Market Authorisation Holder/Sponsor:

Otsuka Pharmaceuticals Netherlands B.V

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Netherlands

EU RISK MANAGEMENT PLAN (RMP) for

Tolvaptan

Version: 15.0

Data Lock Point for this RMP: 18 May 2020

Date of Final Sign Off: 07 Mar 2022

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Signature	Electronically signed
	[redacted]
Signature	Electronically signed
	Emiel van Heumen, MD, MSc./EU QPPV

EU Risk Management Plan for Tolvaptan

(INN or common name): Tolvaptan, OPC- 41061, OPC-61815 (hereafter referred to as "tolvaptan")

RMP version to be assessed as part of this application:

RMP Version number: 15.0

Data Lock Point for this RMP: 18 May 2020

Date of Final Sign Off: 07 Mar 2022

Rationale for submitting an updated RMP: The RMP has been updated in agreement with PRAC recommendations (Assessment report. Procedure No. EMEA/H/C/PSA/S/0078.1).

Summary of significant changes in this RMP

The following changes and updates were made to the RMP in agreement with PRAC recommendations (Assessment report. Procedure No. EMEA/H/C/PSA/S/0078.1).

- Based on the protocol amendment of the PASS Study (156-12-299) the following milestones were updated (Sections 3.2, 3.3, 6.2.4, 7.2, 7.8):
  - LPLV - Q1 2024
  - Final study report - Q1 2025

There are no previously submitted versions of this EU RMP that are still under evaluation by the Agency.

Details of the currently approved RMP:

Version number: 14.6

- Approved with procedure: EMEA/H/C/002788/II/0029
- Date of approval (opinion date): 09 Apr 2021

QPPV name: Emiel van Heumen

QPPV oversight declaration: The content of this RMP has been reviewed and approved by QPPV of the marketing authorisation holder. The electronic signature is available on file and provided on the title page.

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List of In-text Tables

List of Abbreviations, Acronyms, and Definition of Terms

Abbreviation/Acronym	Definition
ADR	Adverse drug reaction
ADPKD	Autosomnal dominant polycystic kidney disease
ARPKD	Autosomnal recessive polycystic kidney disease
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the time-concentration curve
BID	Twice daily
CHF	Congestive heart failure
CKD-EPI	Chronic kidney disease epidemiology collaboration
CI	Confidence interval
C_{max}	Maximum concentration
CrCl	Creatinine clearance
CTD	Common technical document
CYP	Cytochrome P450
eCrClCG	Estimated creatinine clearance using Cockcroft-Gault equation
DLP	Data lock point
EEA	European economic area
eGFR	Estimated glomerular filtration rate
eGFRCKD-EPI	Estimated glomerular filtration rate using CKD-EPI criteria
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ESRD	End-stage renal disease
EU	European Union
GFR	Glomerular filtration rate
HAC	Hepatic Adjudication Committee
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
INN	International nonproprietary name
IR	Immediate-release
MAH	Marketing authorisation holder
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MR	Modified-release
MRI	Magnetic resonance imaging
N	Number of subjects
N/A	Not applicable
NHANES	National Health and Nutrition Examination Survey
NYHA	New York Heart Association

Abbreviation/Acronym	Definition
ODS	Osmotic demyelination syndrome
PASS	Postauthorisation safety study
PD	Pharmacodynamic
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PKD	Polycystic kidney disease
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic safety update report
PT	Preferred term
QD	Daily
QPPV	Qualified person for pharmacovigilance
RMP	Risk management plan
ROW	Rest of world
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
SOC	System organ class
SmPC	Summary of product characteristics
SMQ	Standardised MedDRA query
SSD	Safety data set
TEAE	Treatment-emergent adverse event
US	United States
UTI	Urinary tract infection

1 PART I: PRODUCT(S) OVERVIEW

Table 1-1 Active Substance Information	
Active substance(s) (INN or common name)	Tolvaptan
Pharmacotherapeutic group(s) (ATC code):	Diuretics, Selective vasopressin V2-receptor antagonist: C03XA01
Name of marketing authorisation	Marketing Authorisation Holder: Otsuka Pharmaceuticals Netherlands B.V Herikerbergweg 292 1101 CT, Amsterdam Netherlands
Medicinal products to which this RMP refers:	2
Invented name of the product in the European Economic Area (EEA)	Tolvaptan (Samsca® and Jinarc®)
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Benzazepine derivative synthesized by Otsuka Pharmaceutical Company, Ltd., is a selective vasopressin V2 receptor antagonist.
	Summary of mode of action: The tolvaptan (OPC-41061) clinical development programme was initiated in 1995 and focused on the potential aquaretic effects of the drug and its potential benefits to patients with hyponatraemia and other fluid overload conditions. In 2003, the mechanisms of aberrant response to arginine vasopressin (AVP) in polycystic kidney disease (PKD) animal models were first reported, thus leading to the initiation of the tolvaptan autosomal dominant polycystic kidney disease (ADPKD) development programme at Otsuka. Tolvaptan blocks the effects of vasopressin at the V2 receptor in the kidney. In ADPKD, vasopressin is responsible for promoting cystic cell proliferation and secretion of fluid into the cysts. Nonclinical studies demonstrated that removal of or blocking of vasopressin stops and/or slows cystogenesis and associated consequences in animal models of polycystic kidney disease (PKD). Data from clinical trials supports that tolvaptan blocks vasopressin, slows cystogenesis, and slows the decline in renal function. These effects translated into clinically meaningful reduction in the risk of ADPKD-disease specific outcomes such as pain and worsening renal function.
	Important information about its composition: Tolvaptan tablets are immediate-release tablets of 7.5, 15-, 30-, 45-, 60-, and 90-mg strengths. All excipients are compendial grade and commonly used in tablet formulations.

Table 1-1 Active Substance Information	
eCTD link to the proposed product information, as appropriate	Module 1/Section 131-spclabelpil ema-combined-h-980-en ema-combined-h-2788-en
Indications: approved and proposed	**Samsca Current**: Treatment of adult patients with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH)
	Jinarc Current: Jinarc is indicated to slow the progression of cyst development and renal insufficiency of atuosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1 to 4 at initiation of treatment with evidence of rapidly progressing disease.
	Proposed (if applicable): *Not applicable*
Dosage in the EEA	**Samsca Current**: Treatment with tolvaptan should be initiated at a dose of 15 mg once daily. The dose may be increased to a maximum of 60 mg once daily as tolerated to achieve the desired level of serum sodium. For patients at risk of overly rapid correction of sodium, e.g., patients with oncological conditions, very low baseline serum sodium, taking diuretics or taking sodium supplementation, a dose of 7.5 mg should be considered. Tolvaptan treatment is expected to last until the underlying disease is adequately treated or until such time that hyponatraemia is no longer a clinical issue. Route of administration is oral.
	Jinarc Current: Jinarc is to be administered twice daily in split tolvaptan dose regimens of 45 mg + 15 mg, 60 mg + 30 mg or 90 mg + 30 mg. The morning dose is to be taken at least 30 minutes before the morning meal. The second daily dose can be taken with or without food. According to these split dose regimens the total daily doses are 60, 90, or 120 mg.
	Proposed (if applicable): Not applicable
Pharmaceutical Form(s)	**Samsca Current** Tablets
	Jinarc Current: Tablets
Pharmaceutical Strength(s)	**Samsca Current:** 7.5 mg 15 mg 30 mg
	Jinarc Current: 15 mg 30 mg 45 mg 60 mg 90 mg
Is/will the product subject to additional monitoring in the EU?	Yes

2 PART II: SAFETY SPECIFICATION

2.1 Module SI: Epidemiology of the Indication and Target Population(s)

2.1.1 Indication #1 Hyponatraemia Secondary to SIADH

Brand name of concerned product: Samsca

2.1.1.1 Incidence

A synopsis of literature review for the incidence and prevalence of hyponatraemia in European countries can be found in Table 2.1.1.1-1.

Table 2.1.1.1-1 Synopsis of Literature Review for Prevalence and Incidence of Hyponatraemia in European Countries and United States

Country (Reference)	Study Design	Study Population	Diagnosis Criteria of Hyponatraemia	Prevalence	Incidence
Belgium[6]	Prospective cohort	All patients (3306 admissions) hospitalised in the department of medical oncology of the Institut Jules Bordet, Brussels over 11 months	serum sodium <130 mmol/L	not provided	Incidence per admission: 3.7% (123/3306)for hyponatraemia, and 1.1% for hyponataemia due to SIADH (36/3306)
Ireland[7]	Prospective	All patients (n=1698, mean age=44, male=53%) admitted to the Irish National Neurosciences Centre at Dublin with neurological disorders from Jan 2002 to Sep 2003	plasma sodium < 130 mmol/L	not provided	Incidence during a median hospital stay of 12 days: 11% (187/1698) for hyponatraemia, and 6.8% (116/1698) for hyponatraemia due to SIADH
Netherlands[14]	Cross-sectional	345 Patients older than 60 years (mean age=76 years, male=25%) using antidepressants in a mental health center between Mar 2007 and Apr 2009	serum sodium <135 mmol/L	Period prevalence (duration of antidepressant use: 4 days to >6 months): 9.9% (34/345) for hyponatraemia, and 6.7% (23/345) for hyponatraemia due to SIADH	not provided
Netherlands[10]	Retrospective records review	1438 patients older than 65 years (mean age=78 years, male=45%) in the emergency department for internal medicine at a teaching hospital between September 2010 and August 2011	clinically relevant hyponatraernia: serum sodium < 130 mmol/L	Point prevalence at visit: 6.3% (91/1438) for hyponatraemia, and 0.9% (13/1438) for hyponatraemia due to SIADH	not provided
Portugal[15]	Retrospective records review	1060 patients older than 65 years (mean age = 80 years, male = 52%) admitted in two	plasma sodium < 135 mmol/L (severe: < 125 mmol/L)	Point prevalence at admission: 27.6% (292/1060) for	not provided

Table 2.1.1.1-1 Synopsis of Literature Review for Prevalence and Incidence of Hyponatraemia in European Countries and United States

Country (Reference)	Study Design	Study Population	Diagnosis Criteria of Hyponatraemia	Prevalence	Incidence
		Internal Medicine wards in the University Hospitals of Coimbra from December 2007 to November 2008		hyponatraemia, and 5.9% (63/1060) for severe hyponatraemia	
Sweden[12]	Cross-sectional	1558 elderly adults ≥ 75 years old (mean age=82 years, male=24%) in an urban area of Stockholm in October 1987	serum sodium <136 mmol/L	Point prevalence at study entry: 9.4% (147/1558) for hyponatraemia	not provided
Sweden[16]	Retrospective records review	All patients (n=201675) in the emergency departments at Skane University Hospital in Southern Sweden in 2009 and 2010	plasma sodium <135 mmol/L	Point prevalence at visit: 3% (6461/201675) for hyponatraemia	not provided
Switzerland[11]	Cross-sectional	10249 patients older than 50 years (mean age=68 years, male=57%) in the emergency department at the University Hospital Bern between 2009 and 2010	serum sodium <132 mmol/L	Point Prevalence at visit: 6.1% (628/10249) for hyponatraemia	not provided
United Kingdom[17]	Retrospective records review	All inpatients (n=380, age range: 39-92 years, male=59%) at Queen Elizabeth Hospital over a six month period	severe hyponatraemia: serum sodium < 120 mmol/L	Period prevalence (mean length of hospital stay=22 days): 0.15% (57/380) for severe hyponatraemia	not provided

Table 2.1.1.1-1 Synopsis of Literature Review for Prevalence and Incidence of Hyponatraemia in European Countries and United States

Country (Reference)	Study Design	Study Population	Diagnosis Criteria of Hyponatraemia	Prevalence	Incidence
United Kingdom[5]	Prospective cohort	127 patients aged ≥ 65 years (mean age=79 years, male=22%) admitted with a fragility fracture to a university hospital between January and April 2013	serum sodium< 135 mmol/L	Period prevalence (during mean hospital stay of 7.7 days): 26% for hyponatraemia overall, and 7.1% for hyponatraemia due to SIADH	Incidence during hospital stay (mean length=7.7 days):12.6% (15/127)
United States Verispan HPD Database, 2006	Cross-sectional, cohort, observational study	US hospitalized patients	not provided	not provided	new cases of hyponatraemia (per 1000 person-years) is estimated at 0.25 for SIADH,
Worldwide[9]	Meta-analysis	53 studies in different settings across the world from 1976 to 2006 (18 studies from US, and 23 from Western Europe)	serum sodium < 135 mmol/l (mild:130-134, moderate:125-129, severe: < 125 mmol/l)	Pooled mean prevalence at admission: geriatric wards: mild 10.2%, moderate 3.0%, and severe 4.5%; non-geriatric wards: mild 4.7%, moderate 0.5%, and severe 0.8%	not provided
Worldwide[8]	Cross-sectional (1-day point prevalence study)	13276 adult patients (mean age=61 years, male=60%) of the Extended Prevalence of Infection in Intensive Care study in 1265 ICUs across 76 countries on 8 May 2007	serum sodium < 135 mmol/L (mild:130-134, moderate:125-129, severe: < 125 mmol/L)	Point prevalence: 12·9% for hyponatraemia overall (mild: 9·3%, moderate: 14·8%, and severe: 5·9%)	not provided

Incidence of hyponatraemia was reported as 12.6% (15/127) in elderly patients hospitalised with fracture during a mean hospital stay of 7.7 days in UK.[5] In cancer patients hospitalised in a medical oncology department in Belgium, the incidence per admission was 3.7% (123/3306) and 1.1% (36/3306) for hyponatraemia in general and hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH), respectively.[6] By contrast, in patients hospitalised with neurological disorders in the Irish National Neurosciences Centre, 11% (187/1698) or 6.8% (116/1698) developed hyponatraemia or hyponatraemia secondary to SIADH during a median hospital stay of 12 days.[7]

2.1.1.2 Prevalence

Hyponatraemia is common in patients in ICU, geriatric wards, or emergency department. In a study of 1265 ICUs in 76 countries,[8] prevalence of mild (serum sodium: 130-134 mmol/L), moderate (serum sodium: 125-129 mmol/L), and severe (serum sodium < 125 mmol/L) hyponatraemia was reported as 9.3%, 14.8%, and 5.9%, respectively. In a meta-analysis of 53 studies (23 from Western Europe), the pooled mean prevalence of mild, moderate, and severe hyponatraemia at admission in geriatric wards was 10.2%, 3.0%, and 4.5%, respectively.[9] In older patients admitted to the emergency department, prevalence of hyponatraemia was reported as 6.3% (91/1438) and 6.1% (628/10249) in Netherlands and Switzerland, respectively.[10,11] In population-based studies, prevalence of hyponatraemia was 9.4% (147/1558) in those ≥ 75 years of age in an urban area of Stockholm, Sweden.[12] In a representative sample of civilian, community dwelling US adults 18 years and older in the National Health and Nutrition Examination Survey (NHANES) 1999-2004, the weighted prevalence of hyponatraemia (defined as serum sodium below reference range of 133-145 mmol/L) was 1.72% (301/14697).[13] Hyponatraemia prevalence increased with age and was higher in women compared with men; prevalence was 1.13% in adults 18-44 and 4.52% in adults ages 85 and older and prevalence was 1.32% for men compared with 2.09% in women.

Prevalence of hyponatraemia secondary to SIADH was reported in some EU countries. In elderly patients with fracture at a university hospital in UK, 7.1% (9/127) were diagnosed with hyponatraemia due to SIADH during hospital stay, which account for 27% of all hyponatraemic cases.[5] In elderly patients at a mental health center in the Netherlands, 6.7% (23/345) had hyponatraemia due to SIADH,[14] which accounted for 68% of all hyponatraemic case. In the emergency department, prevalence of hyponatraemia due to SIADH was reported as 0.9% (13/1438) in elderly patients in the Netherlands,[10] and

SIADH accounted for 14% of all hyponatraemic cases. Based on the Verispan US Hospital counts 2006 annual incidence rates for hyponatraemia (new cases per 1000 person years) can be estimated to range around 0.25, 0.6 and 3.4 for SIADH, liver cirrhosis and congestive heart failure, respectively.

2.1.1.3 Demographics of the Target Population in Hyponatraemia Secondary to SIADH

Generally, hyponatraemia, especially severe hyponatraemia, is more prevalent in the elderly than in younger age groups, due to increased prevalence of underlying diseases and decreased control of electrolyte balance in the elderly.[13,18,19] Based on the NHANES survey for 1999-2004 in the US, prevalence of hyponatraemia in 18-44, 45-64, 65-84, >85 years of age groups was 1.1%, 2.0%, 3.1%, and 4.5% respectively.[13] Moreover, odds of severe hyponatraemia was 2.5, 4.3, and 7.7 times higher in the 61-70, 71-80, and >81 years of age groups than that in the reference age group (≤30 years of age) based on a study of 120137 patients in Singapore.[19]

Results of sexual differences in hyponatraemia were not consistent, probably due to the variation in study population and clinical setting.[13,18] There is a lack of study on racial differences in hyponatraemia.

2.1.1.4 Risk Factors for the Disease

As mentioned previously, hyponatraemia or SIADH can be caused by a variety of underlying diseases, such as cancer, neurological surgery, congestive heart failure, liver cirrhosis, and antipsychotics. Other than the underlying diseases, older age is another well-established risk factor for hyponatraemia, especially for severe hyponatraemia.[18,19] In contrast, the role of gender as a risk factor for hyponatraemia is not consistently recognized.[19]

2.1.1.5 Main Treatment Options

There are multiple treatment options for hyponatraemia.

Water restriction: At the present time, water restriction is generally considered the treatment of choice for hyponatraemia secondary to SIADH. However, many patients have difficulties complying with prolonged fluid restriction and hyponatraemia may recur. Moreover, in patients with SIADH part of the water overload may be due to downward resetting of the osmotic threshold for thirst. As thirst is particularly difficult to suppress, water restriction in SIADH frequently leads to non-compliance in the long run.[20]

Isotonic saline: Some patients with SIADH have been successfully treated with isotonic saline.[20]

Hypertonic saline: If a patient is symptomatic due to a rapid decrease in serum sodium concentration, treatment with hypertonic saline should be considered.[20]

Loop diuretics: In order to increase free water excretion rates, loop diuretics have proven effective in the treatment of SIADH. This may be related to an inhibition of the ability of the kidney to maintain a medullary concentration gradient. This treatment strategy is generally reserved to the acute phase of hyponatraemia correction.[20]

Demeclocycline: Its use dates back to the 1970s. This drug has been employed chronically, most often in patients with SIADH due to a malignancy. However, the agent has frequent side effects such as nausea and skin photosensitivity. Moreover, demeclocycline has also been shown to cause nephrotoxicity in some cases leading to irreversible renal failure.[20]

Urea: Urea can be given by mouth, either as a powder or in capsules, and thus results in an osmotic diuresis. Due to its bitter taste, its use has not met wide acceptance.[20]

Extracorporeal treatments: Although rapid correction of hyponatraemia may occur during hemodialysis, in some instances leading to pontine myelinolysis, more gradual forms of dialysis treatment have been advocated. Venovenous hemofiltration has been shown to induce a more gradual correction of hyponatraemia and other forms of slow dialysis treatment, such as slow low-efficiency daily dialysis may be equally effective. However, as most forms of continual renal replacement therapy are performed on intensive care wards, this approach to treat SIADH would lead to a steep increase in costs. In patients with established renal failure, however, dialytic or convective therapies are the treatment of choice.[20]

Vaptans: As current forms of treatment of SIADH have serious limitations, the development of the new class of orally available aquaretic agents was received with great expectation. A study on the effects of conivaptan, a vasopressin V1a/V2-receptor antagonist, in hyponatraemia demonstrated its efficacy in increasing serum sodium, but included predominantly heart failure patients. Although conivaptan may have effects similar to tolvaptan, conivaptan is only available as a parenteral preparation and is authorized only in the USA. Therefore conivaptan is not a treatment option in the EU.[20]

2.1.1.6 Mortality and Morbidity (Natural History)

Symptoms of hyponatraemia are nonspecific and related to both the absolute serum sodium concentration and its rate of change. Patients with mild hyponatraemia are usually asymptomatic. As serum sodium concentration falls below 130 mmol/L, anorexia, nausea, vomiting and abdominal pain may develop. At serum sodium concentration between 115 and 125 mmol/L, agitation, confusion, hallucinations, incontinence and other neurological symptoms predominate. Hyponatraemia below 115 mmol/L may induce serious adverse neurological sequelae, such as seizures, coma, respiratory arrest, brain-stem herniation, permanent brain damage, and death.[1,21] Chronic hyponatraemia (ie, developing in > 48 hours) may present as a relatively asymptomatic condition, whereas acute hyponatraemia (ie, developing in < 48 hours) can accompany severe neurological symptoms at a relatively high serum sodium concentration.[22]

Hyponatraemia is associated with an increased risk of death in both hospitalised and community dwelling patients.[13,23] In a prospective study of 2960 inpatients at a general district hospital in Greater Copenhagen,[23] one-year mortality was higher for hyponatraemic patients than for normonatraemic patients: 27.5% versus 17.7%. Moreover, hyponatraemia was an independent predictor of 1 year and 5 years all-cause mortality respectively: hazard ratio (HR) 1.6 (95% CI: 1.4-1.9) and HR 1.4 (95% CI: 1.3-1.6). Among 14,697 non-institutionalized adults in the National Health and Nutrition Examination Survey for 1999-2004 in US,[13] the overall mortality rate over the period 1999-2006 for hyponatremic subjects was 11% versus 4% for subjects with normonatremia. Hyponatraemia is associated with a significant risk of death in unadjusted (HR 3.61, p<0.001) and adjusted Cox models (HR 2.43, p<0.001).

2.1.1.7 Potential Health Risks (Comorbidities)

As mentioned previously, hyponatraemia or SIADH can be caused by a variety of underlying diseases, such as cancer, neurological surgery, congestive heart failure, liver cirrhosis, and antipsychotics. Other than the underlying diseases, older age is another well-established risk factor for hyponatraemia, especially for severe hyponatraemia.[18,19] In contrast, the role of gender as a risk factor for hyponatraemia is not consistently recognized.[19]

2.1.2 Indication #2 ADPKD

Brand names of concerned products: Jinarc

A synopsis of literature review for the incidence and prevalence of ADPKD in European countries can be found in Table 2.1.2.2-1.

2.1.2.1 Incidence

Incidence of ADPKD phenotype was reported in two studies using data from 1935-1953 in Copenhagen, Denmark[27] and from 1958-1980 in Olmsted County, US,[28] respectively. The age and sex adjusted incidence was higher in US (2.29 per 100,000 person-years) than in Denmark (0.80 per 100,000 person-years), which could be due to differences in study period, case ascertainment method, and population demographics.

2.1.2.2 Prevalence

A comprehensive review of epidemiological studies published from Jan 1980 to Nov 2015 yielded two large, generalizable, population-based studies of ADPKD in Germany and the UK respectively. In 2013, Neumann et al. reported a total point prevalence of ADPKD of 3.3 per 10,000 in southwest Germany.[26] In 2011, Patch et al. reported a 1-year period prevalence of diagnosed cases of 3.9 per 10,000 which corresponds to a total 1-year period prevalence (diagnosed and undiagnosed cases) of 4.3 per 10,000 in the UK.[29]

In addition, the most recent RRT patient counts from national and regional registries (2012), and literature-based assumptions about disease severity and diagnosis rates were used to determine a more generalizable prevalence estimate (covering 19 EU countries and 81% of the EU population).[30] This approach yielded a point prevalence of ADPKD on 31 Dec 2012 of 3.29/10000 (95% CI, 3.27-3.30). Only one study in France reported higher prevalence than the criterion;[31] however, its results are considered less generalizable than other studies due to its much smaller sample size.

Table 2.1.2.2-1 Synopsis of Literature Review for Prevalence and Incidence of ADPKD in European Countries

Country (Reference)	Study Design	Study Population	Prevalence	Incidence
Denmark[27]	Cohort	403, 600 women and 331, 900 men in Copenhagen during 1935 to 1953	not provided	Annual incidence: 0.8 per 10,000
France[31]	Cross-sectional	A population of 410, 000 inhabitants in Brittany in 1993	Point prevalence: 9.0 per 10,000	not provided
Germany[26]	Cross-sectional	A population of 2,727,351 inhabitants in south-west Germany in 2010	Point prevalence: 3.3 per 10,000	not provided
Portugal[32]	Cross-sectional	543,442 inhabitants in Alentejo, south of Portugal in 1999	Point prevalence: 3.3 per 10,000	not provided

Table 2.1.2.2-1 Synopsis of Literature Review for Prevalence and Incidence of ADPKD in European Countries				
Country (Reference)	**Study Design**	**Study Population**	**Prevalence**	**Incidence**
United Kingdom[33]	Cross-sectional	2,100,000 inhabitants in South and Mid-Wales in 1989	Point prevalence: 4.1 per 10,000	not provided
United Kingdom[29]	Cross-sectional	All participants in the UK General Practice Research Database in 2008	Period prevalence (1-year): 3.9 per 10,000	not provided

2.1.2.3 Demographics of the Target Population in ADPKD

Mean age of ADPKD patients was reported as 50-52 years in the UK and Germany populations.[26,29] Incidence of ADPKD is close to 0 before age 10, increases gradually thereafter, and reaches a plateau from age 30 onwards.[27,28] Similarly, prevalence is low before age 20, then increases and reaches the peak in the fifth and sixth decades, and then declines sharply after age 80.[26] Therefore, most cases were not diagnosable until early adulthood, and patients live with the disease as a chronic condition until end-stage renal disease (ESRD) in their fifties or sixties.

There is no apparent sex difference in disease incidence or prevalence, and racial differences in ADPKD are not well studied yet.

2.1.2.4 Risk Factors for the Disease

ADPKD is genetically heterogeneous with 2 genes identified: *PKD1* and *PKD2*. The *PKD1* gene is located on chromosome 16, encodes for polycystin-1, and accounts for about 85% of ADPKD cases.[34] The *PKD2* gene is located on chromosome 4, encodes for polycystin-2, and accounts for about 15% of cases.[34] Compared with *PKD1*, subjects affected with *PKD2* mutations have milder renal disease with fewer renal cysts, delayed onset of hypertension, delayed ESRD by almost two decades, and longer patient survival.[35]

2.1.2.5 Main Treatment Options

Conventional therapies are palliative, directed toward limiting morbidity and mortality from complications of ADPKD, and target only pain, infection, and hypertension which are downstream consequences of cyst expansion but do not address the underlying renal pathophysiology of pathogenomonic cyst formation and kidney enlargement. Often, the only definitive intervention in ADPKD is kidney transplantation, which typically occurs after years of renal dialysis. Before the launch of tolvaptan (Jinarc), no pharmacologic

interventions were available to delay the increase of total kidney volume (a surrogate marker for disease progression).

The concomitant medications would include those intended for the treatment of ADPKD's kidney and non-kidney symptoms, but not the disease pathophysiology itself. High blood pressure is treated with antihypertensive medications, most often inhibitors of the renin-angiotensin system. Pain in the area of the kidneys is treated as needed with typical pain medications ranging from paracetamol to narcotics although non-steroidal anti-inflammatory drugs are often used, they should be avoided due to nephrotoxicity. If acute, pain may often be linked to an underlying cyst rupture, infection or nephrolithiasis where the primary goal of treatment should be the relief of the offending condition. Often chronic pain due to organ displacement/impingement or stretching of the renal capsule requires chronic treatment with narcotics or other nociceptives, typically off-label with antidepressants. When renal function starts to decline, treatment is aimed at slowing down the progression to kidney failure. This involves controlling high blood pressure, restricting protein in the diet, controlling acidosis and hypophosphatemia. When individuals with ADPKD develop renal failure, they need to have dialysis or a renal transplant.

2.1.2.6 Mortality and Morbidity (Natural History)

ADPKD is characterized by progressive development of multiple epithelial-lined kidney cysts and slow, gradual kidney enlargement that eventually results in kidney failure.[36] An estimated 45% to 70% of patients with ADPKD progress to ESRD by age 65.[37,38] The median age at death or ESRD was 53.0 years in patients with *PKD1* and 69.1 years in those with *PKD2*, which were 15 and 9 years earlier than their spouse controls.[35]

Cardiovascular disease is the most common cause of death, followed by infection and malignancy.[39] Moreover, ADPKD is a systematic disease with various renal and extrarenal manifestations, such as pain, hypertension, multiple liver cysts, intracranial aneurysms, nephrolithiasis, and renal failure.[40] Most complications are associated with progressing cyst development[41] and therefore treatment that can slow down the cyst progression has the potential to increase patient survival rate.

2.1.2.7 Potential Health Risks (Comorbidities)

ADPKD is a systematic disease with various extrarenal comorbidities, such as hypertension, left ventricular hypertrophy, liver or pancreatic cysts, and intracranial aneurysms (ICA).

Hypertension and left ventricular hypertrophy occurs frequently in ADPKD patients, which is probably due to the activation of renin-angiotensin-aldosterone system (RAAS) secondary to cyst expansion. Depending on the age and renal function of the patient, hypertension has been observed in 59%-87% of patients with ADPKD.[42,43,44] Left ventricular hypertrophy (LVH), which is an independent risk factor for cardiovascular mortality, occurs more frequently in ADPKD patients than in controls (41% vs. 16%).[45] Cardiovascular diseases were found as the primary cause of death in ADPKD patients (44%) by a large retrospective study in Spain.[43]

A second common organ in which cysts occur in APDKD is the liver. Liver cysts were found in 55%-83% of ADPKD patients among studies,[46,47,48] and the prevalence increases with advancing age and declining glomerular filtration rate.[48] Pancreatic cysts are less common and present in about 6% of ADPKD patients.[46,47]

ICA is the major vascular abnormality reported in ADPKD, and ruptured ICA account for 4% to 7% of deaths in patients with ADPKD.[49] The prevalence of intracranial aneurysm in ADPKD patients increases with aging and declining renal function, and was reported as 5-17% among studies.[50,51,52] Several large prospective studies in North America found the prevalence of ICA was higher in ADPKD patients (4.0 to 11.7%) as compared with a 1% prevalence in the general population.[49]

2.2 Module SII: Nonclinical Part of the Safety Specification

This chapter applies to Hyponatraemia (Samsca) and ADPKD (Jinarc) indications as the pharmaceutical compound is tolvaptan in both indications. The scope of the non-clinical efficacy and safety pharmacology testing was sufficient to fully characterize tolvaptan with regard to its proposed indications and to assess its potential for adverse pharmacodynamic effects on major organ systems.

Tolvaptan was not genotoxic in a wide range of genotoxicity studies. Based on the carcinogenicity studies performed in mice and rats, tolvaptan had no carcinogenic potential at doses of up to 60 and 100 mg/kg/day for male and female mice, and up to 1000 mg/kg/day for male and female rats. Tolvaptan poses no phototoxic risk to humans based on the weight of evidence from the in vitro and in vivo phototoxicity tests completed.

Tolvaptan did not cause any target organ toxicity when administered to rats at doses up to 1000 mg/kg/day for 26 weeks or to dogs at doses of up to 1000 mg/kg/day for 52 weeks. Dose limiting clinical signs in rats and dogs were considered a consequence of exaggerated pharmacologic action of the drug.

The toxicological potential of metabolite DM-4103 found in clinical studies was examined in male rats. No notable toxicity was observed following single subcutaneous administration. Additionally, in a 26-week repeated-dose oral toxicity study of tolvaptan in rats, in which plasma levels of DM-4103 exceeded those expected at the Maximum Recommended Human Dose, no evidence of target organ toxicity was seen.

There were no general safety pharmacology issues identified. There were no non-clinical toxicity findings that preclude safe administration of tolvaptan to humans (see CTD Section 2.4, Non-clinical Overview).

Table 2.2-1 SII-1:Summary of Key Safety Findings from Nonclinical Studies and Relevance to Human Usage

Key safety findings (from nonclinical studies)	Relevance to Human Usage
Single dose toxicity Single oral dose The single oral dose toxicity of tolvaptan was evaluated at doses of up to 2000 mg/kg in rats and beagle dogs. No deaths or toxic signs in general condition were observed in either rats or dogs. In rats, a transient decrease in food consumption and a transient suppression of body weight gain were noted at 2000 mg/kg. The approximate lethal dose was considered to be higher than 2000 mg/kg in both rats and dogs.	These findings after single oral super high doses in rats and dogs are of no relevance to human usage.
Repeat dose toxicity Based on repeat dose oral toxicity studies in rats (4, 13 and 26-week) and dogs (4-, 13- and 52-week) the nontoxic dose of tolvaptan is estimated to be 1000 mg/kg/day in male rats and 100 mg/kg/day in dogs and female rats. The safety margins based on the AUC are 1.9 and 3.2 for male and female rats, and 4.8 and 6.4 for male and female dogs, respectively, following administration of the compound at a dose of 120 mg/day in humans. These safety margins are referring to the ADPKD indication since doses for this indication represent the maximum recommended human dose.	Non-clinical data revealed no special hazard for humans based on conventional GLP studies of safety pharmacology and repeated dose toxicity.
Reproductive toxicity Tolvaptan had no effect on copulation rate or fertility rate, but a prolongation of dioestrus was observed at or above 300 mg/kg/day in female rats. Dose-dependent maternal toxicity (decreased food consumption and body weight) was evident at or above 100 mg/kg/day in rats and 30 mg/kg/day in rabbits. Maternal reproductive performance, as assessed by the ability to maintain pregnancy, was altered at dose levels of 300 mg/kg and higher where a dose-dependent increase in the incidence of abortion was observed in rabbits. The NOAEL was considered to be lower than 100 mg/kg/day in both males and females for general toxicological effects, 1000 mg/kg/day in males and 100 mg/kg/day in females for effects on reproduction.	Clinical trials excluded pregnant or lactating women therefore there are no adequate data from the use of tolvaptan in pregnant women. The potential risk for humans is therefore unknown. Tolvaptan is likely to be used in women of child bearing age, particularly in the treatment of hyponatraemia. Women of childbearing potential should use adequate contraceptive measures during tolvaptan use. Tolvaptan must not be used during pregnancy.

Table 2.2-1 SII-1:Summary of Key Safety Findings from Nonclinical Studies and Relevance to Human Usage

Key safety findings (from nonclinical studies)	Relevance to Human Usage
Developmental toxicity At 1000 mg/kg/day, developmental toxicity of the rat foetuses consisted of decreased body weight and delayed ossification; that of rabbit foetuses consisted of increased incidences of embryo-fetal death, microphthalmia, open eyelids, cleft palate, brachymelia (zygopodium malformations) and fused phalanx. Increased perinatal death and decreased body weight during lactation and after weaning were observed in the 1000 mg/kg/day group. Tolvaptan did not cause any developmental toxicity in rats at maternal doses up to 100 mg/kg/day (the safety margin of 4.4 based on the AUC for humans at the dose of 120 mg/day) or in rabbits at maternal doses up to 300 mg/kg/day (the safety margin of 1.2 based on the AUC for humans at the dose of 120 mg/day). The cause of teratogenicity has not been definitively shown, although dehydration or changes in biotin status were examined as possible causes. These safety margins are referring to the ADPKD indication since doses for this indication represent the maximum recommended human dose.	Clinical trials excluded pregnant or lactating women therefore there are no adequate data from the use of tolvaptan in pregnant women. The potential risk for humans is unknown. The SmPC for tolvaptan contraindicates the use of tolvaptan in pregnancy.
Genotoxicity No observations The genotoxic potential of tolvaptan was evaluated by conducting a bacterial reverse mutation test, a mouse lymphoma assay, a chromosomal aberration test using Chinese hamster lung cells, and a micronucleus test using bone marrow cells from male and female rats. Tolvaptan tested negative for genotoxic effects in all the assay systems used.	No risk to human usage
Carcinogenicity Two 104-weeks carcinogenicity studies, one in mice and one in rat, were conducted to evaluate the carcinogenicity of tolvaptan. In the mouse study, the dose levels were set at 0, 10, 30 and 60 mg/kg/day in males and 0, 10, 30 and 100 mg/kg/day in females. There was no increase in either mortality or tumors in the treated groups as compared with the control group. In the rat study, the dose levels were set at 0, 100, 300 and 1000 mg/kg/day in males and 0, 30, 100, 300 and 1000 mg/kg/day in females. There was no increase in either mortality or tumors in the treated groups as compared with the control group. These results indicated that tolvaptan does not have carcinogenic potential.	No risk to human usage

Table 2.2-1 SII-1:Summary of Key Safety Findings from Nonclinical Studies and Relevance to Human Usage

Key safety findings (from nonclinical studies)	Relevance to Human Usage
Mechanism for drug interaction Cytochrome P450 (CYP): In vitro studies indicated that tolvaptan was metabolized solely by CYP3A and that tolvaptan may be an inhibitor of CYP2C9. In clinic, tolvaptan is a sensitive CYP3A4 substrate with no inhibitory activity at CYP3A4 or CYP2C9. In vitro studies indicate that tolvaptan is a substrate and inhibitor of p-glycoprotein, and tolvaptan or its oxobutyric metabolite may have the potential to inhibit BCRP, OATP1B1, OAT3, and OCT1 transporters.	Clinical studies have confirmed no clinically significant inhibition at BCRP and no interaction at OATP1B1 or OAT3. Clinically relevant drug-drug interaction issues are adequately addressed in the SmPC for tolvaptan. Examples are below: Co-administration of ketoconazole increased tolvaptan AUC 5.3-fold. Tolvaptan Cmax and AUC increased with grapefruit juice. When a single 240-mg dose of tolvaptan was administered with rifampin at steady state (600 mg QD), tolvaptan Cmax and AUC were decreased 85%. No clinically significant changes seen with co-administration with furosemide and hydrochlorothiazide. Digoxin did not cause clinically significant changes in tolvaptan pharmacokinetics. However, digoxin AUC was increased about 20% by co-administration of tolvaptan.
Other toxicity-related information or data	NA

Subsequent to the dossier submitted for the approved indication of hyponatraemia indication, juvenile toxicity studies in rats were undertaken to support paediatric clinical trials for hyponatraemia, and those studies are summarized in the following text.

A 6-week repeated oral dose toxicity study of tolvaptan was conducted in juvenile Sprague-Dawley rats (25 days of age at the start of administration) at doses of 0, 100, 300, and 1000 mg/kg/day. In the juvenile toxicity studies in rats, the treatment-related changes observed were qualitatively comparable to those observed in the adult rat studies. Therefore, the juvenile animal is not considered to be uniquely sensitive to the toxicity associated with tolvaptan.

2.2.1 Need for Additional Nonclinical Data

Nonclinical safety data revealed no special hazard for humans based on conventional tests of safety pharmacology, repeat-dose toxicity, genotoxicity, carcinogenicity, antigenicity, immunotoxicity, or phototoxicity. Toxicologically significant effects were observed only at doses that were sufficiently in excess of the maximum human dose indicating limited to no relevance to clinical use and no additional toxicity studies are planned. However, while no additional nonclinical data are needed, and considering the developmental toxicities noted at high doses in rabbits, tolvaptan is contraindicated in pregnancy.

2.2.2 Conclusions on Nonclinical Data

Table 2.2.2-1 Conclusion on nonclinical safety

Safety concerns
Important identified risks (confirmed by clinical data) None
Important potential risks (not refuted by clinical data or which are of unknown significance) None
Missing information Pregnancy and lactation data.

2.3 Module SIII: Clinical Trial Exposure

Cumulative subject exposure from the clinical trial programme is presented in tables below.

In addition, 204 subjects (193 in completed 5 trials and 11 in ongoing 1 trial) have received OPC-61815 (a phosphate ester of tolvaptan) in clinical trials in Asia (Japan) as of the data lock point (DLP) 18 May 2020. As of the DLP there was an ongoing double-blind, active-control trial with 169 subjects where the treatment assignments were still blinded.

2.3.1 Clinical Trial Exposure by Duration of Exposure

Table 2.3.1-1 SIII.1: Clinical Trial Exposure to Tolvaptan by Duration of Exposure (Cumulative and by Indication)

Duration of Exposure	Persons	Person Time (Patient Days)
Cumulative for All Indications		
<1 m	4151	32675
≥1 m	847	42411
≥3 m	842	116208
≥6 m	748	194741
≥12 m	1309	675525
≥24 m	2066	3536560

Table 2.3.1-1 SIII.1: Clinical Trial Exposure to Tolvaptan by Duration of Exposure (Cumulative and by Indication)		
Duration of Exposure	**Persons**	**Person Time (Patient Days)**
Total person time	9963	4598120
ADPKD		
<1 m	252	3351
≥1 m	293	14445
≥3 m	175	22999
≥6 m	180	46947
≥12 m	547	301552
≥24 m	1948	3423052
Total person time	3395	3812346
Carcinomatous Oedema		
<1 m	43	329
Total person time	43	329
Cardiac Oedema		
<1 m	463	2869
Total person time	463	2869
Chronic Renal Failure		
<1 m	46	324
≥1 m	8	499
≥3 m	69	6668
Total person time	123	7491
Congestive Heart Failure		
<1 m	771	9531
≥1 m	392	22343
≥3 m	591	85636
≥6 m	560	145720
≥12 m	733	359573
≥24 m	68	52996
Total person time	3115	675799
Hepatic Oedema		
<1 m	855	5965
Total person time	855	5965
Hyponatraemia		
<1 m	457	5098
≥1 m	154	5124
≥3 m	7	905
≥6 m	8	2074
≥12 m	29	14400
≥24 m	50	60512
Total person time	705	88113
Renal Impairment		
<1 m	37	37
Total person time	37	37
Healthy		
<1 m	1227	5171
Total person time	1227	5171
Source: CT-1.1-CT-1.10.		

2.3.2 Clinical Trial Exposure by Age Group and Gender

Table 2.3.2-1 SIII.2: Clinical Trial Exposure to Tolvaptan by Age Group and Gender (Cumulative and by Indication)

Age Group (Years)	Persons		Person Time (Patient Days)	
	M	F	M	F
Cumulative for All Indications				
2 to 11	23	18	4217	3195
12 to 17	37	37	11336	8826
18 to 65	4742	2585	2244046	1905692
66 to 75	1003	492	169920	73622
>75	607	415	103450	73808
Unknown	4	0	8	0
Total	6416	3547	2532977	2065143
ADPKD[a]				
2 to 11	10	9	4160	3163
12 to 17	31	30	11317	8794
18 to 65	1691	1623	1959165	1825733
66 to 75	1	0	14	0
Total	1733	1662	1974656	1837690
Carcinomatous Oedema				
18 to 65	7	14	60	109
66 to 75	9	7	67	49
>75	2	4	17	27
Total	18	25	14	185
Cardiac Oedema				
2 to 11	8	6	39	25
12 to 17	5	7	18	32
18 to 65	120	42	757	247
66 to 75	90	38	573	245
>75	82	65	536	397
Total	305	158	1923	946
Chronic Renal Failure				
18 to 65	46	23	3182	1133
66 to 75	34	7	1876	316
>75	11	2	885	99
Total	91	32	5943	1548
Congestive Heart Failure				
18 to 65	1140	364	240669	66874
66 to 75	670	282	160929	60455
>75	440	219	97415	49457
Total	2250	865	499013	176786
Hepatic Oedema				
18 to 65	487	155	3378	1059
66 to 75	109	69	795	498
>75	17	18	120	115
Total	613	242	4293	1672
Hyponatraemia				
2 to 11	5	3	18	7
12 to 17	1	0	1	0

Table 2.3.2-1 SIII.2: Clinical Trial Exposure to Tolvaptan by Age Group and Gender (Cumulative and by Indication)				
Age Group (Years)	**Persons**		**Person Time (Patient Days)**	
	M	**F**	**M**	**F**
18 to 65	271	130	32819	9551
66 to 75	69	72	5586	11960
>75	50	104	4469	23702
Total	396	309	42893	45220
Renal Impairment				
18 to 65	13	10	13	10
66 to 75	10	1	10	1
>75	2	1	2	1
Total	25	12	25	12
Healthy				
18 to 65	967	224	4003	976
66 to 75	11	16	70	98
>75	3	2	6	10
Total	985	242	4087	1084

[a]Paediatric Trial 156-12-298 blinded period completed in Dec 2019.
Source: CT-2.1-CT-2.10.

2.3.3 Clinical Trial Exposure by Dose

Table 2.3.3-1 SIII.3: Clinical Trial Exposure to Tolvaptan by Dose (Cumulative and by Indication)		
Dose of Exposure	**Persons**	**Person Time (Patient Days)**
Cumulative for All Indications		
TLV 3.75 mg	43	151
TLV 5 mg	18	82
TLV 7.5 mg	419	2674
TLV 10 mg	18	162
TLV 15 mg	1175	21628
TLV 3.75-15 mg	3	5
TLV 30 mg	3096	662795
TLV 3.75-30 mg	43	329
TLV 45 mg	107	1798
TLV 60 mg	677	18501
TLV 7.5-60 mg	43	290
TLV 15-60 mg	634	87555
TLV 45-90 mg	80	27434
TLV 90 mg	252	5656
TLV 120 mg	55	259
TLV 180 mg	11	16
TLV 240 mg	27	47
TLV 300 mg	77	414
TLV 360 mg	6	6
TLV 420 mg	6	6
TLV 480 mg	6	6

Table 2.3.3-1 SIII.3: Clinical Trial Exposure to Tolvaptan by Dose (Cumulative and by Indication)

Dose of Exposure	Persons	Person Time (Patient Days)
TLV 30-120 mg	1946	1324685
TLV 60-120 mg	3120	2437498
<60 mg JM	20	24
60 mg JM	16	21
100 mg JM	6	6
150 mg JM	59	290
300 mg JM	28	28
450 mg JM	28	28
TLV MR 20 mg	27	169
TLV SDT 20 mg	28	104
TLV MR 40 mg	17	119
TLV MR 50 mg	45	2320
TLV MR 60 mg	87	437
TLV SDT 60 mg	10	55
TLV MR 80 mg	43	2235
TLV MR 120 mg	12	84
Powder 15 mg	66	154
Syrup 15 mL	14	14
TLV 0.1-0.6 mg/kg suspension	6	21
TLV 1 mg IV	14	14
Total	9963	4598120
ADPKD		
TLV 15 mg	26	71
TLV 30 mg	44	14963
TLV 45 mg	9	45
TLV 60 mg	38	218
TLV 45-90 mg	80	27434
TLV 90 mg	44	2344
TLV 120 mg	20	92
TLV 30-120 mg	1946	1324685
TLV 60-120 mg	3120	2437498
TLV MR 20 mg	17	119
TLV MR 40 mg	17	119
TLV MR 50 mg	45	2320
TLV MR 60 mg	17	119
TLV MR 80 mg	43	2235
TLV MR 120 mg	12	84
Total	3395	3812346
Carcinomatous Oedema		
TLV 3.75-30 mg	43	329
Total	43	329
Cardiac Oedema		
TLV 7.5 mg	10	66
TLV 15 mg	364	2281
TLV 30 mg	36	237
TLV 45 mg	29	171
Powder 15 mg	26	114
Total	463	2869

Table 2.3.3-1 SIII.3: Clinical Trial Exposure to Tolvaptan by Dose (Cumulative and by Indication)

Dose of Exposure	Persons	Person Time (Patient Days)
Chronic Renal Failure		
TLV 15 mg	80	3719
TLV 30 mg	40	3482
TLV 7.5-60 mg	43	290
Total	123	7491
Congestive Heart Failure		
TLV 10 mg	5	62
TLV 15 mg	132	12412
TLV 30 mg	2549	642063
TLV 45 mg	62	1567
TLV 60 mg	278	16524
TLV 90 mg	82	3080
TLV 120 mg	7	91
Total	3115	675799
Hepatic Oedema		
TLV 3.75 mg	19	127
TLV 7.5 mg	333	2418
TLV 15 mg	409	2715
TLV 30 mg	89	574
TLV 60 mg	18	131
Total	855	5965
Hyponatraemia		
TLV 3.75 mg	10	10
TLV 5 mg	12	76
TLV 7.5 mg	10	10
TLV 10 mg	7	94
TLV 15 mg	20	186
TLV 3.75-15 mg	3	5
TLV 30 mg	9	141
TLV 45 mg	1	9
TLV 60 mg	11	137
TLV 15-60 mg	616	87424
TLV 0.1-0.6 mg/kg suspension	6	21
Total	705	88113
Renal Impairment		
TLV 60 mg	37	37
Total	37	37
Healthy		
TLV 3.75 mg	14	14
TLV 5 mg	6	6
TLV 7.5 mg	66	180
TLV 10 mg	6	6
TLV 15 mg	144	244
TLV 30 mg	329	1335
TLV 45 mg	6	6
TLV 60 mg	313	1585
TLV 90 mg	126	232
TLV 120 mg	28	76
TLV 180 mg	11	16

Table 2.3.3-1 SIII.3: Clinical Trial Exposure to Tolvaptan by Dose (Cumulative and by Indication)

Dose of Exposure	Persons	Person Time (Patient Days)
TLV 240 mg	27	47
TLV 300 mg	77	414
TLV 360 mg	6	6
TLV 420 mg	6	6
TLV 480 mg	6	6
<60 mg JM	20	24
60 mg JM	16	21
100 mg JM	6	6
150 mg JM	59	290
300 mg JM	28	28
450 mg JM	28	28
TLV MR 20 mg	10	50
TLV SDT 20 mg	28	104
TLV MR 60 mg	70	318
TLV SDT 60 mg	10	55
Powder 15 mg	40	40
Syrup 15 mL	14	14
TLV 1 mg IV	14	14
Total	1227	5171

Subjects from titration trials are counted multiple times - once per each dose received. ADPKD data provided from Trials 156-04-001, 156-04-248, 156-04-249, 156-04-250, 156-04-251, 156-05-002, 156-06-260, 156-08-271, 156-09-003, 156-09-284, 156-09-285, 156-09-290, 156-10-003, 156-13-210, 156-13-211, 156-12-298, and 156-402-00144.
Source: CT-4.1-CT-4.10.

2.3.4 Clinical Trial Exposure by Ethnic Origin

Table 2.3.4-1 SIII.4: Clinical Trial Exposure to Tolvaptan by Race or Ethnic Origin (Cumulative and by Indication)

Race or Ethnic Origin	Persons	Person Time (Days)
Cumulative		
Caucasian	6100	3899683
Black	597	116693
Hispanic	263	169541
Asian	2606	338309
Other	391	71077
American Indian or Alaska Native	5	2413
Unknown	1	404
Total	9963	4598120
ADPKD		
Caucasian	2706	3235435
Black	81	61824
Hispanic	148	169191
Asian	428	317028
Other	28	26463
American Indian or Alaska Native	4	2405
Total	3395	3812346

Table 2.3.4-1 SIII.4: Clinical Trial Exposure to Tolvaptan by Race or Ethnic Origin (Cumulative and by Indication)		
Race or Ethnic Origin	**Persons**	**Person Time (Days)**
Carcinomatous Oedema		
Asian	43	329
Total	43	329
Cardiac Oedema		
Asian	463	2869
Total	463	2869
Chronic Renal Failure		
Asian	123	7491
Total	123	7491
Congestive Heart Failure		
Caucasian	2473	581675
Black	369	49680
Asian	8	716
Other	264	43324
Unknown	1	404
Total	3115	675799
Hepatic Oedema		
Asian	855	5965
Total	855	5965
Hyponatraemia		
Caucasian	434	80207
Black	34	4664
Hispanic	10	22
Asian	194	2202
Other	33	1018
Total	705	88113
Renal Impairment		
Caucasian	14	14
Black	3	3
Hispanic	20	20
Total	37	37
Healthy		
Caucasian	473	2352
Black	110	522
Hispanic	85	308
Asian	492	1709
Other	66	272
Total	1227	5171
Source: CT-3.1-CT-3.10.		

2.3.5 Brief Overview of Development

The first marketing authorisation for tolvaptan was granted in the United States (US) on 19 May 2009 in the following indication: treatment of clinically significant hypervolemic and euvolemic hyponatraemia as 15, 30, and 60 mg tablets. Tolvaptan has been registered and approved in 46 countries (including the autonomous territory of Hong Kong).

Approved tolvaptan indications include the treatment of clinically significant hypervolemic and euvolemic hyponatraemia in the US, Hong Kong, Canada, Republic of Korea, Indonesia, China, Australia, Turkey, Philippines, Thailand, Egypt, and Vietnam; treatment of hyponatraemia secondary to SIADH in adult patients in European Economic Area (EEA), Taiwan, and Indonesia; treatment of volume overload in heart failure when adequate response is not obtained with other diuretics (eg, loop diuretics) in Japan, Turkey, Philippines, Thailand, and China; treatment of body fluid retention in hepatic cirrhosis when adequate response is not obtained with other diuretics (eg, loop diuretics) in Japan; and to slow the progression of autosomal dominant polycystic kidney disease (ADPKD) in the EEA, Japan, Canada, Republic of Korea, Switzerland, Australia, Hong Kong, Taiwan, Turkey, UK, and US.

2.3.5.1 Clinical Trial Programme - OPC-61815

OPC-61815 is a phosphate ester of tolvaptan which is being developed as an injectable formulation. After intravenous administration, OPC-61815 is rapidly dephosphorylised to tolvaptan by alkaline and acid phosphatase. The affinity of OPC-61815 for the vasopressin V2-receptor is approximately 1/14 of free tolvaptan. The pharmacological effect is due to binding of free tolvaptan to the V2 receptor. OPC-61815 is expected to have a safety profile very similar to tolvaptan, and based on the information available from nonclinical and clinical studies of OPC-61815, there is no new efficacy or safety information related to the mechanism of action of tolvaptan as of the DLP.

2.3.5.2 Hyponatraemia Programme

In the adult hyponatraemia programme, four phase 2 and five phase 3 trials have been conducted in the US, China, and multinationally, and 2 phase 4 trials have been conducted in Korea. In addition, subpopulations of subjects with hyponatremia from 3 trials in the heart failure programme (Trials 156-97-252, 156-98-213, and 156-03-236) are also relevant to the hyponatraemia programme. The population for these hyponatraemia trials was subjects with nonhypovolemic, nonacute hyponatraemia arising from a variety of etiologies including heart failure, cirrhosis, SIADH, and others. Two of the phase 2 trials conducted in the US (Trials 156-96-201 and 156-97-204) were terminated because of insufficient enrollment; one phase 3b trial conducted in the US (Trial 156-08-275) was terminated based on futility analysis results; and one phase 4 trial conducted in Korea (156 KOB 1101i) was terminated due to a change in indication based on safety information. Two studies have been completed: one phase 1b, multinational pharmacokinetic/pharmacodynamic (PK/PD) trial (Trial 156-12-203) in subjects with euvolemic hyponatremia secondary to SIADH and one open-label, phase 4, multinational safety trial (Trial 156-09-101). One hyponatraemia trial in adults is ongoing: a phase 4

placebo-controlled safety and efficacy trial in Korea (Trial 156-KOB-1201i, in subjects with hyponatraemia who are hospitalized with worsening heart failure). Three phase 3b, multinational paediatric trials in subjects (4 weeks to 17 years) with hyponatremia have been terminated due to the inability to enroll subjects: an open-label randomised withdrawal trial (Trial 156-08-276), a long-term safety extension follow-up trial (Trial 156-11-294), and a randomised placebo-controlled safety and efficacy trial (Trial 156-13-207).

2.3.5.3 Cardiac Oedema Programme

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

2.3.5.4 Heart Failure Programme

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

2.3.5.5 Hepatic Cirrhosis Programme

In the hepatic cirrhosis programme, one phase 1 trial in subjects with hepatic impairment in China, three phase 2 trials in subjects with hepatic oedema (two in Japan and one in China), and four phase 3 trials (three in Japan and one in China) have been completed. The phase 1 trial (Trial 156-09-806-01) in China assessed the pharmacokinetics, pharmacodynamics, and safety of tolvaptan in Chinese subjects with Child-Pugh Class B hepatic impairment. For the two completed phase 2 trials in Japan: Trial 156-03-002 was an open-label trial that evaluated subjects with peripheral oedema or ascites secondary to liver disease and Trial 156-06-005 was a double-blind, placebo-controlled trial that evaluated subjects with cirrhosis and ascites despite conventional diuretics. The completed phase 2 and phase 3 trials in China (Trial 156-08-804-01 and Trial 156-08-805-01, respectively) were placebo-controlled trials that evaluated subjects with cirrhosis and ascites despite therapy with conventional diuretics. The three completed phase 3 trials in Japan also evaluated subjects with cirrhosis and ascites despite therapy with conventional diuretics: Trial 156-08-001 was a placebo-controlled trial, Trial 156-08-002 was an open-label trial, and Trial 156-09-004 was a randomised double-blind, parallel-group trial designed to evaluate 2 dose levels of tolvaptan.

2.3.5.6 Carcinomatous Oedema Programme

In the carcinomatous oedema programme, one phase 2 multicentre, open-label, dose-finding trial (Trial 156-12-001) has been completed in Japan to assess the efficacy, pharmacokinetics, pharmacodynamics, and safety of tolvaptan in subjects with volume overload associated with cancer, and to determine the initial and maintenance doses expected to be safe and to have an immediate effect in this population.

2.3.5.7 ADPKD Programme and Renal Impairment Trials

In the adult ADPKD programme, one phase 1 trial (in the US), eight phase 2 trials (five in the US, two in Japan, and one in the Netherlands), and six multinational phase 3/3b trials have been completed (Trials 156-04-251, 156-08-271, 156-09-003, 156-10-003, 256-13-210, and 156-13-211). Two phase 3/4 ADPKD trials have been completed in Japan (Trials 156-09-003 and 156-10-003). In addition, two phase 2 trials have been completed in Japan in subjects with chronic renal failure: Trials 156-12-002 and 156-12-007. One randomised, placebo-controlled trial (Trial 156-12-298) is ongoing in paediatric subjects (ranging from 4 to 17 years) with ADPKD. One phase 4 multicentre, single-arm, open label ADPKD trial (Trial 156-402-00144) has been initiated in Korea.

Phase 2 trials in ADPKD subjects included Trial 156-04-248 and Trial 156-04-249 in the US and a sister Trial 156-04-001 in Japan which investigated ascending single and

multiple doses (5 days) in ADPKD subjects with well-preserved renal function. Subjects from these trials were enrolled into open-label extension trials (Trial 156-04-250 [US] and Trial 156-05-002 [Japan]) in which tolvaptan treatment continued for up to 4 years. Trial 156-06-260 (phase 1, US) and Trial 156-09-284 (phase 2, Netherlands) evaluated changes in renal function and TKV in ADPKD subjects with varying degrees of renal function following 8 and 21 days of tolvaptan dosing, respectively; the effect of tolvaptan withdrawal on these endpoints was studied at 21 days post-treatment in Trial 156-09-284. Trial 156-09-285 was a phase 2 US trial in ADPKD subjects with well-preserved renal function that evaluated the pharmacokinetic/pharmacodynamic and tolerability of modified-release (MR) capsules and spray-dried tablets where each regimen was administered for 7 days. Trial 156-09-290 (US), another phase 2 trial, was a double blind, placebo-controlled trial evaluating the safety and efficacy of MR capsule and immediate-release (IR) tablet formulations in subjects with ADPKD. (The MR programme has been discontinued.)

The following 6 phase 3 trials are completed in the ADPKD programme:

- Trial 156-04-251 (multinational) was a phase 3 double-blind, placebo-controlled trial evaluating the long-term safety and efficacy of tolvaptan for the treatment of ADPKD.
- Trial 156-08-271 (multinational) was a phase 3b open-label, long-term extension trial for subjects who previously completed a phase 1, 2, or 3 tolvaptan ADPKD or renal impairment trial and who have a confirmed diagnosis of ADPKD.
- Trial 156-09-003 (Japan) was a phase 3b open-label extension trial to Trial 156-05-002 to assess the long-term safety of tolvaptan in ADPKD subjects.
- Trial 156-10-003 (Japan) was a phase 3b open-label, long-term extension trial for Japanese subjects who participated in multinational Trial 156-04-251 and who completed 3 years of tolvaptan treatment.
- Trial 156-13-210 (multinational) was a phase 3b randomised-withdrawal, placebo-controlled, parallel-group trial to assess efficacy and safety of tolvaptan in subjects with chronic kidney disease between late stage 2 to early stage 4 due to ADPKD.
- Trial 156-13-211 (multinational) was a phase 3b open-label trial to evaluate the long-term safety of titrated immediate-release tolvaptan in subjects with ADPKD.

Additionally, the following 2 trials are completed in Japan in subjects with chronic renal failure:

- Trial 156-12-002 (Japan) is a phase 2 open-label, dose-finding trial to assess efficacy, PK, PD, and safety of tolvaptan in patients with chronic renal failure who are undergoing peritoneal dialysis.

- Trial 156-12-007 (Japan) is a phase 2 open-label, dose-finding trial to assess efficacy, safety, PK, and PD of tolvaptan in patients with chronic renal failure who are undergoing hemodialysis or hemodiafiltration.

The following trials are ongoing in the ADPKD programme:

- Trial 156-12-298 (multinational) is a phase 3a, two-part, one-year randomised, double-blind, placebo controlled trial to evaluate safety, PK, tolerability, and efficacy of tolvaptan followed by a two-year open-label extension in children and adolescent subjects with ADPKD.
- Trial 156-402-00144 is a phase 4, multicentre, single-arm, open-label trial to evaluate the safety and effectivess in adult Korean patients treated with tolvaptan for management of ADPKD.

2.3.6 Clinical Trial Exposure (Overall ADPKD and Hyponatraemia)

As of the DLP (18 May 2020), 15749 subjects have been included in the tolvaptan clinical programme, of which 9963 subjects have received tolvaptan, and 5829 have received placebo. In the 9 pooled trials in subjects with hyponatremia, a total of 705 subjects were exposed to oral tolvaptan in doses ranging from 3.75 to 60 mg and a 0.1-0.6 suspension for a total person time of 88113. The median exposure for all doses of all oral formulations combined was 13 days, with a mean exposure of 16 days (±12 days).

Short-term ADPKD Trials With or Without Renal Impairment

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

Renal Impairment Without ADPKD

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

2.3.6.1 Hyponatraemia Indications

2.3.6.1.1 Duration of Exposure

Table 2.3.6.1.1-1 Duration of exposure (SIADH)

HYPONATRAEMIA WITH SIADH		
Duration of exposure	**Persons**	**Person time (subject days[a])**
Cumulative up to 30 days (1 month)	213	3177
Cumulative up to 90 days (3 months)	28	953
Cumulative up to 180 days (6 months)	1	106
Cumulative up to 360 days (12 months)	1	353
Cumulative up to 720 days (24 months)	19	9344
>720 days (more than 24 months)	33	39355

[a]Subject days of drug exposure duration is computed based on the actual number of days of medication use (excluding days when dose was missed).
HYPONATRAEMIAS All Hyponatraemia Subjects from Placebo-controlled Multiple Dose HN and HF trials (Trials 156-97-204, 156-02-235, 156-03-238, 156-03-244, 156-04-246, 156-07-802-01, 156-09-101)
Source: Table 1.1

Table 2.3.6.1.1-2 Duration of exposure other indications

HYPONATRAEMIA WITH CIRRHOSIS		
Duration of exposure	**Persons**	**Person time (subject days)**
Cumulative up to 30 days (1 month)	176	2264
Cumulative up to 90 days (3 months)	17	624
Cumulative up to 180 days (6 months)	3	389
Cumulative up to 360 days (12 months)	3	726
Cumulative up to 720 days (24 months)	5	2426
>720 days (more than 24 months)	4	4504
HEART FAILURE (Trials 156-02-235 and 156-03-238)		
Duration of exposure	**Persons**	**Person time (subject days)**
Cumulative up to 30 days (1 month)	150	2117
Cumulative up to 90 days (3 months)	27	1087
Cumulative up to 180 days (6 months)	3	410
Cumulative up to 360 days (12 months)	4	995
Cumulative up to 720 days (24 months)	5	2630
>720 days (more than 24 months)	13	16653

2.3.6.1.2 Exposure by Dose (and Indication in Hyponatraemia)

Table 2.3.6.1.2-1 Exposure by dose and by indications in Hyponatraemia

Maximum Dose of exposure	Persons[1]	Person time (subject days)[2]
HYPONATRAEMIA All Hyponatraemia Subjects from Placebo-controlled Multiple Dose hyponatraemia and heart failure Trials		
<15 mg	11	35
15 mg	2	48
30 mg	1	25
60 mg	188	23784

Table 2.3.6.1.2-1 Exposure by dose and by indications in Hyponatraemia		
Maximum Dose of exposure	**Persons[1]**	**Person time (subject days)[2]**
HYPONATRAEMIA WITH SIADH (Trials 156-97-204, 156-02-235, 156-03-238, 156-03-244, 156-04-246, 156-07-802-01,156-09-101)		
3.75 mg	10	10
7.5 mg	10	10
15 mg	12	69
3.75- 15 mg	1	2
30 mg	1	16
45 mg	1	9
60 mg	2	25
15-60 mg	255	53135
0.1-0.6 mg/kg suspension	3	12
Source: Table 1.2		
HYPONATRAEMIA SUBJECTS WITH HEART FAILURE ETIOLOGY[3] (Trials 156-02-235 and 156-03-238)		
5 mg	6	23
15 mg	2	48
3.75-15 mg	2	3
30 mg	1	25
60 mg	3	43
15-60 mg	185	23741
0.1-0.6 mg/kg suspension	3	9
HYPONATRAEMIA WITH LIVER CIRRHOSIS ETIOLOGY (Trials 156-02-235 and 156-03-238)		
<15 mg	13	147
15 mg	6	69
30 mg	7	100
60 mg	6	69
15-60 mg	176	10548

*[1]Subjects from titration trials are counted multiple times - once per each dose received.

[2]Subject days of drug exposure duration is computed based on the actual number of days of medication use (excluding days when dose was missed).

[3]Subjects with stable heart failure treated for hyponatraemia

[4]Subjects treated for worsening heart failure

2.3.6.1.3 Exposure by Ethnic or Racial Origin (Indication Hyponatraemia)

Table 2.3.6.1.3-1 Exposure by ethnic or racial origin (by indication)		
Exposure by ethnic or racial origin (by indication)		
Ethnic Origin	**Persons**	**Person time (subject days)**
CIRRHOSIS		
Asian	87	644
Black	2	36
Caucasian	105	10003
Other	14	250
HEART FAILURE		
Asian	66	1033

Table 2.3.6.1.3-1 Exposure by ethnic or racial origin (by indication)		
Exposure by ethnic or racial origin (by indication)		
Ethnic Origin	**Persons**	**Person time (subject days)**
Black	16	1365
Caucasian	109	21336
Other	11	158
SIADH/OTHER ETIOLOGY		
Asian	41	525
Black	16	3263
Other	13	619
Caucasian	225	48881

2.3.6.1.4 Exposure by Special Populations Renal, Hepatic and Cardiac Impairment with SIADH/Other Aetiology

Table 2.3.6.1.4-1 Exposure by Special Populations - Hyponatraemia		
Special Population	**Persons**	**Person time (subject days)**
Renal impairment GFR (ml/min/1.73 m^2)		
>80	135	28595
50 - 80	74	14856
30 - <50	27	8340
<30	4	720
Not available	55	777
Hepatic impairment (Child-Pugh class)		
Class A	38	10131
Class B	4	1086
Normal	129	39859
Not available	124	2212
Cardiac impairment (NYHA class)		
NYHA Class I	62	22305
NYHA Class II	9	3237
NYHA Class III	2	137
NYHA Class IV	222	27609
Pregnancy and Lactation		
Pregnant women[1]	0	0
Lactating women	0	0

[1]Women who would not adhere to the reproductive precautions as outlined in the Informed Consent form were excluded. Exposure during pregnancy was observed outside the hyponatraemia programme in patients with polycystic kidney disease (clinical trial 156-04-251); no significant safety information was collected.

Table 2.3.6.1.4-2 Exposure by Special Populations-Hyponatraemia with Other Aetiology		
Special Population	**Persons**	**Person time (subject days)**
HEART FAILURE		
Renal impairment GFR (ml/min/1.73 m^2)		
>80	45	6581
50 - 80	42	8971
30 - <50	31	4236

Table 2.3.6.1.4-2 Exposure by Special Populations-Hyponatraemia with Other Aetiology		
Special Population	**Persons**	**Person time (subject days)**
<30	16	3025
Not available	68	1079
Hepatic impairment (Child-Pugh class)		
Class A	24	3879
Class B	14	1566
Class C	1	14
Normal	55	14423
Not available	108	4010
Cardiac impairment (NYHA class)		
NYHA Class I	14	3395
NYHA Class II	28	6552
NYHA Class III	56	11291
NYHA Class IV	23	1566
Not available	81	1088
Pregnancy and Lactation		
Pregnant women[1]	0	0
Lactating women	0	0
CIRRHOSIS		
Renal impairment GFR (ml/min/1.73 m^2)		
>80	74	5060
50 - 80	33	4812
30 - <50	9	287
<30	2	60
Not available	90	714
Hepatic impairment (Child-Pugh class)		
Class A	14	1972
Class B	56	6324
Class C	42	1877
Normal	3	66
Not available	93	694
Cardiac impairment (NYHA class)		
NYHA Class I	19	1677
NYHA Class II	5	150
NYHA Class III	5	513
NYHA Class IV	1	10
Not available	178	8583
Pregnancy and Lactation		
Pregnant women[1]	0	0
Lactating women	0	0

2.3.6.2 ADPKD Indications

2.3.6.2.1 Overall Exposure ADPKD Clinical Trial Programme

The clinical database for the current ADPKD programme includes 3312 subjects who have been exposed to at least 1 dose of tolvaptan in completed or open-label ongoing clinical trials conducted in North America, South America, Europe, UK, Asia, and

Australia. The ADPKD safety database includes 37 non-ADPKD subjects with normal renal function or varying degrees of renal impairment, and 112 healthy subjects exposed to tolvaptan.

The majority of subjects for the ADPKD programme (3316/3395 subjects [97.7%]) were exposed to tolvaptan doses within the proposed range for marketing (ie, 60 to 120 mg/day). Of the 3395 subjects, 1948 (57.4%) were exposed for 24 months or longer, 547 (16.1%) were exposed for at least 12 months, 180 (5.3%) were exposed for at least 6 months, 175 (5.2%) were exposed for at least 3 months, 293 (8.6%) were exposed for at least 1 month, and 252 (7.4%) were exposed less than 1 month. Cumulative exposure to tolvaptan over the duration of the trial was a person time of 3,812,346.

2.3.6.2.2 Pivotal Trials 156-04-251 and 156-13-210

In the first phase 3 pivotal Trial 156-04-251, 961 of the 1444 subjects (67%) were randomised to tolvaptan. In the second phase 3 pivotal Trial 156-13-210, 683 of 1370 subjects (50%) were randomised to tolvaptan. Thus more than half of subjects in these two pivotal trials (1644/2814 subjects, 58%) were randomised to receive tolvaptan.

Subjects with different degrees of renal failure enrolled in this study are shown below in Table 2.3.6.2.9-1 and Table 2.3.6.2.10-1 Pregnant or lactating women were not enrolled in either study.

In Trial 156-13-210, all subjects who were randomised in the double-blind period (both treatment groups) had received tolvaptan during the tolvaptan run-in period, with an average daily dose of 99.7 mg in the tolvaptan group and 99.4 mg in the placebo group.

In Month 1, 99.7% of subjects in each treatment group received randomised IMP (tolvaptan or placebo). Through Month 12, inclusive, the percentage of subjects continuing on IMP decreased to cumulative 84.5% and 92.6% for the tolvaptan and placebo arms, respectively. At Month 12, the average daily dose was 108.2 mg and 111.8 mg for the tolvaptan and placebo arms, respectively. The majority of subjects received their last dose during Month 12 (78.6% in the tolvaptan arm; 86.8% in the placebo arm).

2.3.6.2.3 Supportive Trials

In addition to Trial 156-04-251, a number of phase 2 and 3 open-label extension trials (156-04-250, 156-05-002, 156-08-271, 156-09-003, and 156-10-003) in ADPKD subjects evaluated safety and efficacy outcomes with tolvaptan. Completed Trials 156-08-271 and Trial 156-10-003 are rollover trials of subjects from Trial 156-04-251. ADPKD subjects from Trial 156-04-250 and Trial 156-05-002 contribute to an understanding of early

effects on estimated glomerular filtration rate (eGFR) and total kidney volume (TKV). In Trial 156-05-002 efficacy and safety was also assessed annually for 3 years.

2.3.6.2.4 Cumulative Exposure to Tolvaptan in all ADPKD Clinical Trials by Duration of Exposure

Table 2.3.6.2.4-1 Cumulative Exposure to Tolvaptan in All Trials in the ADPKD Clinical Programme

Cumulative Exposure	Persons	Person Time
Less than 1 month	252	3351
Greater than or equal to 1 month	293	14445
Greater than or equal to 3 months	175	22999
Greater than or equal to 6 months	180	46947
Greater than or equal to 12 months	547	301552
Greater than or equal to 24 months	1948	3423052
Total	3395	3812346

Includes Trials 156-04-001, 156-04-248, 156-04-249, 156-04-250, 156-04-251, 156-06-260, 156-08-271, 156-09-003, 156-09-284, 156-09-285, 156-09-290, 156-10-003, 156-13-210, 156-13-211, 156-12-298, 156-4020-0144.
Notes: The data lock point for updated exposure data is 18 May 2020.

Table 2.3.6.2.4-2 Dose Levels of Tolvaptan in All Trials in the ADPKD Clinical Programme

Tolvaptan Dose Level	Persons	Person Time
15 mg	**26**	**71**
30 mg	44	14963
45 mg	9	45
60 mg	38	218
45-90 mg	80	27434
90 mg	44	2344
120 mg	20	92
30-120 mg	1946	1324685
60-120 mg	3120	2437498
MR 20 mg	17	119
MR 40 mg	17	119
MR 50 mg	45	2320
MR 60 mg	17	119
MR 80 mg	43	2235
MR 120 mg	12	84
Total	3395	3812346

Notes: MR = modified release (Trial 156-09-290, formulation discontinued). Subjects from titration trials are counted multiple times, once per each dose received.
Includes Trials 156-04-251, 156-08-271, 156-10-003, 156-04-250, 156-05-002, 156-09-003, 156-04-248, 156-04-249, 156-04-001, 156-09-285, 156-06-260, 156-09-284, 156-09-290, 156-13-210, 156 13-211, 156-12-298, S156-402-00144. Excludes Trials 156-07-262, 156-09-282, 156 11 295, and 156-KOA-0801.
The data lock point for updated exposure data is 18 May 2020.

2.3.6.2.5 Cumulative Exposure to Tolvaptan in the ADPKD Pivotal Trial 156-04-251

The cumulative exposure in the ADPKD pivotal Trial 156-04-251 was estimated to be 2226 person years.

Table 2.3.6.2.5-1 Cumulative Exposure to tolvaptan in Trial 156-04-251

Cumulative Exposure	Tolvaptan (N = 961)		Placebo (N = 483)	
	n	Average Daily Dose[a] (mg)	n	Average Daily Dose[a] (mg)
Any exposure	961	95.29	483	110.02
At least 8 months (240 days)	864	101.53	470	112.51
At least 12 months (360 days)	836	99.60	462	112.36
At least 24 months (720 days)	774	97.04	437	110.76
At least 36 months (1090 days)	742	96.45	418	110.55

[a]Average daily doses are the cumulative average daily doses for treated subjects from the initial dose through the time point

2.3.6.2.6 Cumulative Exposure to Tolvaptan in the ADPKD Pivotal Trial 156-13-210

The cumulative exposure in the ADPKD Pivotal Trial 156-13-210 was estimated to be 612.5 person year.

Table 2.3.6.2.6-1 Cumulative Exposure to tolvaptan in Trial 156-13-210

Cumulative Exposure	Tolvaptan (N = 683)		Placebo (N = 687)	
	n	Average Daily Dose[a]	n	Average Daily Dose[a]
Exposure up to 2 months	669	111	678	112.1
Exposure up to 6 months	619	109.3	667	111.8
Exposure up to 12 months	577	108.2	636	111.8

[a]Average daily doses are the cumulative average daily doses for treated subjects from the initial dose through the time point.

2.3.6.2.7 Demographics of ADPKD Subjects: Age, Gender, and Ethnicity Exposed to Tolvaptan in the ADPKD Pivotal Trial 156-04-251

A broader population was enrolled in Trial 156-04-251 than was targeted, such that the demographics were comparable to the anticipated marketed population.

Demographics were comparable across treatment groups for Trial 156-04-251.

The mean age ranged from 18 to 51 years. The gender distribution was equal, 51.6% were male and the majority was Caucasian (84.3%). The trial population included subjects with both early and late-stage PKD (although not as late as Stage 4).

There was limited racial variability among the US subjects; however, there was a good representation of Asian subjects in the population. The subjects could be stratified as Japanese versus non-Japanese for examining some regional differences dependent on intrinsic and extrinsic factors. For instance, when comparing Japanese subjects to subjects from the Americas and Europe/rest of world (ROW), there were lower percentages of Japanese subjects with hypertension, worse renal function (lower creatinine clearance), and smaller kidney volumes; this is in comparison with the EU and US populations, which were generally consistent based on the region in which the trial was conducted.

Demographics of the supportive trials were generally consistent with Trial 156-04-251 with respect to age and gender, but differed in race.

Table 2.3.6.2.7-1 Demographic of ADPKD Subjects in the Phase 3 Pivotal Trial 156-04-251

Characteristic	Tolvaptan (N = 961)	Placebo (N = 484)	Total (N = 1445)
Randomized, n (%)	961 (100.0)	484 (100.0)	1445 (100.0)
Treated, n (%)	961 (100.0)	483 (99.8)	1444 (99.9)
Age (years)			
Mean	38.6	38.8	38.7
SD	7.1	7.1	7.1
Median	39.0	39.0	39.0
Min, Max	18, 51	18, 50	18, 51
<35 years, n (%)[a]	256 (26.6)	109 (22.6)	365 (25.3)
≥35 years, n (%)[a]	705 (73.4)	374 (77.4)	1079 (74.7)
Gender, n (%)			
Male	495 (51.5)	251 (51.9)	746 (51.6)
Female	466 (48.5)	233 (48.1)	699 (48.4)
Race, n (%)			
Caucasian	810 (84.3)	408 (84.3)	1218 (84.3)
Black	16 (1.7)	3 (0.6)	19 (1.3)
Hispanic	13 (1.4)	9 (1.9)	22 (1.5)
Asian	121 (12.6)	62 (12.8)	183 (12.7)
Other	1 (0.1)	2 (0.4)	3 (0.2)

[a]Percent based on total number of subjects treated.
Source: CSR 156-04-251 CT-1.1, CSR 156-04-251 CT-3.1, CSR 156-04-251 CT-3.2, CSR 156-04-251 CT-3.3, CSR 156-04-251 CT-3.9, CSR 156-04-251 CT-8.8.6, CSR 156-04-251 ST-1.15.

2.3.6.2.8 Demographics of Subjects in the ADPKD Pivotal Trial 156-13-210

Baseline demographic characteristics were well balanced across treatment groups in Trial 156-13-210.

The mean age ranged from 21 to 65 years. The gender distribution was equal, 49.6% were male and the majority was white (91.8%). The majority of subjects (94.6%) had Stage 3 (a, b) or Stage 4 CKD.

2.3.6.2.9 Exposure by Special Populations- ADPKD by Renal Function in the Phase 3 Pivotal Trial 156-04-251

Table 2.3.6.2.9-1 Phase 3 Pivotal Trial 156-04-251 Renal Function

Characteristic	Tolvaptan (N = 961)	Placebo (N = 484)	Total (N = 1445)
Randomized, n (%)	961 (100.0)	484 (100.0)	1445 (100.0)
Treated, n (%)	961 (100.0)	483 (99.8)	1444 (99.9)
eCrCLCG[b] at baseline (mL/min)			
$eCrCL_{CG}$ < 80, n (%)	242 (25.2)	130 (26.9)	372 (25.7)
$eCrCL_{CG}$ < 80, n (%)	719 (74.8)	354 (73.1)	1073 (74.3)
eGFRCKD-EPI[c] at baseline (mL/min/1.73 m^2)			
N	958	482	1440
Mean	81.35	82.14	81.61
SD	21.02	22.73	21.60
Median	80.76	80.40	80.74
Min, Max	32.3, 132.8	26.4, 186.7	26.4, 186.7
eGFRCKD-EPI < 30, n (%)[a]	0	1 (0.2)	1 (0.1)
eGFRCKD-EPI 30-60, n (%)[a]	163 (17.0)	84 (17.4)	247 (17.1)
eGFRCKD-EPI > 60, n (%)[a]	795 (82.7)	396 (82.0)	1191 (82.5)
Baseline TKV (mL)			
N	961	483	1444
Mean	1704.8	1667.5	1692.3
SD	921.27	873.11	905.31
Median	1456.7	1468.5	1458.8
Min, Max	750.0, 7555.4	751.1, 6751.1	750.0, 7555.4
TKV < 1000 mL	197 (20.5)	101 (20.9)	298 (20.6)
TKV ≥ 1000 mL	764 (79.5)	383 (79.1)	1147 (79.4)

Abbreviations: CKD-EPI = chronic kidney disease epidemiology collaboration; CrCL = creatinine clearance; eCrCLCG = estimated creatinine clearance using Cockcroft-Gault equation; eGFRCKD-EPI = estimated glomerular filtration rate using CKD-EPI criteria; Min = minimum; Max = maximum; N = number of subjects; SD = standard deviation; TKV =total kidney volume; UTI = urinary tract infection.

[a]Percent based on total number of subjects treated.

[b]Creatinine clearance estimated using Cockcroft-Gault equation.

[c]Estimated GFR calculated using CKD-EPI formula for subjects with available data.

Source: CSR 156-04-251 CT-1.1, CSR 156-04-251 CT-3.1, CSR 156-04-251 CT-3.2, CSR 156-04-251 CT-3.3, CSR 156-04-251 CT-3.9, CSR 156-04-251 CT-8.8.6, CSR 156-04-251 ST-1.15.

2.3.6.2.10 Exposure by Special Populations- ADPKD by Renal Function in the Phase 3 Pivotal Trial 156-13-210

Table 2.3.6.2.10-1 Phase 3 Pivotal Trial 156-13-210 Renal Function

Characteristic	Tolvaptan (N = 683)	Placebo (N = 687)	Total (N = 1370)
Randomized, n (%)	683 (100.0)	687 (100.0)	1370 (100.0)
Treated, n (%)	681 (99.7)	685 (99.7)	1366 (99.7)
$eGFR_{CKD-EPI}$ at baseline[a]			
$eGFR_{CKD-EPI}$ <=45 mL/min/1.73 m^2, n (%)[b]	442 (64.7)	438 (63.8)	880 (64.2)
$eGFR_{CKD-EPI}$ >45 mL/min/1.73 m^2, n (%)[b]	241 (35.3)	249 (36.2)	490 (35.8)
TKV ≤ 2000 mL, N	76 (11.1)	73 (10.6)	149 (10.9)
TKV > 2000 mL, N	60 (8.8)	60 (8.7)	120 (8.8)
$eGFR_{CKD-EPI}$ change from baseline			
Baseline TKV Unknown, N	535	537	N/A
Mean rate of change per year	−2.851	−4.232	N/A
Lsmean	−2.879	−4.242	N/A
Treatment Effect	1.364	N/A	N/A
95% CI	(0.902, 1.825)	N/A	N/A

[a]Percent based on total number of subjects treated.
[b]Estimated GFR calculated using CKD-EPI formula for subjects with available data.
Source: CSR 156-13-210 CT-1.1.2, CSR 156-13-210 CT-3.2.1, CSR 156-13-210 CT-6.1

2.3.6.2.11 Demographics of Subjects Enrolled from ADPKD Trial 156-04-251 into the Long-term Trials

Table 2.3.6.2.11-1 Demographics of Subjects Enrolled from Trial 156-04-251 into the Long-term Trials 156-08-271 or 156-10-003

Characteristic	Trial 156-08-271		Trial 156-10-003
	Early-treated[a] Tolvaptan (N = 557)	Delayed-treated[b] Tolvaptan (N = 314)	Total Tolvaptan[c] (N = 108)
Gender, n (%)			
Male	303 (54.4)	158 (50.3)	63 (58.3)
Female	254 (45.6)	156 (49.7)	45 (41.7)
Age (years)			
Mean (SD)	41.6 (7.1)	43 (6.7)	43.1 (5.6)
Min, Max	21,54 53535354	21, 54	24, 53

Table 2.3.6.2.11-1 Demographics of Subjects Enrolled from Trial 156-04-251 into the Long-term Trials 156-08-271 or 156-10-003			
Characteristic	**Trial 156-08-271**		**Trial 156-10-003**
	Early-treated[a] Tolvaptan (N = 557)	**Delayed-treated[b] Tolvaptan (N = 314)**	**Total Tolvaptan[c] (N = 108)**
Race, n (%)			
Caucasian	535 (96.1)	302 (96.2)	0
Black	9 (1.6)	2 (0.6)	0
Asian	3 (0.5)	2 (0.6)	108 (100.0)
Hispanic	9 (1.6)	7 (2.2)	0
Other	1 (0.2)	1 (0.3)	0

Min = minimum; Max = maximum.

[a]Refers to subjects enrolled from Trial 156-04-251 who received tolvaptan in that trial.

[b]Refers to subjects enrolled from Trial 156-04-251 who received placebo in that trial

[c]Includes 67 subjects who previously received tolvaptan and 41 subjects who previously received placebo in Trial 156-04-251.

Source: CSR 156-08-271 CT-3.1.1, CSR 156-10-003 In-text Table 11.2-1.

2.3.6.2.12 Demographics of ADPKD Subjects Enrolled in Short-term Trials

Table 2.3.6.2.12-1 Demographics of ADPKD Subjects Enrolled in Short-term Trials 156-04-248, 156-04-249, 156-04-001, and 156-09-285				
Characteristic	**Trial 156-04-248**	**Trial 156-04-249**	**Trial 156-04-001**	**Trial 156-09-285**
	Total Tolvaptan (N = 8)	**Total Tolvaptan (N = 37)**	**Total Tolvaptan (N = 18)**	**Total Tolvaptan (N = 25)**
Gender, n (%)				
Male	2 (25.0)	8 (21.6)	9 (50.0)	14 (56.0)
Female	6 (75.0)	29 (78.4)	9 (50.0)	11 (44.0)
Age (years)				
Mean (SD)	38.9 (9.4)	41.8 (7.8)	39.3 (9.3)	38.0 (7.1)
Min, Max	22, 47	25, 58	21, 59	21, 50
Race, n (%)				
Caucasian	7 (87.5)	35 (94.6)	0	25 (100.0)
Black	0	1 (2.7)	0	0
Asian	0	0	18 (100.0)	0
Other	1 (12.5)	1 (2.7)	0	0

Trials 156-04-248, 156-04-249, 156-04-001, and 156-09-285.
Min = minimum; Max = maximum; SD = standard deviation.
Source: CSR 156-04-248 CST-3.1, CSR 156-04-249 CST-3.1, CSR 156-04-001 Table 11.2-2, CSR 156-09-285 CT-3.1.

2.3.6.2.13 Demographics of ADPKD Subjects age: Gender and Ethnicity Exposed to Tolvaptan in the ADPKD Pivotal Trial 156-04-251

A broader population was enrolled in Trial 156-04-251 than was targeted, such that the demographics were comparable to the anticipated marketed population.

Demographics were comparable across treatment groups for Trial 156-04-251.

The mean age ranged from 18 to 51 years. The gender distribution was equal, 51.6% were male and the majority was Caucasian (84.3%). The trial population included subjects with both early and late-stage PKD (although not as late as Stage 4).

There was limited racial variability among the US subjects; however, there was a good representation of Asian subjects in the population. The subjects could be stratified as Japanese versus non-Japanese for examining some regional differences dependent on intrinsic and extrinsic factors. For instance, when comparing Japanese subjects to subjects from the Americas and Europe/rest of world (ROW), there were lower percentages of Japanese subjects with hypertension, worse renal function (lower creatinine clearance), and smaller kidney volumes; this is in comparison with the EU and US populations, which were generally consistent based on the region in which the trial was conducted.

Demographics of the supportive trials were generally consistent with Trial 156-04-251 with respect to age and gender, but differed in race.

Table 2.3.6.2.13-1 Demographic of ADPKD Subjects in the Phase 3 Pivotal Trial 156-04-251

Characteristic	Tolvaptan (N = 961)	Placebo (N = 484)	Total (N = 1445)
Randomized, n (%)	961 (100.0)	484 (100.0)	1445 (100.0)
Treated, n (%)	961 (100.0)	483 (99.8)	1444 (99.9)
Age (years)			
Mean	38.6	38.8	38.7
SD	7.1	7.1	7.1
Median	39.0	39.0	39.0
Min, Max	18, 51	18, 50	18, 51
<35 years, n (%)[a]	256 (26.6)	109 (22.6)	365 (25.3)
≥35 years, n (%)[a]	705 (73.4)	374 (77.4)	1079 (74.7)
Gender, n (%)			
Male	495 (51.5)	251 (51.9)	746 (51.6)
Female	466 (48.5)	233 (48.1)	699 (48.4)
Race, n (%)			
Caucasian	810 (84.3)	408 (84.3)	1218 (84.3)
Black	16 (1.7)	3 (0.6)	19 (1.3)
Hispanic	13 (1.4)	9 (1.9)	22 (1.5)
Asian	121 (12.6)	62 (12.8)	183 (12.7)
Other	1 (0.1)	2 (0.4)	3 (0.2)

[a]Percent based on total number of subjects treated.
Source: CSR 156-04-251 CT-1.1, CSR 156-04-251 CT-3.1, CSR 156-04-251 CT-3.2, CSR 156-04-251 CT-3.3, CSR 156-04-251 CT-3.9, CSR 156-04-251 CT-8.8.6, CSR 156-04-251 ST-1.15.

2.3.6.2.14 Demographics of Subjects in the ADPKD Pivotal Trial 156-13-210

Baseline demographic characteristics were well balanced across treatment groups in Trial156-13-210.

The mean age ranged from 21 to 65 years. The gender distribution was equal, 49.6% were male and the majority was white (91.8%). The majority of subjects (94.6%) had Stage 3 (a, b) or Stage 4 CKD.

2.3.6.2.15 Exposure by Special Populations- ADPKD by Renal Function in the Phase 3 Pivotal Trial 156-04-251

Table 2.3.6.2.15-1 Phase 3 Pivotal Trial 156-04-251 Renal Function

Characteristic	Tolvaptan (N = 961)	Placebo (N = 484)	Total (N = 1445)
Randomized, n (%)	961 (100.0)	484 (100.0)	1445 (100.0)
Treated, n (%)	961 (100.0)	483 (99.8)	1444 (99.9)
$eCrCL_{CG}$[b] at baseline (mL/min)			
$eCrCL_{CG}$ < 80, n (%)	242 (25.2)	130 (26.9)	372 (25.7)
$eCrCL_{CG}$ < 80, n (%)	719 (74.8)	354 (73.1)	1073 (74.3)
eGFRCKD-EPI[c] at baseline (mL/min/1.73 m^2)			
N	958	482	1440
Mean	81.35	82.14	81.61
SD	21.02	22.73	21.60
Median	80.76	80.40	80.74
Min, Max	32.3, 132.8	26.4, 186.7	26.4, 186.7
eGFRCKD-EPI < 30, n (%)[a]	0	1 (0.2)	1 (0.1)
eGFRCKD-EPI 30-60, n (%)[a]	163 (17.0)	84 (17.4)	247 (17.1)
eGFRCKD-EPI > 60, n (%)[a]	795 (82.7)	396 (82.0)	1191 (82.5)
Baseline TKV (mL)			
N	961	483	1444
Mean	1704.8	1667.5	1692.3
SD	921.27	873.11	905.31
Median	1456.7	1468.5	1458.8
Min, Max	750.0, 7555.4	751.1, 6751.1	750.0, 7555.4
TKV < 1000 mL	197 (20.5)	101 (20.9)	298 (20.6)
TKV ≥ 1000 mL	764 (79.5)	383 (79.1)	1147 (79.4)

Abbreviations: CKD-EPI = chronic kidney disease epidemiology collaboration; CrCL = creatinine clearance; eCrCLCG = estimated creatinine clearance using Cockcroft-Gault equation; eGFRCKD-EPI = estimated glomerular filtration rate using CKD-EPI criteria; Min = minimum; Max = maximum; N = number of subjects; SD = standard deviation; TKV = total kidney volume; UTI = urinary tract infection.

[a]Percent based on total number of subjects treated.

[b]Creatinine clearance estimated using Cockcroft-Gault equation.

[c]Estimated GFR calculated using CKD-EPI formula for subjects with available data.

Source: CSR 156-04-251 CT-1.1, CSR 156-04-251 CT-3.1, CSR 156-04-251 CT-3.2, CSR 156-04-251 CT-3.3, CSR 156-04-251 CT-3.9, CSR 156-04-251 CT-8.8.6, CSR 156-04-251 ST-1.15.

2.3.6.2.16 Exposure by Special Populations- ADPKD by Renal Function in the Phase 3 Pivotal Trial 156-13-210

Table 2.3.6.2.16-1 Phase 3 Pivotal Trial 156-13-210 Renal Function

Characteristic	Tolvaptan (N = 683)	Placebo (N = 687)	Total (N = 1370)
Randomized, n (%)	683 (100.0)	687 (100.0)	1370 (100.0)
Treated, n (%)	681 (99.7)	685 (99.7)	1366 (99.7)
eGFRCKD-EPI at baseline[b]			
eGFRCKD-EPI <= 45 mL/min/1.73 m^2, n (%)[a]	442 (64.7)	438 (63.8)	880 (64.2)
eGFRCKD-EPI >45 mL/min/1.73 m^2, n (%)[a]	241 (35.3)	249 (36.2)	490 (35.8)
TKV ≤ 2000 mL, N	76 (11.1)	73 (10.6)	149 (10.9)
TKV > 2000 mL, N	60 (8.8)	60 (8.7)	120 (8.8)
eGFRCKD-EPI change from baseline			
Baseline TKV Unknown, N	535	537	N/A
Mean rate of change per year	-2.851	-4.232	N/A
Lsmean	-2.879	-4.242	N/A
Treatment Effect	1.364	N/A	N/A
95% CI	(0.902, 1.825)	N/A	N/A

[a]Percent based on total number of subjects treated.

[b]Estimated GFR calculated using CKD-EPI formula for subjects with available data.

Source: CSR 156-13-210 CT-1.1.2, CSR 156-13-210 CT-3.2.1, CSR 156-13-210 CT-6.1.

2.3.6.2.17 Demographics of Subjects Enrolled from ADPKD Trial 156-04-251 into the Long-term Trials

Table 2.3.6.2.17-1 Demographics of Subjects Enrolled from Trial 156-04-251 into the Long-term Trials 156-08-271 or 156-10-003

Characteristic	Trial 156-08-271		Trial 156-10-003
	Early-treated[a] Tolvaptan (N = 557)	Delayed-treated[b] Tolvaptan (N = 314)	Total Tolvaptan[c] (N = 108)
Gender, n (%)			
Male	303 (54.4)	158 (50.3)	63 (58.3)
Female	254 (45.6)	156 (49.7)	45 (41.7)
Age (years)			
Mean (SD)	41.6 (7.1)	43 (6.7)	43.1 (5.6)
Min, Max	21,54 53535354	21, 54	24, 53

Table 2.3.6.2.17-1 Demographics of Subjects Enrolled from Trial 156-04-251 into the Long-term Trials 156-08-271 or 156-10-003

Characteristic	Trial 156-08-271		Trial 156-10-003
	Early-treated[a] Tolvaptan (N = 557)	Delayed-treated[b] Tolvaptan (N = 314)	Total Tolvaptan[c] (N = 108)
Race, n (%)			
Caucasian	535 (96.1)	302 (96.2)	0
Black	9 (1.6)	2 (0.6)	0
Asian	3 (0. 5)	2 (0.6)	108 (100.0)
Hispanic	9 (1.6)	7 (2.2)	0
Other	1 ((0.2)	1 (0.3)	0

Min = minimum; Max = maximum.

[a]Refers to subjects enrolled from Trial 156-04-251 who received tolvaptan in that trial.

[b]Refers to subjects enrolled from Trial 156-04-251 who received placebo in that trial

[c]Includes 67 subjects who previously received tolvaptan and 41 subjects who previously received placebo in Trial 156-04-251.

Source: CSR 156-08-271 CT-3.1.1, CSR 156-10-003 In-text Table 11.2-1.

2.3.6.2.18 Demographics of ADPKD Subjects Enrolled in Short-term Trials

Table 2.3.6.2.18-1 Demographics of ADPKD Subjects Enrolled in Short-term Trials 156-04-248, 156-04-249, 156-04-001, and 156-09-285

Characteristic	Trial 156-04-248	Trial 156-04-249	Trial 156-04-001	Trial 156-09-285
	Total Tolvaptan (N = 8)	Total Tolvaptan (N = 37)	Total Tolvaptan (N = 18)	Total Tolvaptan (N = 25)
Gender, n (%)				
Male	2 (25.0)	8 (21.6)	9 (50.0)	14 (56.0)
Female	6 (75.0)	29 (78.4)	9 (50.0)	11 (44.0)
Age (years)				
Mean (SD)	38.9 (9.4)	41.8 (7.8)	39.3 (9.3)	38.0 (7.1)
Min, Max	22, 47	25, 58	21, 59	21, 50
Race, n (%)				
Caucasian	7 (87.5)	35 (94.6)	0	25 (100.0)
Black	0	1 (2.7)	0	0
Asian	0	0	18 (100.0)	0
Other	1 (12.5)	1 (2.7)	0	0

Trials 156-04-248, 156-04-249, 156-04-001, and 156-09-285.
Min = minimum; Max = maximum; SD = standard deviation.
Source: CSR 156-04-248 CST-3.1, CSR 156-04-249 CST-3.1, CSR 156-04-001 Table 11.2-2, CSR 156-09-285 CT-3.1.

2.4 Module SIV: Populations Not Studied in Clinical Trials

2.4.1 SIV.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Table 2.4.1-1 SIV.1-1: Exclusion Criteria in Pivotal Clinical Studies for Hyponatremia

Exclusion Criterion	Reason for Exclusion	Is it considered to be included as missing information?	Rationale
Pregnant women	Unknown effect of drug on foetus	Yes	Potential harm to foetus
Breastfeeding women	Unknown effect of drug on baby	Yes	Potential harm to baby
Hypovolemic Hyponatremia	Risk of dehydration and associated neurological sequalae	No	Untoward effects of dehydration and associated neurological sequalae
Acute Hyponatremia (present <48 hrs)	Risk of rapid correction of seum sodium	No	Risk of neurolgical sequelae (eg. osmotic demyelination)
Hyponatremia due to adrenal insufficiency	Drug mechanism of action not expected to be effective	No	No efficacy expected
Hyponatremia due to uncontrolled hypothyroidism	Drug mechanism of action not expected to be effective	No	No efficacy expected

Table 2.4.1-2 SIV.1-2: Exclusion Criteria in Pivotal Clinical Studies for ADPKD

Exclusion Criterion	Reason for Exclusion	Is it considered to be included as missing information?	Rationale
Pregnant women	Unknown effect of drug on fetus	Yes	Potential harm to fetus
Breasfeeding women	Unknown effect of drug on baby	Yes	Potential harm to baby
eGFR <25 mL/min/1.73 m^2 upon trial entry	Drug site of action in nephron	No	No efficacy expected
End Stage Renal Disease	Drug site of action in nephron	No	No efficacy expected

2.4.2 SIV.2: Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The hyponaetremia and heart failure clinical development programmes are unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure (such as

potential carcinogenic effects, organ toxicity). The pivotal phase 3 trials for ADPKD had a 3-year treatment duration, which allowed for more data to be collected.

2.4.3 SIV.3: Limitations in Respect to Populations Typically Underrepresented in Clinical Trial Development Programmes

Across all indications, tolvaptan is contraindicated in pregnant and breastfeeding women. Table 2.4.3-1 below presents exposure of special populations either included but possibly underrepresented or excluded in the clinical trial development programme by indication. In the ADPKD programme there were 18 women who became pregnant, and 8 subjects whose female partners became pregnant. More information is provided in Section 2.4.3.1.

Table 2.4.3-1 SIV.3-1: Exposure of Special Populations Included or not in Clinical Trial Development Programmes (Overall and by Indication)

Type of Special Population	Exposure
Overall	
Pregnant women	Not included in the clinical development programme
Breastfeeding women	Not included in the clinical development programme
ADPKD	
Children	Limited exposure (1 trial (156-12-298) underway); safety and efficacy in children and adolescents has not yet been established, thus not recommended in the paediatric age group.
Elderly	No trials specifically for elderly, however follow-up trials had patients >65 years old. Limited data on the safety and effectiveness of tolvaptan in ADPKD patients aged over 55 are available. A pre-specified subgroup analysis (Trial 156-13-210) suggested that tolvaptan had less of an effect in patients older than 55 years of age, a small subgroup with a notably slower rate of eGFR decline. Elderly ADPKD patients already in ESRD would unlikely benefit from tolvaptan therapy.
Pregnant or breastfeeding women	Contraindicated during during pregnancy or breastfeeding.
Hepatic Impairment	No ADPKD subjects classified with hepatic impairment.
Renal Impairment	Contraindicated in anuric patients. Dose adjustment is not required in patients with renal impairment. Data for patients in CKD stage 4 are more limited than for patients in stage 1, 2 and 3.
Other relevant comorbidity	Cardiovascular comorbidities are expected in the patient population but are of no significant consequence based on current knowledge.
Disease severity different from the inclusion criteria in the clinical trial population	First pivotal trial chose CKD stages 1 to 3 subjects (TKV > 750 mL before age 50 years) and excluded those with factors that might confound measurement of efficacy. Scecond pivotal trial

Table 2.4.3-1 SIV.3-1: Exposure of Special Populations Included or not in Clinical Trial Development Programmes (Overall and by Indication)	
Type of Special Population	**Exposure**
	chose CKD stage 2 to 4 subjects 18 to 55 years old and CKD stage 3a through 4 subjects aged 56 to 66 years old. ADPKD ESRD not studied and tolvaptan not a valid choice of therapy for these patients.
Subpopulations carrying known and relevant polymorphism	Genetic mapping was not conducted and it is unknown whether this affects the clinical response to tolvaptan for the treatment of PKD.
Routine Medical Practice	Limitied information outside a clinical trial setting due to relatively recent approval processes for tolvaptan for this indication.
ARPKD	
Children	Currently no exposure. One paediatric trial planned in infants followed for 2 years who could then roll over into a proposed second trial for toddlers and older children.
Cardiac Oedema (Japan)	
Children	Limited exposure (1 trial underway); safety including low birth weight infants, neonates, suckling infants, infants, and children, has not been established (there is no clinical experience of the drug for paediatric use)
Elderly	No trials specifically for elderly, ie, >65 years old, but mean subject age in pivotal trial 71 years (range 35 to 85 years). Tolvaptan should be administered with care and the patient's condition should be closely monitored since elderly patients generally have decreased physiological functions and are known to be susceptible to dehydration.
Pregnant or breastfeeding women	Contraindicated during during pregnancy or breastfeeding.
Hepatic Impairment	Patients with hepatic coma or total bilirubin exceeding 3 mg/dL were excluded from the phase 2 and 3 cardiac oedema trials.
Renal Impairment	Patients with anuria, urinary excretion disorders (due to urinary stenosis, urinary calculus, tumour, etc.) or serum creatinine exceeding 3.0 mg/dL were excluded from the pivotal cardiac oedema trial (156-06-002).
Other relevant comorbidity	Patients with poor controlled diabetes mellitus, sustained ventricular tachycardia or ventricular fibrillation or cerebrovascular disorder (excluding asymptomatic cerebral infarction) were excluded from the pivotal cardiac oedema trial.
Disease severity different from the inclusion criteria in the clinical trial population	Patients with acute heart failure, a ventricular assist device, suspected hypovolemia, hypertrophic

Table 2.4.3-1 SIV.3-1: Exposure of Special Populations Included or not in Clinical Trial Development Programmes (Overall and by Indication)

Type of Special Population	Exposure
	cardiomyopathy (excluding dilated-phase hypertrophic cardiomyopathy), severe stenotic valvular disease, acute cardiac infarction, confirmed active myocarditis, amyloid cardiomyopathy, sustained ventricular tachycardia or ventricular fibrillation. The populations for cardiac oedema trials were patients with congestive heart failure with volume overload that had not been resolved despite having received conventional diuretic therapy. When conditions or symptoms due to volume overload are resolved, tolvpatan should be discontinued and it should not be continued after body weight has returned to the target level (body weight at which volume overload is appropriately controlled).
Subpopulations carrying known and relevant polymorphism	Not specifically studied.
Different racial and/or ethnic origin	All patients were Japanese.
Hepatic Oedema (Japan)	
Children	No exposure. Safety including low birth weight infants, neonates, suckling infants, infants, and children, has not been established (there is no clinical experience of the drug for paediatric use)
Elderly	No trials specifically for elderly, ie, >65 years old, but mean subject age in pivotal trial 66 years (range 31 to 80 years). Tolvaptan should be administered with care and the patient's condition should be closely monitored since elderly patients generally have decreased physiological functions and are known to be susceptible to dehydration.
Pregnant or breastfeeding women	Contraindicated during during pregnancy or breastfeeding.
Hepatic Impairment	The patients with hepatic encephalopathy (coma scale ≥ II), hepatocellular carcinoma (with vascular invasion in portal vein trunk or primary branch, inferior vena cava, or hepatic vein trunk), or requirement of new treatment for esophageal/gastric varices, hemoglobin < 8.0 g/dL, or total bilirubin >5 mg/dL were excluded from the pivotal hepatic oedema trial (156-08-001). As serious hepatic function disorder was observed in the ADPKD trial of tolvaptan, the SmPC (Japan) states that administration of tolvpatan to the patients

Table 2.4.3-1 SIV.3-1: Exposure of Special Populations Included or not in Clinical Trial Development Programmes (Overall and by Indication)

Type of Special Population	Exposure
	with body fluid retention in hepatic cirrhosis should be carefully determined by weighing therapeutic benefit and potential risk in consideration that administration of tolvaptan may aggravate hepatic function in patients with hepatic cirrhosis.
Renal Impairment	Patients with anuria, urinary excretion disorders (due to urinary stenosis, urinary calculus, tumour, etc.) or serum creatinine exceeding 3.0 mg/dL were excluded from phase 2 and 3 hepatic oedema trials.
Other relevant comorbidity	Patients with heart failure (NYHA classes III to IV) or cerebrovascular disorder were excluded from the phase 2 and 3 hepatic oedema trials
Disease severity different from the inclusion criteria in the clinical trial population	The populations for hepatic oedema trials were liver cirrhosis patients with ascites that had not been resolved despite having received conventional diuretic therapy. The SmPC (Japan) states that, when conditions or symptoms due to volume overload are resolved, tolvaptan should be discontinued.
Subpopulations carrying known and relevant polymorphism	Not specifically studied.
Different racial and/or ethnic origin	All patients were Japanese.
Hyponaetremia	
Children	No exposure (3 trials discontinued due to inability to enrol); thus not recommended in the paediatric age group.
Elderly	No trials specifically for elderly, although 26% of the subjects included in the clinical trials (2512) were over the age of 65 years. Based on data from these trials, no dose adjustment is needed in elderly patients.
Pregnant or breastfeeding women	Contraindicated during during pregnancy or breastfeeding.
Hepatic Impairment	The Samsca SmPC states that no dose adjustment is needed in patients with mild or moderate hepatic impairment (Child-Pugh classes A and B). Samsca SmPC also states that no information is available in patients with severe hepatic impairment (Child-Pugh class C). In these patients dosing should be managed cautiously and electrolytes and volume status should be monitored.
Renal Impairment	The SmPC states that Samsca is contraindicated in anuric patients. Tolvaptan has not been studied in hyponatraemia patients with severe renal failure. The efficacy and safety of tolvaptan in those with a creatinine clearance <10 mL/min has not been evaluated and is therefore unknown. Based on the

Table 2.4.3-1 SIV.3-1: Exposure of Special Populations Included or not in Clinical Trial Development Programmes (Overall and by Indication)	
Type of Special Population	**Exposure**
	data available, no dose adjustment is required in those with mild to moderate renal impairment.
Disease severity different from the inclusion criteria in the clinical trial population	Hypovolemic hyponatraemia was excluded from all trials, and contraindicated for tolvaptan therapy. The populations for hepatic oedema trials were liver cirrhosis patients with ascites that had not been resolved despite having received conventional diuretic therapy.
Subpopulations carrying known and relevant polymorphism	Not specifically studied.
Different racial and/or ethnic origin	Hispanic ethnicity was not tabulated. Samsca has been marketed in the EU, USA, and several Asian countries for more than three years with no specific safety issues or consequences relating to race or ethnicity.

2.4.3.1 ADPKD Indication, Pregnant or Breastfeeding Women

As of 18 May 2020 a total of 27 cases have been reported among the clinical trials within the ADPKD development programme that describe pregnancy in either tolvaptan treated participants (n = 18) or partners (n = 8) of tolvaptan treated participants (see Table 2.4.3.1-1). In tolvaptan treated participants or partners of tolvaptan treated participants, 14 normal live births, 1 live birth (with neonate who experienced neonatal jaundice and diagnosed with bilaterail renal cysts), 3 spontaneous abortions, 1 missed abortion, 1 miscarriage, 5 elective abortions, 1 stillbirth, and 1 ectopic pregnancy have been reported.

Table 2.4.3.1-1 Case Listing of Pregnancies in either Tolvaptan-treated Participants or Partners of Tolvaptan-treated Participants Across the ADPKD Programme			
Clinical Trial Subjects			
Trial Number	**Subject ID**	**Event**	**Outcome**
156-04-251	[redacted]	Pregnancy of partner	Live birth; no known defects
		Pregnancy of partner	Live birth; no known defects
		Pregnancy	Live birth; no known defects
		Pregnancy	[redacted]
		Pregnancy	
		Pregnancy	
		Pregnancy	Spontaneous abortion
		Pregnancy	[redacted]

Table 2.4.3.1-1 Case Listing of Pregnancies in either Tolvaptan-treated Participants or Partners of Tolvaptan-treated Participants Across the ADPKD Programme

Clinical Trial Subjects			
Trial Number	[redacted]	**Event**	**Outcome**
156-08-271		Pregnancy	Live birth; no known defects
		Pregnancy	Live birth; no known defects
		Pregnancy	Missed abortion
		Gestational hypertension	Recovered; live birth; no known defects
		Pregnancy	Live birth, no known defects
		Pregnancy	Ectopic pregnancy
		Pregnancy	Still birth
156-10-003		Pregnancy	Live birth; no known defects
		Gestational hypertension	
		Pregnancy	Live birth with neonatal jaundice, (Resolved) Relationship to IMP was ruled out, per investigator, since neonatal jaundice is common in newborns. Neonate had abnormality of bilateral renal cysts.
		Pregnancy of partner	Live birth; no known defects
		Pregnancy of partner	Live birth; no known defects
		Pregnancy of partner	Live birth; no known defects
		Pregnancy of partner	Live birth; no known defects
156-09-290		Pregnancy	Miscarriage
156-13-210		Pregnancy	Spontaneous abortion
		Pregnancy	[redacted]
		Paternal exposure before pregnancy	Spontaneous abortion
156-13-211		Pregnancy of partner	Live birth; no defects specified
156-13-211		Pregnancy	Live birth; no known defects[2]

[1]Subject [redacted] nancies during the trial; one resulting in a missed abortion and one with gestational hypertension resulting in a live birth.
[2]Subject [redacted] had updated event outcome based on the follow up added to the case on 22 Jul 2020

Based on available follow-up information, no birth defects have been reported. In animal studies, foetal abnormalities have been observed at doses exceeding the maximum recommended human dose. The potential risk for humans is unknown.

The SmPC states that women of childbearing potential should use adequate contraceptive measures during tolvaptan use. Jinarc must not be used during pregnancy (contraindication).

The SmPC states that 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.

2.5 Module SV: Postauthorisation Experience

2.5.1 SV.1: Postauthorisation Exposure

Otsuka estimates the exposure to marketed product based on worldwide sales and free goods distribution figures. Sales data for tolvaptan have been collected on a monthly as is and was available up to 29 Feb 2020. Tolvaptan is also available as a 1% granule formulation.

2.5.1.1 SV.1.1: Method Used to Calculate Exposure

Patient exposure estimates are based on calculations from product distribution figures, and due to the limitations of this approach, it is not possible to reliably estimate the number of subjects treated with marketed tolvaptan.

It is important to note that the estimated patient-year exposure are not equivalent to the absolute number of patients treated. It should also be noted that the overall patient-year exposure estimates are likely to underestimate the true number of patients exposed to tolvaptan, due to the fact that patient-year estimates are calculated number of patients who could have been treated for one year based on the tablets distributed. However, since many patients do not stay on therapy for a whole year, even for chronic conditions, the real number of patients is likely to be higher.

The PY assumes exposure treated patients have taken one tablet of Samsca per day, i.e. number of tablets equals patient days. Estimates of patient exposure are also provided. This estimation was based upon the following assumptions: Since Samsca and Jinarc are prescribed based on a patient's medical condition, there is no standard dosage and duration of treatment. Therefore, estimated patient-year exposure is calculated for each individual formulation of tolvaptan and assumes that treated patients have taken one full tablet of tolvaptan per day, which means the number of tablets sold for each formulation is equal to the patient-day exposure for that particular formulation. Since patient-year exposure is equal to patient-day exposure divided by 365 days, the patient-year exposure for each individual formulation of tolvaptan is equal to the number of tablets sold divided by 365. Table 2.5.1.2-1, Table 2.5.1.2-2 and Table 2.5.1.2-3 provide an estimate for the interval from 01 Mar 2019 to 29 Feb 2020 and the cumulative estimated patient-year exposure for tolvaptan (Samsca or Jinarc) within the EU/EEA region by brand and formulation.

In the case of Jinarc, patients are typically prescribed 2 tablets of tolvaptan per day, with each tablet being a different dose. Again, exposure to a particular formulation type is being assumed as one tablet per day. However, a direct one-to-one association of patient year exposure to estimated patient numbers is not recommended since individual patients

will be counted in multiple formulation calculations. As a result, the patient-year values for the 15 mg and 30 mg tablets contains patients that are also counted in the patient-year values for 45 mg, 60 mg, and 90 mg tablets. The following table provides an estimate for the interval from 01 Mar 2019 to 29 Feb 2020 and cumulative number patient years of Jinarc within the EU/EEA region by formulation.

2.5.1.2 SV.1.2: Exposure

A summary of the worldwide unit distribution of tolvaptan for the cumulative period from market introduction to 29 Feb 2020 is provided below.

Table 2.5.1.2-1 Samsca Units Distributed and Estimated Patient-Year Exposure in Europe[1]

	Total Number of Tablets Distributed		Estimated Patient Years	
Strength	**Interval 01 Mar 19 to 29 Feb 20**	**Cumulative to 29 Feb 20**	**Interval 01 Mar 19 to 29 Feb 20**	**Cumulative to 29 Feb20**
7.5 mg	115,570	125,670	317	344
15 mg	436,980	2,346,773	1,197	6,430
30 mg	145,620	789,090	399	2,162
Grand Total	**698,170**	**3,261,533**	**1,913**	**8,936**

[1]Countries included are: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Norway, Spain, Sweden, Switzerland, and United Kingdom

Table 2.5.1.2-2 Jinarc Units Distributed and Estimated Patient-Year Exposure in Europe[1]

	Total Number of Tablets Distributed		Estimated Patient Years	
Strength	**Interval 01 Mar 19 to 29 Feb 20**	**Cumulative to 29 Feb 20**	**Interval 01 Mar 19 to 29 Feb 20**	**Cumulative to 29 Feb20**
15 mg	296,254	1,270,073	812	3,480
30 mg	1,535,695	3,053,484	4,207	8,366
45 mg	350,434	1,232,364	960	3,376
60 mg	555,660	864,612	1,522	2,369
90 mg	1,036,560	2,166,388	2,840	5,935
Grand Total	**3,774,603**	**8,586,921**	**10,341**	**23,526**

[1]Countries in the EU/EEA Region include: Austria, Belgium, France, Hungary, Italy, Luxembourg, Netherlands, Spain, Switzerland, United Kingdom, Germany, Sweden, Norway, Denmark, and Finland

A summary of the available worldwide distribution of tolvaptan among the rest of world (ROW) countries and the estimated patient-year exposure for the interval from 01 Mar 2019 to 29 Feb 2020 and cumulative periods are presented in the table below.

Table 2.5.1.2-3 Tolvaptan Units Dr Exposure Among Distributed and Estimated Patient-Year Exposure Among ROW Countries or Regions

Country or Region	Total Number of Tablets Distributed		Estimated Patient-Year	
Strength	**Interval 01 Mar 19 to 29 Feb 20**	**Cumulative to 29 Feb 20**	**Interval 01 Mar 19 to 29 Feb 20**	**Cumulative to 29 Feb 20**
Japan				
Samsca				
7.5 mg				
15 mg				
30 mg				
30 g 1% Granule				
7.5 mg, OD Tablet				
15 mg, OD Tablet				
30 mg, OD Tablet				
Canada				
Samsca				
15 mg				
30 mg				
Jinarc				
15 mg				
30 mg				
45 mg				
60 mg				
90 mg				
Asia and Affiliates				
Samsca				
15 mg	3,378,978	8,520,139	9,257	23,343
30 mg	20,790	118,733	57	325
Jinarc				
15 mg	444,574	461,434	1,218	1,264
30 mg	129,999	133,016	356	364
45 mg	46,144	50,568	126	139
60 mg	21,924	23,114	60	63
90 mg	30,268	31,388	1,218	86
United States				
Samsca				
15 mg				
30 mg				
Jinarc				
15 mg				
30 mg				
45 mg				
60 mg				
90 mg				
Grand Total	**60,355,083**	**201,539,624**	**165,356**	**552,163**

2.6 Module SVI: Additional EU Requirements for the Safety Specification

2.6.1 Potential for Misuse for Illegal Purposes

Tolvaptan is unlikely to be used as an illicit drug for leisure. However, historically use of diuretics to achieve a rapid short-term weight loss through excretion of fluids leading to mis- or illegal use relating to the use of diuretics for weight control has been known. This may be of concern in certain sports (eg, weight lifting, boxing). Recently, tolvaptan has been added to the list of banned substances for Olympic competition. Thus, there is the possibility that any diuretic or aquaretic may be used for this purpose.

2.7 Module SVII: Identified and Potential Risks

2.7.1 SVII.1: Identification of Safety Concerns in the Initial RMP Submission

Table 2.7.1-1	**Summary of safety concerns Samsca**
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 • Medication error: prescribing lower than recommended dose by splitting the Samsca tablet • Anaphylaxis

Table 2.7.1-1	**Summary of safety concerns Samsca**
Important potential risks	• Acute urinary retention (in patients with urinary outflow obstruction) • Allergic skin reactions • Raised intraocular pressure / glaucoma • 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 • Interaction tolvaptan and combined administration of warfarin and antiplatelet agents in heart failure patients • 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 • Liver injury in the hyponatremia population • Teratogenicity
Missing information	• Pediatric data • Pregnancy outcome data • Breast-feeding data • Off-label use • Usage in hepatic impaired patients

Table 2.7.1-2	**Summary of safety concerns Jinarc**
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 ischemiain 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

2.7.2 SVII.2: New Safety Concerns and Reclassification with a Submission of an Updated RMP

Changes were made to the RMP in agreement with PRAC recommendations (Assessment report. Procedure No. EMEA/H/C/PSA/S/0078.1).

No new safety concerns have been identified since this RMP was last updated.

2.7.3 SVII.3: Details of Important Identified Risks, Important Potential Risks and Missing Information

2.7.3.1 SVII.3.1: Presentation of Important Identified Risks and Important Potential Risks

2.7.3.1.1 Details of Important Identified Risks

2.7.3.1.1.1 Liver Injury in ADPKD Patients

MedDRA Terms

- Cholestasis and jaundice of hepatic origin (SMQ) (Narrow)
- Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ) (Narrow)
- Liver-related investigations, signs and symptoms (SMQ) (Narrow)
- Hepatitis, non-infectious (SMQ) (Narrow)
- Liver-related coagulation and bleeding disturbances (SMQ) (Narrow)

Potential Mechanisms

The risk of developing hepatotoxicity involves a complex interplay between the chemical properties of the drug, environmental factors (eg, the use of concomitant drugs or alcohol), age, sex, and underlying diseases. The most extensively documented risk factors are concomitant drug use and diseases.[62,63]

The mechanisms underlying tolvaptan-induced liver injury cannot be determined based on the available data. However, the prolonged latency to onset and the relatively prompt recurrence upon re-challenge would support involvement of the adaptive immune system. Engagement of adaptive immunity could also potentially account for the progression and prolonged resolution phases characteristically observed after discontinuing tolvaptan treatment.[61]

In view of the liver safety signal emerging from review of the ADPKD clinical trial database, liver safety data from the preapproval clinical trials for cirrhosis, congestive heart failure, and hyponatraemia were reviewed by the experts and no signal was found.[61]

Evidence Source(s) and Strength of Evidence

2.7.4 Summary of Clinical Safety and Clinical Study Report 156-04-251, Watkins Tolvaptan Liver Safety Report - Final 28 Oct 2012, a review of the liver safety database for tolvaptan in the treatment of Autosomal Dominant Polycystic Kidney Disease.

During the course of the pivotal, placebo-controlled, phase 3 ADPKD trial (Trial 156-04-251), which was monitored by an Independent Data Monitoring

Committee, a pattern of elevated transaminase levels was identified in a cohort of ADPKD subjects in both treatment groups; however, data were blinded.

Upon unblinding of the trial data, an imbalance in the proportion of subjects with elevated transaminases (tolvaptan > placebo) was revealed. This was unexpected given that no signal for liver injury was observed during the clinical development programmes for hyponatraemia. Transient liver injury was identified as a risk of tolvaptan treatment in some subjects with ADPKD; however, no subjects experienced hepatic failure, hepatic transplantation, or death.

Expert adjudication revealed that 3 subjects in the ADPKD programme met Hy's Law for serious hepatocellular injury (ie, the subjects met Hy's laboratory criteria [alanine aminotransferase/ aspartate aminotransferase (ALT/AST) > 3 × ULN accompanied by total bilirubin (BT) > 2 × ULN], did not have associated evidence of cholestasis [serum alkaline phosphatase < 2 × ULN], and other causes of hepatic injury were excluded by medical differential diagnosis).[61]

In Trial 156-13-210, in which hepatic monitoring was conducted on a monthly basis, no subjects had concurrent transaminase and bilirubin elevations that met Hy's Law laboratory criteria. Hepatic events from the study that met the criteria for adjudication were reviewed by the Hepatic Adjudication Committee.

In the post-marketing setting for ADPKD, a case of acute liver failure resulting in liver transplantation has been reported in Japan. In this report, although the prescribing information recommended the discontinuation of tolvaptan if hepatic abnormalities are observed, tolvaptan dose was instead lowered at the first instance when elvated ALT was observed, and subsequently discontinued 2 weeks later when further elevation of ALT and AST were noted. Two weeks later, ALT peaked at 29 × UL, followed by peak (6.7 × ULN) total bilirubin after an additional week. The hepatic adjudication committee considered the event to be probably related to tolvaptan.

Overall, liver injury is considered to be an important identified risk for treatment of patients with ADPKD.

Characterisation of the Risk

There have been no cases of fulminant liver failure or permanent liver injury/dysfunction in the ADPKD clinical trial programme and all subjects experiencing liver injury have recovered. The liver function test elevations (ALT and AST increases) observed with tolvaptan treatment, (shown in the table below on frequency and CI of events in ADPKD) were reversible within 1 to 4 months. It was estimated in 2012 that long term tolvaptan treatment, with the monitoring regimen (scheduled every 4 months) used in the clinical

trials, carried a risk of liver injury at the incidence of 0.03% (1:3,000) in tolvaptan treated patients.[61] In June 2017, on the basis of 1,940 patients having received tolvaptan through the estimated late onset cutoff for the "window of susceptability" of 18 months, the HAC estimated the incidence of acute liver failure to be about 1:6,200 in ADPKD patients receiving chronic tolvaptan treatment. In late 2017, an acute liver failure requiring liver transplantation report was received through the postmarketing experience for ADPKD. The HAC adjudicated this report as probably related (50% - 74% likelihood) to tolvaptan, but did not recommend any changes to the safety profile of tolvaptan.

MedDRA PT	Tolvaptan Total subjects n=961 n (%)	Placebo/other Total subjects n=483 n (%)	P_a-P_b and 95% CI
Alanine Aminotransferase Increased	39 (4.1)	17 (3.5)	0.0054 (−0.0177, 0.0249)
Aspartate Aminotransferase Increased	36 (3.7)	16 (3.3)	0.0043 (−0.0182, 0.0232)
Bilirubin Increased	2 (0.2)	2 (0.4)	0.0062 (−0.0013, 0.0191)
(Table source: Watkins PB 2012, Line listing Study Report 156-04-251 page 781)			

Risk Groups or Risk Factors

The liver enzyme elevations seen with tolvaptan characteristically had an onset between 3 and 14 months of treatment. The injury typically progressed by biochemical criteria for weeks after discontinuation of treatment, and resolved slowly over one to several months. HLA alleles have been identified as patient risk factors for liver injury due to certain drugs. If HLA alleles that infer risk for liver injury in tolvaptan treated patients are identified (ie, missing information), a personalized medicine approach to improve liver safety might be feasible.

Preventability

For both indications, monthly hepatic function testing and monitoring for signs and symptoms of liver injury are expected to enable earlier detection of liver injury and earlier intervention/drug discontinuation to prevent serious or irreversible outcomes like liver failure.

It is unknown if patients with pre-existing liver disease are at increased risk of tolvaptan-related liver injury, more severe outcome, or irreversibility. Studies in hepatically impaired patients did not show an increased risk of liver injury.

Additional risk minimisation measures are in place for liver injury in ADPKD patients; details provided in Section 5.2.1.

Impact on the Risk-benefit Balance of the Product

The impact on the individual would be variable, correlating with the degree of the liver damage. Most liver enzyme changes are mild and reversible, however in some individuals if undetected and uncorrected, health may deteriorate and the liver injury may prove to be fatal. The individual may have genetic or pharmacogenomics susceptibility that may be may be predictive of risk and outcome.

Public Health Impact

Drug-induced liver injury has become the leading cause for acute liver failure in patients referred for liver transplantation in the US.[64,64] It also has been the most frequent single reason for removing approved drugs from the market.[65] Despite this, drug-induced liver injury is relatively rare, because of extensive efforts to detect toxic drugs by preclinical testing in animals and clinical trials in humans. The majority of patients with symptomatic acute liver injury are expected to completely recover with supportive care after discontinuation of the suspect drug.

2.7.3.1.1.2 Volume Depletion, Dehydration and Associated Sequelae such as Renal Dysfunction

MedDRA Terms

Dehydration, dizziness postural, dry mouth, orthostatic hypotension, syncope, thirst, hypovolemia, or hypovolemic shock, blood creatinine increased, creatinine renal clearance decreased, hypercreatininemia, renal impairment, acute kidney injury, renal failure, prerenal failure, oliguria, anuria, or urine output decreased.

Potential Mechanisms

Tolvaptan is a vasopressin V2 receptor antagonist and promotes aquaresis, the renal excretion of electrolyte-free water. Dehydration is a potential consequence of enhanced free-water clearance when outflow is excessive and not balanced by adequate intake and may be one source of renal damage resulting from hypovolemic compromise of the renal blood flow.

Evidence Source(s) and Strength of Evidence

Hyponatraemia

Tolvaptan Clinical Trials: All Heart Failure and Hyponatraemia subjects from controlled Phase 2 and 3 multiple dose trials. CTD Modules 2.5 Clinical Overview and 2.7.4 Summary of Clinical Safety.

ADPKD

2.7.4 Summary of Clinical Safety and Clinical Study Report 156-04-251 and 2.7.4 Summary of Clinical Safety and Clinical Study Report 156-13-210 for NDA resubmission.

Characterization of the Risk

Hyponatraemia

Dehydration is a potential consequence of enhanced free-water clearance (aquaresis). Management of hyponatraemia requires maintenance of optimal intravascular fluid level and osmolarity and removal of excess extravascular free water. From pooled analysis of all multiple dose trials in heart failure and hyponatraemia, dehydration was less commonly observed than thirst and dry mouth but still more frequent in tolvaptan 15-60 mg subjects (102/3181; 3.2%) than in those receiving placebo (66/2738; 2.4%) (SSD Table 1.2.5.2).

MedDRA Preferred Terms found	Tolvaptan (N = 3294) n (%)	Placebo/other (N = 2738) n (%)
Thirst	597 (18.1)	74 (2.7)
Dry mouth	312 (9.5)	67 (2.4)
Hypotension	301 (9.1)	264 (9.6)
Dizziness	299 (9.1)	225 (8.2)
Dehydration	106 (3.2)	66 (2.4)
Source: SSD Table 1.2.5.2		

ADPKD

Given the aquaretic effects of tolvaptan, TEAEs such as Thirst and Dry Mouth were expected side effects of tolvaptan therapy. Thirst was the most frequently reported TEAE in pivotal Trial 156-04-251, reported by 43.6% of subjects overall (55.3% on tolvaptan and 20.5% on placebo; Dry Mouth was also a frequently reported event in both treatment groups (16.0% on tolvaptan and 12.4% on placebo).

Likewise, in Trial 156-08-271, a long-term extension trial to Trial 156-04-251, events of Thirst and Dry Mouth were frequently reported. Thirst was reported by 43.4% (230/530) of the early-treated tolvaptan subjects and 49.5% (145/293) of delayed-treated tolvaptan subjects, and Dry Mouth was reported by 7.4% (39/530) of early-treated tolvaptan subjects and 13.3% (39/293) of delayed-treated subjects in Trial 156-08-271 (CSR 156-08-271 CT-8.2.2).

MedDRA PT	Tolvaptan Total n=961 n (%)	Placebo/other Total n=483 n (%)	Pa-Pb and 95% CI
Thirst	531 (55.3)	99 (20.5)	0.3476 (0.298, 0.3934)
Dry mouth	154 (16.0)	60 (12.4)	
Dizziness	109 (11.3)	42 (8.7)	0.0265 (−0.0075, 0.0573)
Dehydration	18 (1.9)	11 (2.3)	0.004 (−0.0116, 0.0242)
Source: Line listing TEAE in pivotal Trial 156-04-251			

Other symptoms associated with dehydration (≥3% incidence in the tolvaptan 15-60 mg group as compared to placebo) are hypotension and renal effects [including blood creatinine increased, oligo-/anuria and (acute) renal failure].

Hyponatraemia

MedDRA Preferred Terms found	Tolvaptan (N = 3294) n (%)	Placebo/other (N = 2738) n (%)
Any TEAE	2917 (88.6)	2316 (84.6)
All renal AEs *)	793 (24.1)	515 (18.8)
Renal failure	166 (5.0)	153 (5.6)
Renal failure acute	106 (3.2)	113 (4.1)
Renal failure acute	115 (3.5)	79 (2.9)
Source: SSD Table 1.2.5.1, 1.2.5.2.		

ADPKD

MedDRA Preferred Term found	Tolvaptan n = 961 n (%)	Placebo/other n = 483 n (%)	Pb-Pa and 95% CI
Renal failure	1	0	-
Renal failure acute	0	0	-
Blood creatinine increased	135 (14.0) 0.1405	71 (14.7) 0.147	0.0065 (−0.0306, 0.0466)
Source: Line listing TEAE in pivotal Trial 156-04-251			

Risk Groups or Risk Factors

In both indications, patients with an inability or a compromised capacity to perceive and communicate thirst would be at risk of severe dehydration and subsequent renal impairment without appropriate medical intervention. This would include bedridden and unconscious subjects. Patients who are concomitantly treated with diuretics may be at risk of severe dehydration and subsequent renal impairment.

Special populations which may be at higher risk also include those with a fluid overload in extravascular compartments, but with intravascular contraction. These groups include subjects with hepatic cirrhosis, and potentially some subjects with heart failure.

Preventability

In both indications dehydration is a preventable AE during treatment promoting aquaresis. Careful clinical monitoring of acutely hospitalized subjects should be included as part of routine management. Subjects with an inability or a compromised capacity to perceive or communicate thirst and other early symptoms of dehydration should be provided with special measures to guard against excessive decreases in intravascular volume and the potential for renal impairment. In addition it would be important to exclude hypovolemic subjects from treatment with a vasopressin V2-receptor antagonist. Additional risk minimisation measures are in place for Volume Depletion, Dehydration and Associated Sequelae such as Renal Dysfunction in ADPKD patients (Jinarc Healthcare Professional Education Guide, Jinarc Prescribing Checklist, Jinarc Patient Education Brochure, Jinarc Patient Alert Card); details are provided in Section 5.2.1.

Impact on the Risk-benefit Balance of the Product

Volume depletion and dehydration in the individual patient if uncorrected could lead to serious consequences such as dehydration-associated renal impairment.

In both indications, tolvaptan therapy improves the quality of life of subjects provided the warnings and precautions regarding adequate hydration are followed. Renal impairment in the individual patient will have deleterious effect on health leading to renal failure if it is not immediately corrected.

Public Health Impact

In both indications the difference in incidence between tolvaptan and placebo of the most commonly reported TEAEs in this group were dry mouth, and thirst. However, the public health impact in both indications will be negligible provided the subjects have sufficient access to water and are warned to drink sufficiently. This can be achieved with careful selection of the treated population through effective direction in the SmPC.

In both indications, the impact of renal effects appears to be negligible as their incidence is close to that in the placebo population.

2.7.3.1.2 Details of Important Potential Risks

There are no important potential risks.

2.7.3.2 SVII.3.2: Presentation of Missing Information

2.7.3.2.1 Pregnancy Outcome Data

MedDRA Terms

SMQ: Normal pregnancy conditions and outcomes (Broad)

SMQ: Termination of pregnancy and risk of abortion

SMQ: Pregnancy, labour and delivery complications and risk factor (excl abortions and stillbirth (Broad)

SOC: Pregnancy, puerperium, and perinatal condition

String “Foetal” PTs

Evidence Source(s)

Safety and efficacy of tolvaptan in pregnant women have not been studied. There is no adequate information on the use of tolvaptan during pregnancy. Search of the database is conducted to identify all cases meeting MedDRA Terms specified above. Review and analysis of all cases to date, did not produce direct and clear evidence to justify any change in the benefit-risk balance of tolvaptan.

Population in need of Further Classification

Since no studies have been conducted in pregnant women, use in pregnant women is considered missing information.

Preventability

Pregnancy is listed as contraindication for use for tolvaptan. Patients and heatlh care providers are advised to discontinue Jinarc as soon as they become aware of the pregnancy. Use of reliable methods of contraception is recommended for women of childbearing age. In addition to routine pharmacovigilance activities, additional risk minimisation measures are in place to provide education on the prevention of pregnancy for both, healthcare providers and patients (Jinarc Healthcare Professional Education Guide, Jinar Prescribers Checklist and Jinarc Patient Education Brochure).

Impact on the Risk-benefit Balance of the Product

Overall, there has been no increase in frequency, severity or relatedness of this risk during the data review for the latest reporting period. No update to the characterization of this missing information is warranted. The Company does not consider that there are any impact on the benefit-risk balance of tolvaptan.

2.7.3.2.2 Off-label Use

MedDRA Terms

PT: Off-label use

Evidence Source(s)

Postmarketing reports of off-label use. Review of data will also include the use in breast-feeding, paediatrics and ADPKD patients with renal function other than CKD stage 1-4. As the CKD stage is not always reported in the post marketing settings, the MAH will continue to review this information within PSUR, under the name of "Safety in ADPKD patients with renal function other than CKD stage 1-4" (sub-section within off-label use).

Anticipated Risk/Consequences of the Missing Information

An analysis of AEs associated with off-label use being reviewed will be discussed in the PSUR. During the latest reporting period (19 May 2019 to 18 May 2020) there were 44 cases with reports of "off-label use ". The evaluation of these cases did not reveal any potential safety concerns, which is consistent with the results of the cumulative review.

Impact on the Risk-benefit Balance of the Product

Due to the aquaretic effect of tolvaptan and its potential use in other indications and age groups, the monitoring of off-label use is necessary to help ensure its safe use. Observed changes to the safety profile of tolvaptan as a consequence of off-label use may require revisions to the SmPC. Missing information that have been removed from the list of safety concerns are being incorporated under off-label use evaluation. As of data cut-off, the review of the data within the PSUR does not support an update of the characterisation of this missing information. The Company does not consider that there are any impact on the benefit-risk balance of tolvaptan.

2.7.3.2.3 Use in Hepatic Impaired Patients

MedDRA Terms

Search of safety database for events reported in patients with a medical history of hepatic failure using the following SMQs:

- Cholestasis and jaundice of hepatic origin (Narrow)
- Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (Narrow)
- Hepatitis, non-infectious (Narrow)
- Hepatic disorders specifically reported as alcohol-related (Narrow)

Evidence Source(s)

All cases which are meeting criteria defined above are being analysed. The safe use of tolvaptan in patients with hepatic impairment has not been evaluated in clinical trials. Due to the identified risk of liver injury in ADPKD, the benefits and risks of treatment with tolvaptan in patients with severe hepatic impairment must be evaluated carefully.

Population in need of Further Classification

The limited number of patients with hepatic impairment in both indication of ADPKD and indication of hyponatraemia does not allow for any conclusion regarding use of tolvaptan in these patients.

Preventability

The information in Jinarc SmPC states that in patients with severe hepatic impairment the benefit and risk of treatment with Jinarc must be evaluated carefully. 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. In the section 4.2 of Samsca SmPC it states that no information is available in patients with severe hepatic impairment (Child-Pugh class C). In these patients dosing has to be managed cautiously and electolytes and volume status must be monitored.

Impact on the Risk-benefit Balance of the Product

As of data cut-off, the review of the data within the PSUR does not support an update of the characterisation of this missing information. The Company does not consider that there are any impact on the benefit-risk balance of tolvaptan.

2.7.3.2.4 Use in ADPKD Patients Over the Age of 55 Years

MedDRA Terms

Search of the safety database for events reported in patients ages > 55 years and who was administering tolvaptan for the indication of or has a medical history of ADPKD.

Evidence Source(s)

Population in need of Further Classification

A review of events and case characteristics in patients over the age of 55 years and who were administered tolvaptan for the indication of or has a medical history of ADPKD revealed similar observations in comparison to the other age groups and what had been reported in the past.

The following safety concern under missing information "Use in ADPKD Patients Over 50 Years Old" has been re-characterized to "Use in ADPKD Patients Over 55 Years Old" based on the feedback from EMA provided in the Jinarc Renewal Marketing Authorization CHMP opinion/ Assessment Report [Procedure no.: EMEA/H/C/002788/R/0027]. Based on the early clinical trials the missing information was identified as the "Use in ADPKD patients over the age of 50 years". PASS study (156-12-299) was designed in 2015, with first patient enrollment in the fourth quarter of 2016, and its objectives were consistent with age limit of 50. Upon completion of additional clinical trial (156-13-210) more data became available on the tolvaptan's efficacy and safety in patients under the age of 55. Along with submission of the study CSR in 2018, the SmPC was updated to include this information. During EMA Jinarc Renewal procedure, this missing information was re-characterized to "Use in ADPKD patients over the age of 55 years". While PASS objectives will remain to evaluate data on patients over the age of 50, it is still allowing us to evaluate available data on patients over the age of 55 years. The objective of the PASS study and information provided in the Annex II D will remain unchanged, so that Company can continue to evaluate the use and potential risks in patients over the age of 50 years, which will allow adequate comparison and analysis between baseline, PASS interim reports 1 and 2.

2.7.3.2.5 Long-term Use of Jinarc in Routine Medical Practice

MedDRA Terms

Search of the safety database for events that occurred in patients during long-term use of Jinarc. Long-term use was considered as any patient who completed at least 2 years of therapy with Jinarc.

Evidence Source(s)

The database was reviewed for any cases meeting criteria: event onset latency > 2 years after therapy start date. During the analysis of limited data for long-term Jinarc use (>2 years), there were no events identified that were unique. The Company does not consider the information contained in these infividual safety reports to justify any changes to the benefit-risk balance of tolvaptan.

Population in need of Further Classification

To date, there were no events occuring during long-term use of Jinarc, which were different from events that are observed in patients who use Jinarc for shorter duration. However, the data concerning this population is still very limited.

2.8 Module SVIII: Summary of the Safety Concerns

Table 2.8-1 SVIII-1: Summary of Ongoing Safety Concerns	
Important Identified Risks	• Liver Injury in ADPKD Patients* • Volume depletion, dehydration and associated sequelae such as renal dysfunction
Important Potential Risks	• None
Missing Information	• Pregnancy Outcome Data • Off-label Use • Use in Hepatic Impaired Patients • Use in ADPKD Patients over the age of 55 years* • Long-term Use of Jinarc in Routine Medical Practice*
*Risks which are specific to Jinarc only; all other risks are applicable to both: Samsca and Jinarc.	

3 PART III: PHARMACOVIGILANCE PLAN (Including Postauthorisation Safety Studies)

3.1 III.1: Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: The Otsuka Pharmaceutical Company maintains systems and standard practices for Routine Pharmacovigilance activities to collect reports of suspected adverse reactions (including spontaneous reports, reports from clinical studies, reports of pregnancy/lactation exposures, overdoses and medication errors); prepare reports for regulatory authorities (eg, individual case safety reports, PSURs), and maintain continuous monitoring of the safety profile of approved products (including signal detection and evaluation, updating of labelling, and liaison with regulatory authorities). Hepatotoxicity Adverse Event Follow-up Form is used by the Company to collect PV data for hepatic-related adverse events. The information is collected in stadardized way to ensure the adequate medical assessment of the hepatic-related adverse events. The Otsuka Pharmaceutical Company maintains a Pharmacovigilance System Master File which contains details of these systems and standard practices.

Additional pharmacovigilance activities beyond adverse reactions reporting and signal detection are discussed in Section 3.2.

3.2 Additional Pharmacovigilance Activities

Study short name and title: Protocol 156-12-299 JINARC PASS

A 7.5-year, Multicentre, Non-interventional, Post-authorisation Safety Study for Patients Prescribed JINARC for Autosomal Dominant Polycystic Kidney Disease

Rationale and study objectives:

To characterize and quantify the risk of idiosyncratic liver injury in JINARC treated patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD) in routine clinical practice. Additionally, the following objectives are addressed: Off-label use; Potential risk in pregnant women; Use in ADPKD patients over the age of 50 years; and Long term use of Jinarc in routine medical practice.

Study design:

Retrospective database analysis

Study population:

Patients Prescribed JINARC for Autosomal Dominant Polycystic Kidney Disease

Milestones:

FPFV: 31 Oct 2016

Planned LPLV: 31 Mar 2024

Retrospective database analysis: Predetermined periods post-licensing to be clarified in the full protocol.

Final Study Report: Planned Q1 2025

Title: Hepatic Adjudication Committee (HAC) evaluation of cases of liver injury

Objective: The HAC is a panel of independent hepatic experts who adjudicates cases of liver injury. The HAC's activities serve as additional pharmacovigilance activities to help assess the effectiveness of risk minimisation activitities for liver injury with the use tolvaptan in ADPKD.

Rationale: Follow-up on incidence of cases in clinical trials to assess if rules for withdrawal of tolvaptan are effective.

Milestones: All cases of suspected liver injury, both from the clinical trials and from the postmarketing settings, are assessed by the HAC and 3 quarterly and 1 annual reports are issued.

3.3 Summary Table of Additional Pharmacovigilance Activities

Additional pharmacovigilance activities broken down by indication are described in the tables below.

Information on all completed additional pharmacovigilance activities is provided in Section 7.2.

Please note that there are no ongoing or planned additional pharmacovigilance activities for the hyponatremia indication (Samsca).

Table 3.3-1 III.3-1: Ongoing and Planned Additional Pharmacovigilance Activities for the ADPKD Indication

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1- Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit risk)				
Jinarc PASS 156-12-299 Ongoing	Jinarc PASS: In the EU/EFTA 2,100 patients who are treated according to the decision of the treating physician will be followed prospectively for a minimum of 2 years and a maximum of 5 years to monitor the risk of liver injury in the real life setting. To compliment this prospective study, a large multi-national retrospective database analysis at predetermined periods postlicensing will allow monitoring of off label use. In addition, there will be an assessment of ADPKD related morbidity and mortality, including longer-term effects on GFR decline and progression of disease leading to dialysis or trans-	Hepatotoxicity and missing information: Off label use, Use in patients over the age of 50 years in ADPKD patients, Use and potential risks in pregnant women, including frequency and outcome of pregnancies associated with the use of Jinarc, and Long term use of Jinarc in routine medical practice. In addition, ADPKD related morbidity and mortality will be assessed.	Started: FPFV: Planned LPLV: Retrospective database analysis: Interim Report: Final Study Report:	31 Oct 2016 31 Mar 2024 Predetermined periods post-licensing to be clarified in the full protocol. 31 Dec 2022 Planned Q1 2025

Table 3.3-1 III.3-1: Ongoing and Planned Additional Pharmacovigilance Activities for the ADPKD Indication				
Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
	plantation. 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			
Category 3- Required additional pharmacovigilance activities				
Hepatic Adjudication Committee (HAC) adjudication of cases of liver injury. Ongoing	To help assess the effectiveness of risk minimisation activities for liver injury with the use of tolvaptan in ADPKD	Follow-up on incidence of cases in clinical trials Risk of liver injury in ADPKD patients	All cases of suspected liver injury, both from the clinical trials and from the postmarketing settings are assessed by the HAC, and 3 quarterly and 1 annual reports are issued.	Ongoing

4 PART IV: PLANS FOR POSTAUTHORISATION EFFICACY STUDIES

4.1 Applicability of efficacy to all patients in the target population

Only trials that are part of the terms of current authorisation for tolvaptan will be referenced below.

Table 4.1-1	**IV-1: Planned and Ongoing Post-Authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations for Samsca**			
Study Status	**Summary of objectives**	**Efficacy uncertainties addressed**	**Milestones**	**Due dates**
Efficacy studies which are conditions of the marketing authorisation				
None				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None planned				

Table 4.1-2	**IV-1: Planned and Ongoing Post-Authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations for Jinarc**			
Study Status	**Summary of objectives**	**Efficacy uncertainties addressed**	**Milestones**	**Due dates**
Efficacy studies which are conditions of the marketing authorisation				
None				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None planned				

5 PART V: RISK MINIMISATION MEASURES (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

For identified safety concerns, the product label communicates the risk for the approved indications. Reports of AEs from patients receiving tolvaptan are closely monitored to identify and characterise AEs of special interest and any new emerging safety signal. Risk minimisation measures are planned for each important identified or potential risk.

5.1 V.1: Routine Risk Minimisation Measures

The SmPC text for Samsca and Jinarc has been approved by the EMA. Risk minimisation measures for important identified and potential risks for each product are presented in the tables below.

Table 5.1-1 V.1-1: Description of Routine Risk Minimisation Measures by Safety Concern for Samsca and Jinarc	
Safety Concern	**Routine Risk Minimisation Activities**
Important Identified Risk Liver injury in ADPKD Patients	**Samsca** <u>Routine risk communication:</u> **Samsca SmPC** • Text in Section 4.4 of the SmPC **Samsca PL** • Not applicable <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> • None <u>Other routine risk minimisation measures beyond the Product Information</u>: • Prescription only medication. **Jinarc** <u>Routine risk communication:</u> **Jinarc SmPC** • Text in Section 4.3, 4.4 of the SmPC **Jinarc PL** • Text in Section 2 • Text in Section 4 <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> • Secton 4.4 of SmPC • Section 2 of the PL <u>Other routine risk minimisation measures beyond the Product Information:</u> • Medicinal product subject to restricted medical prescription

Table 5.1-1 V.1-1: Description of Routine Risk Minimisation Measures by Safety Concern for Samsca and Jinarc	
Safety Concern	**Routine Risk Minimisation Activities**
Important Identified Risk Volume depletion, dehydration and associated sequelae such as renal dysfunction	**Samsca** Routine risk communication: **Samsca SmPC** • Text in Sections 4.2, 4.3, 4.4, and 4.8 of the SmPC **Samsca PL** • Text in Sections 2,3 and 4 of the PL Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: • Prescription only medication **Jinarc** Routine risk communication: **Jinarc SmPC** • Text in Section 4.3 and 4.4 of the SmPC **Jinarc PL** • Text in Section 2 and 4 of the PL Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation for monitoring of body weight is included in SmPC sections 4.4 as progressive reduction in body weight could be an early sign of progressive dehydration Other routine risk minimisation measures beyond the Product Information: • Medicinal product subject to restricted medical prescription
Important Potential Risk None	**Not applicable**

Table 5.1-1 V.1-1: Description of Routine Risk Minimisation Measures by Safety Concern for Samsca and Jinarc	
Safety Concern	**Routine Risk Minimisation Activities**
Missing Information Pregnancy outcome data	**Samsca** <u>Routine risk communication:</u> **Samsca SmPC** • Text in Sections 4.3 and 4.6 of the SmPC **Samsca PL** • Text in Sections 2 of the PL <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> • None <u>Other routine risk minimisation measures beyond the Product Information</u>: • Prescription only medication **Jinarc** <u>Routine risk communication:</u> **Jinarc SmPC** • Text in Sections 4.3 and 4.6 of the SmPC **Jinarc PL** • Text in Section 2 of the PL <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> • None <u>Other routine risk minimisation measures beyond the Product Information</u>: • Medicinal product subject to restricted medical prescription

Table 5.1-1 V.1-1: Description of Routine Risk Minimisation Measures by Safety Concern for Samsca and Jinarc	
Safety Concern	**Routine Risk Minimisation Activities**
Missing Information Off-label use	**Samsca** <u>Routine risk communication:</u> **Samsca SmPC** • Text in Section 4.1 of the SmPC **Samsca PL** • Text in Section 1 of the PL <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> • None <u>Other routine risk minimisation measures beyond the Product Information</u>: • Prescription only medication **Jinarc** <u>Routine risk communication:</u> **Jinarc SmPC** • Text in Sections 4.1, 4.2 of the SmPC **Jinarc PL** • Text in Section 1 of the PL <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> • None <u>Other routine risk minimisation measures beyond the Product Information</u>: • Medicinal product subject to restricted medical prescription • Pack size: Jinarc 15 mg tablets Jinarc 30 mg tablets Jinarc 15 mg tablets + Jinarc 45 mg tablets Jinarc 30 mg tablets + Jinarc 60 mg tablets Jinarc 30 mg tablets + Jinarc 90 mg tablets

Table 5.1-1 V.1-1: Description of Routine Risk Minimisation Measures by Safety Concern for Samsca and Jinarc	
Safety Concern	**Routine Risk Minimisation Activities**
Missing Information Use in hepatic impaired patients	**Samsca** <u>Routine risk communication:</u> **Samsca SmPC** • Text in Sections 4.2, 4.4 and 5.2 of the SmPC **Samsca PL** • Text in Section 2 of the PL <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> • None <u>Other routine risk minimisation measures beyond the Product Information</u>: • Prescription only medication **Jinarc** <u>Routine risk communication:</u> **Jinarc SmPC** • Text in Sections 4.2, 4.4 and 5.2 of the SmPC **Jinarc PL** • Text in Sections 2 and 4 of the PL <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> • None <u>Other routine risk minimisation measures beyond the Product Information</u>: • Medicinal product subject to restricted medical prescription

Table 5.1-1 V.1-1: Description of Routine Risk Minimisation Measures by Safety Concern for Samsca and Jinarc	
Safety Concern	**Routine Risk Minimisation Activities**
Missing Information Use in ADPKD patients over the age of 55 years	**Samsca** Routine risk communication: **Samsca SmPC** • Not applicable **Samsca PL** • Not applicable Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: • Prescription only medication **Jinarc** Routine risk communication: **Jinarc SmPC** • Text in Sections 4.2, 5.1 and 5.2 of the SmPC **Jinarc PL** • Not applicable Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: • Medicinal product subject to restricted medical prescription

Table 5.1-1 V.1-1: Description of Routine Risk Minimisation Measures by Safety Concern for Samsca and Jinarc	
Safety Concern	**Routine Risk Minimisation Activities**
Missing Information Long term use of Jinarc in clinical practice	**Samsca** Routine risk communication: **Samsca SmPC** • Not applicable Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: • Prescription only medication **Jinarc** Routine risk communication: **Jinarc SmPC** • Text is Section 5.1 of the SmPC **Jinarc PL** • Not applicable Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: • Medicinal product subject to restricted medical prescription

5.2 V.2: Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product except for liver injury, dehydration and pregnancy prevention in ADPKD patients administering Jinarc.

5.2.1 Additional Risk Minimisation in ADPKD Patients

Objectives:

To inform patients, prescribers and pharmacists about the potential for liver injury, dehydration and pregnancy prevention during tolvaptan treatment in ADPKD.

Details of prescriber's education, certification in the prescriber's registry and reassurance of prescriber's certification prior to the dispensation of Jinarc shall be agreed by the MAH with each National Competent Authority.

The Following aRMM materials are available:

- Healthcare Proffessional Education Guide
- Jinarc Prescribing Checklist
- Patient Education Brochure
- Patient Alert Card

Rationale for the additional risk minimisation activity:

Liver injury: Early identification of elevations in liver enzymes, ALT, AST/bilirubin and prevention of serious liver damage in susceptible individuals.

Dehydration: Jinarc may cause adverse reactions related to water loss such as thirst, polyuria, nocturia and pollakiuria. Therefore, patients must have access to water (or other aqueous fluids) and be able to drink sufficient amounts of these fluids. to prevent dehydration.

Pregnancy prevention: Jinarc is contraindicated in pregnancy. 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.

Target audience and planned distribution path

Liver injury: Patients with ADPKD who are receiveing treatment with Jinarc or are a candidate for initiation of treatment along with prescribing physicians. Information will be available through aRMM educational materials, which include: Jinarc Patient Education Brochure, Healthcare Professional Education Guide, Jinarc Prescribing Checklist, and Patient Alert Card.

Dehydration: Patients with ADPKD who are receiving treatment with Jinarc or are a candidate for initiation of treatmen along with prescribing physicians. Information will be available through aRMM educational materials, which include: Jinarc Patient Education Brochure, Healthcare Professional Education Guide, Jinarc Prescribing Checklist and Patient Alert Card.

Pregnancy prevention: Women of childbearing potential with ADPKD who are receiveing treatment with Jinarc or are a candidate for initiation of treatment along with prescribing physicians. Information will be available through aRMM educational materials, which include: Jinarc Patient Education Brochure, Jinarc Prescribers Checklist and Healthcare Professional Education Guide.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Liver injury: Effectiveness of the risk minimisation measures interventions and criteria for success will be evaluated by a periodic qualitative and quantitative review of the reported cases of liver enzyme changes, liver injury and complication, by the company via routine pharmacovigilance activities and reviewing safety data from PASS 156-12-299 and through external experts adjudication of hepatic adverse events. The HAC is charged with providing an independent, unbiased review of the hepatic adverse events possibly related to liver toxicity with tolvaptan therapy.

Dehydration: Effectiveness of the risk minimisation measures interventions and criteria for success will be evaluated during the PSUR period by a qualitative and quantitative review to assess the frequency, nature, and severity of the reported cases of dehydration.

Pregnancy prevention: Effectiveness of the risk minimisation measures interventions and criteria for success will be evaluated during the PSUR period by a qualitative and quantitative review to assess the frequency and outcome of the reported cases of pregnancy.

Removal of additional risk minimisation activities:

Not applicable.

5.3 V.3: Summary of Risk Minimisation Measures

Table 5.3-1	**V.3-1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern**	
Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
Important Identified Risks		
Liver injury in ADPKD patients	Routine risk minimisation measures: **Samsca SmPC** • **Section 4.4** **Samsca PL** • **Not applicable** Prescription medicine only **Jinarc SmPC** • **Section 4.3** • **Section 4.4** **Jinarc PL** • **Section 2** • **Section 4** Medicinal product subject to restricted medical prescription **Jinarc** Additional risk minimisation measures Details of prescriber's education, certification in the prescriber's registry and reassurance of prescriber's certification prior to the dispensation of Jinarc shall be agreed by the MAH with each National Competent Authority Several education materials are available: • Patient Education Brochure • Healthcare Professional Education Guide • Jinarc Prescribing Checklist • Patient Alert Card	**Samsca** Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: None **Jinarc** Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Hepatotoxicity Adverse Event Follow-up Form Additional pharmacovigilance activities: PASS 156-12-299 Adjudication of cases of liver injury by a panel of independent experts of a Hepatic Adjudication Committee (HAC)
Volume depletion, dehydration and associated sequelae such as renal dysfunction	Routine risk minimisation measures: **Samsca SmPC** • **Section 4.2**	**Samsca** Routine pharmacovigilance activities beyond

Table 5.3-1	**V.3-1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern**	
Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
	• **Section 4.3** • **Section 4.4** • **Section 4.8** **Samsca PL** • **Section 2** • **Section 3** • **Section 4** Prescription only medication **Jinarc SmPC** • **Section 4.3** • **Section 4.4** **Jinarc PL** • **Section 2** • **Section 4** Medicinal product subject to restricted medical prescription **Jinarc** Additional risk minimisation measures • Patient Education Brochure • Healthcare Professional Education Guide • Jinarc Prescribing Checklist • Patient Alert Card	adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: None **Jinarc** Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: None
Important Potential Risks		
None	Not applicable	Not applicable
Missing Information		
Pregnancy outcome data	**Samsca SmPC** • **Section 4.3** • **Section 4.6** **Samsca PL** • **Section 2** Prescription only medication **Jinarc SmPC** • **Section 4.3** • **Section 4.6**	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: None **Jinarc**

Table 5.3-1	**V.3-1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern**	
Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
	Jinarc PL • **Section 2** Medicinal product subject to restricted medical prescription **Jinarc** Additional risk minimisation measures • Healthcare Professional Education Guide • Patient Education Brochure • Jinarc Prescribers Checklist	Routine pharmacovigilance activities: none Additional pharmacovigilance activities: PASS (156-12-299)
Off-label use	**Samsca SmPC** • **Section 4.1** **Samsca PL** • **Section 1** Prescription only medication **Jinarc SmPC** • **Section 4.1** • **Section 4.2** **Jinarc PL** • **Section 1** Medicinal product subject to restricted medical prescription, Pack size **No aRMM required for this risk**	**Samsca** Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: None **Jinarc** Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: PASS 156-12-299

Table 5.3-1	**V.3-1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern**	
Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
Use in hepatic impaired patients	**Samsca SmPC** • **Section 4.2** • **Section 4.4** • **Section 5.2** **Samsca PL** • **Section 2** Prescription only medication **Jinarc SmPC** • **Section 4.2** • **Section 4.4** • **Section 5.2** **Jinarc PL** • **Section 2** • **Section 4** Medicinal product subject to restricted medical prescription **No aRMM required for this risk**	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: None **Jinarc** Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: None
Use in ADPKD patients over the age of 55 years	**Samsca** • **Not applicable** **Jinarc SmPC** • **Section 4.2** • **Section 5.1** • **Section 5.2** **Jinarc PL** • **Not applicable** Medicinal product subject to restricted medical prescription **No aRMM required for this risk**	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None **Jinarc** Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: Protocol PASS 156-12-299

Table 5.3-1	**V.3-1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern**	
Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
Long term use of Jinarc in routine medical practice	**Samsca** • **Not applicable** **Jinarc SmPC** • **Section 5.1** **Jinarc PL** • **Not applicable** Medicinal product subject to restricted medical prescription **No aRMM required for this risk**	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None **Jinarc** Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: Protocol PASS 156-12-299

6 PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

6.1 Summary of the Risk Management Plan for Samsca

6.1.1 VI.1: Summary of the Risk Management Plan for Samsca

This is a summary of the risk management plan (RMP) for Samsca. The RMP details important risks of Samsca, how these risks can be minimised, and how more information will be obtained about these risks and uncertainties (missing information).

Samsca's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how it should be used.

This summary of the RMP for Samsca should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of tolvaptan's RMP.

6.1.2 I: The Medicine and What it is Used for

Samsca is authorised in the EEA for the treatment of adults patients with hypnatraemia secondary to syndrom of inappropriate antidiuretic hormone secretion (SIADH). It contains tolvaptan as the active substance and it is given by oral tablet administration.

Further information about the evaluation of Samsca's benefits can be found in Samsca's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Risk-management-plan_summary/human/002788/WC500183093.pdf

6.1.3 II: Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Samsca, together with measures to minimise such risks and the proposed studies for learning more about tolvaptan's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, prescription only) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Samsca, no additional risk minimisation measures are required.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, (including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Samsca is not yet available, it is listed under 'missing information' below.

6.1.3.1 II.A: A List of Important Risks and Missing Information

Important risks of Samsca are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Samsca. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, pregnancy outcome data).

Table 6.1.3.1-1 II.A-1: List of Important Risks and Missing Information for Samsca (from Part II: Module SVIII)

Important identified risks	• Volume depletion, dehydration and associated sequelae such as renal dysfunction
Important potential risks	• None
Missing information	• Pregnancy outcome data • Off-label use • Use in hepatic impaired patients

6.1.3.2 II.B: Summary of Important Risks for Samsca

Table 6.1.3.2-1 Important Identified Risk: Volume Depletion, Dehydration and Associated Sequelae such as Renal Dysfunction

Evidence for linking the risk to the medicine	**Hyponatraemia** Tolvaptan Clinical Trials: All Heart Failure and Hyponatraemia subjects from controlled Phase 2 and 3 multiple dose trials. CTD Modules 2.5 Clinical Overview and 2.7.4 Summary of Clinical Safety.
Risk factors and risk groups	Patients with an inability or a compromised capacity to perceive and communicate thirst would be at risk of severe dehydration without appropriate medical intervention. This would include bedridden and unconscious patients. Patients who are concomitantly treated with diuretics may be at risk of severe dehydration and subsequent renal impairment. Special populations which may be at higher risk also include those with a fluid overload in extravascular compartments, but with intravascular contraction. These groups include subjects with hepatic cirrhosis, and potentially some subjects with heart failure.

Table 6.1.3.2-1 Important Identified Risk: Volume Depletion, Dehydration and Associated Sequelae such as Renal Dysfunction	
Risk minimisation measures	**Routine risk minimisation measures**: **Samsca SmPC** • **Section 4.2** • **Section 4.3** • **Section 4.4** • **Section 4.8** **Samsca PL** • **Section 2** • **Section 3** • **Section 4** • Prescription only medication **Additional risk minimization measures**: • None **Additional pharmacovigilance activities**: None

Table 6.1.3.2-2 Missing Information: Pregnancy Outcome Data	
Risk minimisation measures	**Routine risk minimisation measures:** **Samsca SmPC** • **Section 4.3** • **Section 4.6** **Samsca PL** • **Section 2** Prescription only medication **Additional risk minimisation measures:** • None **Additional pharmacovigilance activities:** • None

Table 6.1.3.2-3 Missing Information: Off-label Use	
Risk minimisation measures	**Routine risk minimisation measures:** **Samsca SmPC** • **Section 4.1** **Samsca PL** • **Section 1** Pescription only medication **Additional risk minimisation measures:** None **Additional pharmacovigilance activities:** None

Table 6.1.3.2-4 Missing Information: Use in Hepatic Impaired Patients	
Risk minimisation measures	**Routine risk minimisation measures:** **Samsca SmPC** • **Section 4.2** • **Section 4.4** • **Section 5.2** **Samsca PL** • **Section 2** Prescription only medication **Additional risk minimisation measures:** None **Additional pharmacovigilance activities:** None

6.1.4 II.C: Post-authorisation Development Plan (Samsca)

II.C.1. Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation for Samsca.

6.2 Summary of the Risk Management Plan for Jinarc

6.2.1 VI.1: Summary of the Risk Management Plan for Jinarc

This is a summary of the risk management plan (RMP) for Jinarc. The RMP details important risks of Jinarc, how these risks can be minimised, and how more information will be obtained about tolvaptan's risks and uncertainties (missing information).

Jinarc's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how this product should be used.

This summary of the RMP for Jinarc should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of tolvaptan’s RMP.

6.2.2 I: The Medicine and What it is Used for

Jinarc is authorised in the EEA under indication to slow the progression of cyst development and renal insufficiency of atuosomnal dominant polycyctic kidney disease (ADPKD) in adults with CKD stage 1 to 4 at initiation of treatment with evidence of rapidly progressing disease (see SmPC for the full indication). It contains tolvaptan as the active substance and it is given by oral tablet administration.

Further information about the evaluation of Jinarc’s benefits can be found in Jinarc’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage.
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Risk-management-plan_summary/human/002788/WC500183093.pdf

6.2.3 II: Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Jinarc, together with measures to minimise such risks and the proposed studies for learning more about its risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (eg, prescription only) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Jinarc, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, (including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Jinarc is not yet available, it is listed under 'missing information' below.

6.2.3.1 II.A: A List of Important Risks and Missing Information

Important risks of Jinarc are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Jinarc. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table 6.2.3.1-1 II.A-1: List of Important Risks and Missing Information for Jinarc (from Part II: Module SVIII)

Important identified risks	• Liver Injury in ADPKD Patients • Volume depletion, dehydration and associated sequelae such as renal dysfunction
Important potential risks	• None
Missing information	• Pregnancy outcome data • Off-label use • Use in hepatic impaired patients • Use in ADPKD patients over the age of 55 years • Long term use of Jinarc in routine medical practice

6.2.3.2 II.B: Summary of Important Risks for Jinarc

Table 6.2.3.2-1 Important Identified Risk: Liver Injury in ADPKD Patients	
Evidence for linking the risk to the medicine	The risk of developing hepatotoxicity involves a complex interplay between the chemical properties of the drug, environmental factors (eg, the use of concomitant drugs or alcohol), age, sex, and underlying diseases. The most extensively documented risk factors are concomitant drug use and diseases.[62,63] The mechanisms underlying tolvaptan-induced liver injury cannot be determined based on the available data. However, the prolonged latency to onset and the relatively prompt recurrence upon re-challenge would support involvement of the adaptive immune system. Engagement of adaptive immunity could also potentially account for the progression and prolonged resolution phases characteristically observed after discontinuing tolvaptan treatment.[61] In view of the liver safety signal emerging from review of the ADPKD clinical trial database, liver safety data from the preapproval clinical trials for cirrhosis, congestive heart failure, and hyponatraemia were reviewed by the experts and no signal was found.[61]
Risk factors and risk groups	**ADPKD** The liver enzyme elevations seen with Jinarc characteristically had an onset between 3 and 18 month of treatment. The injury typically progressed by biochemical criteria for weeks after discontinuation of treatment, and resolved slowly over one to several months. HLA alleles have been identified as patient risk factors for liver injury due to certain drugs. If HLA alleles that infer risk for liver injury in tolvaptan treated patients are identified (ie, missing information), a personalized medicine approach to improve liver safety might be feasible.

Table 6.2.3.2-1 Important Identified Risk: Liver Injury in ADPKD Patients	
Risk minimisation measures	**Routine risk minimisation measures:** **Jinarc SmPC** • **Section 4.3** • **Section 4.4** **Jinarc PL** • **Section 2** • **Section 4** Medicinal product subject to restricted medical prescription **Additional risk minimisation measures** Details of prescriber's education, certification in the prescriber's registry and reassurance of prescriber's certification prior to the dispensation of Jinarc shall be agreed by the MAH with each National Competent Authority Several education materials are available: • Patient Education Brochure • Healthcare Professional Education Guide • Jinarc Prescribing Checklist • Patient Alert Card
Additional pharmacovigilance activities	**Jinarc** • PASS 156-12-299 • Ajudication of cases of liver injury by a panel of independent experts of a Hepatic Adjudication Committee (HAC)

Table 6.2.3.2-2 Important Identified Risk: Volume Depletion, Dehydration and Associated Sequelae such as Renal Dysfunction	
Evidence for linking the risk to the medicine	**ADPKD** 2.7.4 Summary of Clinical Safety and Clinical Study Report 156-04-251 and 2.7.4 Summary of Clinical Safety and Clinical Study Report 156-13-210 for NDA resubmission.

Table 6.2.3.2-2 Important Identified Risk: Volume Depletion, Dehydration and Associated Sequelae such as Renal Dysfunction	
Risk factors and risk groups	Patients with an inability or a compromised capacity to perceive and communicate thirst would be at risk of severe dehydration without appropriate medical intervention. This would include bedridden and unconscious subjects. Patients who are concomitantly treated with diuretics may be at risk of severe dehydration and subsequent renal impairment. Special populations which may be at higher risk also include those with a fluid overload in extravascular compartments, but with intravascular contraction. These groups include subjects with hepatic cirrhosis, and potentially some subjects with heart failure.
Risk minimisation measures	**Routine risk minimisation measures:** **Jinarc SmPC** • **Section 4.3** • **Section 4.4** **Jinarc PL** • **Section 2** • **Section 4** Medicinal product subject to restricted perscription **Additional risk minimization measures**: • Healthcare Professional Education Guide • Jinarc Prescribing Checklist • Patient Education Brochure • Patient Alert Card **Additional pharmacovigilance activities**: None

Table 6.2.3.2-3 Missing Information: Pregnancy Outcome Data	
Risk minimisation measures	**Routine risk minimisation measures:** **Jinarc SmPC** • **Section 4.3** • **Section 4.6** **Jinarc PL** • **Section 2** Medicinal product subject to restricted medical prescription **Additional risk minimisation measures:** • Healthcare Professional Education Guide • Jinarc Prescribing Checklist • Patient Education Brochure **Additional pharmacovigilance activities:** • PASS (156-12-299)

Table 6.2.3.2-4 Missing Information: Off-label Use	
Risk minimisation measures	**Routine risk minimisation measures:** **Jinarc SmPC** • **Section 4.1** • **Section 4.2** **Jinarc PL** • **Section 1** Medicinal product subject to restricted medical prescription. Pack size **Additional risk minimisation measures:** None **Additional pharmacovigilance activities:** PASS 156-12-299

Table 6.2.3.2-5 Missing Information: Use in Hepatic Impaired Patients	
Risk minimisation measures	**Routine risk minimisation measures:** **Jinarc SmPC** • **Section 4.2** • **Section 4.4** • **Section 5.2** **Jinarc PL** • **Section 2** • **Section 4** Medicinal product subject to restricted medical perscription **Additional risk minimisation measures:** None **Additional pharmacovigilance activities:** None

Table 6.2.3.2-6 Missing Information:Use in ADPKD Patients over the age of 55 years	
Risk minimisation measures	**Routine risk minimisation measures:** **Jinarc SmPC** • **Section 4.2** • **Section 5.1** • **Section 5.2** **Jinarc PL** • **Not applicable** Medicinal product subject to restricted medical prescription **Additional risk minimisation measures:** None **Additional pharmacovigilance activities:** Protocol PASS 156-12-299

Table 6.2.3.2-7 Missing Information: Long-term Use of Jinarc in Routine Medical Practice	
Risk minimisation measures	**Routine risk minimisation measures:** **Jinarc SmPC** • **Section 5.1** **Jinarc PL** • **Not applicable** Medicinal product subject to restricted medical prescription **Additional risk minimisation measures:** None **Additional pharmacovigilance activities:** PASS 156-12-299

6.2.4 II.C: Post-authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

Table 6.2.4-1 Ongoing and Planned Additional Pharmacovigilance Activities for the ADPKD Indication (Jinarc)				
Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1- Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit risk)				
Jinarc PASS 156-12-299 Ongoing	Jinarc PASS: In the EU/EFTA 2,100 patients who are treated according to the decision of the treating physician will be followed prospectively for a minimum of 2 years and a maximum of 5 years monitor the risk of liver injury in the real life setting. To compliment this prospective study, a large multi-national retrospective database analysis at predetermined periods postlicensing will allow monitoring of off label use. In addition, there will be an assessment of ADPKD related morbidity and mortality, ncluding longer-term effects on GFR decline and progression of disease leading to dialysis or trans-plantation. 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 missing information: Off label use, Use in patients over the age of 50 years in ADPKD patients, Use and potential risks in pregnant women, including frequency and outcome of pregnancies associated with the use of Jinarc. and Long term use of Jinarc in routine medical practice. In addition, ADPKD related morbidity and mortality will be assessed.	Started FPFV: Planned LPLV: Retrospective database analysis: Interim Report Final Study Report:	31 Oct 2016 31 Mar 2024 Predetermined periods post- licnsing to be clarified in the full protocol 31 Dec 2022 Planned Q1 2025

II.C.2 Other Studies in Post-authorisation Development Plan

Table 6.2.4-2 Other Studies in Post-authorisation Development Plan for the ADPKD Indication (Jinarc)				
Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Hepatic Adjudication Committee (HAC) adjudication of cases of liver injury. Ongoing	To help assess the effectiveness of risk minimisation activities for liver injury with the use of tolvaptan in ADPKD.	Follow-up on incidence of cases in clinical trials to assess if rules for withdrawal of tolvaptan are effective Risk of Liver injury in ADPKD patients	All cases of suspected liver injury, both from the clinical trials and from the postmarketing settings. are assessed by the HAC and 3 quarterly reports are issued in addition to Annual liver safety summary (LSS) report being produced on ongoing basis.	Ongoing

7.4 Annex 4: Specific Adverse Drug Reaction Follow-up Forms

Jinarc®▼ (Tolvaptan) Hepatotoxicity Adverse Event Follow-up Form

Patient ID:	**Patient Initials:**	**Birth Date (dd/mmm/yyyy):**
Follow up to reported hepatic adverse event		
INSTRUCTIONS: Please complete this form **as completely as possible** to provide relevant information associated with your initial report of a hepatic event which was submitted to Otsuka PV. This will help Otsuka to better assess the reported event. Please return to <insert email address>		
Demographic Data:		
Case #	Sex: ☐ Female ☐ Male	Ethnicity: ☐ Caucasian ☐ Indian ☐ Asian ☐ Other: (specify):
Medicinal Product (Jinarc): _____ Information:		
Start Date:	Stop Date:	☐ Continuing
Indication:		
Hepatic Event Information:		
Please provide the onset date of the hepatic event: _____		
Please provide the final diagnosis for the hepatic event:		
Please provide a brief description of the hepatic event (use additional pages if needed).		
Was a hepatologist or gastroenterologist consulted with reference to the hepatic events? ☐ Yes ☐ No If yes, provide diagnosis and assessment.		
After discontinuing Jinarc therapy in response to the hepatic event, did you observe any changes in the patient's clinical data that may further explain the observed hepatic event?		
Was treatment/intervention provided for this hepatic event ☐ Yes ☐ No		
Date of Treatment/Intervention (M/D/Y)	Treatment/Intervention (specify)	

Outcome of hepatic event:	**Assessment**		
☐ Recovered/resolved Date: _____ ☐ Recovering/ Resolving ☐ Not recovered	☐ Life-threatening ☐ Not Life-threatening ☐ Serious/Medically significant ☐ Non-serious	☐ Other: _____	☐ Fatal Cause of Death: _____ _____ Date of Death: _____

Was the patient hospitalized due to the hepatic event? ☐ Yes ☐ No If yes: Date of Admission Date of Discharge
Did the patient need a liver transplant due to the hepatic event? ☐ Yes: Date _____ ☐ No
Did the hepatic event abate after Jinarc was stopped? ☐ Yes ☐ No ☐ Not Applicable (Jinarc was not stopped)
Was Jinarc restarted? ☐ Yes: Restart Date _____ ☐ No

If Jinarc was restarted, did the hepatic event reoccur? ☐ Yes: Date _____ ☐ No

Was the hepatic event related to MP? ☐ Yes ☐ No

Is there any other explanation or an alternative etiology for the hepatic event? ☐ Yes (specify below)
☐ No

Patient ID:	**Patient Initials:**	**Birth Date (dd/mmm/yy):**

Laboratory Findings (Include all available results):

	Immediately Prior to start of Jinarc		**First Abnormal**		**Most Abnormal**		**Resolution**		
Serum Tests	**Value (unit)**	**Date of Test (M/D/Y)**	**Value (unit)**	**Date of Test (M/D/Y)**	**Value (unit)**	**Date of Test (M/D/Y)**	**Value (unit)**	**Date of Test (M/D/Y)**	**Reference Normal Values (units)**
ALT									
AST									
Total Bilirubin									
Alkaline Phosphatase									
INR									
GGT									
Albumin									
Serum Ammonia									
Hepatitis A serology									
Hepatitis B serology									
Hepatitis C serology									
EBV serology									
Eosinophils									
Anti-smooth muscle Ab*									
Immunoglobulin G (IgG)									
Anti-actin Ab									
Anti-mitochondrial Ab									
Anti-nuclear Ab									
Anti-native DNA Ab									
Other (Please specify):									

Concomitant Medications: Please list all medications taken prior to starting or during Jinarc treatment including prescription medications, over-the counter medications, dietary supplements, and or herbal products). If list of concomitant medications exceeds the rows provided, please attach an additional page using the column headers**.**

Medication	Dose (units)	Start Date	Stop Date	Indication

Do you consider any of the concomitant medications to be related to the hepatic event (i.e. a suspect medication)? ☐ Yes ☐ No If yes, list medication and rationale:		
Patient ID:	**Patient Initials:**	**Birth Date (dd/mmm/yy):**

Relevant History and Concurrent Disorders: (Check all that apply and include start and stop dates)

☐ None	☐ Drug Abuse	☐ Granulomatosis	☐ Recent general anaesthesia
☐ Alcohol Abuse	☐ Diabetes	☐ Hypertriglyceridemia	☐ Blood product transfusion
☐ Cirrhosis	☐ Sepsis	☐ Ischemic Hepatitis	☐ Psoriasis
☐ Biliary Tract Disorders	☐ Gilbert's syndrome	☐ Heart Failure/Heart Disease	☐ Recent Travel to Foreign Countries
☐ Viral Hepatitis	☐ Illicit drugs	☐ Obesity	☐ Wilson's disease
☐ Auto-Immune Hepatitis	☐ Non-Alcoholic Steatohepatitis (NASH)	☐ Hypotensive episodes	☐ Liver disease in pregnancy
☐ Anorexia	☐ Rigorous physical activity/exercise	☐ Family history of liver disease	☐ Documented Hypotension
☐ Familial hyperbilirubinemia	☐ Hepatic Cyst/Polycystic kidney disease	☐ Hyperlipoproteinemia	☐ Trauma/Falls
☐ Gallbladder Disease Gall stones/ Bile duct occlusion	☐ Malignancy (including metastasis and grading): Please specify site	☐ Occupational exposure (benzine, carbon tetrachloride, chloroform, methylene chloride)	☐ Poisoning/Toxicity (eg. Poisonous mushrooms or organic solvents)
☐ Other (Please specify):			

Symptoms / Clinical Presentation: (Check all that apply)

☐ No symptoms	☐ Jaundice	☐ Bleeding disorder	☐ Purpura
☐ Abdominal pain	☐ Nausea	☐ Hepatic tenderness	☐ Asterixis
☐ Abdominal distension	☐ Vomiting	☐ Dark urine	☐ Splenomegaly
☐ Anorexia	☐ Fever	☐ Hepatomegaly	☐ Joint pain
☐ Ascites	☐ Rash	☐ Pruritus	☐ Weight gain
☐ Asthenia	☐ Weakness	☐ Lymphadenopathy	☐ Encephalopathy
☐ Fatigue	☐ Other (Please specify):		

Diagnostic Tests

Test	Date of Test (M/D/Y)	Findings
Ultrasound of the Abdomen		

Liver Biopsy		
Abdominal X-Ray		
Abdominal CT		
MRI of Abdomen		
Other (Please specify):		

Name: _____

Signature: _____

Date: _____

7.6 Annex 6: Details of Proposed Additional Risk Minimisation Activities (if applicable)

The following materials for additional risk minimisation plan are provided as appendices:

Appendix 1 Healthcare Professional Education Guide

Appendix 2 Otsuka Jinarc Patient Education Brochure

Appendix 3 Otsuka Jinarc Patient Alert Card

Appendix 4 JINARC® (tolvaptan) Prescribing Checklist

Appendix 1 Healthcare Professional Education Guide

Jinarc®▼

(tolvaptan)

Healthcare Professional Educational Guide

Date of preparation: August 2021

Contents

1. Glossary

ADPKD	Autosomal dominant polycystic kidney disease
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AP	Alkaline phosphatase
BT	Bilirubin-total
eGFR	Estimated glomerular filtration rate
HCP	Healthcare professional
INR	International normalized ratio
mL/min	Milliliters per minute
mg	Milligram
SmPC	Summary of product characteristics
WCBP	Women of child bearing potential
ULN	Upper limit of normal

2. What is the purpose of this guide?

This guide is provided by Otsuka Pharmaceutical Europe Limited for prescribers and other healthcare professionals (HCPs) who are responsible for the treatment of patients with autosomal dominant polycystic kidney disease (ADPKD) using Jinarc® (tolvaptan).

This guide will enable you to:

- Understand what Jinarc® is indicated for and how it should be used
- Be aware of the important side effects of Jinarc® (in particular idiosyncratic hepatic toxicity and the risk of dehydration) and how they can be prevented, identified and managed
- Provide important safety information to your patients receiving Jinarc® and the need for regular monitoring
- Be aware of tools available to support the safe use of Jinarc® and their purpose
- Be aware of the mechanism to report adverse events.

Important: This guide summarises specific important information about Jinarc®. Before prescribing or dispensing Jinarc®, please read the Summary of Product Characteristics (SmPC) carefully, as it contains all the important information you need to know about Jinarc®.

3. What is Jinarc® and what is it indicated for?

Jinarc® contains tolvaptan, which blocks the effects of vasopressin at the V_2 receptor in the kidney, and 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 4 at initiation of treatment with evidence of rapidly progressing disease.

4. When should treatment not be initiated with Jinarc®?

The physician will need to determine if their patient is appropriate to receive Jinarc® therapy (please see section 4.3 of the Jinarc® SmPC for the complete information on contraindications for Jinarc therapy). Due to the risk of hepatic toxicity with Jinarc® therapy for ADPKD, Jinarc® should not be used in patients with any of the following:

- Elevated liver enzymes and/or signs or symptoms of liver injury prior to initiation of treatment that meet the requirements for permanent discontinuation of Jinarc®

- Inability or unwillingness to comply with monthly liver function testing.

Additionally, Jinarc® should not be used in patients with any of the following (included but not limited to):

- Volume depletion
- Inability to perceive or respond to thirst
- Female patients trying to become pregnant, Pregnant, or breastfeeding

5. What dose of Jinarc® should I prescribe?

The initial dosage for Jinarc® in patients with ADPKD is 60mg per day as a split-dose regimen of 45mg + 15mg (45mg taken upon waking and 15mg taken 8 hours later). Up titration to a split regime of 90mg (60mg + 30mg) per day, and then to a split dose regime of 120mg (90mg + 30mg) per day, if tolerated, should be attempted with at least weekly intervals between titration steps.

It is important to follow Jinarc® SmPC for the complete dosing instructions, including special considerations and information about interaction with other medications and supplements (see Jinarc® SmPC, section 4.2).

6. What are some of the special warnings and precautions for use pertaining to Jinarc therapy?

Please read section 4.2 (Posology and method of administration), section 4.4 (Special warnings and precautions for use) and section 4.5 (Interaction with other medicinal products and other forms of interaction) of the SmPC as they contain the complete and important information, including but not limited to hepatic toxicity and dehydration which are important to consider prior to prescribing Jinarc®.

Jinarc® has been associated with idiosyncratic elevations of blood ALT and AST with infrequent cases of concomitant elevations in BT. In post-marketing experience with tolvaptan in ADPKD, acute liver failure requiring liver transplantation has been reported.

7. How should I manage patients with existing hepatic impairment?

Dose adjustment is not needed in patients with mild or moderate hepatic impairment (Child-Pugh classes A and B). Limited information is available in patients with severe hepatic impairment (Child-Pugh class C). These patients should be managed cautiously and liver enzymes should be monitored regularly. Jinarc® should be used in cirrhotic patients only when the need to treat outweighs the risk of treatment.

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.

8. How should I evaluate the liver function of patients on Jinarc therapy?

To mitigate the risk of significant and/or irreversible liver injury, blood testing for hepatic transaminases and bilirubin is required prior to initiation of Jinarc®, continuing monthly for 18 months and at regular intervals (every 3 months) thereafter.

Prior to initiation:

If a patient has abnormal blood ALT, AST or BT levels prior to initiation of treatment which fulfil the criteria for permanent discontinuation, the use of Jinarc® is contraindicated. In case of abnormal baseline levels below the limits for permanent discontinuation, treatment can only be initiated if the potential benefits of treatment outweigh the potential risks and liver function monitoring must continue at increased time frequency. The advice of a hepatologist is recommended.

During the first 18 months of treatment:

During the first 18 months of treatment, Jinarc® will only be supplied to patients whose physician has determined that monitored liver function supports continued therapy.

At the onset of symptoms or signs consistent with hepatic injury or if clinically significant abnormal ALT or AST increases are detected during treatment, Jinarc® administration must be immediately stopped and repeat tests including ALT, AST, BT and alkaline phosphatase (AP) must be obtained as soon as possible (ideally within 48-72 hours). Testing must continue at increased time frequency until symptoms/signs/laboratory abnormalities stabilise or resolve, at which point Jinarc® may be re-initiated.

Jinarc® therapy should be stopped upon confirmation of sustained or increasing transaminase levels and permanently discontinued if significant increases and/or clinical symptoms of hepatic injury persist.

Recommended guidelines for permanent discontinuation include:

- ALT or AST >8 x ULN
- ALT or AST >5 x ULN for more than 2 weeks
- ALT or AST >3 x ULN and (BT >2 x ULN or international normalised ratio (INR) >1.5)
- ALT or AST >3 x ULN with persistent symptoms of hepatic injury noted as above.

If ALT and AST levels remain below 3-times the upper limit of normal (ULN), Jinarc® therapy may be cautiously re-started, with frequent monitoring at the same or lower doses, as transaminase levels appear to stabilise during continued therapy in some patients.

A Jinarc® prescribing checklist has been developed to help HCPs decide whether to continue treatment in patients exhibiting signs and symptoms of liver injury and elevated liver enzymes.

It is important to report adverse events involving liver injury, including any AST or ALT rise exceeding 3 x ULN.

Please report Adverse Drug Reactions to Otsuka Pharmaceutical Europe LTD. Pharmacovigilance Department on telephone: +44 (0) 203 747 5000 (including out of hours), fax: +44 (0) 1895 207 115. Email: vigilance@otsuka-europe.com

9. What are some of the safety issues should I discuss with patients prescribed Jinarc®?

Liver injury

Patients should be informed about regular blood testing required to monitor and manage the risk of liver injury while taking Jinarc®. 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) should also be discussed. Patients should be advised to report these side effects immediately if they occur.

Water loss and the risk of dehydration

Jinarc® may cause undesirable effects related to water loss such as thirst, polyuria, nocturia, and pollakiuria. Patients should be instructed to drink water or other aqueous fluids ahead of thirst, in order to avoid excessive thirst or dehydration. Additionally, patients should be advised to drink 1-2 glasses of fluid before bedtime regardless of perceived thirst, and to replenish fluids overnight with each episode of nocturia.

Ensure that patients are aware of diseases that may impair appropriate fluid intake or conditions that may increase the risk of water loss e.g. in case of vomiting or diarrhoea. Patients should be instructed to contact you in case they have experienced such conditions or have signs or symptoms of dehydration.

Fertility/Pregnancy/Lactation information

Jinarc® is contraindicated during conception and pregnancy as it may result in developmental abnormalities in the foetus. It is also contraindicated while breastfeeding.

Women of child-bearing potential (WCBP) should be advised to use effective and reliable method of contraception at least four weeks before starting therapy, during therapy and even in the case of dose interruptions, and for at least a further four weeks after stopping Jinarc®.

Female patients should be advised to report to the treating physician immediately if they are pregnant or think they may be pregnant while taking Jinarc® or within 30 days after stopping Jinarc®. Women should be advised not to breastfeed while taking Jinarc®.

Please refer to section 4.6, Fertility, pregnancy and lactation, of the Jinarc® SmPC for additional information.

10. What other tools are available to support the safe use of Jinarc®?

In addition to this guide, other tools available to support Health Care Professionals' and patients' use of Jinarc® include a Prescribing Checklist, Patient Education Brochure and Patient Alert Card. These are described in more detail below:

Prescribing Checklist:

The Prescribing Checklist is designed to assess the suitability of patients who have been identified as candidates for Jinarc® therapy. The checklist can be used at treatment initiation and regularly thereafter for monitoring patients to support the appropriate use of Jinarc®. At initiation, the checklist helps check contraindications and precautionary conditions to enable appropriate prescribing; it reminds the HCP to educate the patient in the correct use of the medicine. In the case of patients receiving on-going treatment, the checklist helps the HCP perform key checks to monitor the patient's condition and provides an algorithm to assist in optimising dosing based on tolerability.

Patient Education Brochure:

The Patient Education Brochure contains a summary of the key information that the patient should be aware of while on Jinarc® therapy. It should be given to

patients so they can learn more about dosing plan, correct intake, and the safety issues to be aware of while taking Jinarc®. The Patient Education Brochure also advises patients to contact their prescribing doctor if they are concerned that they may be experiencing signs and symptoms of hepatic injury on treatment.

Patient Alert Card:

The Patient Alert Card contains important safety information about Jinarc® for patients and emergency carers. It includes information on hepatotoxicity, severe dehydration and advice should such symptoms occur. The Patient Alert Card should be filled out and given to the patient by their prescribing doctor or nurse. The patient should keep it with them in their wallet or bag at all times.

11. How should I report adverse drug reactions with Jinarc®?

Please report all suspected adverse drug reactions to Otsuka Pharmaceutical Europe LTD Pharmacovigilance Department on +44 (0) 203 747 5000 (including out of hours), by fax on +44 (0) 1895 207 115, email vigilance@otsuka-europe.com.

12. Where can I obtain further information?

For further information, please go to:

https://www.ema.europa.eu/en/medicines/human/EPAR/jinarc

Appendix 2 Otsuka Jinarc Patient Education Brochure

Jinarc®▼

(tolvaptan)

Patient Education Brochure

Contents

1. What is the purpose of this brochure?

This Patient Education Brochure is provided by Otsuka Pharmaceutical Europe LTD. for patients with autosomal dominant polycystic kidney disease (ADPKD) who are receiving treatment with Jinarc® (tolvaptan).

This brochure will:

- Explain what Jinarc® is, what medical condition it is used for and how it should be used
- Provide some of the important safety information with respect to the risk that Jinarc can cause your liver to not work properly ®, as well as cause excessive water loss, and what to do if they occur.
- Inform you on the importance of pregnancy prevention while being treated with Jinarc.

Important: Please read the "Package leaflet: Information for the patient" (found in the medicine package) which contains the complete information, including other precautions, you need to know when taking Jinarc. Talk to your doctor if you have any questions about your treatment with Jinarc®.

2. What is Jinarc®?

You have been prescribed Jinarc® because you have "autosomal dominant polycystic kidney disease" or "ADPKD". Jinarc is used to treat ADPKD in adults with chronic kidney disease (CKD) stages 1 to 4 with evidence of rapidly progressing disease.

Jinarc contains the active substance tolvaptan which blocks the effect of the hormone vasopressin. By blocking the effect of vasopressin, Jinarc increases urine production and slows the growth of kidney cysts in patients with ADPKD.

3. Which patients are not eligible for treatment with Jinarc®?

Your doctor will determine whether it is appropriate for you to receive treatment with Jinarc. Due to the some of the risks associated with Jinarc therapy, such as potential effects which may cause your liver not to work properly, and the potential to cause dehydration, you should not take Jinarc® if any of the following applies to you:

- If you have been told that you have raised levels of liver enzymes in your blood which do not allow treatment with Jinarc®

- If you are unable or unwilling to comply with monthly blood test for checking liver function.
- If you have any condition which is associated with a very low blood volume
- If you have difficulty realising when you are thirsty or are unable to drink sufficient amounts of water

Avoid treatment with Jinarc if you are a female, and you are planning to get pregnant, are pregnant, or breastfeeding.

4. Which patients should take special care when taking Jinarc®?

You should take care while taking Jinarc® and tell your doctor:

- If you suffer from liver disease, or other medical conditions or illness
- If you cannot drink enough water or if you have to limit your fluid intake or you are at an increased risk of water loss
- If you are not sure that Jinarc therapy may be appropriate for you

5. What are some of the important side effects of Jinarc® that should I be aware of?

Jinarc® may cause your liver not to work properly and increase the level of liver enzymes and bilirubin in your blood. You may need to get additional blood testing. Treatment with Jinarc® will be stopped and may be restarted if the blood tests for liver function are normal.

To check for any changes in your liver function, your doctor will conduct blood tests:

- before starting treatment with Jinarc®
- every month for the first 18 months of treatment
- every 3 months thereafter.

The following symptoms indicate that you may have potential liver problems:

- tiredness
- loss of appetite
- pain in the abdomen

- dark urine
- yellowing of skin or eyes (jaundice)
- severe dehydration
- nausea
- vomiting
- itching
- Flu-like syndrome (joint and muscle pain)
- fever

It is important that you contact your doctor if you develop any of the symptoms listed above.

6. Is it important to drink plenty of fluids when taking Jinarc®?

Jinarc also causes water loss because it increases your urine production. This water loss may result in side effects such as dry mouth and thirst or even more severe side effects like kidney problems or severe dehydration.

Symptoms of dehydration may include:

- increased thirst
- dry mouth
- feeling tired or sleepy
- decreased urination
- headache
- dry skin
- dizziness
- rapid heart rate
- confusion
- poor skin elasticity

It is important that you contact your doctor if you develop any of the symptoms listed above.

Jinarc® will make you pass urine more often than before and this may make you more thirsty than usual. You should drink plenty of water or other watery drinks

whether or not you feel thirsty in order to avoid excessive thirst or dehydration. You should drink 1-2 glasses of fluid before bedtime and drink more if you pass urine during the night time. Special care must be taken if you have diseases that increase the risk of water loss, e.g. in case of vomiting or diarrhoea.

7. Is it safe to take Jinarc® while trying to become pregnant, during pregnancy or while breastfeeding?

You must not take Jinarc® if you are trying to become pregnant or during pregnancy as it may result in side effects to you and developmental abnormalities in your unborn baby. Women of childbearing potential must use effective and reliable method of pregnancy prevention at least four weeks before therapy is initiated, during therapy and even in the case of dose interruptions, and for at least a further four weeks after stopping Jinarc®. You must not breastfeed while taking Jinarc®. In case you become pregnant, stop taking Jinarc® and inform your prescribing doctor immediately so that your pregnancy can be monitored.

8. What is the Jinarc® Patient Alert Card and how should I use it?

When you are first prescribed Jinarc® you will be given the Jinarc® Patient Alert Card by your doctor or nurse. This card contains important safety information regarding the risks of liver injury and dehydration while taking Jinarc® and what to do should signs or symptoms occur. It also contains the emergency contact details of your doctor or treatment centre. The contact details will be added to the card by your healthcare provider. You should keep it with you in your wallet or bag at all times in case of emergency.

If you have not received the Patient Alert Card please contact your doctor or nurse.

Appendix 3 Jinarc Patient Alert Card

Otsuka **Jinarc®▼ (Tolvaptan)** Patient Alert Card

Patient's Name:

_____

Date Jinarc® first prescribed:

_____

Doctor's Name:

_____

Hospital name and telephone number:

_____

Important safety information for patients

Jinarc® **can affect how your liver works**.

Consult your doctor if you experience symptoms of tiredness, loss of appetite, upper abdominal pain or discomfort, fever, dark urine or yellowing of skin or eyes, joint and muscle pain with fever (flu-like syndrome), itching, nausea and vomiting.

Jinarc® **can cause severe dehydration.**

Drink plenty of fluids to avoid dehydration or excessive water loss and consult your doctor if you are not able to drink fluids by mouth.

Important safety information for emergency carers

Jinarc® may cause liver injury. Blood tests for liver function must be performed periodically (monthly for the first 18 months, then every 3 months of continuing treatment). Therapy should be stopped or discontinued if significant increase of liver enzymes and/or clinical symptoms of hepatic injury persist.

Jinarc® can produce significant increase in urination which may lead to severe dehydration or excessive water loss. Symptoms of dehydration may include increased thirst, dry mouth, feeling tired or sleepy, decreased urination, headache, dry skin, dizziness, rapid heart rate, confusion and poor skin elasticity.
For more info please visit <<product website>>

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Appendix 4 Jinarc (Tolvaptan) Prescribing Checklist

JINARC®▼ (tolvaptan) Prescribing Checklist For Treatment Initiation

Patient name		**Patient hospital number**	

JINARC® (tolvaptan) 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 4 at initiation of treatment and evidence of rapidly progressing disease. This checklist should be used before treatment initiation (**Sections A** and **B**) and during ongoing treatment (**Section C**) with JINARC®.

Section A: Check patient's eligibility for initiating Jinarc® treatment

For the following statements, please tick 'Yes' if the statement applies to the patient, or 'No' if it does not

CONTRAINDICATIONS – if any of the following apply to the patient then they should **not** be treated with JINARC®	**Yes**	**No**
Elevated liver enzymes as follows: • ALT or AST >8 x upper limit of normal (ULN); • ALT or AST >5 x ULN for more than 2 weeks; • ALT or AST >3 x ULN and (BT >2 x ULN or international normalized ratio [INR] >1.5) • ALT or AST >3 x ULN with persistent symptoms of hepatic injury (such as fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, dark urine or jaundice)		
Hypersensitivity to the active substance or any of its excipients (e.g. lactose or galactose intolerance, benzazepine or benzazepine derivatives)		
Anuria		
Volume depletion		
Hypernatraemia		
Inability to perceive or respond to thirst		
Trying for a pregnancy, Pregnant or breastfeeding		
Unwilling/unable for monthly monitoring visits		
PRECAUTIONARY CONDITIONS – If any of the following apply to the patient, caution along with appropriate monitoring should be used	**Yes**	**No**
Raised liver enzymes, AST and/or ALT stabilised at no greater than 3 x ULN **In case of abnormal baseline levels below the limits for permanent discontinuation, treatment can only be initiated if the potential benefits of treatment outweigh the potential risks and liver function testing must continue at increased time frequency. The advice of a hepatologist is recommended.**		
Severe hepatic impairment (Child-Pugh class C)		
Limited access to water and signs of dehydration		
Partial obstruction of urinary outflow (e.g. prostatic hypertrophy)		
Fluid and electrolyte imbalance		
Serum sodium abnormalities		
History of anaphylaxis		
Lactose and galactose intolerance		
Diabetes Mellitus		
Elevated uric acid concentration		
Decreased glomerular filtration rate		
Use of medicines likely to interact with Jinarc® such as CYP3A inhibitors (e.g. ketoconazole, fluconazole, grapefruit juice), CYP3A inducers (e.g. rifampin), CYP3A substrates, transporter substrates, digoxin, drugs increasing serum sodium concentration, diuretics or non-diuretic anti-hypertensive medicinal products, and vasopressin analogues. *Jinarc® is to be administered in daily doses of 15mg or 30mg in patients taking drugs that are moderate or strong CYP 3A inhibitors, as concomitant use of these drugs increases Jinarc® exposure. Please see Jinarc SmPC for detailed information. (See Jinarc SmPC, Sections 4.2 and 4.5 for the complete information)*		
PRESCRIBING DECISION (Initiation)	**Yes**	**No**
I intend to initiate treatment with JINARC® (select one dose below):		

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○ 60mg per day (split dose 45mg and 15mg) ○ Split dose 15mg and 15mg (if patient is also on moderate CYP3A inhibitor) ○ 15mg per day (if patient is also on strong CYP3A inhibitor)		
If you have decided to prescribe JINARC® please complete **Section B**		

Section B: Patient education

Please tick the corresponding box if the statement applies to the patient

I have reminded the patient of the risk of liver toxicity with use of Tolvaptan therapy, need for monthly blood liver function test for the first 18 months of therapy and 3 monthly thereafter on continuing therapy.			
I have reminded the patient to be vigilant for signs and symptoms of hepatic injury, to drink adequate fluids ahead of thirst sensation and to drink 1-2 glasses of fluid before bedtime.			
I have advised a female patient to use adequate contraception and to report pregnancy if it occurs while on treatment. **Or the patient is male or a woman of non-childbearing potential**			
I have given the patient a Patient Education Brochure and Patient Alert Card.			
Prescriber signature		**Date**	

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JINARC®▼ (tolvaptan) Prescribing Checklist For Patient Monitoring

Patient name		Patient hospital number	

Section C: Check patient's on-going eligibility for Jinarc® treatment

The following sections should be completed monthly for Jinarc® (tolvaptan) patients who are being treated for ADPKD for the first 18 months, and then every 3 months thereafter.

All adverse events should be reported to Otsuka using the reporting mechanism below.

Please tick 'Yes' if the statement applies to the patient, 'No' if it does not

HEPATIC INJURY	Yes	No
Is the patient showing any signs or symptoms of liver injury (fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, icterus, dark urine or jaundice)**? If the answer is Yes, treatment with Jinarc® should be stopped, the cause investigated and the occurrence reported using the reporting mechanisms below.**		

Liver function test results	Recommended action
ALT or AST abnormal	**Stop Jinarc® treatment and investigate the cause of the raised liver enzyme(s) including repeat tests as soon as possible (ideally within 48-72 hours). Report decision to Otsuka using the reporting mechanism below. Continue monitoring.**
Liver Function results stabilise If ALT and AST levels remain below 3 x ULN	**Re-start Jinarc® treatment cautiously at same or lower dose with frequent monitoring and report decision to Otsuka using the reporting mechanism below**
ALT or AST >8-times ULN	**Permanently discontinue treatment and report decision to Otsuka using the reporting mechanisms below.**
ALT or AST >5-times ULN for more than 2 weeks	
ALT or AST >3-times ULN and (BT >2-times ULN or International Normalized Ratio [INR] >1.5)	
ALT or AST > 3-times ULN with persistent symptoms of hepatic injury (such as fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, dark urine or jaundice).	

PRESCRIBING DECISION (On-going treatment) **Titrate dose upward, if tolerated, with at least weekly intervals between up-titrations.**	
Based on tolerability and other tests performed on this patient (select one option below)	
• **I intend to prescribe Jinarc® (select one dose below)**	
○ 15mg (for patients also taking strong CYP3A inhibitors)	
○ 30mg (for patients also taking strong CYP3A inhibitors)	
○ 30mg per day (15mg and 15mg split dose) for patients also taking moderate CYP3A inhibitors ○ 45mg per day (30mg and 15mg split dose) for patients also taking moderate CYP3A inhibitors ○ 60mg per day (45mg and 15mg split dose) for patients also taking moderate CYP3A inhibitors ○ 60mg per day (45mg and 15 mg split dose)	
○ 90mg per day (60mg and 30mg split dose)	
○ 120mg per day (90mg and 30mg split dose)	
• **I have decided to interrupt treatment**	
• **I have decided to permanently discontinue treatment**	
○ Liver function contraindications	
○ Patient has been lost to follow-up	
○ Patient has died	
○ Patient choice	
○ Other	

Prescriber signature		Date	

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Please report Adverse Drug Reactions to <insert local comapny name> Department on telephone: (including out of hours), fax: <insert local telephone and fax number> or by email: <<insert local PV email address

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