February 2016

Drug	tolvaptan (Jinarc)
Indication	To slow the progression of kidney enlargement in patients with autosomal dominant polycystic kidney disease (ADPKD)
Listing Request	As per indication
Dosage Form	45 + 15 mg, 60 + 30 mg, and 90 + 30 mg tablets
NOC Date	February 25, 2015
Manufacturer	Otsuka Canada Pharmaceutical Inc.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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ABBREVIATIONS

ADPKD	autosomal dominant polycystic kidney disease
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AVP	arginine vasopressin
BUN	blood urea nitrogen
CDR	CADTH Common Drug Review
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CrCl	creatinine clearance
CT	computed tomography
DBP	diastolic blood pressure
DT	delayed treatment
eCrCl	estimated creatinine clearance
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
GFR	glomerular filtration rate
HR	hazard ratio
htTKV	height-adjusted total kidney volume
ITT	intention-to-treat population
MAP	mean arterial pressure
MCID	minimal clinically important difference
MDRD	Modification of Diet in Renal Disease
MMRM	mixed model repeated measures
MRI	magnetic resonance imaging
QoL	quality of life
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SBP	systolic blood pressure
SCr	serum creatinine
TEAE	treatment-emergent adverse events
TKV	total kidney volume
UTI	urinary tract infection

EXECUTIVE SUMMARY

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is a genetically inherited condition that results in the development of multiple fluid-filled cysts in both kidneys. It is the most common genetic disease of the kidneys and the fourth leading cause of end-stage renal disease (ESRD). In Canada, about 35,000 (0.1%) people are affected. The severity of disease follows a spectrum determined by the type of genetic mutation. Patients with non-truncating polycystic kidney disease 1 gene (PKD1) and polycystic kidney disease 2 gene (PKD2) mutations have lower risk for progression to ESRD, whereas in patients with truncating PKD1 mutation, dialysis is often required by 50 to 55 years of age. Supportive treatments are used to manage the symptoms of ADPKD, such as pain management for abdominal and back pain, antibiotics for lower and upper urinary infections, and treatment for nephrolithiasis. A major gap in the current management of ADPKD is the absence of treatments that inhibit disease progression. This review will evaluate the efficacy and safety of tolvaptan (Jinarc) 45 + 15 mg, 60 + 30 mg, or 90 + 30 mg administered orally as a twice-daily split-dose regimen for 36 months. Tolvaptan is the first drug in class under review indicated to slow the progression of kidney enlargement in adults with ADPKD.

Results and Interpretation

Included Studies

TEMPO 3:4 (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes) is the pivotal trial that evaluated the efficacy and safety of tolvaptan for ADPKD. TEMPO 3:4 is a phase 3 randomized, double-blind, placebo-controlled trial that was conducted in 1,445 adult patients with ADPKD across 129 sites in North and South America, Europe, Japan, and Australia. Patients were randomized to receive tolvaptan or placebo for 36 months.

The primary outcome was the percentage annual rate of change in total kidney volume (TKV) (both kidneys, unadjusted for age or height) from baseline, assessed by magnetic resonance imaging (MRI) at months 12, 24, and within two weeks before or after month 36. The key secondary outcome was a composite of time to clinical progression (definition: worsening kidney function based on 25% reduction in reciprocal of serum creatinine (SCr); clinically significant kidney pain that required medical leave, pharmacologic treatment, or invasive intervention; worsening hypertension; or worsening albuminuria).

Other secondary outcomes were change in slope of kidney function ascertained by the reciprocal of SCr and secondarily by estimated glomerular filtration rate (eGFR) determined by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, the Modification of Diet in Renal Disease (MDRD) equation, and estimated creatinine clearance (eCrCl) using the Cockcroft-Gault equation. Change from baseline in mean arterial pressure (MAP) and time to progression to high pre-hypertension or requiring antihypertensive therapy was evaluated in patients who were non-hypertensive at baseline. For patients taking antihypertensive therapy at baseline, percentage with clinically sustained decrease in blood pressure leading to sustained reduction in antihypertensive therapy compared with baseline was measured. Lastly, kidney pain was assessed with a 0 to 10 Likert scale.

TEMPO 3:4 reported exploratory analyses on several subgroups. For this review, the protocol-specified subgroups of importance were age, genetic mutation (PKD1 and PKD2), baseline TKV, and baseline kidney function. No data were available for PKD1 or PKD2 mutation.

The main limitations of TEMPO 3:4 were the potential for unblinding of patients and/or investigators due to the higher prevalence of specific adverse events (AEs) experienced in the tolvaptan group, potential bias in effect estimates due to the larger number of patients who discontinued in the tolvaptan group, and the absence of evaluation of some clinically important outcomes, such as time to ESRD, cardiovascular complications, and patient quality of life (QoL). In addition, there are limitations with rate of change in TKV as an outcome and its correlation with clinical outcomes (e.g., delaying ESRD, need for dialysis, and mortality). Hence, there is a nontrivial degree of uncertainty in the findings from TEMPO 3:4. Based on the inclusion criteria of the trial, the efficacy results are specific to patients at risk for disease progression but who have not yet reached later stages of the disease. Therefore, careful patient selection, taking into consideration baseline TKV and kidney function, will be required prior to initiating therapy with tolvaptan to identify patients at high risk of progression to ESRD. The higher incidence of liver enzyme elevations in patients who received tolvaptan is notable. Health Canada and the manufacturer have agreed that strategies to reduce the risks of adverse liver-related events should be implemented. This will include the creation of a Canadian ADPKD registry and a mandatory hepatic safety monitoring program (HSMP).

Efficacy

End-Stage Renal Disease/Dialysis

No data were identified for this outcome.

Disease Complications

Tolvaptan statistically significantly delayed the time to the composite outcome of clinical progression compared with placebo (incidence rate 43.94 versus 50.04 events per 100 person-years, hazard ratio [HR] 0.87; 95% confidence interval [CI], 0.78 to 0.97) (Table 1). This result was driven by fewer events of kidney function decline and clinically relevant episodes of kidney pain with tolvaptan (HR 0.39; 95% CI, 0.26 to 0.57 and HR 0.64; 95% CI, 0.47 to 0.89, respectively). No differences were found for worsening hypertension or worsening albuminuria. In subgroup analyses, tolvaptan was superior to placebo in delaying the composite outcome in patients who were ≥ 35 years of age, with height-adjusted TKV (htTKV) < 600 mL/m, or with eCrCl < 80 mL/min.

In exploratory analyses of time to 13 ADPKD-related events (i.e., hypertension, kidney pain, hepatic cysts, hematuria, albuminuria, nephrolithiasis, urinary tract infection, anemia, colonic diverticuli, vascular/cardiac abnormality, abdominal/inguinal hernia, other cysts, and significant decline in kidney function) and nine events more closely related to kidney enlargement [redacted].

In patients who were non-hypertensive at baseline, tolvaptan and placebo performed similarly on progression to hypertensive events (incidence rate 31.80 versus 29.60 events per 100 person-years, HR 0.99; 95% CI, 0.81 to 1.23) and resting MAP (difference in slope –0.25 mm Hg per year, 95% CI, –1.06 to 0.57). Also, in patients who were hypertensive at baseline, the relative risk (RR) of experiencing sustained reduction in blood pressure leading to reduction in antihypertensive therapy up to month 36 was not statistically significant (RR 1.10; 95% CI, 0.60 to 2.02).

Fatal and Non-fatal Cardiovascular Events

Cardiovascular outcomes were not formally evaluated as efficacy outcomes, rather, the following were reported as harms: palpitations (tolvaptan versus placebo: [redacted]), ventricular extrasystoles ([redacted]

[redacted]), atrial fibrillation ([redacted]), acute myocardial infarction ([redacted]), angina pectoris ([redacted]), and coronary artery disease ([redacted]).

Extrarenal Manifestations

Extrarenal manifestations were not formally evaluated as an efficacy outcome, but rather, the following were reported as harms[redacted] and intracranial aneurysm (0.3% versus 0.2%).

Hospitalization

No data were identified for this outcome.

Mortality

There were no deaths in the tolvaptan or placebo groups during the trial.

Quality of Life

No data were identified for this outcome.

Patient-Reported Outcomes

No difference was found in mean change in area under the curve (AUC) from baseline of kidney pain score, measured on a 10-point Likert scale, between tolvaptan and placebo in patients not taking pain medication at baseline (difference –0.08; 95% CI, –0.20 to 0.03).

Total Kidney Volume

Compared with placebo, the annual percentage increase in TKV was significantly less, statistically and clinically, with tolvaptan (2.8% versus 5.5%, 49.2% reduction in growth rate). A mixed model repeated measures (MMRM) sensitivity analysis found that the largest difference occurred after year 1. Tolvaptan was superior to placebo in all subgroup analyses for the annual percentage increase in TKV.

Kidney Function

There was statistically significant less decline in kidney function with tolvaptan as measured by the slope of reciprocal of SCr (difference in slope 1.20 $[mg/mL]^{-1}$ per year; 95% CI, 0.62 to 1.78). This result was confirmed by using slope of $eGFR_{CKD-EPI}$, $eGFR_{MDRD}$, and eCrCl. Subgroup analyses of reciprocal of SCr found results in favour of tolvaptan for patients ≥ 35 years, with TKV ≥ 1,500 mL, or with htTKV ≥ 600 mL/m. The open-label extension study, TEMPO 4:4, found sustained reduction in eGFR slope in patients continuing on tolvaptan and decelerated slope in patients switched to tolvaptan over an additional two-year period.

Need for Supportive Treatments

No data were identified for this outcome**.**

Harms

Adverse Events

Nearly all patients experienced at least one AE (97.9% in tolvaptan group and 97.1% in placebo group). [redacted].

Serious Adverse Events

Serious adverse events (SAEs) were experienced by 18.4% of patients in the tolvaptan group and 19.7% of patients in the placebo group. More patients in the tolvaptan group experienced SAEs

related to elevation in liver enzymes (2.2% versus 0.8%), chest pain (0.8% versus 0.4%), and headache (0.5% versus 0). Basal cell carcinoma was more frequent in the tolvaptan group (0.8% versus 0.2%).

Withdrawal Due to Adverse Events

More patients receiving tolvaptan withdrew from the trial due to an AE (15.4% versus 5.0%). The most common AE leading to withdrawal of tolvaptan was polyuria (4.2% versus 0), followed by pollakiuria (1.6% versus 0), nocturia (0.9% versus 0.2%), thirst (0.6% versus 0.2%), abnormal liver function (0.6% versus 0), and fatigue (0.5% versus 0).

Notable Harms

More patients in the tolvaptan group experienced alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevation greater than 2.5 times the upper limit of normal (4.9% versus 1.2% and 3.2% versus 0.8%, respectively). Serious liver-related events and serious elevations in ALT, AST, and transaminase levels were more common in the tolvaptan group and more patients on tolvaptan discontinued treatment due to abnormal liver function (numbers reported above). In the tolvaptan group, two patients met Hy's criteria. No events of liver failure or liver transplant were reported during the trial.

Hypernatremia (serum sodium > 150 mmol/L) occurred in 4% of patients receiving tolvaptan and 1.4% of patients receiving placebo. Clinically significant increases in uric acid and gout were higher in patients receiving tolvaptan (6.2% versus 1.7% and 2.9% versus 1.4%, respectively). Polyuria and thirst were much more common in the tolvaptan group (38.3% versus 17.2% and 55.3% versus 20.5%, respectively).

Potential Place in Therapy[1]

There is currently no specific treatment for delaying progression of ADPKD other than optimizing blood pressure control. Tolvaptan (Jinarc) has been shown to significantly slow the growth of TKV in pre-clinical studies[1] and in the largest randomized controlled trial (RCT) for ADPKD (TEMPO 3:4) to date.[2] In the RCT, tolvaptan also slowed the rate of decline of kidney function. However, TEMPO 3:4 was not powered to evaluate the treatment effect using traditional outcomes such as percentage of patients (on treatment versus placebo) with a doubling of SCr (or halving of eGFR) and mean time delay for progression to ESRD. Nevertheless, given the pre-clinical and clinical findings, tolvaptan is presently the most promising disease modifier drug available for slowing the progression of ADPKD.

Patients with ADPKD display a wide spectrum of disease severity depending largely on their mutation class.[3,4] Patients with truncating PKD1 mutations typically will have severe disease, with half of them requiring ESRD treatment by age 50 to 55 years. By contrast, patients with PKD2 and many with non-truncating PKD1 mutations typically will have mild disease, with half of them needing ESRD treatment only by late 70 years of age. Moreover, patients with large TKV at a younger age are also at high risk for progression to early ESRD. Given its costs and potential adverse effects as well as incomplete efficacy data, it may be prudent at this time to select patients who are at "high risk" for progression to early ESRD for tolvaptan treatment. "High-risk" patients may be selected based on their genotype (i.e., truncating PKD1 mutations),[3,4] family history of at least one older affected relative who developed ESRD before age 50 years (i.e., highly predictive of truncating PKD1 mutations),[5] or age-adjusted TKV (as measured by MRI or computed tomography [CT] but not ultrasound).[6,7]

[1] Based on information provided in draft form by the clinical expert consulted by CADTH Common Drug Review (CDR) reviewers for the purpose of this review.

Conclusions

Tolvaptan is a selective vasopressin V_2 receptor antagonist indicated to slow progression of kidney enlargement in adults with ADPKD. It was evaluated in one multi-centre RCT, TEMPO 3:4, which included 1,445 patients and follow-up of 36 months, and in one open-label extension study, TEMPO 4:4, which included 904 patients and follow-up of two years. Compared with placebo, tolvaptan demonstrated benefit on the primary outcome of change in TKV. Although there is evidence that TKV growth predicts rates of GFR decline, there remains uncertainty about how well TKV predicts clinically relevant outcomes such as delaying ESRD, need for dialysis, and mortality. Tolvaptan was also shown to be superior to placebo on rate of change in kidney function and a composite outcome of clinical progression, providing further evidence for a potential benefit of tolvaptan. No differences between groups were observed for hypertension outcomes. Based on the inclusion criteria of the trial, the efficacy results are specific to patients at risk for disease progression but who have not yet reached later stages of the disease. Therefore, careful patient selection, taking into consideration baseline TKV and kidney function to identify high-risk patients who are most likely to develop ESRD,[7] will be required prior to initiating therapy with tolvaptan. Important harms associated with tolvaptan were thirst, polyuria, nocturia, pollakiuria, and elevation in liver enzymes. Long-term data of efficacy and safety as well as assessment of clinical outcomes are needed to make firm conclusions about tolvaptan's risk-benefit profile. Based on the results of TEMPO 3:4 and TEMPO 4:4, tolvaptan potentially fills an important therapeutic need in the management of adults with ADPKD.

TABLE 1: SUMMARY OF RESULTS (ALL PRE-SPECIFIED PRIMARY AND SECONDARY OUTCOMES OF TEMPO 3:4)

	TEMPO 3:4	
	Tolvaptan N = 961	Placebo N = 484
Clinical progression (composite)[a]		
N (% group total)	961 (100)	483 (99.8)
HR (95% CI)	0.87 (0.78 to 0.97)	
P value	0.01	
Progression to hypertensive events in patients non-hypertensive at baseline		
N (% group total)	174 (18.1)	79 (16.3)
N (% non-hypertensive subset)	174/196 (88.8)	79/102 (77.4)
HR (95% CI)	0.99 (0.81 to 1.23)	
P value	0.97	
Resting MAP in patients non-hypertensive at baseline		
N (% group total)	129 (13.4)	74 (15.3)
N (% non-hypertensive subset)	129/196 (65.8)	74/102 (72.5)
Mean (mm Hg increase per year)	2.56	2.59
Slope (linear mixed effect model)	0.84	1.08
Difference in slope (95% CI)	–0.25 (–1.06 to 0.57)	
P value	0.55	
Reduction of antihypertensive therapy in patients hypertensive at baseline		
N (% group total)	481 (50.0)	267 (55.2)
N (% hypertensive subset)	481/765 (62.9)	267/382 (69.9)
No. patients with event	30	15
RR (95% CI)	1.10 (0.60 to 2.02)	
P value	0.75	

	TEMPO 3:4	
	Tolvaptan N = 961	**Placebo N = 484**
Kidney pain score in patients not taking pain medications at baseline		
N (% group total)	926 (96.4)	467 (96.5)
Mean change in AUC from baseline	0.00	0.08
Difference (95% CI) (ANCOVA)	–0.08 (–0.20 to 0.03)	
P value	0.16	
TKV		
N (% group total)	819 (85.2)	458 (94.6)
Mean change (% increase per year)	2.78	5.61
Slope (% increase per year) (95% CI) (linear mixed effect model)[b]	2.80 (2.46 to 3.14)	5.51 (5.06 to 5.96)
Difference in slope (95% CI)	–2.71 (–3.27 to –2.15)	
P value	< 0.001	
Kidney function (reciprocal of SCr)		
N (% group total)	842 (87.6)	464 (96.1)
Mean change ($[mg/mL]^{-1}$ per year)	–2.56	–3.68
Slope ($[mg/mL]^{-1}$ per year) (linear mixed effect model)[b]	–2.61	–3.81
Difference in slope (95% CI)	1.20 (0.62 to 1.78)	
P value	< 0.001	

ANCOVA = analysis of covariance; AUC = area under the curve; CI = confidence interval; HR = hazard ratio; MAP = mean arterial pressure; RR = relative risk; SCr = serum creatinine; TKV = total kidney volume.

[a] Defined as worsening kidney function based on 25% reduction in reciprocal of SCr; clinically significant kidney pain that required medical leave, pharmacologic treatment, or invasive intervention; worsening hypertension; or worsening albuminuria.

[b] Slope was derived from a linear mixed model that included time-treatment interaction.

Source: Torres VE et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med 2012; 367(25): 2407-18[2] and Clinical Study Report for TEMPO 3:4.[8]

1. INTRODUCTION

1.1 Disease Prevalence and Clinical Features

Autosomal dominant polycystic kidney disease (ADPKD) is a genetically inherited condition that results in the development of multiple fluid-filled cysts in both kidneys.[9] It is the most common genetic disease of the kidneys and the fourth leading cause of end-stage renal disease (ESRD).[9] In Canada, about 35,000 (0.1%) people are estimated to be affected.[10] Precise estimates of disease prevalence, however, are difficult to obtain because clinical symptoms may be silent for many years. The total prevalence, including subclinical cases, may be close to 1 in 500 and prevalence of clinically important cases between 1 in 1,000 and 1 in 2,000. The disease is usually diagnosed in the second or third decade of life.[11] Normal renal tissue is progressively replaced by cyst growth, which results in kidney enlargement, fibrosis, and ultimately ESRD, necessitating dialysis or kidney transplant. Common complications include hypertension, kidney pain, urinary tract infection (UTI), pyelonephritis, nephrolithiasis, and hematuria.[11] Extrarenal manifestation may also develop, such as pancreatic and hepatic cysts and intracranial aneurysm.[12]

ADPKD is caused by mutations in polycystic kidney disease 1 gene (PKD1) or polycystic kidney disease 2 gene (PKD2), which code for the proteins polycytin-1 and polycystin-2, respectively.[12] These proteins are involved in signalling pathways that maintain normal renal tubular structure.[12] The PKD1 mutation is more prevalent than PKD2 mutation (85% versus 15%, respectively, in patients ascertained from kidney disease clinics or dialysis centres) and causes a more severe disease phenotype.[9] In patients with truncating PKD1 mutation, dialysis is often required by 50 to 55 years of age, whereas in patients with PKD2 mutation dialysis may be delayed until 70 years of age or older. More recently, non-truncating PKD1 mutation has been shown to cause a milder form of kidney disease intermediate of truncating PKD1 and PKD2 mutations.[4] Genetic testing for PKD1 or PKD2 is not routinely conducted in clinical practice. Diagnosis is based on presenting clinical symptoms such as enlarged kidneys and cysts and presence of positive family history.[13] Creatinine-based tests of kidney function are typically within the normal range for several decades until late in the clinical course and are not sensitive for use to detect disease progression. Total kidney volume (TKV) as measured by magnetic resonance imaging (MRI) has been used as a biomarker for kidney disease severity and outcome measure in clinical trials.

ADPKD impacts all aspects of a person's life, both physically and psychologically. The symptoms, complications, and management of ADPKD interfere with daily chores, limit physical activities, and can lead to social stigma. Common symptoms experienced by patients include fatigue, anxiety, abdominal and back pain, and abdominal distension. Given the significant morbidity and increased risk of mortality imposed by ADPKD, therapeutic strategies that slow disease progression and prevent disease complications are needed.

1.2 Standards of Therapy

The Kidney Disease: Improving Global Outcomes (KDIGO) conference brought together an international panel of experts to discuss areas of consensus and gaps in knowledge related to the evaluation, management, and treatment of ADPKD.[14] Management of ADPKD focuses on addressing the symptoms and related complications of ADPKD through lifestyle modifications and pharmacotherapy.

A cornerstone of ADPKD treatment is the control of blood pressure to a target of ≤ 140/90 mm Hg and reducing the risk of cardiovascular events. Patients are encouraged to restrict sodium intake, maintain a healthy diet, exercise, limit alcohol to moderate levels, not smoke, and to self-monitor blood pressure. If

pharmacotherapy for high blood pressure is required, first-line medications target the renin-angiotensin-aldosterone system.

Arginine vasopressin (AVP), also known as antidiuretic hormone (ADH), has been implicated in the pathogenesis of ADPKD. Patients may be advised to increase water consumption to 2.5 L to 4 L per day to suppress endogenous AVP.[15]

Supportive treatments are used to manage other symptoms of ADPKD, such as pain management for abdominal and back pain, antibiotics for lower and upper urinary infections, and treatment for nephrolithiasis. At later stages of the disease with onset of ESRD, renal replacement therapy with dialysis (hemodialysis or peritoneal dialysis) or kidney transplantation are implemented.

A major gap in the current management of ADPKD is the absence of treatments that inhibit disease progression. The available treatment strategies do not slow progression to ESRD, need for renal replacement therapies, other disease complications, or mortality. Therefore, treatments that delay progression to ESRD and that improve quality and prolong life by targeting the underlying pathology of ADPKD are needed.

1.3 Drug

This review evaluates the efficacy and safety of tolvaptan (Jinarc) 45 + 15 mg, 60 + 30 mg, or 90 + 30 mg, administered orally as a split-dose, twice-daily regimen. Tolvaptan is the first drug in class under review indicated to slow the progression of kidney enlargement in adults with ADPKD. Tolvaptan is also marketed under the brand name of Samsca in strengths of 15 mg and 30 mg for clinically important non-hypovolemic hyponatremia. Samsca was reviewed by the CADTH Common Drug Review (CDR) in 2012.[16]

Tolvaptan is a selective vasopressin V_2 receptor antagonist with 1.8 times greater affinity for the receptor compared with endogenous AVP.[17] When AVP binds to V_2 receptors, which are found in kidney collecting ducts, adenylyl cyclase is stimulated to produce cyclic adenosine monophosphate (cAMP). cAMP has a major role in cyst formation and in stimulating fluid secretion into the cystic lumen.[12] The inhibition of V_2 receptors by tolvaptan, therefore, is proposed to reduce cyst burden and kidney growth.

Indication under review
To slow the progression of kidney enlargement in patients with ADPKD.[a]
Listing criteria requested by sponsor
As per indication.[a]

[a] The product monograph specifies the following regarding patient identification: "In order to select patients who might best benefit from the effects of Jinarc, clinical trials evaluated ADPKD patients having a total kidney volume (TKV) ≥ 750 mL, with relatively preserved renal function, i.e., estimated creatinine clearance (eCrCl) ≥ 60 mL/min, generally corresponding to a CKD-EPI eGFR ≥ 30 mL/min/1.73m^2, at the time of initiation of treatment."[17]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of tolvaptan (45 + 15 mg, 60 + 30 mg, or 90 + 30 mg) for the treatment of ADPKD in adults.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase 3 studies were selected for inclusion based on the selection criteria presented in Table 2. Grey literature and databases were also searched to identify trials that meet the selection criteria.

TABLE 2: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults 18 years of age or older with ADPKD
	Subgroups:
	• Age
	• Genetic mutation
	  ○ PKD1 — truncating, non-truncating
	  ○ PKD2
	• Total kidney volume at baseline
	• Kidney function at baseline
	  ○ Normal
	  ○ Abnormal (evidence of advanced disease)

Intervention	Tolvaptan split-dose regimens (45 + 15 mg, 60 + 30 mg, or 90 + 30 mg)
Comparators	Placebo Standard care • Blood pressure control • Fluid consumption • Other supportive treatments such as pain management

Outcomes	**Key efficacy outcomes:**
	• ESRD/dialysis (presence and time to)
	• Disease complications
	  ○ Hematuria
	  ○ Hypertension
	  ○ Infections (lower UTI, pyelonephritis)
	  ○ Nephrolithiasis
	• Fatal and non-fatal cardiovascular events
	• Extrarenal manifestations
	  ○ Liver cysts
	  ○ Pancreatic cysts
	  ○ Intracranial aneurisms
	• Hospitalization
	• Mortality (all-cause and disease specific)
	• QoL
	• Patient-reported outcomes:[a]
	  ○ Fatigue
	  ○ Anxiety
	  ○ Abdominal distension
	  ○ Back pain
	  ○ Abdominal pain

	○ Limitation of physical tasks ○ Missed work days **Other efficacy outcomes:** • Total kidney volume (adjusted for age or height) • Kidney function (GFR, SCr, albuminuria) • Need for supportive treatments **Harms outcomes:** • AEs • SAEs • WDAEs • AEs of interest: ○ Elevated liver enzymes ○ Liver toxicity — injury, failure, idiosyncratic toxicity ○ Hypernatremia ○ Hyperkalemia ○ Hyperglycemia ○ Hyperuricemia ○ Dehydration ○ Polyuria ○ Thirst
Study Design	Published and unpublished phase 3 RCTs

ADPKD = autosomal dominant polycystic kidney disease; AE = adverse event; ESRD = end-stage renal disease; GFR = glomerular filtration rate; PKD1 = polycystic kidney disease 1 gene; PKD2 = polycystic kidney disease 2 gene; QoL = quality of life; RCT = randomized controlled trial; SAE = serious adverse event; SCr = serum creatinine; UTI = urinary tract infection; WDAE = withdrawal due to adverse event.
[a] These outcomes were specified in the patient input summary (see Appendix 1).

The literature search was performed by an information specialist using a peer-reviewed search strategy (see Appendix 2). Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's Medical Subject Headings (MeSH) and keywords. The main search concepts were Jinarc (tolvaptan) and kidney disease. No methodological filters were applied to limit retrieval. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on June 26, 2015. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on October 21, 2015. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the CADTH *Grey Matters* checklist (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine). Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

TWO CDR CLINICAL REVIEWERS INDEPENDENTLY SELECTED STUDIES FOR INCLUSION IN THE REVIEW BASED ON TITLES AND ABSTRACTS, ACCORDING TO THE PREDETERMINED PROTOCOL. FULL-TEXT ARTICLES OF ALL CITATIONS CONSIDERED POTENTIALLY RELEVANT BY AT LEAST ONE REVIEWER WERE ACQUIRED. REVIEWERS INDEPENDENTLY MADE THE FINAL SELECTION OF STUDIES TO BE INCLUDED IN THE REVIEW, AND DIFFERENCES WERE RESOLVED THROUGH DISCUSSION.

INCLUDED STUDIES ARE PRESENTED IN TABLE 3; EXCLUDED STUDIES (WITH REASONS) ARE PRESENTED IN

Appendix 3.

3. RESULTS

3.1 Findings From the Literature

ONE STUDY WAS IDENTIFIED FROM THE LITERATURE FOR INCLUSION IN THE SYSTEMATIC REVIEW (FIGURE 1). THE INCLUDED STUDY IS SUMMARIZED IN TABLE 3 AND DESCRIBED IN SECTION 3.2. A LIST OF EXCLUDED STUDIES IS PRESENTED IN

Appendix 3.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

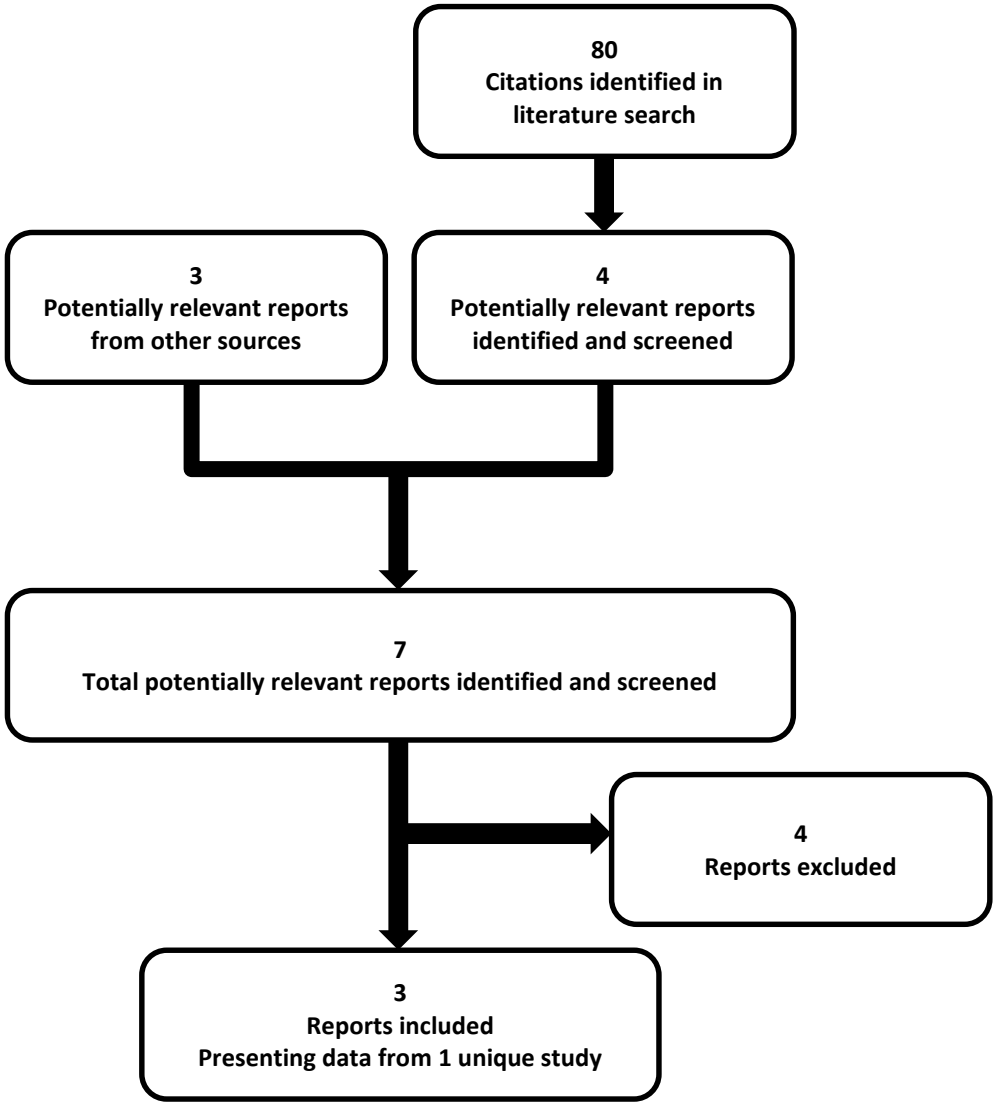


TABLE 3: DETAILS OF INCLUDED STUDIES

		TEMPO 3:4
DESIGNS & POPULATIONS	**Study Design**	DB RCT
	Locations	129 sites worldwide • North America • South America • Europe • Japan • Australia
	Randomized (N)	1,445 (2:1 ratio tolvaptan: placebo)
	Inclusion Criteria	• 18 to 50 years of age with diagnosis of ADPKD • TKV ≥ 750 mL • eCrCl ≥ 60 mL/min (Cockcroft-Gault formula)
	Exclusion Criteria	• Contraindications to, or interference with MRI assessments • Taking medications or having concomitant illnesses that may confound end points • Taking other experimental therapies, approved therapies for affecting ADPKD cysts, or history of tolvaptan use
DRUGS	**Intervention**	Split-dose b.i.d. PO regimen (morning and afternoon) starting at 45 + 15 mg Weekly increases to 60 + 30 mg and then to 90 + 30 mg as tolerated Patients took highest dose that was tolerated throughout trial
	Comparator(s)	Placebo
DURATION	**Phase**	
	Run-in	Not reported
	Double-blind	36 months
	Follow-up	6 weeks
OUTCOMES	**Primary End Point**	TKV (annual rate of percentage change)
	Other End Points	• Time to clinical progression (composite of worsening kidney function, clinically significant kidney pain requiring medical leave, pharmacologic treatment with narcotics or last-resort analgesics, invasive intervention, worsening hypertension, and worsening albuminuria) • Change in slope of kidney function (reciprocal of SCr and $GFR_{CKD-EPI}$) • For patients non-hypertensive at baseline, change in resting mean arterial pressure • For patients non-hypertensive at baseline, time of progression to high prehypertension (SBP > 129 and/or DBP > 84 mm Hg), hypertension (SBP > 139 and/or DBP > 89 mm Hg), or requiring antihypertensive therapy • For patients taking antihypertensive therapy at baseline, percentage with clinically sustained decreases of blood pressure leading to reduction in antihypertensive therapy • Kidney pain (change from baseline) • Safety
NOTES	**Publications**	Torres et al.;[2] Clinical Study Report.[8]

ADPKD = autosomal dominant polycystic kidney disease; b.i.d. = twice daily; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; DPB = diastolic blood pressure; eCrCl = estimated creatinine clearance; DB = double-blind; GFR = glomerular filtration rate; MRI = magnetic resonance imaging; PO = orally; RCT = randomized controlled trial; SCr = serum creatinine; SPB = systolic blood pressure; TKV = total kidney volume.
Note: 1 additional report was included.[19]
Source: Torres VE et al., 2012[2] and Torres VE et al., 2011.[18]

3.2 Included Studies

3.2.1 Description of Studies

TEMPO 3:4 (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes) is the pivotal trial that evaluated the efficacy and safety of tolvaptan for ADPKD.[2,8] TEMPO 3:4 is a phase 3, randomized, double-blind, placebo-controlled trial that was conducted in over 1,400 patients across 129 sites in North and South America, Europe, Japan, and Australia. Patients were randomized in a 2:1 ratio to receive tolvaptan or placebo and were followed for three years. Randomization was conducted centrally and was stratified by baseline hypertension status, estimated creatinine clearance (eCrCl) (< 80 mL/min and ≥ 80 mL/min), TKV (< 1,000 mL and ≥ 1,000 mL), and geographic area. Blinding was carried out by providing tolvaptan and matched placebo in kits of blister cards containing 15 mg or 30 mg tablets. The manufacturer of tolvaptan, Otsuka Pharmaceuticals, funded the trial and collected and analyzed the data.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

Patients 18 to 50 years of age diagnosed with ADPKD and fulfilling the following criteria were included in the trial: eCrCl ≥ 60 mL/min (chronic kidney disease [CKD] Stages 1 to 3) according to the Cockcroft-Gault equation within 31 days of randomization and TKV ≥ 750 mL by MRI. Patients were excluded if there were any contraindications to or interference with MRI measurements, if they were taking medications or had concomitant illnesses with potential to confound the end points of the trial, or if they were taking other experimental therapies, approved therapies for ADPKD cysts, or had used tolvaptan previously.

b) Baseline Characteristics

Patients randomized to tolvaptan or placebo were balanced with respect to demographic, disease-related, and medication-use characteristics (Table 4). The majority of the study population was Caucasian (approximately 84%) with an average age of 39 years. Males and females were nearly equally represented. Randomization was stratified according to hypertension status, eCrCl, and TKV, all of which were balanced. Systolic and diastolic blood pressure, TKV, estimated glomerular filtration rate (eGFR), serum creatinine (SCr), and eCrCl on continuous scale were also similar among groups. The number of patients with baseline clinical symptoms of hematuria, kidney pain, nephrolithiasis, UTI, anemia, and proteinuria and who were taking antihypertensive medication were nearly similar in those taking tolvaptan and placebo.

TABLE 4: SUMMARY OF BASELINE CHARACTERISTICS

Characteristic	Tolvaptan (N = 961)	Placebo (N = 484)
Males — no. (%)	495 (51.5)	251 (51.9)
Race — no. (%)		
Caucasian	810 (84.3)	408 (84.3)
Asian	121 (12.6)	62 (12.8)
Other	30 (3.1)	14 (2.9)
Age — years (SD)	39 (7)	39 (7)
Weight — kg (SD)	79 (18)	79 (18)

Characteristic	Tolvaptan (N = 961)	Placebo (N = 484)
Blood pressure — mm Hg (SD)		
Systolic	128.6 (13.5)	128.3 (13.5)
Diastolic	82.5 (9.9)	82.5 (9.3)
Hypertension — no. (%)	765 (79.6)	382 (78.9)
TKV — mL (SD)	1,705 (921)	1,668 (873)
htTKV — mL/m (SD)	979 (515)	958 (483)
TKV < 1,000 mL — no. (%)	197 (20.5)	101 (20.9)
eGFR — mL/min/1.73 m^2 (SD)	81.35 (21.02)	82.14 (22.73)
SCr — mg/dL (SD)	1.05 (0.30)	1.04 (0.32)
eCrCl — mL/min (SD)	104.08 (32.76)	103.80 (35.60)
eCrCl < 80 mL/min — no. (%)	242 (25.2)	130 (26.9)
Hematuria — no. (%)	338 (35.2)	164 (33.9)
Kidney pain — no. (%)	496 (51.6)	239 (49.4)
Nephrolithiasis — no. (%)	187 (19.5)	109 (22.5)
UTI — no. (%)	290 (30.2)	164 (33.9)
Anemia — no. (%)	105 (10.9)	48 (9.9)
Urinary albumin/creatinine — ratio (SD)	7.2 (14.3)	8.6 (21.7)
Proteinuria — no. (%)	233 (24.2)	116 (24.0)
Medications — no. (%)		
ACEI	419 (43.6)	199 (41.1)
ARB	307 (31.9)	165 (34.1)
ACEI, ARB, or both	683 (71.1)	350 (72.3)
Beta-blocker	171 (17.8)	94 (19.4)
CCB	180 (18.7)	104 (21.5)
Diuretic	32 (3.3)	14 (2.9)

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; eCrCl = estimated creatinine clearance; eGFR = estimated glomerular filtration rate; htTKV = height-adjusted total kidney volume; SCr = serum creatinine; SD = standard deviation; TKV = total kidney volume; UTI = urinary tract infection.
Source: Torres VE et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med 2012; 367(25): 2407-18.[2]

3.2.3 Interventions

Tolvaptan was administered in a split-dose morning and afternoon regimen starting at 45 + 15 mg. The dose was increased weekly based on patient tolerability to 60 + 30 mg and then to 90 + 30 mg. Patients continued on the highest tolerable dose for 36 months. If patients could not tolerate a dose increase they were resumed on the previous tolerated dose. Patients who could not tolerate the lowest dose of 45 + 15 mg were withdrawn from the trial. Diuretics and medications that inhibit cytochrome 3A4 were avoided during the trial. Angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) were recommended as first-line treatment for hypertension. All patients were provided with recommendations to maintain adequate water consumption to prevent thirst during daytime and to ingest one to two cups of water before bedtime. Dietary restrictions on sodium and protein intake were provided as appropriate according to site-specific guidelines.

3.2.4 Outcomes

Assessments were conducted at baseline, at randomization, weekly during dose escalation, every four months during treatment, and at two follow-up visits after 36 months (trial end) between weeks one and six. Measurements of blood pressure, kidney function, and kidney pain score were taken at each of these time points. Adherence to treatment was assessed through self-report and pill counts.

The primary outcome was the percentage annual rate of change in TKV (both kidneys, unadjusted for age or height) from baseline, assessed by MRI at months 12, 24, and within two weeks before or after month 36. The relationship between TKV and clinically important end points (such as delaying or preventing ESRD or need for hemodialysis) remains to be elucidated. It is considered a surrogate outcome for cyst development in ADPKD.[8] The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) observational study found that height-adjusted TKV (htTKV) was correlated inversely with glomerular filtration rate (GFR) and had potential to predict development of Stage 3 CKD.[20] No minimal clinically important difference (MCID) for change in TKV was identified. (See Appendix 5 for more detail.)

The key secondary outcome was a composite of time to clinical progression (definition: worsening kidney function based on 25% reduction in reciprocal of SCr; clinically significant kidney pain that required medical leave, pharmacologic treatment, or invasive intervention; worsening hypertension; or worsening albuminuria). These events were assessed by investigators for primary analyses and also by an independent Clinical Events Committee for sensitivity analyses. Other secondary outcomes were:

- Change in slope of kidney function from post-dose baseline to last on-drug trial visit, ascertained by the reciprocal of SCr. Exploratory analyses were also conducted using eGFR estimated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, the Modification of Diet in Renal Disease (MDRD) equation, and eCrCl estimated with the Cockcroft-Gault equation.
- For patients who were non-hypertensive at baseline, change from baseline in mean arterial pressure (MAP) and time to progression to high prehypertension (systolic blood pressure [SBP] > 129 mm Hg and/or diastolic blood pressure [DBP] > 84 mm Hg), hypertension (SBP > 139 mm Hg and/or DBP > 89 mm Hg), or requiring antihypertensive therapy.
- For patients taking antihypertensive therapy at baseline, percentage with clinically sustained decrease in blood pressure leading to sustained reduction in antihypertensive therapy compared with baseline.
- Change from baseline in kidney pain as assessed with a non-validated Likert scale of 0 to 10, with 0 representing no pain (recall period: four months) in patients not taking pain medications at baseline.

Safety end points included reported adverse events (AEs) and serious adverse events (SAEs), vital signs, and electrocardiography (ECG).

3.2.5 Statistical Analysis

The trial was designed to have 85% power to detect a 20% reduction in the growth rate of TKV. Using a two-sided alpha threshold of 0.045 and assuming a 20% withdrawal rate, 600 patients were needed to detect this effect size. The target for enrolment was doubled to 1,200 to 1,500 patients.

The primary outcome — rate of change in TKV — was analyzed by transforming TKV to $\log_{10}$ values and fitting slopes with a linear mixed effect Laird-Ware model that included group (tolvaptan or placebo), time in unit of years from date of randomization to the MRI visit, and group-time interaction. In addition, a mixed model repeated measures (MMRM) analysis was conducted, using the repeated

measures of change from baseline in TKV, as a sensitivity analysis. The MMRM included covariates of hypertension status, eCrCl, geographic region, visit, treatment, baseline kidney volume, treatment-visit interaction, and baseline kidney volume-visit interaction. Slope of kidney function based on SCr reciprocal or eGFR and change from baseline in MAP were analyzed using similar methodology.

The secondary composite end point was analyzed with an extended Cox model to analyze time to multiple events. Treatment was the only variable in the model and data were censored if patients were withdrawn from the trial. Time to progression to prehypertension, hypertension, or antihypertensive therapy for patients who were non-hypertensive at baseline was analyzed in a similar manner. The number of hypertensive patients at baseline experiencing clinically sustained decreases in blood pressure leading to sustained reduction in blood pressure medication compared with baseline was examined with a Cochran-Mantel-Haenszel analysis, stratified by baseline stratification factors (i.e., hypertension status, kidney volume, eCrCl, etc.).

Area under the curve (AUC) of kidney pain score was analyzed using analysis of covariance (ANCOVA) with treatment, baseline stratification factors, and baseline pain score entered in the model as covariates. An MMRM of change from baseline in kidney pain score was also conducted as a sensitivity analysis.

A hierarchical approach with a pre-specified order for testing outcomes and a two-sided alpha of 0.05 was used to account for multiple statistical tests. The order of testing outcomes was TKV, composite of clinical progression, kidney function based on reciprocal of SCr, resting MAP in non-hypertensive patients, kidney pain based on 10-point Likert scale, progression to hypertensive events or needing antihypertensive therapy in non-hypertensive patients, and sustained decrease in blood pressure leading to decrease in blood pressure medication in hypertensive patients.

Subgroup analyses were conducted by gender, age (< 35 versus ≥ 35 years), hypertension status (yes versus no), eCrCl (< 80 mL/min versus ≥ 80 mL/min), TKV (< 1,000 mL versus ≥ 1,000 mL or < 1,500 mL versus ≥ 1,500 mL), htTKV (< 600 mL versus ≥ 600 mL), microalbuminuria status (present versus absent), region (Japan, non-Japan, Americas, Europe/rest of world), and ethnicity (Caucasian versus non-Caucasian). For this review, the protocol-specified subgroups of importance were age, genetic mutation (PKD1 and PKD2), baseline TKV, and baseline kidney function.

In exploratory analyses, individual components of the key secondary composite outcome were examined. Also explored were outcomes of albuminuria (urine albumin/creatinine ratio), SCr, and time to multiple ADPKD events from month 4 onwards. The time to multiple ADPKD events included two separate analyses, with the first incorporating 13 ADPKD-related events and the second incorporating nine events related more closely to kidney enlargement.

a) Analysis Populations

The intention-to-treat (ITT) population included all patients who were randomized (961 to tolvaptan and 484 to placebo). The observed cases dataset consisted of all data points from patients who were evaluated at baseline, post-baseline, and at end of trial, thereby requiring no imputation for missing data. The double-blind trial period was the time from the first dose of tolvaptan or placebo (or after titration phase for kidney function) to 14 days after the last dose.

For the primary outcome of TKV, the observed cases dataset within the double-blind treatment period was analyzed. This analysis included 85.2% and 94.6% of patients in tolvaptan and placebo groups,

respectively (Table 5). The secondary composite outcome included all events that occurred within the double-blind treatment period for all ITT patients. Other secondary outcomes were also based on data collected within the double-blind treatment period; the rate of renal function change analysis (using reciprocal of SCr as primary measure) included patients within the treatment period (using week 3 as baseline), with at least four months of follow-up, and excluded observations that investigators deemed to be unreliable.

Safety outcomes were assessed on all patients who consumed at least one dose of trial medication.

The non-hypertensive subset was defined as all ITT patients with no hypertension at baseline (SBP ≤ 139 mm Hg, DBP ≤ 89 mm Hg, and not taking antihypertensive medication). The hypertensive subset was defined as all ITT patients with hypertension at baseline (SBP > 139 mm Hg, DBP > 89 mm Hg, or taking antihypertensive medication).

3.3 Patient Disposition

Of those screened, 68% were included in the trial (1,445/2,122), with 961 randomized to receive tolvaptan and 484 placebo (Table 5). A greater percentage of patients in the tolvaptan group discontinued treatment (23% versus 13.8%), with many more discontinuing due to an AE with tolvaptan compared with placebo (15.4% versus 5.0%). Other reasons for discontinuation, which were balanced among groups, were withdrawal of consent (5.2% versus 6.2%), loss to follow-up (1.6% versus 1.7%), withdrawn by investigator (0.3% versus 0.8%), and protocol deviation (0.1% versus 0.2%). From the primary outcome of TKV, 11.6% of randomized patients were excluded (14.8% in the tolvaptan group and 5.4% in placebo) due to absence of follow-up MRI scan within the double-blind treatment period.

TABLE 5: PATIENT DISPOSITION

	TEMPO 3:4	
	Tolvaptan	**Placebo**
Screened, N	2,122	2,122
Randomized, N (%)	961 (45.3)	484 (22.8)
Treated, N (%)	961 (100)	483 (99.8)
Discontinued, N (%)	221 (23.0)	67 (13.8)
AE	148 (15.4)	24 (5.0)
Withdrawal of consent	50 (5.2)	30 (6.2)
Loss to follow-up	15 (1.6)	8 (1.7)
Met withdrawal criteria	4 (0.4)	0
Withdrawn by investigator	3 (0.3)	4 (0.8)
Protocol deviation	1 (0.1)	1 (0.2)
N (primary outcome)	819 (85.2)	458 (94.6)
N (key secondary analyses)	961 (100)	483 (99.8)
N (slope of kidney function)	842 (87.6)	464 (95.9)
Safety, N	961 (100)	483 (99.8)

AE = adverse event.
Source: Torres VE et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med 2012; 367(25): 2407-18[2] and Clinical Study Report for TEMPO 3:4.[8]

3.4 Exposure to Study Treatments

Of the patients randomized to tolvaptan, 88% were more than 90% adherent to treatment. In the placebo group, 93% of patients were more than 90% adherent to treatment. Greater than 50% of patients in the tolvaptan group and greater than 80% of patients in the placebo group received the highest dose of 90 + 30 mg. At trial end (month 36), 42% of patients in the tolvaptan group were on the highest daily dose (90 + 30 mg), 16.3% were on the middle dose (60 + 30 mg), and 18.6% were on the lowest dose (45 + 15 mg), resulting in an average daily dose of 96.45 mg. In comparison, the daily average placebo dose was 110 mg. In the tolvaptan group, 336 patients (35.0%) were down-titrated to a lower dose by trial end, and in the placebo group, 70 patients (14.5%) were down-titrated.

Dietary restrictions (sodium, protein, caffeine) [redacted].[8] Antihypertensive medications and medications for kidney pain [redacted].[8]

3.5 Critical Appraisal

3.5.1 Internal Validity

Randomization was conducted centrally, but details of how the randomization sequence was generated or how allocation was concealed were not reported. Demographic and other disease-related characteristics were well balanced among groups, suggesting that randomization was effective. The principal investigators, trial personnel, and patients were blinded to treatment. Due to the higher rate of specific AEs in the tolvaptan group, such as thirst, polyuria, and nocturia, and down-titration to lower doses in the tolvaptan group, there is a possibility that patients and/or investigators became unblinded to treatment allocation during the trial. Patient-reported outcomes, such as kidney pain, could be biased by unblinding of treatment allocation.

Standard care recommendations, such as increased fluid intake, dietary restrictions, and antihypertensive therapy, were implemented in both groups. Although there were differences in clinical standards among centres (e.g., higher sodium intake allowed and more frequent visits on a monthly basis in the Japanese population compared with other centres), this likely did not bias results because randomization was stratified by region. However, patient compliance to standard of care recommendations (e.g., volume of fluid actually consumed) is unclear, as it was not formally assessed with patient intake diaries or at follow-up visits. If there was a difference in the amount of fluid consumed between the tolvaptan and placebo groups, then treatment estimates may be biased due to the effect of water on AVP suppression. Higher fluid intake in the placebo group would likely dilute treatment effect whereas higher fluid intake in the tolvaptan group would augment treatment effect. The Health Canada review of tolvaptan indicated that the recommendation of increasing fluid intake in the placebo group may have diluted treatment estimates.[19] Based on findings of similar TKV growth rate among placebo patients in TEMPO 3:4 and patients from other trials,[20,21] as well as only modest suppression of urine osmolality, the manufacturer concluded that fluid intake would not have had significant effect on disease progression.[19] These data provide indirect evidence of the absence of effect of fluid consumption.

The conduct of the trial might potentially have led to a biased estimation of treatment effect. A large number of patients dropped out of the trial, with more dropouts in the tolvaptan group compared with placebo (23% versus 13.8%). In addition, about [redacted] of patients in the tolvaptan group were excluded from TKV analysis and [redacted] were excluded from secondary kidney function analysis (verses [redacted] in placebo group, respectively). Many of the exclusions from TKV may have been early discontinuations

within the first six months because a minimum interval of six months from a prior MRI scan was needed for inclusion in the outcome. The exclusion of these patients may have compromised randomization. Those patients who discontinued the treatment early in the trial may systematically differ from those patients who successfully completed the entire three-year treatment period, thus leading to a certain degree of imbalance between the two groups. Of note, the statistical analyses of TKV were based on the observed cases dataset rather than the ITT population with no imputation of missing data. In addition, the primary analysis for kidney function included patients with at least four months of follow-up and excluded observations deemed unreliable by investigators. Post-hoc sensitivity analyses examined the effect of excluding patients from TKV and kidney function by imputing missing data with the placebo TKV growth rate or placebo kidney function slope, respectively. Results remained significant in favour of tolvaptan for TKV and kidney function after imputation of missing data. However, since data may not be missing at random, this still leaves the question of whether the comparison of the annual per cent increase rate in TKV and slope of kidney function could have been biased due to the imbalances between treatment groups. For kidney function, this is less of a concern as the results were corroborated with three other measures (i.e., $eGFR_{CKD-EPI}$, $eGFR_{MDRD}$, and eCrCl).

In time to event outcomes, patients who dropped out were censored in primary analyses. Given the differential dropout rate among groups, this may have introduced bias in effect estimates. In a sensitivity analysis of the key secondary composite outcome, values for patients who dropped out were imputed with a percentage of the placebo risk. The result remained significant in favour of tolvaptan when up to 110% of the placebo risk was imputed. Similar sensitivity analyses were conducted for kidney pain and worsening kidney function, with results remaining significant in favour of tolvaptan when up to 120% and 200% of the placebo risk were imputed, respectively. Despite these sensitivity analyses, the potential bias due to differential discontinuation between tolvaptan and placebo remains.

3.5.2 External Validity

Males and females were equally represented and the average age was 39 years. No patient was over 51 years of age and, therefore, the results cannot be generalized to patients over 50 years of age. The average age of ADPKD diagnosis was 27.4 years (range: 0 to 50 years). Caucasians composed the majority of the study population (approximately 84%), Asians about 13%, and other ethnicities about 3%. There were a total of 423 (29.3%) patients from North America, with 379 (26.2%) from the United States and 44 (3.0%) from Canada. While baseline data on prevalence of hypertension and other ADPKD-related outcomes were reported, the presence of other types of comorbidities is not known.

The patients in TEMPO 3:4 were primarily CKD Stages 1 (tolvaptan versus placebo: 34.4% versus 35.9%) or 2 (48.5% versus 46.5%) and fewer patients were CKD Stage 3 (17.0% versus 17.4%). There was only one placebo patient in Stage 4 and none in Stage 5. According to the inclusion criteria, all patients had baseline TKV ≥ 750 mL based on MRI and, therefore, were at risk for disease progression.[18] In addition, the majority of patients (approximately 79%) had hypertension at baseline. The study population likely represented a spectrum of disease stages based on distribution of age and TKV.

The placebo comparator was appropriate given the limited drug therapy options for treating ADPKD. The implementation of other standard care interventions and treatment of hypertension, in addition to tolvaptan or placebo, makes the trial more reflective of clinical practice. The three-year length of follow-up was likely adequate to detect changes in TKV but longer-term follow-up would be needed to elucidate the performance of tolvaptan on clinical outcomes such as progression to ESRD, development of cardiovascular complications, and to determine if the reduction in TKV is sustainable. The open-label

extension study, TEMPO 4:4, provides evidence of sustained reduction in slope of eGFR with tolvaptan for up to five years (see Appendix 6).

TEMPO 3:4 examined several efficacy and harm end points that are relevant to ADPKD. The primary outcome was annual rate of change in TKV, based on three-year data with MRI measurements at the end of each year (12 months, 24 months, and around 36 months). TKV has some correlation with GFR and potential to predict risk of Stage 3 CKD (Appendix 5).[20] Other measures of kidney function, such as CrCl and GFR, may not show abnormality until decades into the disease. TKV, therefore, is more suitable for evaluating earlier stages of ADPKD. TKV of both kidneys was measured using MRI, which is the gold standard approach. However, since it remains unknown if there are accumulated beneficial effects beyond the three-year treatment period, the generalizability of effect on TKV after three years is uncertain. Moreover, the treatment effect was actually just a delay of the increase of patients' TKV (49% slower over the three-year period compared with placebo) but not a complete halt of growth. Therefore, given the relatively young population (39 years), at some point in life patients will still end up with enlarged kidney.

Although TKV is an important marker for ADPKD progression, its correlation with clinical outcomes that can take up to decades to develop, such as need for renal replacement therapy and disease complications, is uncertain. The trial did measure some clinical outcomes as secondary end points, such as a composite of clinical progression and individual components of the composite outcome (i.e., worsening kidney function, kidney pain, hypertension, and worsening albuminuria). The individual components of the secondary outcome are not of equal clinical importance. For instance, while kidney pain is clinically important, worsening albuminuria is less informative. Other clinical outcomes that were evaluated were progression to hypertensive events, and kidney pain score. The latter was assessed on a non-validated 10-point Likert scale with a long recall period of four months. Other important clinical outcomes, such as progression to ESRD/dialysis, quality of life (QoL), hospitalization, extrarenal complications, and infections were not systematically evaluated as efficacy end points and, therefore, the effect of tolvaptan on these outcomes is currently not known.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below. See Appendix 4 for detailed efficacy data.

3.6.1 End-Stage Renal Disease/Dialysis

No data were identified for this outcome.

3.6.2 Disease Complications

Time to clinical progression, which was a composite and key secondary outcome of the trial, was statistically delayed with tolvaptan compared with placebo (incidence rate 43.94 versus 50.04 events per 100 person-years, hazard ratio [HR] 0.87; 95% confidence interval [CI], 0.78 to 0.97) (Table 6). A sensitivity analysis based on independently adjudicated events found similar effect size. The statistically significant result was driven by kidney function decline and kidney pain (note: the individual components of the composite outcome are described in more detail in the following paragraphs). In subgroup analyses, tolvaptan was superior to placebo in delaying progression in patients ≥ 35 years of age, females, Caucasians, hypertension or microalbuminuria present, baseline htTKV < 600 mL/m, and eCrCl < 80 mL/min (Appendix 4, Table 9).

In patients who were non-hypertensive at baseline, there was no statistically significant difference between tolvaptan and placebo on progression to hypertensive events (incidence rate 31.80 versus 29.60 events per 100 person-years, HR 0.99; 95% CI, 0.81 to 1.23) and resting MAP (difference in slope –0.25 mm Hg per year, 95% CI, –1.06 to 0.57). MMRM sensitivity analysis found similar results. Also, in patients who were hypertensive at baseline, the relative risk (RR) of experiencing sustained reduction in blood pressure leading to reduction in antihypertensive therapy up to month 36 using last observation carried forward was not statistically significant (RR 1.10, 95% CI, 0.60 to 2.02).

The individual components of the composite outcome were examined in exploratory analyses. There were fewer events of kidney function decline and clinically relevant episodes of kidney pain (defined as clinically significant episodes requiring medical leave, pharmacologic treatment, or invasive intervention) with tolvaptan (HR 0.39; 95% CI, 0.26 to 0.57 and HR 0.64; 95% CI, 0.47 to 0.89, respectively). No differences were found for worsening hypertension or worsening albuminuria (Appendix 4, Table 10). In subgroup analyses, there were fewer events of kidney function decline in the tolvaptan group by age (< 35 years and ≥ 35 years), gender (males and females), ethnicity (Caucasians and non-Caucasians), hypertension status (absent and present), eCrCl (< 80 mL/min and ≥ 80 mL/min), TKV (< 1,500 mL and ≥ 1,500 mL), htTKV ≥ 600 mL, and microalbuminuria present (data not shown). For kidney pain, there were fewer events in the tolvaptan group in patients less than 35 years of age, females, Caucasians, hypertension present, eCrCl (< 80 mL/min and ≥ 80 mL/min), TKV < 1,500 mL, htTKV ≥ 600 mL, and microalbuminuria present (data not shown).

In the exploratory analyses of time to 13 ADPKD-related events (i.e., hypertension, kidney pain, hepatic cysts, hematuria, albuminuria, nephrolithiasis, urinary tract infection, anemia, colonic diverticuli, vascular/cardiac abnormality, abdominal/inguinal hernia, other cysts, and significant decline in kidney function), and nine events more closely related to kidney enlargement (i.e., hypertension, kidney pain, hematuria, albuminuria, nephrolithiasis, UTI, anemia, abdominal/inguinal hernia, significant decline in kidney function), [redacted]. Results for the individual events are reported in Appendix 4, Table 12.

The following disease complications were not formally evaluated as efficacy outcomes but were reported as harms: anemia (2.8% versus 5.0%), hematuria (7.8% versus 14.1%), renal cyst hemorrhage (0.3% versus 0.8%), nephrolithiasis (1.6% versus 2.9%), cystitis (1.1% versus 2.5%), renal cyst infection (0.9% versus 2.7%), UTI (8.4% versus 12.6%), and pyelonephritis (0.5% versus 1.0%).

3.6.3 Fatal and Non-fatal Cardiovascular Events

The following disease complications were not formally evaluated as efficacy outcomes but were reported as harms: palpitations (tolvaptan versus placebo: 3.5% versus 1.2%), ventricular extrasystoles (0.9% versus 0%), atrial fibrillation (0.3% versus 0.2%), acute myocardial infarction (0.1% versus 0.4%), angina pectoris (0.2% versus 0%), and coronary artery disease (0.1% versus 0%).

3.6.4 Extrarenal Manifestations

The following disease complications were not formally evaluated as efficacy outcomes but were reported as harms: hepatic cyst (tolvaptan versus placebo: 1.4% versus 2.1%), other cysts (1.9% versus 4.1%), and intracranial aneurysm (0.3% versus 0.2%).

3.6.5 Hospitalization

No data were identified for this outcome.

3.6.6 Mortality

There were no deaths in the tolvaptan or placebo groups during the trial.

3.6.7 Quality of Life

No data were identified for this outcome.

3.6.8 Patient-Reported Outcomes

No statistical difference was found in mean change in AUC from baseline for kidney pain score between tolvaptan and placebo in patients not taking pain medication at start of trial (difference –0.08; 95% CI, –0.20 to 0.03) (Table 6). MMRM sensitivity analysis found similar results. In subgroup analyses, reductions in pain score in females and in patients with microalbuminuria in the tolvaptan group were observed (Appendix 4, Table 9). The result for the kidney pain domain, which was part of the composite clinical progression outcome, is reported in Section 3.6.2.

The following patient-reported outcomes were not formally evaluated as efficacy outcomes but were reported as harms: abdominal discomfort (tolvaptan versus placebo: [redacted]), abdominal distension ([redacted]), abdominal pain (6.5% versus 6.6%), fatigue (13.6% versus 9.7%), back pain (13.8% versus 18.2%), and anxiety ([redacted]).

3.6.9 Total Kidney Volume

The primary outcome of the trial was annual percentage change in TKV (Table 7). Compared with placebo, the annual percentage increase in TKV was significantly less, statistically and clinically, with tolvaptan (2.8% versus 5.5%, difference in slope –2.7% per year; 95% CI, –3.3 to –2.1, 49.2% reduction in growth rate). The MMRM sensitivity analysis also demonstrated benefit of tolvaptan compared with placebo and found the largest difference occurred after year 1. Tolvaptan was superior to placebo in all subgroup analyses for the annual percentage increase in TKV (Appendix 4, Table 9).

3.6.10 Kidney Function

Kidney slope function, based on reciprocal of SCr, was a secondary outcome (Table 7). Kidney function slopes based on $GFR_{CKD\text{-}EPI}$, GFR_{MDRD}, and eCrCl are presented in Appendix 4, Table 13. Baseline and follow-up laboratory measurements for SCr, blood urea nitrogen (BUN), and urine albumin to creatinine ratio are provided in Appendix 4, Table 14.

There was statistically significant less decline in kidney function with tolvaptan versus placebo as measured by the slope of reciprocal of SCr (difference in slope 1.20 $[mg/mL]^{-1}$ per year; 95% CI, 0.62 to 1.78). This result was confirmed by using slope of eGFR estimated with the CKD-EPI equation, the MDRD equation, and eCrCl estimated with the Cockcroft-Gault equation (Appendix 4, Table 13). MMRM analyses of SCr and eGFR also demonstrated beneficial effect of tolvaptan. Subgroup analyses of reciprocal of SCr found results in favour of tolvaptan for patients ≥ 35 years, males and females, Caucasians, hypertension or microalbuminuria present, and TKV ≥ 1,500 mL or htTKV ≥ 600 mL/m (Appendix 4, Table 9).

In exploratory analysis, urine albumin to creatinine ratio was not different between tolvaptan and placebo (Table 14). However, MMRM analysis found that tolvaptan was associated with a lower ratio

compared with placebo from month 12 onwards. In addition, there were fewer clinically significant abnormalities in SCr or BUN in the tolvaptan group compared with placebo (16.7% versus 21% and 15.6% versus 29.4%, respectively). For SCr, [redacted] ([redacted] mg/dL) was [redacted] ([redacted] mg/dL).[8]

3.6.11 Need for Supportive Treatments

No data were identified for this outcome.

TABLE 6: KEY EFFICACY OUTCOMES

	TEMPO 3:4	
	Tolvaptan	**Placebo**
Clinical progression (composite)[a]		
N (% of group total)	961 (100)	483 (99.8)
HR (95% CI)	0.87 (0.78 to 0.97)	
P value	0.01	
Progression to hypertensive events in patients non-hypertensive at baseline		
N (% group total)	174 (18.1)	79 (16.3)
N (% non-hypertensive subset)	174/196 (88.8)	79/102 (77.4)
HR (95% CI)	0.99 (0.81 to 1.23)	
P value	0.97	
Resting MAP in patients non-hypertensive at baseline		
N (% group total)	129 (13.4)	74 (15.3)
N (% non-hypertensive subset)	129/196 (65.8)	74/102 (72.5)
Mean (mm Hg increase per year)	2.56	2.59
Slope (linear mixed effect model)	0.84	1.08
Difference in slope (95% CI)	–0.25 (–1.06 to 0.57)	
P value	0.55	
Reduction of antihypertensive therapy in patients hypertensive at baseline		
N (% group total)	481 (50.0)	267 (55.2)
N (% hypertensive subset)	481/765 (62.9)	267/382 (69.9)
No. patients with event	30	15
RR (95% CI)	1.10 (0.60 to 2.02)	
P value	0.75	
Kidney pain score in patients not taking pain medication at baseline		
N (% group total)	926 (96.4)	467 (96.5)
Mean change in AUC from baseline	0.00	0.08
Difference (95% CI) (ANCOVA)	–0.08 (–0.20 to 0.03)	
P value	0.16	

ANCOVA = analysis of covariance; AUC = area under the curve; CI = confidence interval; HR = hazard ratio; MAP = mean arterial pressure; RR = relative risk.

[a] Defined as worsening kidney function based on 25% reduction in reciprocal of SCr; clinically significant kidney pain that required medical leave, pharmacologic treatment, or invasive intervention; worsening hypertension; or worsening albuminuria.

Source: Torres VE et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med 2012; 367(25): 2407-18[2] and Clinical Study Report for TEMPO 3:4.[8]

TABLE 7: OTHER EFFICACY OUTCOMES

	TEMPO 3:4	
	Tolvaptan	Placebo
TKV		
N (% group total)	819 (85.2)	458 (94.6)
Mean change (% increase per year)	2.78	5.61
Slope (% increase per year) (95% CI) (linear mixed effect model)[a]	2.80 (2.46 to 3.14)	5.51 (5.06 to 5.96)
Difference in slope (95% CI)	–2.71 (–3.27 to –2.15)	
P value	< 0.001	
Kidney function (reciprocal of SCr)		
N (% group total)	842 (87.6)	464 (96.1)
Mean change ($[mg/mL]^{-1}$ per year)	–2.56	–3.68
Slope ($[mg/mL]^{-1}$ per year) (linear mixed effect model)[a]	–2.61	–3.81
Difference in slope (95% CI)	1.20 (0.62 to 1.78)	
P value	< 0.001	

CI = confidence interval; SCr = serum creatinine; TKV = total kidney volume.
[a] Slope was derived from a linear mixed model that included time-treatment interaction.
Source: Torres VE et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med 2012; 367(25): 2407-18[2] and Clinical Study Report for TEMPO 3:4.[8]

3.7 Harms

3.7.1 Adverse Events

Nearly all patients experienced at least one AE (97.9% in the tolvaptan group and 97.1% in the placebo group) (Table 8). Thirst, polyuria, nocturia, pollakiuria, polydipsia, and decreased appetite were much more frequent with tolvaptan. Clinically significant increases in levels of uric acid, sodium, and liver enzymes also occurred in more patients receiving tolvaptan compared with placebo. In addition, eye disorders (glaucoma, ocular hyperemia, photophobia, and blurred vision) occurred in seven patients receiving tolvaptan compared with no patients receiving placebo.

3.7.2 Serious Adverse Events

SAEs were experienced by 18.4% of patients in the tolvaptan group and 19.7% of patients in the placebo group. More patients in the tolvaptan group experienced SAEs related to elevation in liver enzymes, chest pain, and headache. In addition, basal cell carcinoma was more frequent in the tolvaptan group (0.8% versus 0.2%).

3.7.3 Withdrawals Due to Adverse Events

More patients receiving tolvaptan withdrew from the trial due to an AE (15.4% versus 5.0%). The most common AE leading to withdrawal of tolvaptan was polyuria, followed by pollakiuria, nocturia, thirst, abnormal liver function, and fatigue.

3.7.4 Mortality

No deaths were reported during the trial.

3.7.5 Notable Harms

More patients in the tolvaptan group experienced alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevation greater than 2.5 times the upper limit of normal (4.9% versus 1.2% and 3.2% versus 0.8%, respectively). More patients in the tolvaptan group also had ALT or AST elevation that was greater than three, five, or 10 times the upper limit of normal (data not shown).[8] Serious liver-related events and serious elevations in ALT, AST, and transaminase levels were more common in the tolvaptan group, and more patients on tolvaptan discontinued treatment due to abnormal liver function.

According to Hy's criteria, risk of serious liver injury is heightened if AST or ALT is greater than three times the upper limit of normal, bilirubin is greater than two times the upper limit of normal (without signs of cholestasis), and other medical reasons for liver injury are excluded. In the tolvaptan group, two patients met Hy's criteria.

No events of liver failure or liver transplant were reported during the trial.

Hypernatremia (serum sodium > 150 mmol/L) occurred in 4% of patients receiving tolvaptan and 1.4% of patients receiving placebo (Table 8). Hyperkalemia was similar in tolvaptan and placebo groups (3.1% versus 3.7%). Hyperglycemia was lower in the tolvaptan group (0.6% versus 2.1%). Clinically significant increases in uric acid and gout were higher in patients receiving tolvaptan (6.2% versus 1.7% and 2.9% versus 1.4%, respectively). Dehydration occurred in 1.9% of patients in tolvaptan group and 2.3% in placebo group. Polyuria and thirst were much more common in the tolvaptan group (38.3% versus 17.2% and 55.3% versus 20.5%, respectively).

TABLE 8: HARMS

	TEMPO 3:4	
	Tolvaptan (N = 961)	Placebo (N = 483)
AEs		
Patients with > 0 AEs, N (%)	941 (97.9)	469 (97.1)
Thirst	531 (55.3)	99 (20.5)
Polyuria	368 (38.3)	83 (17.2)
Nocturia	280 (29.1)	63 (13.0)
Pollakiuria	223 (23.2)	26 (5.4)
Dry mouth	154 (16.0)	59 (12.2)
Fatigue	131 (13.6)	47 (9.7)
Dizziness	109 (11.3)	42 (8.7)
Polydipsia	100 (10.4)	17 (3.5)
Constipation	81 (8.4)	12 (2.5)
Dyspepsia	76 (7.9)	16 (3.3)
Decreased appetite	69 (7.2)	5 (1.0)
Clinically significant increase — uric acid	59 (6.2)	8 (1.7)
ALT > 2.5 times upper limit of normal	47 (4.9)	6 (1.2)
Serum sodium > 150 mmol/L	38 (4.0)	7 (1.4)
Palpitations	34 (3.5)	6 (1.2)
AST > 2.5 times upper limit of normal	31 (3.2)	4 (0.8)

	TEMPO 3:4	
	Tolvaptan (N = 961)	**Placebo (N = 483)**
Clinically significant increase — potassium	30 (3.1)	18 (3.7)
Gout	28 (2.9)	7 (1.4)
Dehydration	18 (1.9)	11 (2.3)
Bilirubin > 1.5 times upper limit normal	9 (0.9)	9 (1.9)
Eye disorders (glaucoma, ocular hyperemia, photophobia, and blurred vision)	7 (0.7)	0
Hyperglycemia	6 (0.6)	10 (2.1)
SAEs		
Patients with > 0 SAEs, N (%)	177 (18.4)	95 (19.7)
Combined liver-related events (e.g., cholestasis, jaundice, liver failure, fibrosis, cirrhosis, noninfectious hepatitis)	22 (2.3)	5 (1.0)
Malignant tumours Basal cell carcinoma	16 (1.7) 8 (0.8)	2 (0.4) 1 (0.2)
ALT elevation	9 (0.9)	2 (0.4)
AST elevation	9 (0.9)	2 (0.4)
Transaminase elevation	4 (0.4)	0
Chest pain	8 (0.8)	2 (0.4)
Headache	5 (0.5)	0
Hepatitis	1 (0.1)	0
WDAEs		
WDAEs, N (%)	148 (15.4)	24 (5.0)
Polyuria	[redacted]	[redacted]
Pollakiuria	[redacted]	[redacted]
Nocturia	[redacted]	[redacted]
Thirst	[redacted]	[redacted]
Abnormal liver function	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Deaths		
Number of deaths, N (%)	0	0

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

Source: Torres VE et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med 2012; 367(25): 2407-18[2] and Clinical Study Report for TEMPO 3:4.[8]

4. DISCUSSION

4.1 Summary of Available Evidence

The efficacy and safety of tolvaptan compared with placebo for ADPKD has been evaluated in one large, multi-centre, phase 3 randomized controlled trial (RCT) (TEMPO 3:4) that followed patients for three years and one open-label extension trial (TEMPO 4:4) that followed patients for an additional two years. Statistically significant benefits of tolvaptan were demonstrated with respect to TKV, kidney function, and clinical progression (driven by kidney pain and worsening kidney function). Additional exploratory analyses also suggested benefit of tolvaptan for time to 13 ADPKD-related events and nine events more closely related to kidney enlargement. No differences were found for hypertension-related outcomes. Other clinical outcomes, such as time to ESRD, need for dialysis, cardiovascular events, or QoL were not evaluated in the trial. The primary harms with tolvaptan were those related to its mechanism of action, such as thirst, polyuria, and nocturia, as well as elevation in liver enzymes.

The main limitations of TEMPO 3:4 were the potential for unblinding of patients and/or investigators due to the higher prevalence of specific AEs experienced in the tolvaptan group, potential bias in effect estimates due to the larger number of patients who discontinued in the tolvaptan group, and the absence of evaluation of some clinically important outcomes.

4.2 Interpretation of Results

4.2.1 Efficacy

The therapeutic management of ADPKD is limited by the lack of disease-modifying drugs. Patients with ADPKD currently have access to symptomatic treatments and surgical interventions, none of which slow kidney growth.[19] Tolvaptan, therefore, through its effects on TKV and kidney function, potentially fills an important therapeutic gap in the management of ADPKD. The use of tolvaptan for ADPKD has been approved by Health Canada,[19] Japan,[19] and the European Medicines Agency (EMA).[22] The Food and Drug Administration (FDA), however, did not approve tolvaptan for ADPKD, because of lack of long-term follow-up data and the use of TKV as the primary outcome, which was thought to be an inadequate surrogate marker.[23] The FDA has released draft guidance that supports the use of TKV as a baseline biomarker, in combination with patient age and baseline eGFR, to identify patients with ADPKD at high risk of progressive decline in kidney function for inclusion in clinical trials.[24]

Tolvaptan is the first drug therapy to demonstrate statistically significant benefit in the treatment of ADPKD: it was superior to placebo in reducing TKV over 36 months, the primary outcome in TEMPO 3:4. It remains unknown if there are accumulated beneficial effects beyond the 36-month treatment period. The open-label extension study, TEMPO 4:4, reported sustained reduction in eGFR slope in patients continuing on tolvaptan and decelerated slope in patients switched to tolvaptan over an additional two-year period (for total treatment period of five years) (see Appendix 6: SUMMARY OF OPEN-LABEL EXTENSION TRIAL). A key consideration, also, is that change in TKV is a surrogate for kidney function and key clinical outcomes. There is no defined MCID for TKV; however, based on discussion with the clinical expert involved in the review, the approximately 50% less increase in annual slope of TKV with tolvaptan compared with placebo over the course of the trial is a notable effect size and is likely clinically significant.

Nevertheless, there are limitations with rate of change in TKV as an outcome (see Appendix 5) and hence there is a nontrivial degree of uncertainty in the findings from TEMPO 3:4. The CRISP study used MRI to measure the rates of change in TKV, total cyst volume, and GFR over eight years.[20] The

prospective, observational, longitudinal, multi-centre study (N = 241 adults with ADPKD) showed a statistically significant negative correlation between rates of GFR decline and TKV growth. The correlation was moderate in association after eight years of follow-up. A limitation of these analyses is they assumed that the rates of GFR decline and TKV growth were constant and linear. The CRISP study demonstrated that TKV is dependent on age in addition to patient height; it therefore remains uncertain that GFR would be constant over time. As well, clinical outcomes such as ESRD and need for dialysis often manifest after decades; the evidence for a correlation between rates of GFR decline and TKV growth and the TEMPO 3:4 study are therefore relatively short compared with the natural history of ADPKD. Hence, it remains to be answered through longer-term studies whether tolvaptan can impact those outcomes that are ultimately of concern to patients, such as delaying the need for dialysis, ability to carry out chores of daily living, hypertension, disease complications, and mortality. In addition, future studies should evaluate tolvaptan's effects on health-related quality of life.

The lower decline in kidney function with tolvaptan, which was demonstrated by four different measures, is also supportive of the potential benefit of tolvaptan. Importantly, for both TKV and kidney function outcomes, a large percentage of patients were differentially excluded from the tolvaptan group in primary analyses. Although post-hoc sensitivity analyses with data imputation were conducted, there is still potential for results of these outcomes to be biased due to data not missing at random.

The inconsistency between the results of kidney pain score (no statistically significant difference) and the kidney pain domain of the clinical progression outcome (statistically significant difference in favour of tolvaptan) is likely due to the differences in the definitions of the outcomes. The 10-point scale method to assess kidney pain asked patients to recall pain episodes over a period of four months; episodes of pain may have fluctuated greatly over that time period and, therefore, any potential differences between tolvaptan and placebo may have been masked by the assignment of a single score for each four-month interval. The kidney pain domain, however, assessed clinically significant episodes of pain that required medical leave or some intervention, which is a more objective measure than pain score.

4.2.2 Harms

The commonly experienced AEs associated with tolvaptan were thirst, polyuria, nocturia, and pollakiuria, and these were also reasons for patients discontinuing treatment with tolvaptan. These effects may impact a patient's overall experience with the medication and QoL and, therefore, it will be important for health care providers to monitor patients for these effects on an ongoing basis. Other AEs that should be evaluated are gastrointestinal-related (i.e., constipation, dyspepsia, decrease in appetite), increase in uric acid and sodium, gout, eye disorders, and basal cell carcinoma.

Elevation in liver enzymes and progression to liver injury or failure has been identified as an important AE associated with the use of tolvaptan that requires careful monitoring. Patients taking tolvaptan must be regularly monitored for liver function and appropriate action taken if enzymes are elevated to prevent progression to overt liver failure. Health Canada, in collaboration with the manufacturer, have agreed to the establishment of a Canadian ADPKD registry for the purposes of monitoring long-term clinical outcomes such as time to ESRD or dialysis, mortality, and cause of mortality in all patients receiving tolvaptan for ADPKD in Canada.[19] In addition, the manufacturer has established a mandatory hepatic safety monitoring program (HSMP) to ensure that liver function tests are conducted and liver safety signals are monitored.[19] These measures, along with patient and provider education and ongoing post-marketing surveillance, should help to minimize the risks of hepatic harms of tolvaptan. The

monitoring of long-term safety (beyond five years) through studies and post-marketing surveillance should also be a continuing priority.

4.3 Potential Place in Therapy[2]

There is currently no specific treatment for delaying progression of ADPKD other than optimizing blood pressure control. However, multiple promising drugs have been identified in pre-clinical studies and some tested in RCTs.[25,26] Among these drugs, tolvaptan has been shown to significantly slow the growth of total kidney volume in pre-clinical studies[1] and in the largest RCT for ADPKD (TEMPO 3:4) to date.[2] In the RCT, tolvaptan also slowed the rate of decline of kidney function. However, TEMPO 3:4 was not powered to evaluate the treatment effect using traditional outcomes such as percentage of patients (on treatment versus placebo) with a doubling of serum creatinine (or halving of eGFR) and mean time delay for progression to ESRD. Nevertheless, given the pre-clinical and clinical findings, tolvaptan is presently the most promising disease-modifying drug available for slowing the progression of ADPKD.

Patients with ADPKD display a wide spectrum of disease severity depending largely on their mutation class.[3,4] Patients with truncating PKD1 mutations typically will have severe disease, with half of them requiring ESRD treatment by age 50 to 55 years. By contrast, patients with PKD2 and many with non-truncating PKD1 mutations typically will have mild disease, with half of them needing ESRD treatment only by late 70 years of age. Moreover, patients with large TKV at a younger age are also at high risk for progression to early ESRD. Given its costs and potential adverse effects as well as incomplete efficacy data (see earlier), it may be prudent at this time to select patients who are at "high risk" for progression to early ESRD for tolvaptan treatment. "High-risk" patients may be selected based on their genotype (i.e., truncating PKD1 mutations),[3,4] family history of at least one older affected relative who developed ESRD before 50 years of age (i.e., highly predictive of truncating PKD1 mutations),[5] or age-adjusted TKV (as measured by MRI or CT but not ultrasound).[6,7,20]

[2] Based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

5. CONCLUSIONS

Tolvaptan is a selective vasopressin V_2 receptor antagonist indicated to slow progression of kidney enlargement in adults with ADPKD. It was evaluated in one multi-centre RCT, TEMPO 3:4, which included 1,445 patients and follow-up of three years, and in one open-label extension study, TEMPO 4:4, which included 904 patients and follow-up of two years. Compared with placebo, tolvaptan demonstrated benefit on the primary outcome of change in TKV. Although there is evidence that TKV growth predicts rates of GFR decline, there remains uncertainty about how well TKV predicts clinically relevant outcomes such as delaying ESRD, need for dialysis, and mortality. Tolvaptan was also shown to be superior to placebo on rate of change in kidney function and a composite outcome of clinical progression, providing further evidence for a potential benefit of tolvaptan. No differences between groups were observed for hypertension outcomes. Based on the inclusion criteria of the trial, the efficacy results are specific to patients at risk for disease progression but who have not yet reached later stages of the disease. Therefore, careful patient selection, taking into consideration baseline TKV and kidney function to identify high-risk patients who are most likely to develop ESRD,[7] will be required prior to initiating therapy with tolvaptan. Important harms associated with tolvaptan were thirst, polyuria, nocturia, pollakiuria, and elevation in liver enzymes. Long-term data of efficacy and safety as well as assessment of clinical outcomes are needed to make firm conclusions about tolvaptan's risk-benefit profile. Based on the results of TEMPO 3:4 and TEMPO 4:4, tolvaptan potentially fills an important therapeutic need in the management of adults with ADPKD.

APPENDIX 1: PATIENT INPUT SUMMARY

1. Brief Description of Patient Group(s) Supplying Input

One patient group, Polycystic Kidney Disease Foundation of Canada (PKDFC) provided input for this review. The mission of PKDFC is to promote programs of research, advocacy, education, support and awareness in order to discover treatments and a cure for polycystic kidney disease (PKD), and improve the lives of all it affects. Over the past three years, PKDFC has received project sponsorship from Otsuka Canada Pharmaceutical Inc. including website translation (French), front-line initiative capacity building, and the PKD Canadian Symposium. Additionally, Otsuka Canada Pharmaceutical Inc. has been a corporate sponsor of the Walk for PKD campaign since 2013. No funding from other pharmaceutical companies was reported in PKDFC's submission. No conflict of interest was declared in preparing the patient input for this submission.

CADTH also received a letter from the Kidney Foundation of Canada, BC & Yukon Branch that supported the input provided by PKDFC. As the letter was received after the deadline for patient input, it was not included within the review. The perspectives shared, however, align with those of PKDFC.

2. Condition-Related Information

Information was obtained through personal knowledge, patient telephone interviews, and an online survey.

Patients with PKD believe that the most important aspects in the management of PKD are to control high blood pressure, kidney function, and to slow the progression of cyst development and growth on both the liver and kidneys. Based on an online survey that asked respondents to rank three options in terms of "how important you feel they are in determining whether or not you feel your PKD is under control," 63% of respondents chose "my kidney function is not declining rapidly"; 15% chose "I am not experiencing many PKD symptoms," and 13% selected "my kidneys are not growing too quickly." Respondents of the online survey also indicated that PKD impacts every aspect of their daily lives, such as how they get dressed and what they wear. In addition, respondents indicated having to wrap bandages around their abdomens daily to prevent pain and or hernias, limitations on physical tasks, social stigma, and emotional toll because of the way they look as key issues associated with PKD. Online survey respondents also noted they were unable to do simple maintenance and household chores, ride a bicycle, play sports, exercise, walk, play with their children, and drive long distances because of having PKD. The most frequent symptoms reported by respondents were fatigue (72%), anxiety (55%), high blood pressure (54%), abdominal distension (51%), back pain (48%), abdominal pain (46%), and liver cysts (43%). The online survey also provided the following quotes about the impact of PKD on patients:

- "It becomes the centre of your existence, and early death sentence. Treatment becomes the focus of your life versus your family. Especially having seen your parent go through the same affliction."
- "High blood pressure, pain, infection, physical changes in your body shape and the worry about needing dialysis or a transplant can cause anxiety and uncertainty."
- "It is a disease that totally takes over your life, from the minute you are diagnosed. It affects everything and everybody that is in your life."

Almost two-thirds (62%) of respondents expressed being either extremely concerned or very concerned about the impact of PKD on their current overall health.

Caregivers of people with PKD also responded to the online survey and indicated a number of challenges they faced in caring for someone with PKD. These included financial hardships, intimacy issues, changes in lifestyle, and physical challenges. Caregivers were fearful of their loved one with PKD having liver failure, kidney failure, a heart attack, or dying. They also feared the disease would be passed to their children, and were therefore very conscious of testing and monitoring their children for the signs and symptoms of PKD.

One caregiver expressed the importance of having treatments that delay the progression of PKD and/or prevent it from developing in the first place. Another became a living kidney donor to support his spouse and children who all have PKD.

3. Current Therapy-Related Information

Information was obtained through personal experience and patient telephone interviews.

All patients interviewed were currently taking tolvaptan (were part of the tolvaptan TEMPO trial), as well as medications for high blood pressure. In a survey, 63% of respondents indicated they thought, "There are no effective treatments available for PKD." With respect to adverse effects associated with current therapies, respondents indicated that the most difficult to tolerate were large amounts of fluid intake and urine output, advanced daily planning to manage fluid intake and urine output, and temporary increase in liver enzymes.

Patients indicated hardships related to accessing tolvaptan, including travel time and discomfort related to clinic visits. All of the interviewees noted that without a clinical trial or private drug coverage, none of them could afford tolvaptan.

Patients indicated that the symptoms of PKD that tolvaptan managed well were depression, fewer major kidney pain events (such as pain medication needed, trips to the emergency room, missed workdays, etc.), and fewer symptoms overall. The symptoms managed less well included high blood pressure and pain in other organs (e.g., liver, pancreas, and back). For some patients, tolvaptan did not improve their emotional outlook and had a negative impact on their day-to-day life. Patients pointed out that they still had unmet needs despite treatment with tolvaptan, including impact on their liver (elevated liver enzymes requiring close monitoring), cyst development, hernias, impact on family life, ability to obtain life insurance, risk to employment (due to medication costs), and risk of passing PKD on to their children. The adverse effects caused by tolvaptan that were seen as unacceptable, in addition to its effects on liver enzymes, were the large amount of fluid intake and frequent urination (although some patients stated this became acceptable), increased tiredness, dry mouth, thirst, and dizziness (if taking both tolvaptan and a blood pressure medication concurrently). Overall, patients reported tolvaptan was easy to use (although the twice-daily administration was a drawback) and believed that it was helping to slow the progression of their disease.

4. Expectations About the Drug Being Reviewed

Information was obtained through personal experience and patient telephone interviews.

Patients expect tolvaptan will delay the need for dialysis and/or kidney transplantation, as well as prolong their lives with improved quality of life. Additional expectations for tolvaptan treatment included allowing individuals to work longer without taking sick leave and reducing financial burden for retirement, and allowing them to contribute to society more without succumbing to the PKD lifestyle.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	June 26, 2015
Alerts:	Weekly search updates until (October 21, 2015)
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded
SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY
1. (tolvaptan* or jinarc* or OPC-41061 or OPC41061 or 0150683-30-0 or 150683-30-0).ti,ot,ab,kw,sh,rn,hw,nm,rn.
2. (adpkd or pkd or ((renal or kidney) adj4 (autosomal or cys* or polycys*))).ti,ab.
3. Polycystic kidney, autosomal dominant/
4. 2 or 3
5. 1 and 4
6. 5 use pmez
7. (tolvaptan* or jinarc* or OPC-41061 or OPC41061 or 0150683-30-0).ti,ab.
8. *tolvaptan/
9. 7 or 8
10. *kidney polycystic disease/
11. 2 or 10
12. 9 and 11
13. 12 use oemezd
14. 6 or 13

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	No date limits were used
Keywords:	Jinarc (tolvaptan) AND Kidney disease
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Muto S, et al.[27]	Japanese subgroup analysis of TEMPO 3:4
Clinical Report Synopsis for Protocol: 156-08-271[28]	Open-label study
Boertien WE, et al.[29]	Study design not of interest
Higashihara E, et al.[30]	Study design not of interest

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 9: SUBGROUP DATA FOR PRE-SPECIFIED PRIMARY AND SECONDARY OUTCOMES

	Age		Gender		Ethnicity		Hypertension		TKV (mL)		htTKV (mL/m)		eCrCl (mL/min)		Microalbuminuria	
	< 35	≥ 35	M	F	Caucasian	Non-Caucasian	Present	Absent	< 1,500	≥ 1,500	< 600	≥ 600	< 80	≥ 80	Present	Absent
Clinical progression — composite (no. events per 100 person-years)																
$N_{Tolvaptan}$																
$N_{Placebo}$																
Tolvaptan																
Placebo																
HR																
LCI (95%)																
UCI (95%)																
Resting MAP slope in non-hypertensive patients (mm Hg increase per year)																
$N_{Tolvaptan}$																
$N_{Placebo}$																
Tolvaptan																
Placebo																
Difference																
LCI (95%)																
UCI (95%)																
Progression to hypertensive events in non-hypertensive patients (no. events per 100 person-years)																
$N_{Tolvaptan}$																
$N_{Placebo}$																
Tolvaptan																
Placebo																
HR																
LCI (95%)																
UCI (95%)																

	Age		Gender		Ethnicity		Hypertension		TKV (mL)		htTKV (mL/m)		eCrCl (mL/min)		Microalbuminuria	
	< 35	≥ 35	M	F	Caucasian	Non-Caucasian	Present	Absent	< 1,500	≥ 1,500	< 600	≥ 600	< 80	≥ 80	Present	Absent
Reduction of antihypertensive therapy in hypertensive patients up to month 36 (no. patients with event)																
$N_{Tolvaptan}$																
$N_{Placebo}$																
Tolvaptan																
Placebo																
RR																
LCI (95%)																
UCI (95%)																
Kidney pain score difference (change in AUC from baseline)																
$N_{Tolvaptan}$																
$N_{Placebo}$																
Tolvaptan																
Placebo																
Difference																
LCI (95%)																
UCI (95%)																
TKV slope (% increase per year)																
$N_{Tolvaptan}$																
$N_{Placebo}$																
Tolvaptan																
Placebo																
Difference																
LCI (95%)																
UCI (95%)																

	Age		Gender		Ethnicity		Hypertension		TKV (mL)		htTKV (mL/m)		eCrCl (mL/min)		Microalbuminuria	
	< 35	≥ 35	M	F	Caucasian	Non-Caucasian	Present	Absent	< 1,500	≥ 1,500	< 600	≥ 600	< 80	≥ 80	Present	Absent
Kidney function slope — reciprocal of SCr ([mg/mL]$^{-1}$ per year)																
$N_{Tolvaptan}$	[redacted]															
$N_{Placebo}$	[redacted]															
Tolvaptan	[redacted]															
Placebo	[redacted]															
Difference	[redacted]															
LCI (95%)	[redacted]															
UCI (95%)	[redacted]															

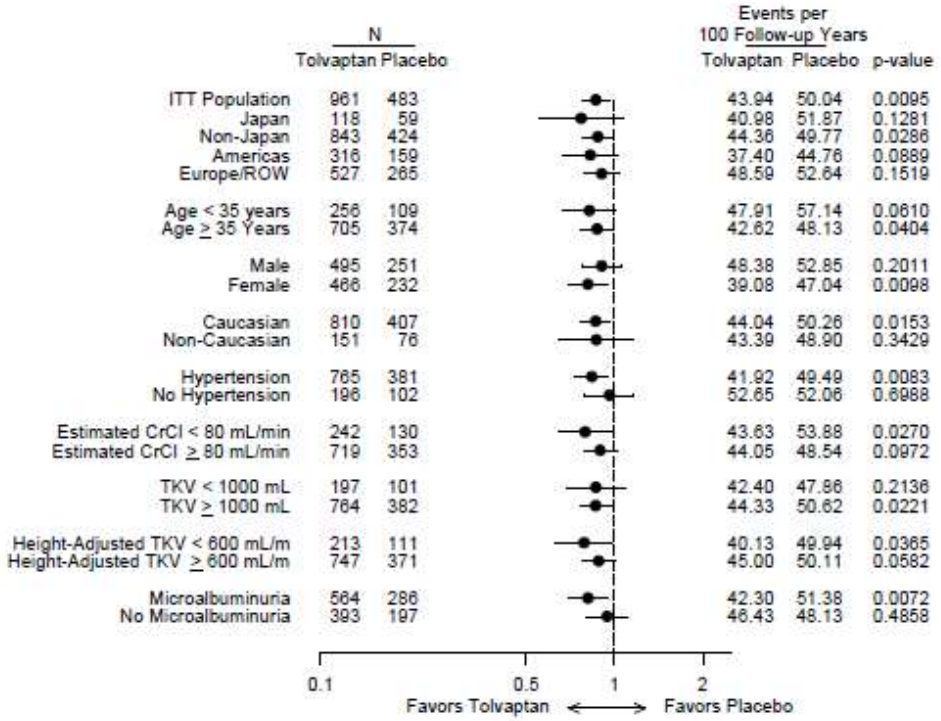
AUC = area under the curve; eCrCl = estimated creatinine clearance; F = female; HR = hazard ratio; htTKV = height-adjusted total kidney volume; LCI = lower confidence interval; M = male; MAP = mean arterial pressure; NA = not applicable; P = favours placebo; RR = relative risk; SCr = serum creatinine; T = favours tolvaptan; TKV = total kidney volume; UCI = upper confidence interval.

[a] Statistically significant at least at *P* = 0.05 level.

Source: Clinical Study Report for TEMPO 3:4.[8]

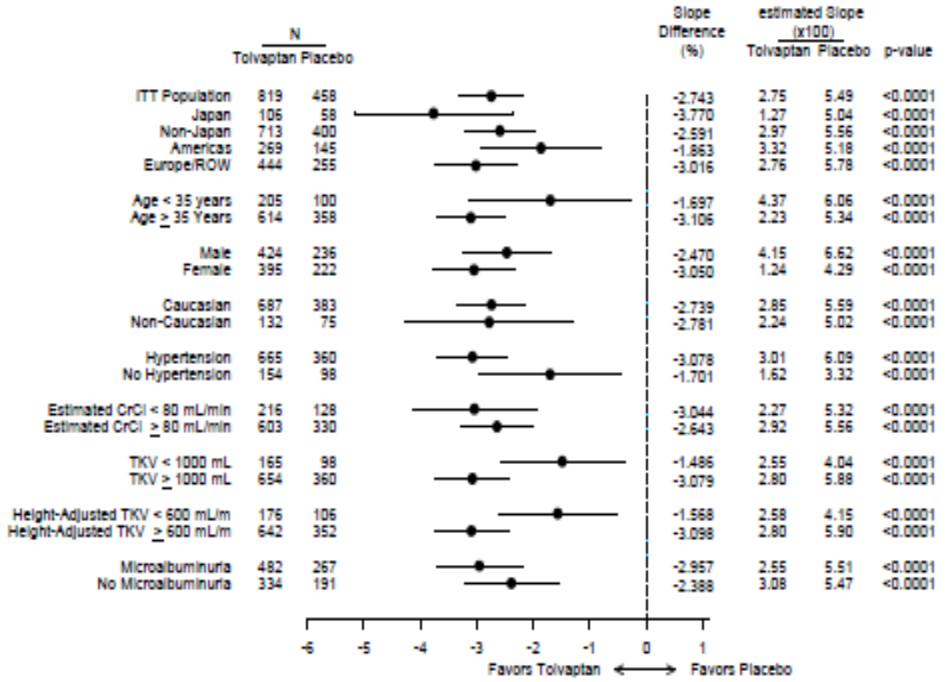
The following forest plots of subgroup analyses have been obtained from the manufacturer-submitted Clinical Study Report for trial (TEMPO 3:4).[8] Note that the data shown in the forest plots for region (Japan, Non-Japan, Americas, Europe/ROW) were not extracted in Table 9. Also, data for TKV < 1,500 mL and ≥ 1,500 mL were extracted rather than TKV < 1,000 mL and ≥ 1,000 mL as shown in the forest plots.

FIGURE 2: KEY SECONDARY OUTCOME OF CLINICAL PROGRESSION (COMPOSITE)



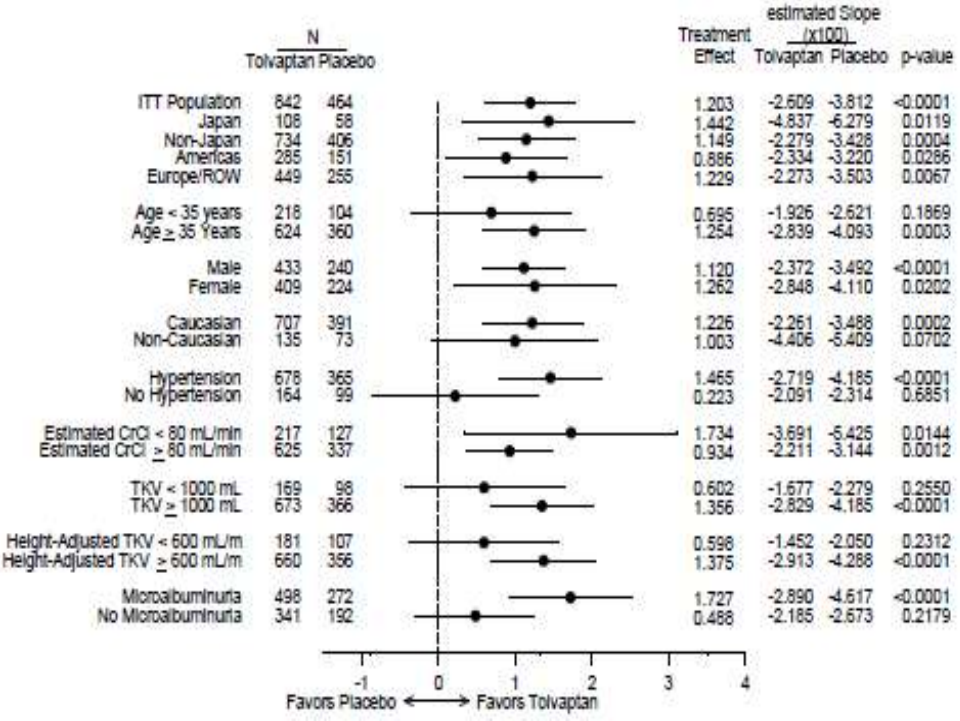
CrCl = creatinine clearance; ITT = intention-to-treat; ROW = rest of world; TKV = total kidney volume.
Source: Clinical Study Report for TEMPO 3:4.[8]

FIGURE 3: TKV SLOPE DIFFERENCE



CrCl = creatinine clearance; ITT = intention-to-treat; ROW = rest of world; TKV = total kidney volume.
Source: Clinical Study Report for TEMPO 3:4.[8]

FIGURE 4: KIDNEY FUNCTION (1/SCR) SLOPE DIFFERENCE



CrCl = creatinine clearance; ITT = intention-to-treat; ROW = rest of world; TKV = total kidney volume.
Source: Clinical Study Report for TEMPO 3:4.[8]

TABLE 10: EXPLORATORY ANALYSIS — INDIVIDUAL COMPONENTS OF THE SECONDARY COMPOSITE OUTCOME OF CLINICAL PROGRESSION

	TEMPO 3:4	
	Tolvaptan	Placebo
Worsening kidney function		
N (%)	917 (95.4)	476 (98.3)
No. events per 100 person-years	1.85	4.84
HR (CI)	0.39 (0.26 to 0.57)	
P value	< 0.0001	
Worsening kidney pain		
N (%)	961 (100)	483 (99.8)
No. events per 100 person-years	4.73	7.30
HR (CI)	0.64 (0.47 to 0.89)	
P value	0.0071	
Worsening hypertension		
N (%)	961 (100)	483 (99.8)
No. events per 100 person-years	30.74	32.05
HR (CI)	0.94 (0.81 to 1.09)	
P value	0.42	
Worsening albuminuria		
N (%)	961 (100)	483 (99.8)
No. events per 100 person-years	8.17	7.75
HR (CI)	1.04 (0.84 to 1.28)	
P value	0.74	

CI = confidence interval; HR = hazard ratio.
Source: Clinical Study Report for TEMPO 3:4.[8]

TABLE 11: EXPLORATORY ANALYSIS — TIME TO MULTIPLE AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE EVENTS

	TEMPO 3:4	
	Tolvaptan	Placebo
All 13 Items		
N (%)	[redacted]	[redacted]
No. events per 100 person-years	[redacted]	[redacted]
HR (CI)	[redacted]	
P value	[redacted]	
Nine Items related to kidney enlargement[a]		
N (%)	[redacted]	[redacted]
No. events per 100 person-years	[redacted]	[redacted]
HR (CI)	[redacted]	
P value	[redacted]	

CI = confidence interval; HR = hazard ratio.
[a] Hypertension, kidney pain, hematuria, albuminuria, nephrolithiasis, UTI, anemia, abdominal/inguinal hernia, significant decline in kidney function.
Source: Clinical Study Report for TEMPO 3:4.[8]

TABLE 12: EXPLORATORY ANALYSIS — INDIVIDUAL COMPONENTS OF MULTIPLE AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE EVENTS

	Tolvaptan	Placebo
N (%)	961 (100)	484 (100)
Hypertension, N (%)	336 (35.0)	173 (35.7)
Kidney pain, N (%)	252 (26.2)	184 (38.0)
Hepatic cysts, N (%)	17 (1.8)	8 (1.6)
Hematuria, N (%)	73 (7.6)	67 (13.8)
Albuminuria, N (%)	5 (0.52)	7 (1.4)
Nephrolithiasis, N (%)	17 (1.8)	17 (3.5)
UTI, N (%)	95 (9.9)	71 (14.7)
Anemia, N (%)	22 (2.3)	22 (4.5)
Colonic diverticuli, N (%)	4 (0.42)	0
Vascular/cardiac abnormality, N (%)	42 (4.4)	22 (4.5)
Abdominal/inguinal hernia, N (%)	30 (3.1)	18 (3.7)
Other cysts, N (%)	13 (1.4)	9 (1.9)
Decline in kidney function, N (%)	9 (0.94)	5 (1.0)

UTI = urinary tract infection.
Source: Clinical Study Report for TEMPO 3:4.[8]

TABLE 13: EXPLORATORY ANALYSIS — KIDNEY SLOPE FUNCTIONS BASED ON $GFR_{CKD-EPI}$, GFR_{MDRD}, AND eCRCL

	TEMPO 3:4	
	Tolvaptan	Placebo
Kidney Function ($GFR_{CKD-EPI}$)		
N (%)	842 (87.6)	464 (96.1)
Slope (mL/min/1.73 m^2 per year) (linear mixed effect model)	–2.72	–3.70
Difference (CI)	0.98 (0.60 to 1.36)	
P value	< 0.001	
Kidney Function (GFR_{MDRD})		
N (%)	[redacted]	[redacted]
Slope (mL/min/1.73 m^2 per year) (linear mixed effect model)	[redacted]	[redacted]
Difference (CI)	[redacted]	
P value	[redacted]	
Kidney Function (eCrCl)		
N (%)	[redacted]	[redacted]
Slope (mL/min per year) (linear mixed effect model)	[redacted]	[redacted]
Difference (CI)	[redacted]	
P value	[redacted]	

CI = confidence interval; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eCrCl = estimated creatinine clearance; GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease.
Source: Clinical Study Report for TEMPO 3:4.[8]

TABLE 14: EXPLORATORY ANALYSIS — BASELINE AND FOLLOW-UP LEVELS OF SERUM CREATININE, BLOOD UREA NITROGEN, AND URINE ALBUMIN-CREATININE RATIO

	TEMPO 3:4	
	Tolvaptan	Placebo
SCr (mg/dL)		
Baseline (SD)	1.05 (0.3)	1.04 (0.3)
Month 12	1.16 (0.4)	1.13 (0.4)
Month 24	1.19 (0.4)	1.17 (0.5)
Month 36 (SD)	1.25 (0.5)	1.26 (0.60)
Last follow-up visit (SD)	1.21 (0.5)	1.27 (0.6)
BUN (mg/dL)		
Baseline (SD)	19.4 (5.4)	19.3 (5.4)
Month 12 (SD)	15.9 (6.0)	19.8 (5.7)
Month 24 (SD)	17.0 (6.6)	20.6 (6.6)
Month 36 (SD)	18.3 (7.6)	21.8 (7.9)
Last follow-up visit (SD)	21.0 (7.4)	22.0 (7.6)
Urine Albumin-Creatinine Ratio		
Baseline (SD)	7.2 (14.3)	8.6 (21.7)
Month 12 (SD)	7.0 (11.8)	8.9 (23.1)
Month 24 (SD)	7.2 (13.3)	9.2 (25.1)
Month 36 (SD)	8.3 (20.7)	9.4 (19.0)
Last follow-up visit (SD)	7.5 (18.7)	9.1 (20.1)

BUN = blood urea nitrogen; SCr = serum creatinine; SD = standard deviation.
Source: Torres VE et al., 2012.[31]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity of total kidney volume (TKV) as a surrogate outcome for kidney function.

Findings

Common Methods Used for Measuring Total Kidney Volume

TKV is usually measured with magnetic resonance imaging (MRI) or by computed tomography (CT) scan.[32-35] Although ultrasound is currently the method of choice for a diagnosis of autosomal dominant polycystic kidney disease (ADPKD), its use for assessing disease progression is limited because ultrasonography is highly operator dependent and its images are less sensitive and reproducible than CT or MRI. Furthermore, the kidneys are located in a slanted orientation relative to the sagittal body plane, making the determination of the true longitudinal axis inaccurate. This is an important source of error by ultrasound, because an ellipsoid formula based on three orthogonal kidney axes is often used for the TKV measurement. Contrast-enhanced CT is an acceptable method for measuring TKV in patients with ADPKD and has similar accuracy and reliability to MRI.[34,36] It is more readily available and relatively faster than MRI; however, the disadvantages of CT include ionizing radiation and the use of nephrotoxic contrast agents.[34] MRI accurately and reliably measures TKV in ADPKD.[20] As noted earlier for TKV measurement, conventional ultrasound is not as reliable as MRI or contrast-enhanced CT and should not be used. MRI is the gold standard test for measuring TKV; however, limited access to MRI for regular monitoring of TKV limits its use in clinical practice. In clinical research, height-adjusted total kidney volume (htTKV) was commonly used as a surrogate outcome in the study of ADPKD.[11,32] The rationale for adopting htTKV as an adjusted TKV marker was to minimize the differences in TKV values between men and women.[20,36] In the pivotal study included in this review (TEMPO 3:4), TKV (not adjusted for age or height) was measured with MRI.[8]

Correlation of Total Kidney Volume With Kidney Function Outcomes

There is very limited information on the correlation of TKV and kidney function outcomes. The association of TKV with kidney function was assessed in an eight-year observational study (CRISP)[20] and the pivotal study (TEMPO 3:4).[8]

CRISP was a prospective, observational, longitudinal, multi-centre study that included 241 adults with ADPKD, aimed to determine if htTKV predicts the onset of renal insufficiency. MRI and iothalamate clearance were used to measure htTKV and glomerular filtration rate (GFR), respectively. The correlation of htTKV and kidney function impairment (defined as Stage 3 chronic kidney disease [CKD], GFR < 60 mL/min per 1.73 m^2) during eight-year follow-up was assessed. It was reported that in the group of patients who had data at every visit (n = 93), increase in htTKV was statistically significant from baseline each year ($P < 0.001$), reaching a mean increase of 55% after eight years. In contrast, GFR decline was statistically significant from baseline much later, beginning in year 6 (–10.6%, 95% confidence interval [CI] not reported; $P < 0.001$) and continuing in year 8 (–22.3%, 95% CI not reported; $P < 0.001$). Similar changes in htTKV and GFR were seen over time when data from the entire cohort was analyzed (data presented in figure, not extractable). Based on the calculation of Pearson correlation coefficients and corresponding *P* values, a statistically significant negative correlation between htTKV and GFR, which increased from a weak correlation at baseline (r = –0.22, $P = 0.02$) to a moderate correlation at year 8 (r = –0.65, $P = 0.001$), was found. Similar increases in the strength of the association between baseline

htTKV and GFR were found when data from the entire cohort were analyzed (data not extractable). Therefore, htTKV is considered a good biomarker for kidney disease progression, although it is not perfect.

In addition, in a post-hoc exploratory analysis of the pivotal study (TEMPO 3:4), [redacted] was reported between per cent change in TKV and worsening kidney function (r = [redacted]).[8] But the association of htTKV change with Stage 3 CKD was not reported in the study.

Predicted Value of Baseline Height-Adjusted Total Kidney Volume for Stage 3 Chronic Kidney Disease
The prediction value of baseline TKV for future Stage 3 CKD was assessed in an eight-year observational study (CRISP).[20] After a mean follow-up of eight years, 194 of 241 patients remained in the study. Stage 3 CKD developed in 31% of patients. Multivariable analyses of the independent contribution of baseline htTKV (in 100 mL/m increments) to a decline to Stage 3 CKD or to a > 20% or > 40% decline in GFR showed significant odds ratio (OR) of 1.48, 1.39, and 1.47, respectively. For each 100 mL/m change in htTKV, a 48% (95% CI, 29% to 70%) increase in odds of progression to Stage 3 CKD was estimated. Similar ORs and levels of significance were seen with estimated glomerular filtration rate (eGFR) determinations. In area under receiver operator characteristic (AUROC) analysis, it was reported that baseline htTKV of 600 mL/m most accurately defined the risk of developing Stage 3 CKD within eight years with an AUROC of 0.84 (95% CI, 0.79 to 0.90). It was also reported that htTKV was a better predictor than baseline age, SCr, BUN, or urinary albumin (P = 0.05).

A limitation of these analyses is the assumption that the rates of GFR decline and TKV growth were constant and linear. The CRISP study demonstrated that TKV is dependent on age; it remains uncertain that GFR would be constant over time.

Health Canada and the National Institute for Health and Care Excellence (NICE), in their evaluations of the TEMPO 3:4 study, considered the correlation of TKV and worsening kidney function as imperfect, but accepted TKV as a valid outcome for use in clinical trials on ADPKD.[19,37]

No MCID of change in unadjusted or htTKV were identified for ADPKD.

Conclusion

TKV is gaining clinical and regulatory acceptance as a valid surrogate marker to assess outcomes of drug interventions for ADPKD. MRI is considered the gold standard method for measuring TKV, though it is not easily accessible or feasible in the routine monitoring of patients. Ultrasound is not a sufficiently sensitive or reliable substitute for MRI. Limited evidence has shown a weak negative correlation between htTKV and GFR at baseline and early stages of ADPKD, and moderate correlation at the end of eight years of follow-up. In addition, baseline htTKV ≥ 600 mL/m may forecast the risk of developing Stage 3 CKD in ADPKD patients at high risk for kidney disease progression within eight years of follow-up. Therefore, baseline htTKV may be a prognostic biomarker in ADPKD. However, because clinical outcomes such as ESRD and need for dialysis may take decades to occur, longer-term studies are needed to show that TKV correlates with outcomes of ADPKD progression. No MCID for TKV was identified for ADPKD.

APPENDIX 6: SUMMARY OF OPEN-LABEL EXTENSION TRIAL: RESULTS OF INTERIM ANALYSES OF TWO YEARS

Aim

To summarize the findings of the extension study (TEMPO 4:4).

Findings

Study Objectives and Baseline Disease Characteristics

The two-year extension study (TEMPO 4:4) was a phase 3b multi-centre, international, open-label, extension trial using oral tolvaptan tablets in patients with autosomal dominant polycystic kidney disease (ADPKD).[11,38,39] The objective of this extension study was to assess longer-term (up to eight years) effects and harms of tolvaptan. The safety end points included a descriptive summary of treatment-emergent adverse events (TEAEs) and clinical laboratory tests, such as liver function. Limited efficacy data were presented in the Clinical Summary.[11] This summary is based on a two-year interim analysis (data cut-off March 2012). Updated data were requested from the manufacturer but no updated reports are yet available.[40]

[redacted] (Table 15).

TABLE 15: PATIENT DISPOSITION

	ET TLV, n (%)	DT TLV, n (%)	Other TLV, n (%)	Total, N (%)
Screened				[redacted]
Prior treatment	[redacted]	[redacted]	[redacted]	[redacted]
TEMPO 3:4	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Completed	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Met withdrawal criteria	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawn by the investigator	[redacted]	[redacted]	[redacted]	[redacted]
Withdrew consent to participate	[redacted]	[redacted]	[redacted]	[redacted]
Analyzed for safety	[redacted]	[redacted]	[redacted]	[redacted]

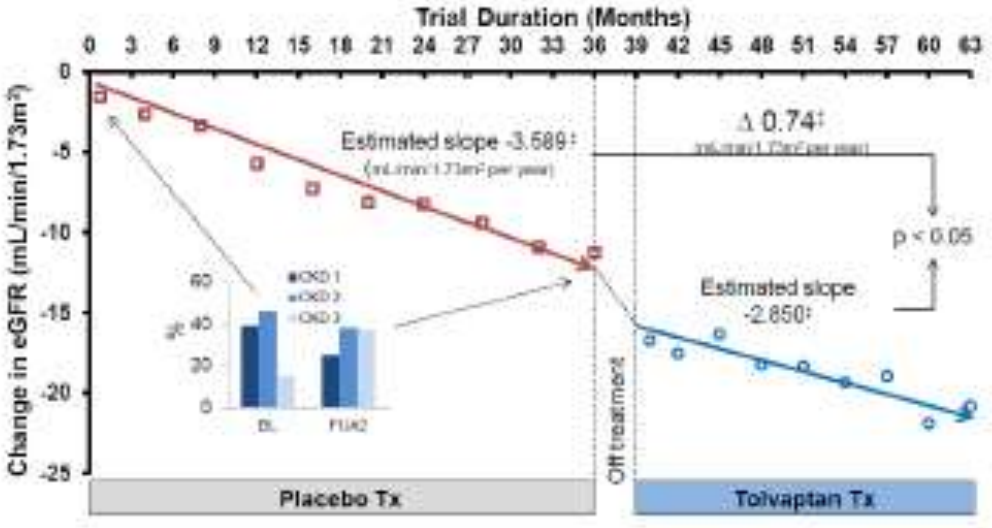
AE = adverse event; DT= delayed treatment with TLV indicating patients in placebo group in TEMPO 3:4; ET = early treatment with TLV indicating patients in TLV group in TEMPO 3:4; Other TLV = treatment with TLV from other studies; TLV = tolvaptan.
Note: Percentages are based on the number of patients enrolled.
Source: TEMPO 4:4, Clinical Study Report: p. 56, Table 7.1-1.

Results

Efficacy

Efficacy data were presented in the Clinical Summary provided in the manufacturer submission[11] and in a conference abstract, Torres et al.[39] A total of 871 ADPKD patients were included in the interim analysis. A comparison of delayed-treatment (DT) patients (N = 314) participating in both trials showed a statistically significant improvement in the mean estimated glomerular filtration rate (eGFR) slope after switching from placebo to tolvaptan (from –3.59 to –2.85 mL/min/1.73 m^2 per year, treatment effect 21%, *P* = 0.048), despite the time difference leading to an increased proportion of patients starting in Stage 3 chronic kidney disease (CKD) at baseline of TEMPO 4:4 (Figure 5).[11,39]

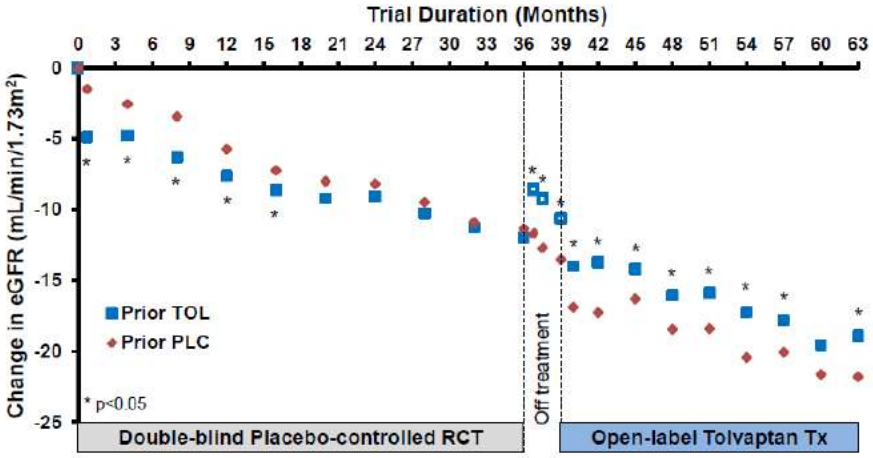
FIGURE 5: CHANGE IN ESTIMATED GLOMERULAR FILTRATION RATE OF PLACEBO PATIENTS FROM TEMPO 3:4 SWITCHING TO TOLVAPTAN IN TEMPO 4:4



BL = baseline; eGFR = estimated glomerular filtration rate; FU#2 = follow-up number 2; Tx = treatment.
Source: Clinical summary provided in submission.[11]

Analysis of the separation in eGFR between early treatment (ET) and DT patients post-treatment withdrawal in the pivotal trial suggested sustained protection of kidney function during the two-year open-label extension (*P* < 0.05 for 11/12 time points) (Figure 6).[11,39]

FIGURE 6: TREATMENT EFFECT ON ESTIMATED GLOMERULAR FILTRATION RATE IS MAINTAINED DURING TEMPO 4:4 AFTER WASHOUT IN TEMPO 3:4



eGFR = estimated glomerular filtration rate; PLC = placebo; RCT = randomized controlled trial; TOL = tolvaptan; Tx = treatment.
Source: Clinical summary provided in submission.[11]

The study concluded that initiation of tolvaptan treatment in placebo patients resulted in a deceleration in eGFR decline and that continuous tolvaptan treatment conferred sustained protection of kidney function. The slope of eGFR decline during tolvaptan treatment remains improved relative to placebo through five years of therapy.

Harms

Safety analysis was conducted in three treatment groups: the ET group (i.e., patients treated with tolvaptan in previous randomized controlled trials [RCTs]), the DT group (i.e., patients treated with placebo in previous RCTs) and the other tolvaptan group (i.e., patients treated with tolvaptan from other ADPKD trials). [redacted].

The main adverse events (AEs) are presented in Table 16. TEAEs were reported in [redacted] of patients. Serious TEAEs were reported in [redacted]. No detailed information of serious adverse events (SAEs) was reported. TEAEs that led to discontinuation of tolvaptan were reported for [redacted], with the highest percentage of patients reporting TEAEs that led to discontinuation of therapy in the [redacted] and the lowest in the [redacted] receiving tolvaptan treatment died due to a self-inflicted gunshot wound.

Hepatic safety: the incidence of elevated alanine aminotransferase (ALT) (more than three times the upper limit of normal) for patients in the [redacted] was higher than for patients in the [redacted]. At the earliest, ALT elevations of more than three times the upper limit of normal were observed at approximately [redacted] after initiation of treatment. [redacted] experienced liver failure, liver transplantation, or death. [redacted]. Based on a recent publication[41] that re-examined data from TEMPO 3:4 and TEMPO 4:4, as well as from long-term (> 14 months) non-ADPKD tolvaptan trials, using the 5-point Drug-Induced Liver Injury Network classification, the author concluded that although

liver injury following long-term tolvaptan treatment in patients with ADPKD was infrequent and reversible, the potential for serious irreversible injury exists. Therefore, regular monitoring of transaminase levels is warranted in patients with ADPKD.[41]

TABLE 16: ADVERSE EVENTS

	ET TLV n (%)	DT TLV n (%)	Other TLV n (%)	Total n (%)
Patients treated	[redacted]	[redacted]	[redacted]	[redacted]
Patients with AEs	[redacted]	[redacted]	[redacted]	[redacted]
Patients with TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Patients with serious TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation from TLV due to AE	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]
Thirst	[redacted]	[redacted]	[redacted]	[redacted]
Polyuria	[redacted]	[redacted]	[redacted]	[redacted]
Pollakiuria	[redacted]	[redacted]	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]	[redacted]	[redacted]
CRF	[redacted]	[redacted]	[redacted]	[redacted]
ARF	[redacted]	[redacted]	[redacted]	[redacted]
Kidney impairment	[redacted]	[redacted]	[redacted]	[redacted]
Kidney pain	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; ARF = acute renal failure; CRF = chronic renal failure; DT = delayed treatment with TLV indicating patients in placebo group in TEMPO 3:4; ET = early treatment with TLV indicating patients in TLV group in TEMPO 3:4; OT = Treatment with TLV from other studies; TEAE = treatment-emergent adverse event; TLV = tolvaptan.
Note: Percentages are based on the number of patients enrolled.
Source: TEMPO 4:4 Clinical Study Report.

Limitation

A key limitation for the findings of the extension study is the non-randomized, open-label design. Another limitation is the results are based on an interim analysis and, therefore, the conclusion that treatment effect persists seems premature. Also, no formal sample size calculation was performed for this extension portion. Its sample size was limited to those patients with ADPKD from previous phase 1, 2, and 3 trial population completers.

Summary

Tolvaptan administered as a split-dose regimen was generally well tolerated in adult patients with ADPKD. The most frequently reported TEAEs during the treatment period were consistent with the mechanism of action of tolvaptan or the natural history of ADPKD disease progression. The safety profile in the extension study was consistent with that observed in the pivotal study. The TEAE of increased serum creatinine (SCr) was similar among treatment groups. Hepatic injury remained an AE of concern in the extension study. The open-label design and interim duration of the extension study preclude any firm conclusions of whether the efficacy of tolvaptan persists in the long term. Therefore, longer-term analyses are needed to draw conclusions about the maintenance of benefits and safety of tolvaptan, especially regarding potential liver toxicity and late onset adverse effects.

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