaptan was hoped to lead to structural as well as functional improvements in the kidney. The findings in hypertension and albuminuria components of the composite endpoint are disappointing, as these are adverse prognostic factors in ADPKD. In particular, hypertension aggravates the progressive renal disease of ADPKD, and cardiovascular disease is the main cause of death in these patients. The lack of significance of the hypertension endpoint was attributed by the applicant to the relatively high prevalence of treated hypertension seen in the population at baseline. This is plausible. By the time cyst formation starts, the renin-angiotensin system is already activated and reduction of already formed but microscopic cysts might not reverse that trend. If treatment were started well before cyst formation starts, then we might see a change in prevalence in hypertension in comparison to placebo, but this population has not been studied.

Worsening in albuminuria is also an adverse prognostic factor in ADPKD and the lack of effect on this endpoint is noted, although *post-hoc* analyses suggested a possibility for a late effect. This endpoint might again be affected by time of initiation of treatment.

Rate of renal function decline

In the pre specified 3rd endpoint, Tolvaptan treatment slowed the rate of renal function decline (reciprocal of serum creatinine) by one-third compared to placebo, for which the predefined statistical criteria were met. This was confirmed by other estimation methods and demonstrated a significant association with the rate of change in TKV. The mean rate of change per year in estimated GFR CKD-EPI was around -2.7 mL/min/1.73 m^2 for the tolvaptan group and -3.6 for the placebo group. The rate of GFR decline in ADPKD is inexorable but relatively slow. To put the eGFR results into context, rapid progression of renal impairment is generally defined in CKD as a sustained decline in eGFR of more than 5 ml/min/1.73 m2/year. Once eGFR decreases below 30 mL/min, there is a progressive impact of complications related to renal impairment. Although primarily dependent on symptoms, the need for renal replacement therapy often occurs in a GFR range between 5 and 10 ml/min/1.73 m2. These later stages of CKD are therefore of particular interest for verification of the clinical effect of tolvaptan. Further long-term data to show that tolvaptan continues to slow the rate of renal function decline and delay the onset of end-stage renal disease will be provided post authorisation within the long term extension study of the pivotal trial as well as from an ongoing efficacy study in patients with later stages of renal insufficiency and with a primary endpoint related to GFR as outlined in Annex II and RMP.

Other endpoints

Beyond the third endpoint of renal function decline, none of the other planned secondary endpoints yielded clear trends. In any case, the rate of renal function change was the last endpoint for which the null hypothesis was rejected; therefore subsequent analyses must be considered in the light of potential type 1 error. In an exploratory analysis, treatment with tolvaptan was associated with an improvement in selected ADPKD-related conditions. A smaller proportion of subjects on tolvaptan reported renal pain, nephrolithiasis, haematuria, UTI, and anaemia as compared with subjects on placebo. However these results should be viewed with caution.

Additional analyses

Subgroup analyses of pivotal study

For the primary endpoint, generally consistent results were seen in all subgroups, including those related to stratification factors, baseline disease severity, adverse prognostic factors, age, gender, and race. For the secondary and third efficacy endpoints, subgroup analyses produced nominal point estimates that generally favoured tolvaptan.

The CRISP study suggested that both TKV and renal function worsen more quickly for those with larger kidney volumes; however efficacy was also suggested for subjects with TKV ≥1000 ml at

baseline, and for subjects with TKV ≥1500 ml at baseline. Efficacy was also shown in subjects grouped by estimated creatinine clearance less than, or greater than 80 mL/min. An exploratory analysis by CKD stage was also submitted (Stage 1, 2, 3A, 3B, based on eGFRCKD-EPI). The favorable effects of tolvaptan on kidney volume were consistent at various stages of ADPKD. Stage 2 CKD is a wide grouping; however the treatment effect on kidney growth and eGFR decline is significant both in patients with baseline eGFR 60-74 and patients with baseline eGFR 75-89.

Supportive studies

Supportive evidence of efficacy in ADPKD is available from two separate 3-year, open-label extension trials, study and 156-05-002. Study 250 is more informative, as study 156-05-002 was in a smaller number of patients and involved a dose of 15mg b.d. The mean results from study 156-04-250 suggest an acute decrease in renal volume of 3-4% in the first month. This is uncertain given the small numbers, intersubject variability and the lack of a control arm; however a small acute effect on renal volume was also suggested in the shorter studies 156-06 and 156-09-284. In this exploratory data-set, TKV appeared to have a slower rate of decrease in the higher-dose group, and increased in the off-treatment period between month 36 and the start of the extension period. These data at the 45/15 and 60/30 mg regimes suggests a dose-response for slowing TKV volume progression, and appear to confirm that continuous treatment with tolvaptan may be important.

The progression of ADPKD, as evidenced by both increasing total kidney volume and declining estimated glomerular filtration rate, was significantly slowed after 3 years of tolvaptan treatment compared with historical control data, and there was a significant negative correlation between annualized slope of TKV and slope of eGFR. The limitations to this historical comparison include the small number of patients in the open-label studies, the fact that tolvaptan dosing was not the same as in the pivotal study, and the age of the MRDR data.

Based on preliminary data of the long term extension of the pivotal study (trial 156- 08-271) the beneficial effect of tolvaptan was maintained during the 2-years of treatment.

2.5.4. Conclusions on the clinical efficacy

For the primary efficacy endpoint, total kidney volume increased by 18.8% in placebo subjects over 3 years but by around half that (9.6%) in tolvaptan subjects. A large total kidney volume has been associated with hypertension, gross hematuria, nephrolithiasis, and pain in cross-sectional and longitudinal studies. The applicant has supported the use of total kidney volume as a primary endpoint with good clinical arguments and literature. The data to show a reduction in cyst development are considered clinically compelling.

Whereas a relevant effect on renal function decline could be shown in the secondary composite endpoint of the pivotal study and the rate of renal function decline showed significant association with the rate of change in TKV (as in other recent literature), effects of tolvaptan on renal pain or other clinical manifestations and symptoms of ADPKD are not considered robust at this time.

In the pivotal trial a patient population with a relatively large renal volume consistent with rapid cystic growth, but reasonably preserved renal function was evaluated (patients with early but rapidly progressive disease).

The indication was therefore, and also in view of safety considerations as discussed below, amended to reflect patients in whom clinically relevant benefit has been clearly shown.

Furthermore, considering that efficacy assessment and extrapolation to long term outcomes, is largely based on the surrogate parameter TKV more extensive long term data and data on patients in later stages of the disease is needed to confirm efficacy assumption based on hard clinical outcomes. This will be done within two post authorisation efficacy studies as described in Annex II and RMP.

The SPC clearly states that data are not currently available to show whether long-term therapy with Jinarc continues to slow the rate of renal function decline and affect clinical outcomes of ADPKD, including delay in the onset of end-stage renal disease.

The combination of a targeted indication to a population where the benefits have been conclusively demonstrated, adequate information to the prescriber and the post approval follow up leads to a relevant net benefit even if balanced against the risks discussed further below.

The CHMP considers the following measures necessary to address issues related to efficacy:

Description	Due date
Post Authorisation Efficacy Study (PAES): In order to further define the efficacy of tolvaptan in patients with more advanced renal dysfunction on a primary endpoint related to GFR rather than TKV the MAH should submit the Final study report of Study 156-13-210 by:	Feb-2018
Post Authorisation Efficacy Study (PAES): In order to show whether the observed short-term effects of tolvaptan on the rate of renal function decline translate into favourable long-term outcomes such as ADPKD related morbidity and mortality, including longer-term effects on GFR decline and progression of disease leading to dialysis or transplantation the MAH should submit the results of the open-label extension to the pivotal trial study 156-08-271. A comparison of progression shall be made to the expected untreated progression rate. The final clinical study report should be submitted by:	June-2016

2.6. Clinical safety

Patient exposure

Thirteen clinical trials in the ADPKD program have been completed. Four trials are currently on-going, including 1 multinational trial, 1 in the US and 2 in Japan. Of the 4 on-going trials, Trial 156-09-290 is a randomized, double-blind, placebo-controlled trial investigating safety and efficacy of tolvaptan (modified release formulation) in subjects with ADPKD. Because this trial is still blinded, only preliminary safety information with all treatment groups combined are described in this safety summary, and enrolled subjects are not included in estimates of tolvaptan exposure. In the remaining 3 on-going trials, all subjects are receiving open-label tolvaptan.

At the cut-off date 31 March 2012, approximately 6331 adult patients worldwide were exposed to oral tolvaptan in clinical trials in ADPKD and other indications. Since the first date of marketing approval of tolvaptan (19/5/09 through to 18/5/12) total post-marketing exposure to tolvaptan based on worldwide sales figures in indications other than ADPKD is estimated at approximately 3790 patient-years.

The safety database for the ADPKD submission includes 1581 subjects exposed to at least 1 dose of immediate-release tolvaptan in completed or on-going clinical trials. This population includes 1432 subjects with ADPKD, 37 non-ADPKD subjects with normal renal function or varying degrees of renal impairment, and 112 healthy subjects. Of the 1432 ADPKD subjects exposed, 1292 have been exposed for up to 6 months, 1017 for up to 12 months, and 801 for up to 36 months. 961 subjects with ADPKD were randomized to tolvaptan in the phase 3 pivotal Trial 156-04-251, with 864 subjects exposed for at least 8 months and 836 subjects exposed for 1 year or longer. The average daily dose of tolvaptan received at Month 36 was 96.45 mg.

Table 11: Cumulative exposure to tolvaptan in ADPKD subjects according to dose received

Cumulative Exposure	Tolvaptan, n (%)		
	15 to 45 mg (N = 53)	60 to 120 mg (N = 1412)	Total (N = 1432)
Any exposure	53 (100.0)	1412 (100.0)	1432 (100.0)
At least 2 weeks	17 (32.1)	1366 (96.7)	1383 (96.6)
At least 6 months	17 (32.1)	1275 (90.3)	1292 (90.2)
At least 12 months	15 (28.3)	1002 (71.0)	1017 (71.0)
At least 24 months	14 (26.4)	825 (58.4)	839 (58.6)
At least 36 months	13 (24.5)	788 (55.8)	801 (55.9)
At least 48 months	13 (24.5)	214 (15.2)	227 (15.9)
At least 60 months	11 (20.8)	26 (1.8)	38 (2.7)

The primary safety dataset is from the pivotal, placebo-controlled Trial 156-04-251. Based on findings from the pivotal trial, safety analyses were extended to include supportive ADPKD program trial datasets, as well as clinical datasets and post marketing surveillance from other indications (e.g., hyponatraemia, heart failure) when necessary to further explore important potential safety signals.

Adverse events

Table 12: Pivotal trial: adverse events (all causalities) within the treatment period

	Tolvaptan (N = 961)	Placebo (N = 484)	Total (N = 1445)
Number of subjects treated	961	483	1444
Subject years of drug exposure	2334.5	1305.5	3640.0
Subjects with AEs, n (%)	941 (97.9)	469 (97.1)	1410 (97.6)
Number of AEs	10909	4968	15877
Subjects with TEAEs, n (%)	941 (97.9)	469 (97.1)	1410 (97.6)
Number of TEAEs[a]	8544	3775	12319
Subjects with serious TEAEs, n (%)	177 (18.4)	95 (19.7)	272 (18.8)
Subjects with severe TEAEs, n (%)	203 (21.1)	88 (18.2)	291 (20.2)
Subjects who discontinued IMP due to an AE, n (%)	144 (15.0)	21 (4.3)	165 (11.4)
Number of subjects who died	0	0	0

97.9% of tolvaptan-treated subjects and 97.1% of placebo treated subjects had at least one treatment-emergent adverse event (TEAE) in the pivotal study. Treatment-emergent AEs reported in ≥ 10% of subjects in either or both treatment group included thirst, polyuria, hypertension, nocturia, renal pain, headache, pollakiuria, nasopharyngitis, dry mouth, blood creatinine increased, back pain, fatigue, diarrhoea, dizziness, polydipsia, nausea, urinary tract infection, and haematuria.

Adverse events directly associated with the aquaretic effects of tolvaptan (e.g., thirst, polyuria, nocturia, pollakiuria and dry mouth) were observed in a higher proportion of tolvaptan subjects in the first 3 months following initiation of therapy than during maintenance treatment.

TEAEs that led to discontinuation of study drug were reported in approximately 15% of subjects on tolvaptan compared with approximately 4% of subjects on placebo. The most frequently reported events resulting in treatment discontinuation were polyuria, nocturia, pollakiuria, thirst, abnormal hepatic function and fatigue. Overall, TEAEs associated with ADPKD (including renal pain, haematuria, anaemia, urinary tract infection and nephrolithiasis) were reported at a relatively uniform rate throughout the trial. There were numerical reductions in favour of tolvaptan for haematuria, urinary tract infection and anaemia. There was no indication that tolvaptan had a clinically meaningful effect on the occurrence of vascular abnormalities associated with ADPKD, or on other cysts outside of the kidney.

Flank pain or renal pain were reported in a smaller proportion of subjects treated with tolvaptan (27.7%) compared with subjects treated with placebo (36.9%) and fewer such events in tolvaptan subjects were reported as severe or serious.

Across the whole ADPKD program, frequently reported TEAEs in other long-term and short-term trials of tolvaptan were consistent with those observed in Trial 156-04-251, and AEs leading to treatment discontinuation were similar in the 2 long-term open studies.

Adverse events of particular interest

Hepatic toxicity

In the pivotal trial, the incidence of elevated transaminase levels for tolvaptan subjects (> 3 × ULN) was approximately 3 to 4-fold higher than for placebo subjects. The overall incidence of serious hepatic TEAEs was also higher for tolvaptan subjects (2.3%, 22/961) than for placebo subjects (1.0%, 5/483)

The applicant formed an independent, blinded, expert Hepatic Adjudication Committee for the *post-hoc* sequential evaluation and adjudication of these events in the ADPKD program (data from completed trials and data from on-going trials received through 31 Mar 2012). This process will continue for on-going trials.

59 subjects from ADPKD clinical trials were identified as meeting the hepatic event criteria for further evaluation. The criteria for "potentially serious liver injury" were:

- ALT/AST > 3 × ULN accompanied by total bilirubin > 2 × ULN

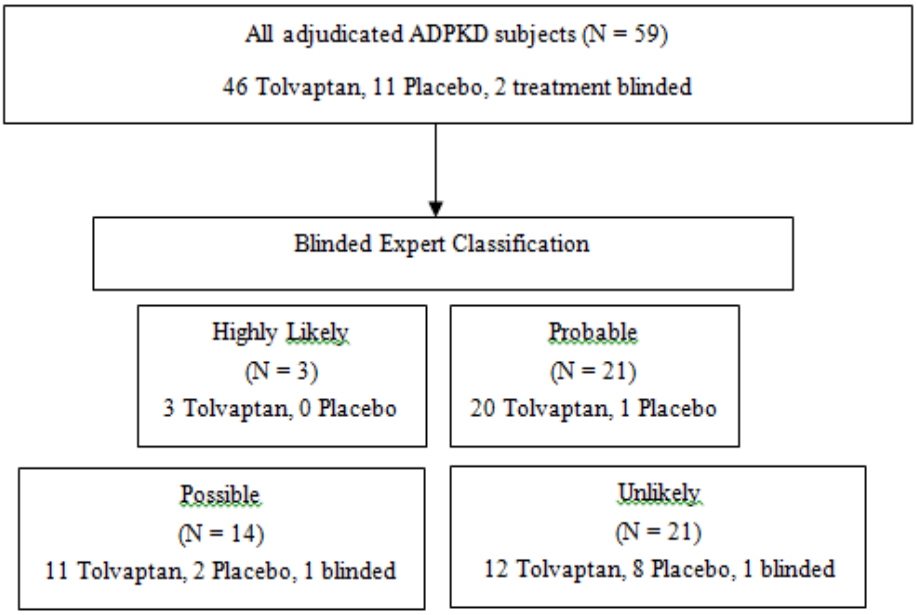
-Total bilirubin elevation occurring within 30 days of the transaminase elevation

- No evidence of cholestasis (serum alkaline phosphatase < 2 × ULN)

- Other causes of hepatic injury were excluded by medical differential diagnosis

This adjudication revealed that 3 tolvaptan subjects in the ADPKD program met requirements for potentially serious liver injury. 2 of these were from the pivotal study, 1 from the extension study 156-08-271. The onset of hepatocellular injury, as manifested by transaminase values exceeding 3 × ULN, was characteristically observed after at least 3 months of treatment, but could occur after 1 year.

Figure 9: Adjudication Results for the ADPKD Program, cases meeting criteria for potentially serious liver injury



Transaminase 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, permanent liver

injury or dysfunction. No subjects experienced hepatic failure, hepatic transplantation, or death resulting from hepatocellular injury. For the 3 cases adjudicated as highly likely, the safety report mentions liver biopsy in 1 case – this was a picture of cytolytic hepatitis with evidence of centrilobular necrosis.

No association with tolvaptan dose or exposure was found. Given the small numbers, a clear association between tolvaptan and demographic characteristics, or disease characteristics was inconclusive. TEAEs of increased ALT/AST were however more common in tolvaptan subjects with a baseline eCrCLCG < 80 mL/min compared to those with better renal function (5.4% compared to 3.2 and 3.6% respectively)

An updated report was submitted during the procedure, which includes an additional 2 years of data (31 Mar 2012 to 28 February 2014) from the extension study. As of March 2014, 1275 patients had received tolvaptan through the estimated "window of susceptibility" of 18 months, up from 838 in the 2012 adjudication report. There were no new cases meeting criteria for potentially serious liver injury in this update.

Retrospective evaluation of data from the separate hyponatraemia and heart failure clinical development programs did not reveal an imbalance of subjects with elevated AST/ALT between tolvaptan and placebo groups, nor were any of the subjects adjudicated as "highly likely" or "probable". Tolvaptan as the Samsca licence (hyponatraemia indication) was first approved in 2009. Since the first date of approval of tolvaptan through to 18/5/12, worldwide post marketing exposure to tolvaptan is estimated at approximately 3790 patient years. No signal of tolvaptan-induced hepatotoxicity has been detected during this post marketing experience.

Electrolyte balance

Tolvaptan did not have a clinically meaningful effect on serum potassium or calcium concentrations in subjects with ADPKD. The rate of potentially clinically significant increased sodium abnormalities (sodium > 150 mEq/L) was higher in the tolvaptan group (4.0%) compared with the placebo group (1.4%) in the pivotal trial. Following titration of tolvaptan in the first 3 weeks, mean changes (± standard deviation) from baseline to Week 3 in serum sodium were 2.24 ± 2.71 mEq/L on tolvaptan compared with 0.02 ± 2.45 mEq/L on placebo. A higher incidence in TEAEs related to increased sodium concentrations was also observed in tolvaptan subjects (5.2%) compared with placebo subjects (1.4 %), which were predominantly mild in severity and reported early following initiation of treatment. No events were serious, and none led to study drug discontinuation.

Hyperuricaemia

In the pivotal trial, an increased level of uric acid (greater than 10 mg/dL) was reported at a higher rate in the tolvaptan group (6.2%) compared with the placebo group (1.7%). Similarly, TEAEs related to increases in uric acid were more frequent in the tolvaptan group (5.1%) than the placebo group (2.7%). There was a higher incidence of the ADR "Increased blood uric acid" (2.5% vs. 1.2%) and of "gout" (2.9% vs. 1.4%) in tolvaptan subjects compared with placebo subjects. No events were considered serious and none led to study drug discontinuation. In the safety population, the use of allopurinol at any time during trial treatment was documented in 65/961 tolvaptan subjects (6.8%) and 25/483 placebo subjects (5.2%)

Renal impairment

The rate of significantly increased creatinine abnormalities was lower in the tolvaptan group (16.7%) compared with the placebo group (21.0%) in the pivotal trial. A slightly lower incidence of acute renal failure TEAEs was observed in tolvaptan subjects, TEAEs of increased creatinine were similar between the 2 treatment groups. All reports of increased blood creatinine were rated as mild to moderate in severity. TEAEs of increased blood creatinine led to discontinuation of study drug in 3 tolvaptan subjects (0.3%) during the pivotal trial.

Upon withdrawal of treatment, serum creatinine concentrations decreased to concentrations that were significantly lower in tolvaptan than placebo subjects, indicating that tolvaptan subjects had had smaller net increases in serum creatinine during the trial. This corresponds to an increase from baseline to follow-up Visit 2 in the mean serum creatinine level from 1.05 mg/dL to 1.21 mg/dL in the tolvaptan group, as compared with an increase from 1.04 mg/dL to 1.27 mg/dL in the placebo group.

Cardiovascular effects and thrombosis

Reports of TEAEs in the myocardial infarction SMQ were comparable between the 2 treatment groups (0.7% on tolvaptan, 0.6% on placebo) and overall, tolvaptan did not appear to increase cardiovascular risk in subjects with ADPKD. A higher proportion of subjects on tolvaptan (7.4%) reported events related to arrhythmia compared with subjects on placebo (4.6%) This difference was primarily due to a higher incidence of palpitations and syncope in the tolvaptan group. All TEAEs of palpitations or syncope were mild or moderate in severity. Four tolvaptan subjects experienced serious TEAEs in the arrhythmia-related investigations, signs, and symptoms SMQ (1 with palpitations, 1 with palpitations and syncope, and 2 with loss of consciousness) compared with 1 placebo subject (bradycardia). None of the events in this analysis resulted in study drug discontinuation.

Hyperglycaemia

Increased glucose concentrations were observed less frequently in subjects on tolvaptan (5.5%) compared with subjects on placebo (6.8%) and potentially clinically significant decreased glucose concentrations occurred at similar rates in the tolvaptan and placebo groups (3.8% and 3.7%, respectively). Mean changes from baseline to Month 36 in serum glucose concentrations were 0.90 ± 17.38 mg/dL in the tolvaptan group and -0.36 ± 17.36 mg/dL in the placebo group.

Reported TEAEs in the hyperglycaemia/new onset diabetes mellitus SMQ were however more frequent in subjects on tolvaptan (76.9%) compared with subjects on placebo (41.2%). This difference was primarily due to an increased incidence of thirst and polyuria. Excluding these lead to more similar events between the 2 treatment groups (18.4% vs. 17.0%), although still a numerical increase in the tolvaptan group. The proportions of subjects who experienced serious TEAEs were however similar between the 2 treatment groups and discontinuations due to hyperglycaemia TEAEs were infrequent.

While theoretical mechanisms exist whereby tolvaptan might affect glucose homeostasis, the proportion of subjects with changes in glucose concentrations and the incidence of TEAEs related to hyperglycaemia during the trial were similar between the 2 treatment groups. In contrast, TEAEs of diabetes were reported exclusively in tolvaptan subjects in the pivotal trial; however, the total number of cases was small (n = 7). Overall however, the applicant concludes that an association between tolvaptan use and hyperglycaemia/new onset diabetes TEAEs cannot be excluded. This has now been reflected in the SmPC (see also discussion on safety).

Glaucoma

In the pivotal study, TEAEs in the glaucoma SMQ (glaucoma, eye pain, increased intraocular pressure, blurred vision, and reduced visual acuity) were reported in 2.1% (20/961) of subjects in the tolvaptan group and 1.0% (5/483) of subjects in the placebo group. For the 3 terms most specific to glaucoma (glaucoma, open angle glaucoma, and intraocular pressure increased) the incidences were 0.7% (7/961) in the tolvaptan group vs. 0.4% (2/483) in the placebo group. Treatment-emergent AEs of glaucoma, increased intraocular pressure, eye pain, and blurred vision were all mild to moderate in severity, with the exception of 1 tolvaptan subject who reported a serious TEAE of severe glaucoma. Also, 2 early-treated tolvaptan subjects in trial 156-08-271 reported TEAES of mild glaucoma during treatment, one of which was a subject who had an event of glaucoma in the pivotal trial that worsened in trial 156-08-271.

The applicants review of all reported cases of glaucoma or open angle glaucoma did not reveal associated AEs, laboratory abnormalities, concomitant medications, or physical examination findings that indicated a clear pattern of exacerbating factors, or suggested a causal link to tolvaptan. With the exception of 1 case that occurred on day 4 (placebo subject), the remaining events appeared to occur later in treatment (many after 2 to 3 years of treatment). The sponsor engaged an external independent expert in ophthalmology and glaucoma, to complete a blinded review of the 7 cases from trial 156-04-251 for possible attribution of causality. Following this review, the expert found no clear and consistent pattern that would attribute these events to study drug. However, glaucoma will be investigated in the PASS and will be subject to targeted follow up (see also discussion on safety).

Neoplasia

A further potential new safety signal in Trial 156-04-251 was an increased incidence of TEAEs in the malignant neoplasms SMQ (1.7% vs. 0.4%), in particular basal cell carcinoma (0.8% vs. 0.2%) on tolvaptan. In the wider SOC of "neoplasms benign, malignant, and unspecified (including cysts and polyps)," TEAEs were recorded in 45 subjects (4.7%) in the tolvaptan group and 19 (3.9%) in the placebo group. Treatment-emergent AEs in the "malignant tumour" SMQ were reported in 1.7% of subjects in the tolvaptan group and 0.4% of subjects in the placebo group with a calculated OR for the treatment-group comparison of 4.072 (95% CI 0.932, 17.782). None of the reported TEAEs in the malignant tumour SMQ were considered potentially related to study drug by the investigator.

Table 13: Incidence of Treatment-emergent Adverse Events in the Neoplasm SMQs in Trial 156-04-251 by MedDRA System Organ Class and Preferred Term

MedDRA Query PT	Tolvaptan (N = 961) n (%)	Placebo (N = 483) n (%)	Total (N = 1444) n (%)
Malignant tumors SMQ, Total[a]	16 (1.7)	2 (0.4)	18 (1.2)
Basal Cell Carcinoma	8 (0.8)	1 (0.2)	9 (0.6)
Breast Cancer	3 (0.3)	1 (0.2)	4 (0.3)
Cervix Carcinoma Stage 0	1 (0.1)	0	1 (0.1)
Chronic Myeloid Leukaemia	1 (0.1)	0	1 (0.1)
Kaposi's Sarcoma	1 (0.1)	0	1 (0.1)
Malignant Melanoma	2 (0.2)	0	2 (0.1)
Malignant Melanoma In Situ	1 (0.1)	0	1 (0.1)
Squamous Cell Carcinoma	0	1 (0.2)	1 (0.1)
Tumors of unspecified malignancy SMQ, Total[a]	0	1 (0.2)	1 (0.1)
Thyroid Neoplasm	0	1 (0.2)	1 (0.1)

Overall, for the 16 tolvaptan subjects in the pivotal trial with malignant neoplasm events, the majority (10/16 subjects) had relevant history or presence of a risk factor for development of the neoplasm. The time to onset (regardless of neoplasm type) in the pivotal trial ranged from 121 to 1088 days after initiation of tolvaptan. No imbalance in overall malignant tumours was seen in the controlled data from non-ADPKD studies. Combined with controlled data from non-ADPK studies, the overall incidence of basal cell carcinoma was 15/4255 (0.4%) vs. 6/3221 (0.2%)

The baseline prevalence and incidence of new occurrences of skin neoplasm (basal cell carcinoma) will be further characterized in the proposed PASS. The assessment of this safety signal will be performed through routine pharmacovigilance and communicated as appropriate.

Serious adverse event / deaths / other significant events

There were no deaths in the pivotal study. As of 31/3/12, a total of 2 subjects died due to TEAEs while participating in tolvaptan trials in the ADPKD program. One was due to a self-inflicted gunshot wound, the other assessed as due to subarachnoid haemorrhage secondary to ruptured cerebral aneurysm. Neither were assessed as related to tolvaptan by the investigator.

In the pivotal trial safety population, the proportion of subjects on tolvaptan who experienced at least 1 serious TEAE (18.4%) was nominally lower than on placebo (19.7%). Tolvaptan treatment was associated with a decreased incidence of serious TEAEs associated with ADPKD worsening or complications, such as urinary tract infection, pyelonephritis, renal pain, hypertension, and haemorrhage into renal cysts. Serious TEAEs reported in tolvaptan subjects at ≥ 0.5% higher incidence than in placebo subjects included increased ALT, increased AST, and headache. The events relating to hepatic toxicity are discussed above. Otherwise, no particular pattern arises.

Serious TEAEs in long-term supportive trials of tolvaptan in ADPKD subjects were infrequent and most reported TEAE terms were consistent with those observed in Trial 156-04-251. Across supportive short-term trials, only 2 subjects experienced serious TEAEs (polyuria, angina) and there were no serious TEAEs in the healthy subject trials.

Laboratory findings

Events relating to renal and liver function tests, uric acid, potassium, sodium, glucose and calcium are discussed in other sections. No significant differences in other biochemistry or haematology parameters were seen.

Safety in special populations

Pregnancy and breast feeding

As of 31/3/12, there have been 6 documented live births, 3 reported spontaneous abortions, and 5 reported elective abortions in tolvaptan trials within the ADPKD program. Based on available follow-up information, no birth defects have been reported. It is unknown whether tolvaptan is excreted in human milk; however, excretion of tolvaptan in breast milk in animal studies has been demonstrated. Breastfeeding should be discontinued (contraindication) when receiving tolvaptan, and it is contra-indicated in pregnancy (refer to non-clinical assessment above (chapter 2.3 of this assessment report).

Children

There are no existing or new data in children; the proposed indication is restricted to adults.

Gender, race and age

Overall, there were no conclusive and clinically important differences in adverse events attributable to treatment with tolvaptan, based on gender, race, or age. The mean age of subjects at randomization was however 38.7 years in the pivotal trial, as the inclusion criteria restricted to patients up to 50 years old. The SmPC was updated to state that, the safety and effectiveness of tolvaptan in ADPKD patients aged over 50 has not yet been established. Additional safety information is available for tolvaptan in other indications, which typically included elderly subjects. In these programs, no significant age-related risks were identified.

Renal impairment

The incidence of specific adverse events of interest in this group is covered separately in the sections above where appropriate. Overall, the proportions of subjects in each treatment group who reported TEAEs during the pivotal trial were similar regardless of baseline renal function in the pivotal trial. As detailed in the pharmacology section, subjects with or without ADPKD and varying degrees of renal function were enrolled in 3 completed short-term trials (Trials 156-09-282, 156-06-260, and 156-09-284). No differences of concern emerged, although the numbers of subjects were small.

TEAEs associated with the aquaretic effects of tolvaptan such as thirst and excessive urination occurred at a lower incidence in subjects with reduced renal function compared with subjects who had

normal or preserved renal function. This effect was considered to be due to a smaller increase in urine output relative to a higher baseline urine output, attributable to a smaller number of fully functioning nephrons and decreased sensitivity to AVP.

Hepatic impairment

No new formal studies in patients with hepatic impairment are submitted for the ADPKD indication, nor is an integrated analysis of adverse events according to baseline degree of hepatic impairment submitted. The safety overview does note that in subjects with cirrhosis treated with tolvaptan in prior hyponatraemia trials, an increased incidence of GI bleeding was noted in subjects on tolvaptan compared with subjects on placebo. However, there were no subjects with late-stage cirrhosis in the ADPKD trials.

Immunological events

The TEAE of rash was seen in 4.2% tolvaptan subjects in the pivotal trial, vs. 1.9% of placebo subjects. TEAEs in the anaphylactic reaction SMQ were reported in 25.3% of subjects in the tolvaptan group and 20.1% of subjects in the placebo group in the pivotal trial. This difference was primarily due to increased incidences of rash and dyspnoea in the tolvaptan group. Events of urticaria, pruritus, and chest discomfort were also slightly more frequent in subjects on tolvaptan compared with subjects on placebo. All reports of rash, pruritus, or chest discomfort were mild or moderate in severity in both treatment groups. Serious anaphylaxis-related TEAEs were reported in 1.0% of subjects on tolvaptan and 0.2% of subjects on placebo. Two tolvaptan subjects (0.2%) and 1 placebo subject (0.2%) experienced serious treatment emergent AEs related to anaphylaxis, with reported terms of anaphylactic reaction and respiratory failure.

The case of anaphylaxis on tolvaptan was reported 3 to 6 months after the initiation of treatment and was moderate in severity. The case narrative reports a temporal relationship with amoxicillin, the sponsor assessed the event as unrelated to tolvaptan, and the patient continued on tolvaptan. The case of respiratory failure was also moderate and occurred after month 33, and occurred in the context of advancing hepatic involvement and pleural/pericardial effusion. Neither of these 2 events led to discontinuation of trial therapy.

Safety related to drug-drug interactions and other interactions

No AEs with the preferred term of ‘drug interaction’ were reported by investigators during the pivotal trial, and no unexpected signals arise from review of adverse events in patients taking various drug categories.

Discontinuation due to adverse events

Table 14: Incidence of treatment-emergent adverse events resulting in discontinuation of investigational medicinal product in at least 0.5% of subjects in any group in trial 156-04-251 by MedDRA System Organ Class and Preferred Term

SOC PT	Tolvaptan (N = 961)	Placebo (N = 483)	Total (N = 1444)
Total[a]	144 (15.0)	21 (4.3)	165 (11.4)
General disorders and administration site conditions			
Fatigue	5 (0.5)	0	5 (0.3)
Thirst	6 (0.6)	1 (0.2)	7 (0.5)
Hepatobiliary disorders			
Hepatic Function Abnormal	6 (0.6)	0	6 (0.4)
Renal and urinary disorders			
Nocturia	9 (0.9)	1 (0.2)	10 (0.7)
Pollakiuria	15 (1.6)	0	15 (1.0)
Polyuria	38 (4.0)	0	38 (2.6)
Renal Pain	2 (0.2)	3 (0.6)	5 (0.3)

Post marketing experience

At the time of submission the product was not authorized in any country for the treatment of patients with ADKPD. From the last PSUR interval (19 May 2013 – 18 May 2014) on Samsca (tolvaptan authorised for the treatment of clinically significant hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone (SIADH) in adult patients) no safety concerns have arisen.

2.6.1. Discussion on clinical safety

General

As initially submitted, of the 1432 ADPKD subjects exposed to tolvaptan, 1292 were exposed for up to 6 months, 1017 for up to 12 months, and 801 for up to 36 months. 961 subjects with ADPKD were randomized to tolvaptan in the phase 3 pivotal Trial 156-04-251, with 864 subjects exposed for at least 8 months and 836 subjects exposed for 1 year or longer. The average daily dose of tolvaptan received at Month 36 was 96.45 mg. Some supportive information is available from clinical studies and post-marketing data relating to use in hypernatraemia. Overall the number of exposed individuals and treatment duration is reasonable for an application of this nature.

In the pivotal study, there were significantly more discontinuations due to adverse events in the tolvaptan arm compared to the placebo group (15% vs. 4.3%) The commonest adverse events associated with tolvaptan in the ADPKD program were as expected from its aquaretic effect. These included thirst, polyuria, nocturia, pollakiuria, and dry mouth. In the pivotal trial, aquaresis-related adverse events led to the discontinuation of tolvaptan in approximately 8% of participants, mostly within the first month. Fluid intake must be adjusted to balance increased urine output, particularly important in subjects with impaired renal function. These adverse events are inconvenient, and for some patients the frequent need to urinate and replace with fluids is intolerably disruptive. Any change in serum sodium appears manageable clinically through appropriate guidance regarding fluid intake, clinical monitoring and dose reduction.

At the initiation of tolvaptan therapy there is a small and reversible reduction in GFR, the mechanism is not fully defined (refer to discussion in clinical pharmacology section). Data suggest that the absolute decrease is lower in patients with more severe renal impairment, but the numbers of such patients are limited. Even if the decline is small, in patients with more severe renal impairment it can become more significant as a percentage of residual renal function.

Generally, other adverse events in the ADPKD program linked to tolvaptan have previously also been established in the separate Samsca licence.

Significant hepatic toxicity however appears to be limited to the ADPKD population. Potential new signals from the ADPKD program of glaucoma/intra-ocular pressure and basal cell carcinoma are also highlighted both will be monitored with in the PASS (as described in the RMP).

There were no deaths in the pivotal study, or other deaths in the ADPKD program assessed as related to tolvaptan. Overall, the proportion of subjects on tolvaptan who experienced at least 1 serious TEAE (18.4%) was similar to the placebo group.

Hepatic toxicity

In the pivotal trial, the incidence of elevated transaminase levels for tolvaptan subjects (> 3 × ULN) was approximately 3 to 4-fold higher than for placebo subjects. The overall incidence of serious hepatic TEAEs was higher for tolvaptan subjects (2.3%, 22/961) than for placebo subjects (1.0%, 5/483). An independent, blinded, expert Hepatic Adjudication Committee reviewed all available data in ADPKD patients. This process will continue for on-going trials. 59 subjects from ADPKD clinical trials were identified as meeting the hepatic event criteria for further evaluation. This adjudication revealed that 3 tolvaptan subjects in the ADPKD program met the criteria for potentially serious liver injury, based on the extent of transaminase and total bilirubin rise, lack of evidence for cholestasis and exclusion of other causes (as detailed above). 2 of these cases were from the pivotal study, 1 from the extension study 156-08-271.

The onset of hepatocellular injury, as manifested by transaminase values exceeding 3 × ULN, was characteristically observed after at least 3 months of treatment, but could occur after 1 year. The transaminase 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. No subjects experienced hepatic failure, hepatic transplantation, or death resulting from hepatocellular injury. However, as concluded by the submitted liver safety report, in patients with ADPKD, tolvaptan has the potential to cause liver injury that could progress to liver failure. The number of subjects with ADPKD currently exposed is insufficient to rule out less common but severe hepatic toxicity.

Overall, the association of tolvaptan with significant elevations of liver function tests is a clear signal. There is a characteristic pattern of hepatocellular injury after 3-15 months of treatment, with a continued rise in serum ALT/AST for weeks to months after discontinuation of therapy, followed by gradual resolution over 1-4 months. 2 cases had a positive rechallenge. The dose difference between the non-ADPKD population and the ADPKD population could account for the absence of a safety signal in the non-ADPKD trials, however tolvaptan plasma concentrations in the heart failure population significantly overlap those observed in the ADPKD population. The pattern of liver disease is also probably idiosyncratic, so may not have a dose-response, indeed no association with tolvaptan dose or exposure was found.

As of March 2014, 1275 patients have received tolvaptan through the estimated “window of susceptibility” of 18 months, up from 838 in the 2012 adjudication report. There have been no new cases meeting the criteria for potentially serious liver injury, which offers some reassurance.

The 3 cases correspond to about 1:400 patients treated for at least 18 months. Assuming 10% of such cases will progress to acute liver failure the estimate of incidence of acute liver failure in ADPKD patients chronically receiving treated with tolvaptan might be estimated at 1 in 4,000. Obviously, more cases had elevations of LFTs with a less certain causal link, and the available cases do not allow a definitive estimate of event frequency.

Jinarc is to be prescribed with blood testing for hepatic transaminases and bilirubin required prior to initiation of Jinarc, continuing monthly for 18 months and three monthly thereafter. Additional safety profiling to evaluate further the risk of hepatic injury with Jinarc use in a real world setting will be carried out within a post authorisation safety study as mentioned in Annex II and described in the RMP. For concurrent monitoring for symptoms that may indicate liver injury clear stopping rules related to LFTs or symptoms/signs consistent with hepatic injury have been included in the SmPC, along with guidelines for permanent discontinuation.

There are a number of features to take into account. Whilst reversible to date, the typical presentation is progression of injury for several weeks after stopping drug treatment. So far, cases of potentially severe liver injury have been restricted to the ADPKD population and there may be a genetic or other basis for this (the mechanism is not currently known). However post-marketing data and trial data from other study programs may give reassurance on the event incidence.

Based on limited data, liver injury appears to occur after 3 months - however it is not possible to implement stopping rules based on lack of efficacy within this timeframe. Cystic liver disease is common in ADPKD patients; this may pose additional problems or confer further risk, although on the limited data available, there is no clear relationship between cystic liver disease at baseline and subsequent risk of hepatic events. No subgroup has been identified with a particular risk that can be excluded from taking tolvaptan – although in general terms, factors like age, alcohol intake and poor nutrition can influence the risk of drug-induced liver injury. Whilst the mechanism is currently unknown, the prolonged latency and relatively prompt recurrence upon re-challenge may support an immunological mechanism.

Other notable adverse events

There was an excess of events relating to raised intraocular pressure and glaucoma in the pivotal trial compared to the placebo group. No mechanism is known, but overall a plausible relationship for raised intra-ocular pressure/glaucoma cannot be excluded. Glaucoma will be investigated in the PASS.

There was also a small increased incidence of malignant neoplasms in the pivotal trial in the tolvaptan group. These were driven by basal cell carcinoma (0.8% vs. 0.2%). This is not predicted from previous clinical trials, from preclinical and *in vivo* background work, or from a mechanistic point of view. The number of observed events is small, the observation may be a chance finding, and causality is not clear at this time. The applicant suggests there is a higher background incidences of such lesions in ADPKD patients, however there is still an imbalance between the tolvaptan and placebo group and an association with tolvaptan cannot be ruled out. Basal cell carcinoma itself is a slow-growing condition, manageable with routine monitoring. There is no signal for an association with tolvaptan and other malignancies, however in the context of proposed long-term use, in a patient population with additional risk of renal malignancy this is a potential concern in the safety evaluation which must be monitored. The baseline prevalence and incidence of new occurrences of skin neoplasm (basal cell carcinoma) will be further characterized in the proposed PASS (as described in the RMP).

There are a number of other adverse events which given their frequency, seriousness and reversibility are manageable. These include changes in serum sodium and uric acid. There are no signals of particular clinical concern regarding cardiovascular and thrombotic adverse events. An association between tolvaptan use and hyperglycaemia/new onset diabetes TEAEs has already been picked up in the Samsca licence, and cannot be excluded in the proposed ADPKD setting - this has been reflected in the Jinarc SmPC. No significant differences in biochemistry or haematology parameters were seen, other than those already discussed. Whilst any hepatic toxicity of tolvaptan may have an immunological basis, other serious allergic reactions are not signalled.

Special populations

There are no adequate data on the use of tolvaptan in pregnancy or during breast-feeding; this is reflected in the SmPC. However, as Studies in animals have shown reproductive toxicity and excretion into the milk tolvaptan the product is contraindicated in pregnant of breasfeeding women. The proposed indication is also restricted to adults. Overall, there were no conclusive and clinically important differences in adverse events attributable to treatment with tolvaptan based on gender or race.

No assessment can be made on adverse events in the elderly, as the ADPKD clinical program focused on treating relatively young patients, with the pivotal trial excluding patients over 50. However, long-term treatment with tolvaptan in ADPKD is anticipated and there are a number of adverse events for which the elderly are potentially more susceptible. It is reflected in 4.2 of the SmPC that safety and efficacy in ADPKD patients aged over 50 years has not been established and the PASS will monitor the use in this patient population as described in the RMP.

The proposed indication is a condition characterised by progressive renal impairment, which the product aims to slow. The ADPKD study program focused however on patients with relatively intact renal function so there are few ADPKD patients with more severe renal dysfunction taking tolvaptan long-term. Tolvaptan causes a short-term and reversible reduction in GFR at the start of treatment. Furthermore, TEAEs of increased ALT and AST were more common in tolvaptan subjects with a baseline eCrCLCG < 80 mL/min compared to those with better renal function.

Furthermore the SmPC states that the risk of hepatic damage in patients with severely reduced renal function (i.e. eGFR < 20) may be increased and that these patients should be carefully monitored for hepatic toxicity. The SPC also notes the more limited data in CKD stage 3 patients.

The initial reduction in GFR is small and the patient numbers too limited to conclude an increased risk of hepatotoxicity. However taking also into account the lack of data or therapeutic rationale in ADPKD patients with already advanced renal disease, this is a further argument which led to narrow the indication to CKD stage I to III patients at the initiation of the treatment. As the treatment is supposed to be long term patients will reach later stages of renal insufficiency and further data on the treatment of patients in more advanced stages will be generated within the ongoing clinical trials 156-09-290 and 156-08-271 as defined in Annex II and described further in the RMP.

It is not clear how many patients with hepatic impairment were in the pivotal study as the exclusion criteria were pragmatic, and hepatic status was not formally assessed at baseline. As the risk: benefit for tolvaptan in ADPKD patients with significant hepatic failure is questionable, given its intrinsic potential for serious hepatotoxicity the SmPC contra-indicates use in patients with elevated liver enzymes and/or signs or symptoms of liver injury that meet the requirements for permanent discontinuation of tolvaptan.

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

2.6.2. Conclusions on the clinical safety

In general the safety profile of tolvaptan in the treatment of adult patients with ADPKD has been well described, with an adequate subject exposure for an application of this nature. The majority of adverse events associated with tolvaptan were expected given its known pharmacodynamic properties, are tolerable given the expected benefit and the seriousness of the proposed indication, and are clinically manageable for most patients in practice. However, discontinuations due to AEs are more frequent in the tolvaptan arm, and it is clear that for some patients adverse events related to aquaresis are intolerable and lead to discontinuation.

The most serious risk is idiosyncratic hepatic toxicity, which so far appears specific to ADPKD patients. Generally it has been seen at 3 and 14 months, but this cannot be confirmed given the limited cases. The incidence is relatively low. The real incidence with more patients treated outside of the study setting could be higher, although the size of the ADPKD population is relatively limited. All cases to date have been reversible and not associated with hepatic failure.

For marketing authorisation the risk can be considered manageable with the final SmPC statements including contraindication and stopping rules concerning patients with elevated liver enzymes and signs or symptoms of liver injury. Nevertheless further data on the risk of progression to acute hepatic

failure on tolvaptan - including the progression of hepatic impairment for several weeks after stopping tolvaptan, and the prevalence of polycystic liver disease in ADPKD patients are needed post approval. At this point in time there is no identified subgroup with a particular risk that can be excluded from taking tolvaptan and data in a real live setting under strict monitoring will add further clarification. A Post authorisation safety study will investigate further on hepatotoxicity, basal cell carcinoma glaucoma and other risks as defined in the RMP. As the exact frequency and severity of hepatotoxic events which might impact on the benefit risk of the product cannot be defined with certainty based on the current data this study is made condition to the marketing authorisation. Submission of the study protocol is requested within 2 months after Marketing Authorisation as defined in the RMP.

As mentioned above the risk of liver injury can be considered acceptable for marketing of the product in view of the appropriate patient and prescriber education, strong monitoring requirements (more frequent than employed in the ADPKD studies) and other measures in the risk: management plan.

The CHMP considers the following measures necessary to address issues related to safety:

Description	Due date
A non-interventional post authorization safety study (PASS)to investigate the risks of: Hepatotoxicity Basal cell carcinoma • Glaucoma associated with the use of Jinarc. In addition the study should also provide information on Pregnancy outcomes, in patients treated with Jinarc Patterns of drug utilisation, especially with regards to off-label use and use in patients over 50 years old ADRs associated with long term use of Jinarc Final study report should be submitted by:	Quarter 2022

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 12.0, the PRAC considered by consensus that the risk management system for tolvaptan (JINARC) in the amended indication: to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease could be acceptable if the MAH implemented the changes to the RMP as

described in the PRAC assessment report. It should be noted that the Risk Management Plan is a joint one for Jinarc and the previously authorised product Samsca.

The applicant implemented during the procedure the changes in the RMP as requested by PRAC. The CHMP endorsed the Risk Management Plan version 12.2 with the following content:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Volume depletion and dehydration • Dehydration associated renal dysfunction • Too rapid rise of serum sodium and neurologic sequelae (encephalopathy, osmotic demyelination) • Hyper - / hypoglycemia • Hyperuricemia, gout • Hypernatremia in heart failure patients • Hyperkalaemia in heart failure patients • Interaction with CYP3A4 Inhibitors • Interaction with CYP3A4 Inducers • Interaction with vasopressin receptor agonists • Pharmacodynamic Interaction tolvaptan and combined administration of diuretics leading to dehydration and renal dysfunction • Liver injury in ADPKD patients • Anaphylaxis
Important potential risks	Acute urinary retention (in patients with urinary outflow obstruction) • Allergic skin reactions • Raised intraocular pressure / glaucoma Interaction tolvaptan and combined administration of warfarin and antiplatelet agents in heart failure patients • Interaction tolvaptan and serum potassium concentration-increasing substances • Pharmacodynamic Interaction tolvaptan and combined administration ACE-I possibly leading to dehydration and renal dysfunction • Pharmacodynamic Interaction tolvaptan and combined administration ARB possibly leading to dehydration and renal dysfunction • Cardiac arrhythmias secondary to electrolyte shifts in Heart Failure patients • Post-treatment myocardial ischemia in worsening Heart Failure patients • Dyspnea in Heart Failure patients • Hypercoagulability (stroke, myocardial infarction) in Heart Failure patients • Gastrointestinal bleeding in cirrhotic patients • Skin Neoplasms (basal cell carcinoma) in ADPKD patients • Teratogenicity
Missing information	Pediatric data • Pregnancy outcome data • Breast-feeding data • Off-label use • Usage in hepatic impaired patients • Use in ADPKD patients with renal function other than stage 1-3 kidney disease • Use of Jinarc in patients over 50 years • Long term use of Jinarc in clinical practice

Pharmacovigilance plan

Ongoing and planned studies in the PhV development plan

On-going and planned Additional PhV studies/activities in the Pharmacovigilance Plan				
Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports**
Category 3 An Observational Prospective Registry USA: Up to 1500 hypervolemic & euvolemic hyponatremia patients Europe: A maximum of 1005 euvolemic hyponatremic hospitalized patients followed through the duration of their hospital stay	1.Obtain demographic and clinical characteristics of patients who are being treated 2. Demonstrate comparative effectiveness of available treatments 3. Define and compare the resource utilization in the hospital setting	None in particular	Ongoing	2016
Category 3 Study I 15600-001 - Drug Use-Results Survey of Samsca Tablets 15 mg	To obtain details on the occurence of AEs in the post-marketng phase	Any adverse events with Samsca in cardiac failure patients	Ongoing	2017
Category 3 Study I156-00-003 Study Drug Use-Results Survey of Samsca in ADPKD in Japan	To obtain details on the occurence of AEs in the post-marketng phase in Japan	Adverse events with Sasmca in ADPKD patients in Japan in particular liver injury	Started	Third Quarter 2023
Category 1 Jinarc Post authorisation safety study 156-12-299	Jinarc PASS: The objective of the PASS is to prospectively collect information on the safety of Jinarc when used in a real-life setting. A retrospective study to assess safety concerns associated with longer term use will also be included.	Hepatotoxicity, and other identified and potential risks including glaucoma and skin neoplasms and missing information. In addition, ADPKD related morbidity and mortality will be assessed.	Planned for Q4 2015	Full Protocol Submission 2 months after EC decision. Planned final report Q4 2022
Category 3 Study 156-14-216	A Phase 1, Single Center, Open-Label Trial to Investigate the Effects of 400 and 200 mg Oral Fluconazole, a Moderate CYP3A4 Inhibitor, on	Study effects of tolvaptan on Moderate CYP3A4 inhibitors	Planned FPFV June 2015 and Planned LPLV June 2015 Planned Final study report June 2016	Planned submission of Final report August 2016

On-going and planned Additional PhV studies/activities in the Pharmacovigilance Plan				
Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports**
	Tolvaptan Pharmacokinetics and Pharmacodynamics of 30 mg Tolvaptan in Healthy Adult Subjects			
Category 3 The potential of DM-4103 as an inhibitor of P-glycoprotein study	To study in-vitro the potential for tolvaptan/DM-4103 to cause increases in concentrations of other drugs transported by P-glycoprotein	Study potential interactions with p-glycoprotein inhibitors	On-going	Planned submission of final report August 2016

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product and that the Jinarc post authorization safety study be a condition of the marketing authorization..

The PRAC also considered that the proposed study in the post-authorisation development plan is sufficient to monitor the effectiveness of the risk minimisation measures and that a full protocol should be submitted including questionnaires and other methods for data collection.

Risk minimisation measures

Safety concern	Routine Risk Minimization measures Using the Product Label as a tool and when deemed necessary Additional Risk Minimization is proposed	Additional risk minimization measures
Important Identified Risk		
Volume depletion and dehydration	Current SIADH SmPC Samsca •Contraindication in Section 4.3 of the SmPC for subjects with volume depletion and subjects who cannot perceive thirst •Warning in Section 4.4 of the SmPC that subjects should have access to water and be able to drink sufficient amounts of water •Warning in Section 4.8 of the SmPC that thirst and dehydration are very common undesirable effects ADPKD indication Jinarc In section 4.4 of the SmPC: Special warnings and precautions for use; the text states: .•Tolvaptan may cause undesirable effects related to water loss such as thirst, dry mouth and dehydration (see section 4.8). Therefore, patients should have access to water (or other aqueous fluids) and be able to drink sufficient amounts of these fluids (see section 4.2). Patients should be instructed to drink water or other aqueous fluids at the first sign of thirst in order to avoid excessive thirst or dehydration. •Additionally, patients should ingest 1-2 glasses of fluid before bedtime regardless of perceived thirst and replenish fluids overnight with each episode of nocturia •In section 4.3 Contraindications: Volume depletion is added.	None
Too rapid rise /correction of serum sodium and neurologic sequelae (encephalo-pathy, osmotic demyelination)	•Samsca Contraindication in Section 4.3 of the SmPC for subjects with volume depletion and subjects who cannot perceive thirst •Warning in section 4.4 of the SmPC that subjects should have access to water and be able to drink sufficient amounts of water. A statement in Section 4.4 of the SmPC that patients should be carefully monitored with respect to serum sodium and volume status, with detailed information on how and for how long a patient should be monitored.	**YES for Samsca® only** DHPC

	This section also provides information on which patients might be at higher risk, details the potential neurologic consequences of a too rapid correction of hyponatremia, and provides practical guidance to avoid a too fast correction of the sodium concentration. In addition, this section warns for a higher risk in patients who received other treatment for hyponatremia or medicinal products which increase serum sodium concentration prior to initiation of treatment with tolvaptan. •Statement in section 4.5 of the SmPC that medicinal products with high sodium content such as effervescent analgesic preparations and certain sodium containing treatments for dyspepsia may also increase serum sodium concentration. In addition, concomitant use of tolvaptan with other treatments for hyponatremia or other medicinal products that increase serum sodium concentration may result in a higher risk for developing rapid correction of serum sodium and is therefore not recommended. •Inclusion in section 4.8 of the SmPC that rapid correction of hyponatremia, sometimes leading to neurological symptoms, is an undesirable effect of tolvaptan **Additional risk Minimization Action** Samsca® After adoption of positive opinions on 15-Mar-2012 updated safety information concerning rapid correction of serum sodium and potential interaction with products increasing serum sodium was communicated by means of a direct healthcare professional communication (DHPC). For variations II/005 **(Rapid Rise in Sodium)** and II/007(Co-administration of tolvaptan with medicines with high sodium content or other treatments for hyponatremia is not recommended), the EMA requested communication of the new safety information by means of a DHPC. The DHPC letter was distributed in all EEA countries where Samsca is marketed or available by other means and where the national competent authorities agreed with the dissemination of the national DHPC, i.e. in Austria, Denmark, Finland, Germany, Ireland, Italy, Luxembourg, Netherlands, Norway, Spain, Sweden and United Kingdom. Jinarc ADPKD indication in SmPC	

	In section 4.4 Special warnings and precautions for use; the text states: Fluid and electrolyte status should be monitored in all patients. Administration of tolvaptan induces copious aquaresis and may cause dehydration and increases in serum sodium (see section 4.8) and is contraindicated in hypernatremia patients (see section 4.3). Therefore, serum creatinine, electrolytes and symptoms of electrolyte imbalances (e.g. dizziness, fainting, palpitations, confusion, weakness, gait instability, hyper-reflexia, seizures, coma) should be assessed prior to and after starting tolvaptan to monitor for dehydration. During long-term treatment electrolytes should be monitored at least every three months. Pre-treatment sodium abnormalities (hyponatremia or hypernatremia) must be corrected prior to initiation with tolvaptan therapy.	
Dehydration associated renal dysfunction	Current SIADH SmPC Samsca •contraindication in Section 4.3 of the SmPC for subjects with volume depletion and subjects who cannot perceive thirst •contraindication in Section 4.3 of the SmPC for subjects with anuria •warning in Section 4.8 of the SmPC that increases in blood creatinine are common undesirable effects Jinarc ADPKD indication •SmPC 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. Special care should be taken in patients having diseases that impair appropriate fluid intake or who are at an increased risk of water loss e.g. in case of vomiting or diarrhoea.	None
Acute urinary retention in patients with urinary outflow	Samsca Urinary outflow obstruction Urinary output must be secured. Patients with partial obstruction of urinary outflow, for example patients with	None

obstruction	prostatic hypertrophy or impairment of micturition, have an increased risk of developing acute retention. Jinarc 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.	
Hypernatremia	Current SIADH SmPC Samsca •Contraindication in Section 4.3 of the SmPC for subjects with hypernatremia •Warning in Section 4.4 of the SmPC that rapid change in serum sodium: tolvaptan may cause rapid increases in serum sodium; therefore after initiation of treatment, subjects should be carefully monitored for serum sodium and volume status. Particular care should be applied in subjects at risks for demyelination syndromes (e.g. hypoxia, alcoholism, malnutrition) •Statement in Section 4.8 of the SmPC that hypernatremia is a common undesirable effect Jinarc ADPKD indication In section 4.3 of the SmPC Hypernatremia is a contraindication. • Statement in Section 4.8 of the SmPC that hypernatremia is a common undesirable effect In section 4.4 Serum Sodium Abnormalities Pre-treatment sodium abnormalities (hyponatremia or hypernatremia) must be corrected prior to initiation with tolvaptan therapy.	None
Hyperkalemia	Current SIADH SmPC Samsca •Statement in Section 4.8 of the SmPC that hyperkalaemia is a common undesirable effect Jinarc ADPKD indication •Statement in Section 4.8 of the SmPC that hyperkalaemia is a common undesirable effect	None
Hyper - / hypoglycemia	Current SIADH SmPC Samsca •statement in Section 4.8 of the SmPC that hypo and	None

	hyperglycemia are common undesirable effects • In section 4.4 Warnings and Precautions of SmPC it states that Diabetic patients with an elevated glucose concentration (e.g. in excess of 300 mg/dl) may present with pseudohyponatremia. This condition should be excluded prior and during treatment with tolvaptan. Tolvaptan may cause hyperglycemia. Therefore, diabetic patients treated with tolvaptan should be managed cautiously. In particular this applies to patients with inadequately controlled type II diabetes Jinarc ADPKD indication •statement in Section 4.8 of the SmPC that hyperglycemia is a common undesirable effects A class effect warning that diabetic patients treated with tolvaptan should be managed cautiously will be added to the proposed Jinarc label in section 4.4 Special warnings and precautions for use as follows:"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.	
Hyperuricemia, gout	rrent SIADH SmPC Samsca •Hyperuricemia is a common adverse event Jinarc ADPKD indication •SmPC section 4.8 in clinical trials with other indications hyperuricemia is a common adverse event •SmPC section 4.4 states : Decreased uric acid clearance by the kidney is a known effect of tolvaptan. In a double-blind, placebo-controlled trial of patients with ADPKD, potentially clinically significant increased uric acid (greater than 10 mg/dL) was reported at a higher rate in tolvaptan-patients (6.2%) compared to placebo-treated patients (1.7%). Adverse reactions of gout were reported more frequently in tolvaptan-treated patients (28/961, 2.9%) than in patients receiving placebo (7/483, 1.4%). In addition, increased use of allopurinol and other drugs used to manage gout were observed in the double-blind, Placebo-controlled trial. Effects on serum uric acid are	None

	attributable to the reversible renal hemodynamic changes that occur in response to tolvaptan's effects on urine osmolality and may be clinically relevant. However, events of increased uric acid and/or gout were not serious and did not cause discontinuation of therapy in the double-blind, placebo-controlled trial. Uric acid concentrations should be evaluated prior to initiation of Jinarc therapy, and as indicated during treatment based on symptoms.	
Liver injury	**Additional Risk Minimization Measures in** Jinarc for ADPKD The section 4.4 on warning and precautions describes in detail the findings in the ADPKD clinical trial program. In addition this section contains instructions on the need for and frequency of liver function testing. **Additional Risk Minimization Measures for Jinarc® (see also section 3.2.2)** **Physician Education and Certification Registry** Prescriber's education, certification in the prescriber's registry and reassurance of prescriber's certification prior to the dispensation of Jinarc in accordance with local legislation. **Additional Educational materials for Jinarc prescribers** A document pack containing the following educational material will be delivered to each prescribing physician and hospital pharmacies upon request: • Educational material on need for liver monitoring while on tolvaptan and guide to early recognition of liver injury Checklist for the prescriber to evaluate eligibility of ADPKD patient for tolvaptan treatment. **Patient education brochure and medication alert card for the patient on tolvaptan** Educational Materials will stipulate: 1. Blood testing for hepatic transaminases (AST and ALT) and bilirubin (BT) is mandatory prior to initiation of Jinarc therapy. When Jinarc treatment is continued perform monthly transaminase and bilirubin monitoring for 18 months, and 3 monthly thereafter	For ADPKD: 1. Prescriber's education, certification in the prescriber's registry reassurance of prescriber's certification prior to the dispensation of Jinarc in accordance with local legislation. 2. Checklist for prescribers on appropriateness of ADPKD patient for tolvaptan treatment. 3. Patient education brochure and patient alert card

	2. Be alert for ALT >3 times the upper limit of normal. This would warrant weekly monitoring of ALT, AST and BT at a minimum. 3. Monitoring for symptoms that may indicate liver injury (such as fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, icterus, dark urine or jaundice). 4. Recommendations for tolvaptan therapy termination in relation to patient's liver status.	
Anaphylaxis	Samsca A variation procedure to include anaphylaxis in SmPC section 4.8 undesirable effects (anaphylactic shock and rash generalized) and a warning statement in SmPC section 4.4 was finalised with a positive opinion on 23-Jan-2014. Section 4.4 *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. Jinarc Jinarc SmPC: In section 4.8 undesirable effects (anaphylactic shock and rash generalized) and a warning statement in SmPC section 4.4 : *Anaphylaxis* In post-marketing experience, anaphylaxis (including anaphylactic shock and rash generalised) has been reported very rarely following administration of tolvaptan. This type of reaction occurred after the first administration of tolvaptan. If an anaphylactic reaction or other serious allergic reactions occur, administration of tolvaptan must be discontinued immediately and appropriate therapy initiated. Since hypersensitivity is a contraindication (see section 4.3) treatment must never be restarted after an anaphylactic reaction or other serious allergic reactions.	
Interaction with CYP3A4 Inhibitors	SIADH •Warning in SmPC Section 4.5 of increased tolvaptan plasma concentrations after the administration of strong CYP3A4 inhibitors and after intake of grapefruit juice ADPKD	None

	Warning in SmPC Section 4.5 the following: Concomitant use of medicinal products that are moderate (e.g. amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil) or strong (e.g., itraconazole, ketoconazole, ritonavir, clarithromycin) CYP 3A inhibitors increase tolvaptan exposure. Co-administration of tolvaptan and ketoconazole resulted in a 440% increase in area under time-concentration curve (AUC) and 248% increase in maximum observed plasma concentration (C_{max}) for tolvaptan. Co-administration of tolvaptan with grapefruit juice, a moderate to strong CYP3A inhibitor, produced a doubling of peak tolvaptan concentrations (C_{max}). Dose reduction of tolvaptan is recommended for patients while taking moderate or strong CYP 3A inhibitors (see section 4.2).	
Interaction with CYP3A4 Inducers	Samsca SmPC Section 4.5 of decreased tolvaptan plasma concentrations after the administration of CYP3A4 inducers. ADPKD Warning in SmPC Section 4.5 •Tolvaptan plasma concentrations have been decreased by up to 87% (AUC) after the administration of CYP3A4 inducers. Caution should be exercised in co-administering CYP3A4 inducers (e.g. rifampicin, barbiturates) with tolvaptan. •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.	None
Interaction with vasopressin receptor agonists	SIADH A statement in Section 4.5 of the SmPC that the effect of vasopressin analogs such as desmopressin may be attenuated in patients using such analogs to prevent or control bleeding when co-administered with tolvaptan ADPKD • Section 4.5 of the SmPC 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)	None

	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.	
Pharmaco-dynamic Interaction with diuretics leading to dehydration and renal dysfunction	Samsca SmPC changes Section 4.4 Dehydration Volume status should be monitored in patients taking tolvaptan as 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: interrupt or reduce the dose of tolvaptan and increase fluid intake. Section 4.5 Diuretics While there does not appear to be a synergistic nor 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: interrupt or reduce doses of tolvaptan and/or diuretics, increase fluid intake, evaluate and address other potential causes of dehydration. Section 4.8 Renal impairment uncommon ADPKD Section 4.5 of the SmPC Diuretics Tolvaptan has not been extensively studied in ADPKD in combination with 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, appropriate action must be taken which may include the need to interrupt or reduce doses of tolvaptan and/or diuretics and increased fluid intake. Other potential causes of renal dysfunction or dehydration must be evaluated and addressed.	
Important Potential Risks		
Acute urinary retention (in patients with	Current SIADH SmPC •contraindication in Section 4.3 of the SmPC for subjects with anuria	None

urinary outflow obstruction)	•warning in Section 4.4 of the SmPC that urinary output must be secured and that "subjects with partial obstruction of urinary outflow, for example subjects with prostatic hypertrophy or impairment of micturition, have an increased risk of developing acute retention and require careful monitoring" ADPKD indication •Special warnings and precautions of the SmPC section 4.4 state 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.	
Allergic skin reactions	Current SIADH SmPC •Contraindication for hypersensitivity to the active substance or to any of the excipients For the indication of ADPKD •Section 4.3 Contraindications: Hypersensitivity to the active substance or to any of the excipients •Section 4.8 of SmPC- Pruritic rash is an uncommon adverse event in clinical trials with other indications	None
Teratogenicity based on preclinical findings	SIADH Current SmPC section 5.3 text reads: 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. •contraindication in Section 4.3 that tolvaptan shall not be used during pregnancy •adequate contraceptive practice requested for fertile women in Section 4.6 ADPKD Section 5.1 in the SmPC 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	None

	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. •The toxic potential of tolvaptan was also investigated in juvenile rats by 6-week repeated oral administration starting from 25 days of age (4 days after weaning). Tolvaptan was orally administered by gavage at doses of 30, 100, and 1000 mg/kg/day. No animal died and, overall, treatment-related changes were generally qualitatively comparable to those observed in adult rat toxicity studies of tolvaptan. •Section 4.3 contraindication: tolvaptan shall not be used during pregnancy •One pregnancy in an ADPKD trial resulted in spontaneous abortion. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. •Section 4.6 Women of childbearing potential should use adequate contraceptive measures during tolvaptan use. Jinarc must not be used during pregnancy (see section 4.3).	
Interaction tolvaptan and combined administration of warfarin and antiplatelet agents	SIADH As this is still only a potential risk to be confirmed, there is no text in the SmPC for this potential risk under evaluation •Warning in SmPC Section 4.5 •In healthy subjects, tolvaptan, a CYP3A4 substrate, had no effect on the plasma concentrations of some other CYP3A4 substrates (e.g. warfarin or amiodarone). •Warfarin There is no evidence of clinically significant interactions with warfarin. ADPKD Warning in SmPC Section 4.5 There is no evidence of clinically significant interactions with warfarin.	None
Skin Malignancies (basal cell carcinoma) in the ADPKD population	ADPKD No risk minimisation activity is warranted for this potential safety risk.	None
Missing Information		
Pediatric data	SIADH indication	None

	•Statement in Section 4.2 of the SmPC that there is no experience in children and adolescents under the age of 18 years. Additionally the SmPC states that Samsca is not recommended in the pediatric age group. For the indication of ADPKD: The safety and efficacy of Jinarc in children and adolescents has not yet been established. Jinarc is not recommended in the pediatric age group	
Pregnancy outcome data	• SmPC section 4.3 pregnancy is a contraindication •SmPC section 4.6 Pregnancy and lactation states that there are no adequate data from the use of tolvaptan in pregnant women. Studies in animals have shown reproductive toxicity. •The potential risk for humans is unknown. •Women of childbearing potential should use adequate contraceptive measures during tolvaptan use. ADPKD indication : Section 4.6 of the SmPC Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Women of childbearing potential should use adequate contraceptive measures during tolvaptan use. Jinarc must not be used during pregnancy (see section 4.3).	None
Breast-feeding data	SIADH indication •contraindication in Section 4.3 of the SmPC in breast feeding •warning in Section 4.6 of the SmPC that tolvaptan is contraindicated during breast-feeding ADPKD indication Section 4.6 of the SmPC •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. Jinarc is contraindicated during breastfeeding (see section 4.3).	None
Usage in hepatic impaired patients	SIADH •Warning in SmPC section 4.4 that fluid and electrolyte status should be monitored in all patients and particularly in those with renal and hepatic impairment.	None

	• No dose adjustment is needed in patients with hepatic impairment • In addition the following text will be added: 'Healthcare providers should perform liver function tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. If hepatic injury is suspected, Samsca should be promptly discontinued, appropriate treatment should be instituted, and investigations should be performed to determine probable cause. Samsca should not be re-initiated in patients unless the cause for the observed liver injury is definitively established to be unrelated to treatment with Samsca ADPKD Section 4.2 of the SmPC states The effect of hepatic impairment on the treatment of ADPKD has not been investigated. In patients with severe hepatic impairment the benefits and risks of treatment with Jinarc must be evaluated carefully. Patients must be managed carefully and liver enzymes must be monitored regularly (see section 4.4). Jinarc is contraindicated in patients with elevated liver enzymes and/or signs or symptoms of liver injury prior to initiation of treatment that meet the requirements for permanent discontinuation of tolvaptan (see sections 4.3 and 4.4). No dose adjustment is needed in patients with mild or moderate hepatic impairment (Child-Pugh classes A and B).	
Off-label use	SIADH SmPC and package information leaflet instruct prescribers and patients on proper use of tolvaptan in SIADH ADPKD SmPC and package information leaflet instruct prescribers and patients on proper use of tolvaptan in ADPKD. The Jinarc PASS will survey the drug utilisation pattern.	None
Use in ADPKD patients outside CKD stage 1-3	In the SmPC, Section 4.1, Therapeutic Indications, language is included to highlight the intended use in adults with ADPKD who have CKD stage 1 to 3 at initiation of treatment. Additionally in Section 4.2, Renal impairment, language includes the following: "Dose adjustment is not required in patients with renal impairment. No clinical trials in subjects with a creatinine clearance <10 mL/min or in patients undergoing dialysis have been conducted. The risk of hepatic damage in patients with severely reduced renal function (i.e. eGFR < 20) may be increased; these patients should be carefully monitored for	None

	hepatic toxicity. Data for patients in CKD stage 3 are more limited than for patients in stage 1 or 2"	
Use of Jinarc in patients over 50	In the Jinarc SmPC, section 4.2 under the Elderly Population states that "Increasing age has no effect on tolvaptan plasma concentrations. However,Safety and effectiveness of tolvaptan in ADPKD patients aged over 50 years has not yet been established".	None
Long term use of Jinarc in clinical practice	In the Jinarc SmPC, Section 5.1 of the SmPC states that *'Data are not currently available to show whether long-term therapy with Jinarc continues to slow the rate of renal function decline and affect clinical outcomes of ADPKD, including delay in the onset of end-stage renal disease.'*	None

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications

The CHMP endorsed this advice without changes.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

The primary endpoint in the single pivotal study was the rate of change in TKV for subjects randomised to tolvaptan (normalized as percentage) to the rate of change for subjects randomized to placebo. Total kidney volume increased by 18.8% in placebo subjects over 3 years but by only half that (9.6%) in tolvaptan subjects. The rate of growth was 2.80% per year (tolvaptan) vs. 5.51% per year (placebo) (ratio of geometric mean 0.974; 95% confidence interval [CI] 0.969 to 0.980; $p < 0.0001$), for a difference of −2.71% per year with a 49.2% reduction in growth rate in the tolvaptan group compared with the placebo group. The effect of treatment with tolvaptan on TKV was greatest in the first year but effects treatment 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 years. The incremental treatment effect for reduction in TKV from the first year to the second year was −1.92% ($p < 0.0001$) and from the second year to the third year was −1.78% ($p = 0.0005$). These results were replicated in sensitivity analyses, including re-analyses to

account for differing model assumptions and datasets, potential MRI quality or reading errors, and analyses by study centre and country.

The finding of slowed TKV progression is supported by *in vivo* data and preclinical disease models. The submitted literature also suggests that a reduction in the rate of renal enlargement may correlate with benefit in clinical outcomes. Data from 2 open-label studies was matched to historical data in a case-control study. The progression of ADPKD, as evidenced by both increasing total kidney volume and declining estimated glomerular filtration rate, was significantly slowed after 3 years of tolvaptan treatment compared with historical control data, and there was a significant negative correlation between annualized slope of TKV and slope of eGFR.

In the secondary composite endpoint, there was a statistically significant 13.5 % rate reduction compared to placebo. This was driven by changes in 2 out of the 4 components of the composite variable. These were the events of renal function decline (based on a 25% decrease in the reciprocal of serum creatinine, an increase in serum creatinine of 33%) and renal pain (severe renal pain requiring medical intervention)

The hazard ratio relating to renal function decline was 0.386 (95% CI 0.263 to 0.566) and for renal pain the HR was 0.642 (95% CI 0.466 to 0.887). These correspond to a relative improvement of 61.4% and 35.8% respectively. The numbers of worsening renal function events are low, but perhaps consistent with the relatively intact renal function, the relatively slow rate of renal function decline, and the length of the study. Events that signaled a decline in renal function were delayed in both groups until around a year, with the separation of tolvaptan treatment from placebo treatment evident at approximately Month 18. The effect of tolvaptan on renal pain was observed earlier in the treatment period.

In the 3rd endpoint, tolvaptan treatment slowed the rate of renal function decline (reciprocal of serum creatinine) by one-third compared to placebo, for which the predefined statistical criteria were met. This was confirmed by other estimation methods and demonstrated a significant association with the rate of change in TKV. The mean rate of change per year in estimated GFR CKD-EPI was around -2.7 mL/min/1.73 m2 for the tolvaptan group and -3.6 for the placebo group.

Uncertainty in the knowledge about the beneficial effects.

Whilst the key secondary composite endpoint showed an overall rate reduction compared to placebo, this was driven by changes in 2 out of the 4 components of the composite variable. For the 2 components that did show a change (renal function decline, severe renal pain), the numbers of events were small. Whilst the short duration of the trial might have hampered to show clearer and direct effects on clinical parameters the effect on renal pain could not been convincingly shown and the claim to slow the progression of “kidney disease” was considered too broad at this time in relation to the patients studied and the specific benefits seen and is reflected in the amended indication.

As discussed in more detail in the efficacy part of this assessment TKV is an acceptable surrogate parameter and suits as a primary endpoint in this setting. Measures of renal volume, as shown in literature as well as in the pivotal trial, are clearly linked to the characteristic progressive development of renal cysts in ADPKD, and correlate with renal function. Whereas the indication has been adapted to reflect the patient population who is benefiting best further assurance on the correlation between renal volume and other clinical endpoints is to be provided post authorisation, although a correlation was clinically plausible *a priori*. Furthermore, considering the short duration of the pivotal trial and the long course of the disease further assurance needs to be provided if the promising short term effects will be maintained in the long term.

This will be done with two post authorisation efficacy studies, the one being the long-term extension of the pivotal trial, the other designed to provide data on clinical endpoints in later stages of the disease. The aim will be to show that tolvaptan continues to slow the rate of renal function decline and

delay the onset of end-stage renal disease, particularly as the so far studied population had relatively preserved renal function at baseline.

Furthermore provision of the results of these on-going efficacy studies is made condition to the marketing authorisation in Annex II. Furthermore on-going studies are expected to provide further clarity of APKD related morbidity and mortality, including longer-term effects on GFR decline and progression of disease leading to dialysis or transplantation. Long term use in clinical practice will also be investigated in the PASS as described in the RMP and outlined in Annex II.

Risks

Unfavourable effects

The commonest adverse events associated with tolvaptan were as expected from its aquaretic effect. These included thirst, polyuria, nocturia, pollakiuria, and dry mouth. In the pivotal trial, aquaresis-related adverse events led to the discontinuation of tolvaptan in approximately 8% of participants, mostly within the first month. Fluid intake must be adjusted to balance increased urine output, particularly important in subjects with impaired renal function. These adverse events can be clinically managed and monitored in the majority of patients.

The most serious risk is idiosyncratic hepatic toxicity, which so far appears specific to ADPKD patients. The incidence is relatively low. All cases to date have been reversible and not associated with hepatic failure. For marketing authorisation the risk can be considered manageable with the final SmPC statements including contraindication and stopping rules concerning patients with elevated liver enzymes and signs or symptoms of liver injury.

Furthermore the risk of liver injury can be considered acceptable for marketing of the product in view of the appropriate patient and prescriber education, strong monitoring requirements (more frequent than employed in the ADPKD studies) and other measures in the risk: management plan.

Uncertainty in the knowledge about the unfavourable effects

Hepatotoxicity

The adverse event of most concern, which is specific to the ADPKD program, is hepatic toxicity. The incidence is relatively low and thus far, all hepatic adverse events have been reversible and not associated with hepatic failure.

A total of 1275 patients had received tolvaptan through the estimated “window of susceptibility” of 18 months. After adjudication, 3 tolvaptan subjects in the ADPKD program met the criteria for potentially serious liver injury so there is a total incidence of about 1:400 patients treated for at least 18 months.

Assuming 10% of these 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. Whilst all cases to date have been reversible and not associated with hepatic failure, the number of subjects exposed is too low to exclude that tolvaptan has the potential to cause liver injury capable of progression to liver failure.

As already mentioned the risk can be considered balanced for marketing of this product in view of the appropriate patient and prescriber education, strong monitoring requirements and contraindication in patients with elevated liver enzymes as described in the SmPC

However, considering that patients will be treated for periods longer than assessed within the clinical trials and in later stages of this progressive disease further investigation on ADRs associated with long term use of the product is considered key to the benefit risk and data thereto will be provided in particular from the PASS as described in the RMP and Annex II.

Special populations

Tolvaptan causes a short-term and reversible reduction in GFR at the start of treatment. Data suggest that the absolute decrease is lower in patients with more severe renal impairment, but the numbers of such patients are limited and even if the decline is small, in patients with more severe renal impairment it may become more significant.

Furthermore, TEAEs of increased ALT and AST were more common in tolvaptan subjects with a baseline eCrCLCG < 80 mL/min compared to those with better renal function. The initial reduction in GFR is small and the patient numbers too limited to conclude an increased risk of hepatotoxicity. However taking also into account the lack of efficacy data or therapeutic rationale in ADPKD patients with more advanced renal disease the indication statement was amended to CKD stage I to III at the initiation of treatment and tolvaptan should be discontinued if renal insufficiency progresses to CKD stage 5 as described in the SmPC.

As the risk: benefit for tolvaptan in ADPKD patients with significant hepatic failure is questionable, given above mentioned intrinsic potential for serious hepatotoxicity the SmPC also contra-indicates use in patients with elevated liver enzymes and/or signs or symptoms of liver injury that meet the requirements for permanent discontinuation of tolvaptan.

Further confirmative data on later stages of renal insufficiency will be provided post authorisation from the ongoing PEAS and, under the monitored use of the product, safety data in the real life setting will be generated within the planned PASS both studies being Annex II conditions.

No assessment can be made on adverse events in the elderly, as the ADPKD clinical program focused on treating relatively young patients, with the pivotal trial excluding patients over 50 and this is appropriately reflected in the SmpC. However, as long-term treatment with tolvaptan in ADPKD is anticipated and there are a number of adverse events for which the elderly are potentially more susceptible further data on this potential risk will also be provided within the post authorisation safety study.

Benefit-risk balance

Importance of favourable and unfavourable effects

As there is no other specific treatment in ADKPD a clear unmet medical need for the treatment of ADPKD exists which is taken into account. Current drug therapy is focused on the treatment of symptoms and complications. ADPKD is a serious condition, with around half of patients requiring renal replacement therapy by 60 years of age. The effects of tolvaptan compared to placebo on the rate of kidney volume increase are considered to reflect a clinically meaningful slowing of cystic kidney disease progression, which correlated in the pivotal study and in previous literature with a significant effect on the rate of decline in renal function. These results are most clear in patients with CKD stage 1 to 3 at initiation of treatment and evidence of rapidly progressing disease.

Whilst long-term data on harder clinical endpoints are to be provided post authorisation to verify that tolvaptan continues to slow the rate of renal function decline and delay the onset of end-stage renal disease, the provided evidence on the favourable effects is considered satisfactory for approval. Long term use in clinical practice, use in patients over 50 years, Glaucoma and other risks will be investigated in the PASS made condition to the marketing authorisation.

The commonest adverse events relate to aquaresis. They may be unpleasant and inconvenient but their risks are manageable with appropriate advice in the product information. Nevertheless for some patients the frequent need to urinate and replace with fluids is intolerably disruptive, particularly as long-term therapy is anticipated.

Hepatotoxicity is the most important aspect in the safety evaluation, and as discussed above there are gaps in the understanding of this. The incidence is low. The real incidence with more patients treated

outside of the study setting could be higher, although the size of the ADPKD population is relatively limited. Importantly, all cases to date have been reversible and not associated with hepatic failure. However, the number of subjects exposed is too low to confirm this, and tolvaptan has the potential to cause liver injury capable of progression to liver failure.

As discussed above, taking the number of exposed patients, the number of potentially serious hepatic AEs, and past experience with drug induced liver injury, we might assume the incidence of acute liver failure in ADPKD patients chronically receiving treated with tolvaptan to be 1 in 4,000. With further data this could turn out to be higher, lower, or negligible, but the potential for serious hepatotoxicity clearly should be weighed against the benefits and therefore justifies the inclusion of the PASS in Annex II of the marketing authorisation. The risk is mitigated by restricting the indication to a patient population for whom a compelling clinical benefit has been shown and clear stopping and permanent discontinuation rules are included in the SmPC based on test results and signs/symptoms of liver disease. The risk of liver injury can be considered acceptable for marketing authorisation with the strong monitoring requirements (more frequent than employed in the ADPKD studies) as outlined in SmPC and RMP.

Agreed risk minimisation measures include a prescriber educational programme. Education materials for prescribers and patients and a patient alert card are required, and a prospective long-term follow-up cohort study and retrospective database study , both described in the RMP and the former being condition of the MA will be carried out primarily to evaluate the hepatic safety of Jinarc. Furthermore 3 monthly reports summarising severe hepatic adverse events, as well as 6 monthly reports on hepatic events from an expert advisory panel to assure early detection of signals will be submitted.

The prescription of tolvaptan in ADPKD is to be initiated and monitored under the supervision of physicians with special expertise in managing ADPKD, and a full understanding of the risks of tolvaptan therapy including hepatic toxicity and monitoring requirements. The prognostic factors in ADPKD are complex, and an individual discussion between the specialist prescriber and the patient would always be required. The relatively small number of patients with ADPKD likely to be treated with tolvaptan and the specialist setting further increase the feasibility of adequately inclusive and meaningful post-marketing safety studies.

Benefit-risk balance

ADPKD is a potentially life-threatening condition, and there are currently no approved therapies to slow its inexorable progression. Whilst there are currently no compelling data to show a benefit in the other clinical manifestations of ADPKD, there is a clinically meaningful effect of tolvaptan on the progression of total kidney volume (reflecting cyst development) and on the progression of renal function in patients with CKD stage 1 to 3 at initiation of treatment and evidence of rapidly progressing disease.

The slow evolution of ADPKD would require an impracticably long study to show further and sustained benefit on clinical outcome parameters of the disease and in patients progressing to later stages. Given the rarity of ADPKD, the seriousness of the disease and the lack of other therapies the benefit risk balance in the agreed amended indication together with the risk minimisation measures as described above can be considered positive.

Nevertheless a concern on a potential lack of clinical efficacy in the long term and in later stages of ADPKD persists and requires confirmation. Lack of verification would lead to a re-evaluation of the benefit risk of the product and therefore two post authorisation efficacy studies are made condition to the marketing authorisation. The one, as an open label extension of the pivotal trial, will provide longer term data on the progression of ADKPD, including patients continuing on tolvaptan after the pivotal trial and making comparison of progression to the expected untreated progression rate the other will contribute data on later stages of the disease.

The main safety issue is the significant rise in liver function tests in a small number of patients. To date these have been reversible and not associated with severe clinical outcomes. However the pattern suggests idiosyncratic toxicity, and more serious hepatotoxicity cannot be ruled out. The range of measures described above would be expected to significantly mitigate the risk but to further define the safety profile in a real life setting, in particular the hepatotoxicity is considered key to the benefit risk and a post authorisation safety study was made condition to the marketing authorisation

Discussion on the benefit-risk balance

The CHMP considers that the net clinical benefit outweighs the risk in the granted therapeutic indication. Provisions in the SmPC and the requirements of the risk management plan and Annex II are suitable to mitigate the identified and potential risks in particular the risk of hepatotoxicity.

Furthermore, as the clinical efficacy assessment is largely based on a surrogate parameter and due to the slow evolution of this rare disease requiring an impracticably long study to show further and sustained benefit on clinical outcome parameters of the disease and in patients progressing to later stages post authorisation efficacy follow up was made condition to the Marketing authorisation.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Jinarc indicated to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, 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.

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.

- **Additional risk minimisation measures**

Prior to launch of Jinarc in each Member State the Marketing Authorisation Holder must agree the content and format of the educational programme, including communication media and distribution modalities with each National Competent Authority. The MAH must ensure that all healthcare professionals and patients/carers who are expected to prescribe and/or use JINARC have access to/are provided with the following educational package

- Physician educational material
- Patient information pack

The educational programme is aimed at ensuring awareness about the potential risk of hepatotoxicity and providing guidance on how to manage this risk and the importance of pregnancy prevention prior to the initiation and during the treatment with Jinarc.

The physician educational material should contain:

- The Summary of product Characteristics
- Healthcare professionals training material

The healthcare professional training material shall contain the following key elements

- the risk of hepatotoxicity associated with the use of Jinarc
- the importance of pregnancy prevention, before and during treatment with Jinarc

The patient information pack should contain:

- The Patient information leaflet
- Patient/Carer educational material
- A Patient Alert Card

The Patient/Carer educational material shall contain the following key messages:

- the risk of hepatotoxicity associated with the use of Jinarc
- the importance of pregnancy prevention, before and during treatment with Jinarc

The Patient Alert Card shall contain the following key messages:

- Signs or symptoms of liver toxicity and severe dehydration
- Advice if such symptoms occur

- **Obligation to complete post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
A non-interventional post authorization safety study (PASS) to investigate the risks of: Hepatotoxicity	

Description	Due date
Basal cell carcinoma • Glaucoma associated with the use of Jinarc. In addition the study should also provide information on Pregnancy outcomes, in patients treated with Jinarc Patterns of drug utilisation, especially with regards to off-label use and use in patients over 50 years old ADRs associated with long term use of Jinarc Final study report should be submitted by:	4 Quarter 2022
Post Authorisation Efficacy Study (PAES): In order to further define the efficacy of tolvaptan in patients with more advanced renal dysfunction on a primary endpoint related to GFR rather than TKV the MAH should submit the Final study report of Study 156-13-210 by:	Feb-2018
Post Authorisation Efficacy Study (PAES): In order to show whether the observed short-term effects of tolvaptan on the rate of renal function decline translate into favourable long-term outcomes such as ADPKD related morbidity and mortality, including longer-term effects on GFR decline and progression of disease leading to dialysis or transplantation the MAH should submit the results of the open-label extension to the pivotal trial study 156-08-271. A comparison of progression shall be made to the expected untreated progression rate. The final clinical study report should be submitted by:	June-2016

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Additional Data/Market exclusivity

Furthermore, the CHMP reviewed the data submitted by the applicant, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers, by consensus, that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.