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Original Investigation

Rationale and Design of the TEMPO (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes) 3-4 Study

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Background: Current management of autosomal dominant polycystic kidney disease (ADPKD) is focused on treating disease complications, not on slowing cyst development or preventing progression to kidney failure. Tolvaptan, a selective vasopressin V2 (vasopressin 2) receptor antagonist, has been proved to inhibit kidney cyst growth and preserve kidney function in multiple animal models of polycystic kidney disease. The TEMPO (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes) 3-4 Study will examine the long-term effectiveness and safety of tolvaptan in patients with ADPKD. We report baseline characteristics and revised power calculations for the trial.

Study Design: A prospective, 3-year, multicenter, double-blind, placebo-controlled trial of tolvaptan, a selective V2 receptor antagonist. Primary outcome is total kidney volume percentage of change from baseline for tolvaptan relative to placebo. Secondary outcome parameters include time to ADPKD-associated complications (kidney function decrease, blood pressure control, renal pain, and albuminuria) and safety end points.

Setting & Participants: This trial includes patients with ADPKD with relatively preserved kidney function (baseline estimated creatinine clearance ≥60 mL/min), aged 50 years or younger, and with total kidney volume measured using magnetic resonance imaging ≥750 mL.

Intervention: Administration of placebo or tolvaptan, dose titrated to tolerance.

Outcomes: Number of subjects enrolled and baseline characteristics.

Measurements: Total kidney volume, kidney function, albuminuria, kidney pain, and vital signs.

Results: 1,445 patients with ADPKD were enrolled between March 2007 and January 2009. Preliminary baseline median total kidney volume was 1.46 L, and estimated creatinine clearance was 105 ± 34 mL/min. A prespecified blinded sample-size recalculation at two-thirds enrollment confirmed the likely power of the study to detect 20% differences from placebo in the primary and key secondary end points at $P < 0.05$.

Limitations: This is a preselected ADPKD population chosen for its risk of progression to kidney failure and may not represent the general ADPKD population. If study results are positive with regard to the primary end point, positive effects on other secondary clinical outcomes will be required to assess overall benefit.

Conclusions: This randomized trial is the largest clinical study of a proposed ADPKD intervention to date. It targets patients with ADPKD with early disease who are projected to have rapid cyst growth and accelerated outcomes. Blockade of vasopressin V2 receptor is hypothesized to inhibit cyst growth, thereby delaying additional adverse clinical outcomes.

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INDEX WORDS: Clinical trial; autosomal dominant polycystic kidney disease (ADPKD); polycystic kidney disease; vasopressin.

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Autosomal dominant polycystic kidney disease (ADPKD) is the most common kidney hereditary disease (caused in most cases by a mutation in the *PKD1* or *PKD2* gene[1,2]). ADPKD is a systemic disorder characterized by progressive cyst formation in both kidneys, with progressive kidney enlargement often leading to end-stage renal disease. Other kidney symptoms include pain, hypertension, gross hematuria, nephrolithiasis, and mild albuminuria. Current therapies are directed toward limiting morbidity and mortality from complications of ADPKD,[3] but not specifically targeting the inhibition of cyst formation.

Although kidney failure is the most feared consequence of the disease, glomerular filtration rate (GFR) is a poor marker of disease severity and progression in early phases of the disease. GFR remains intact during a prolonged period (typically decades) through compensatory hyperfiltration, but ultimately decreases sharply thereafter. Gradual anatomic distortion likely parallels the loss of functioning glomeruli.[4] The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) showed that total kidney volume at entry into the study predicted future kidney function deterioration and identified a potential method for study of therapies targeted at inhibition of cyst formation.[5] Therefore, in early ADPKD, total kidney volume is likely to be a more sensitive marker of disease progression than kidney function.

Improved knowledge of genetic, molecular, and cellular mechanisms underlying cyst formation in ADPKD has resulted in the discovery of potentially effective therapeutic targets.[6] Vasopressin, acting on vasopressin 2 (V2) receptors, increases intracellular cAMP (cyclic adenosine monophosphate) in distal nephron segments and collecting ducts, promoting chloride-driven fluid secretion. cAMP also stimulates B-RAF/MEK/extracellular signal–regulated signaling, mitogenesis, and proliferation of polycystic kidney epithelial cells or wild-type kidney epithelial cells under experimental conditions of calcium deprivation.[7,8] Localization of the V2 receptors in the distal nephron and collecting duct[9] corresponds to the main site of cystogenesis in autosomal recessive polycystic kidney disease (ARPKD) and arguably in ADPKD,[10] and increased circulating levels of vasopressin in animal models[11,12] and patients with ADPKD[13,14] provided the rationale for experimental studies with vasopressin V2 receptor antagonists. The vasopressin V2 receptor antagonist OPC-31260 inhibited cyst formation in animal models for ARPKD, nephronophthisis,[11] and ADPKD.[12] Tolvaptan, another vasopressin V2 receptor antagonist with high potency and selectivity for human vasopressin V2 receptor, proved effective in a rat model for ARPKD.[15] Moreover, genetic elimination of arginine vasopressin in this model yielded animals relative free of cysts unless an exogenous V2 receptor agonist was administered.[16]

Tolvaptan induces free-water clearance and is approved by the US Food and Drug Administration for hypervolemic and euvolemic hyponatremia and the European Medicines Agency for hyponatremia associated with syndrome of inappropriate secretion of antidiuretic hormone. These approvals were based on studies of the efficacy and safety of this vasopressin V2 receptor antagonist in hyponatremia.[17-19] Phase 2 studies in patients with ADPKD showed that split-dose administration of tolvaptan was more effective than a single dose in achieving sustained suppression of vasopressin action, evidenced by 24-hour urine osmolality decrease to $<$300 mOsm/L.[20] A phase 2 open-label trial in 46 and 17 patients with ADPKD investigating the long-term safety, tolerability, and efficacy of split-dose regimens has completed 3 years of treatment and is ongoing in the United States[21] and Japan,[22] respectively.

Based on promising results in animal models and early clinical studies with respect to efficacy and safety, we have designed and initiated a large clinical trial to examine the effectiveness of tolvaptan in patients at relatively early stages of ADPKD.

METHODS

Study Population

Patients with ADPKD (diagnosis based on Ravine criteria[23]) aged 18-50 years with estimated creatinine clearance (eCCr) using the Cockcroft-Gault[24] equation $>$60 mL/min and measured total kidney volume (sum of right and left kidney volumes) $>$750 mL using magnetic resonance (MR) imaging (MRI) were eligible for study-participation. Detailed study inclusion and exclusion criteria are listed in Box 1.

Study Design and Setting

The TEMPO (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes) 3-4 study was designed as a multicenter, double-blind, placebo-controlled, parallel-arm trial in patients with ADPKD. Patients were enrolled worldwide (North and South America, Europe, Japan, and Australia). After determining eligibility (Box 1), patients were randomly assigned with stratification to 1 of 2 treatment groups (2:1 ratio of tolvaptan to placebo). Stratification factors include baseline hypertension (present or absent), eCCr ($\geq$80 or $<$80 mL/min), and total kidney volume ($\geq$1,000 or $<$1,000 mL). Hypertension is defined as systolic blood pressure $>$139 mm Hg and/or diastolic blood pressure $>$89 mm Hg or use of antihypertensive treatment.

Figure 1 schematically represents the trial design. Three split-dose regimens of oral tolvaptan and matching placebo are

Box 1. Eligibility Criteria of the TEMPO 3-4 Study

Inclusion Criteria

- Adult patients providing informed consent (defined as men or women aged ≥18 y and ≥ regional legal age of maturity to age 50 y)
- Patients with a diagnosis of ADPKD
- Willingness to comply with reproductive precautions (women capable of becoming pregnant must be willing to comply with approved birth control from 2 wk before to 60 d after using investigational product)
- eCCr ≥60 mL/min within −31 d of randomization (established using Cockcroft-Gault formula[24])
- Rapid estimated rate of kidney volume increase based on total kidney volume ≥750 mL using MRI at randomization (excluding those meeting volumetric criterion solely due to ≤6 predominant cysts)

Exclusion Criteria

- Patients who, in the opinion of the study investigator or sponsor, may present a safety risk
- Patients unlikely to adequately adhere to the trial's procedures (due to medical conditions likely to require an extended interruption or discontinuation or history of substance abuse or nonadherence)
- Patients having contraindications to or interference with MRI assessments
- Patients using medications or having concomitant illnesses likely to confound end point assessments
- Patients using other experimental (ie, nonmarketed) therapies or approved therapies for the purpose of affecting ADPKD cysts or those using or having a history of using tolvaptan

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; eCCr, estimated creatinine clearance; MRI, magnetic resonance imaging; TEMPO, Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes.

tested: low (45/15 mg), medium (60/30 mg), and high (90/30 mg). Patients begin treatment with the lowest dose, and after each 1-week safety assessment, doses are titrated to the next higher dose treatment group until a level of intolerability or the highest dose of treatment is reached. After the titration phase, participating patients remain on the highest tolerable dose until 36 months of treatment are completed. Patients are evaluated every 4 months during treatment and twice between 1-6 weeks after treatment concludes.

Trial Treatments

Tolvaptan or placebo tablets are given orally twice daily to allow for effective drug concentrations over 24 hours. Dosing occurs on waking and approximately 9 hours later, irrespective of meals. Exact timing is adjusted based on wake/sleep habits. Patients may downtitrate at any time. Patients unable to tolerate the lowest dose are discontinued from investigational product use, yet are asked to continue participation in study exploratory ADPKD outcomes assessment (Box 2) in the trial. Medication adherence is monitored using pill counts as the drug is returned. Nonadherent patients (defined as discontinuation of investigational product for 30 consecutive days or >30% missed dosages intended for a period, without investigator and medical monitor approval) are withdrawn from the trial.

Safety of patients and optimal testing of tolvaptan efficacy requires standardization of background clinical care. Therefore, this trial includes a requirement for antihypertensive therapy in patients with hypertension (systolic blood pressure >139 mm Hg and/or diastolic blood pressure >89 mm Hg). Because deterioration in kidney function in patients with ADPKD is likely to be accelerated by hypertension, treatment also is required (unless otherwise contraindicated) in patients with reproducible systolic blood pressure of 130-139 mm Hg and/or diastolic blood pressure of 85-89 mm Hg. The protocol recommends first-line use of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. Long-term use of diuretics is not allowed because they may affect certain assessments (such as urine sodium or osmolality). Recommendation for dietary restrictions (such as restrictions for salt, protein, and caffeine) is left to the discretion of the principal investigator and therefore is site specific. Additional site- or region-specific additions to the visit schedule have been allowed when requested by local regulatory authorities or ethics committees.

Patients are given standard fluid ingestion recommendations to help avoid dehydration and reflex vasopressin increases. They are asked to drink enough water to prevent thirst throughout the daytime period and an additional 1-2 cups of water before bedtime. During the titration phase, patients were asked to self monitor changes in body weight, reporting changes >3% in body weight over any 7-day period to the trial physician.

Primary Outcome

The primary end point of the TEMPO 3-4 trial is the rate of total kidney volume change (normalized as percentage) for tolvaptan (combining all doses) relative to placebo.

Secondary Outcomes

Secondary outcomes involve a composite secondary efficacy end point and noncomposite secondary efficacy end points. Additional safety, pharmacokinetic, pharmacodynamic, and exploratory end points have been formulated.

The composite secondary efficacy end point is time to multiple investigator-reported ADPKD clinical progression events (changes in blood pressure category or onset or worsening of hypertension requiring adjustment to hypertensive treatment), severe kidney pain (requir-

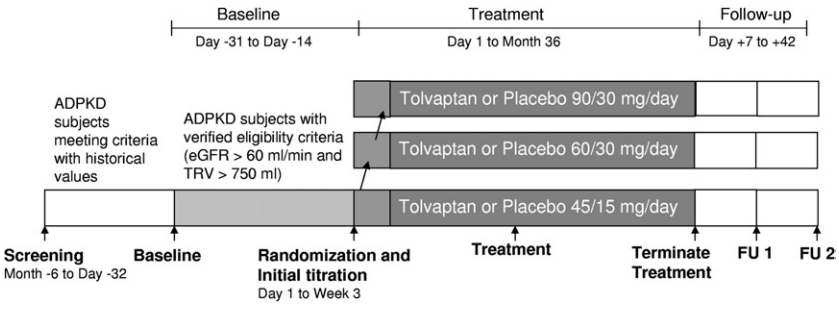

Figure 1. Schematic trial design of the TEMPO (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes) 3-4 Study. Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; eGFR, estimated glomerular filtration rate; FU, follow-up; TRV, total renal volume.

Box 2. Primary and Secondary End Points of the TEMPO 3-4 Study

Primary Outcome End Point

Primary efficacy end point: Rate of total kidney volume change (normalized as percentage) for tolvaptan (combining all doses) relative to placebo.

Secondary Outcome End Points

Composite secondary efficacy end point: Time to investigator-reported multiple ADPKD clinical progression events (ie, onset or progression of hypertension, need for hypertensive treatment), severe kidney pain (requiring medical intervention), worsening albuminuria (by category), worsening kidney function (33% increase in SCr) for tolvaptan (combining all doses) relative to placebo while on treatment.

Noncomposite secondary efficacy end points: For tolvaptan compared with placebo:
1. Rate of eGFR change from postdose baseline (end of titration) to last on-drug trial visit (using 1/SCr as primary measure).
2. For patients who are nonhypertensive at baseline, change from baseline for mean arterial pressure at rest at scheduled clinic visits up to point of exposure to antihypertensive therapy for any reason.
3. Change from baseline in kidney pain assessed using 0-10 pain scale as average area under the concentration-time curve between baseline and last trial visit or last visit before initiating medical or surgical therapy for pain.
4. For patients who are nonhypertensive at baseline, time to progress to any of:
   a) High prehypertension (SBP >129 and/or DBP >84 mm Hg).
   b) Hypertension (SBP >139 and/or DBP >89 mm Hg).
   c) Requiring antihypertensive therapy.
5. For patients on antihypertensive therapy at baseline, percentage with clinically sustained decreases in blood pressure leading to a sustained decrease in antihypertensive therapy compared with baseline (while using investigational product) at visits months 12, 24, and 36.

Safety end points: Safety end points to be analyzed will include a descriptive summary of the following:
1. Reported adverse events.
2. Vital signs.
3. Clinical laboratory tests.
4. ECG data.

Pharmacokinetic end point: Determination of tolvaptan and metabolite plasma concentrations.

Pharmacodynamic end points: For tolvaptan compared with placebo:
1. For urine, using spot osmolality and MCP1 to creatinine ratios.
2. For blood, cystatin C and SUN concentrations.

Exploratory End Point

1. Fasting urine osmolality (at randomization and follow-up visit 2 only).
2. ADPKD outcomes and medical resource use: Analysis of additional events attributed to ADPKD for tolvaptan-treated patients compared with placebo, including health-economic outcomes.

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; DBP, diastolic blood pressure; ECG, electrocardiography; eGFR, estimated glomerular filtration rate; MCP1, monocyte chemoattractant protein 1; SBP, systolic blood pressure; SCr, serum creatinine; SUN, serum urea nitrogen; TEMPO, Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes.

ing medical intervention), worsening albuminuria (by category), and worsening kidney function (33% increase in serum creatinine level) for tolvaptan (combining all doses) relative to placebo.

Trial end points were constructed based on advice obtained at scientific advisory boards and meetings with regulatory agencies from Japan, the European Union, and the United States. End points were chosen to represent potentially clinically meaningful changes in levels of laboratory or physiologic parameters and patient symptoms reasonably expected to develop or worsen with progressive ADPKD. Sporadic symptoms or symptoms subject to external influences (eg, nephrolithiasis and hematuria) were not included as end points, but are collected for exploratory analysis. A detailed description of all secondary, pharmacokinetic, pharmacodynamic, and exploratory end points is listed in Box 2.

Safety end points include a descriptive summary of reported adverse events, vital signs, clinical laboratory tests, and electrocardiogram recordings.

Data Collection

Data as listed in Table 1 are obtained. Patients are seen every 4 months. During each visit, medical history, concomitant medication, adverse events, and tolerability are assessed. Blood is drawn and a spot urine sample is obtained to assess safety end points. Patients are asked about investigational product tolerability and pain attributed to their kidneys (on a 0-10 scale).

Annually, MRI of the kidneys using standardized procedures (discussed next) is performed. An electrocardiogram is obtained at the beginning (baseline and end of titration) and end of the study (month 36 or early termination and second follow-up visit). All blood and urine chemistry, electrocardiographic, and MRI end point data are analyzed and read centrally. Data for PKD outcome assessments are collected using standardized case report forms and entered into a central database. Monitoring and auditing of participating centers takes place to ensure that data are obtained correctly. Two follow-up visits (7-21 days

Table 1. Ongoing Data Collection of the TEMPO 3-4 Study

Assessment	No. of Times Performed	Visit
MRI	4	Baseline, M12, 24, 36/ET
ADPKD outcomes: composite end point components, in-clinic blood pressure, serum creatinine, albumin, kidney pain score, origin of kidney pain using examination or history, review of disease burden and health care use attributable to ADPKD	12	All visits
Tolerability	12	All visits
Pharmacokinetics (determination of tolvaptan and metabolite (DM-4103 and DM-4107) plasma concentrations	5	Baseline, wk 3, M12, 24, 36/ET
Laboratory (hematology, serum chemistry, urinalysis, and urine pregnancy)	12	All visits
Physical examination	2[a]	Baseline and M36/ET[a]
ECG	3	Screening, M36/ET, and FU 2

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ECG, electrocardiogram; ET, early termination; FU, follow-up; M, month; MRI, magnetic resonance imaging; TEMPO, Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes.

[a]For all other visits, a directed examination should be conducted at the investigators' discretion if deemed necessary to assess changes in medical history, adverse events, or other medically indicated parameters.

after the prior visit) are performed to assess the persistence of treatment effects and participant safety after termination of double-blind treatment (after 36 months or earlier for patients withdrawing from the trial).

MRI for Determination of Kidney Volume

Patients undergo a standardized protocol for MRI of the abdomen without use of intravenous contrast at baseline and months 12, 24, and 36. In the case of early termination, MRI is performed when the last MRI was more than 6 months before. The MRI acquisition protocol includes T2-weighted single-shot fast spin-echo/half-Fourier acquired single turbo spin echo (SSFSE/HASTE) images with fat saturation and 3-dimensional spoiled gradient interpolated T1-weighted images without fat saturation. At some sites, T2/T1-weighted fast imaging with steady state precession (true FISP/fast imaging employing steady state acquisition [FIESTA]) series are added to improve the delineation of kidney borders. All MR images are acquired in the coronal plane at 4-mm slice thickness covering the entire kidneys during breath-hold(s).

MR images are sent to the central reading facility for quality control and measurement of kidney volume using T1- and T2-weighted MR images as defined in a study-specific imaging charter. Alice software (Perceptive Informatics; www.perceptive.com) is used to measure total kidney volume by calculating the volume of serial kidney outlines that have been verified by independent radiologists familiar with ADPKD. To maintain objectivity in the evaluations, the radiology reviewers are blinded to patient name, site identifiers, assessments, determinations, and sequence of acquisition.

Estimation of Power and Sample Size

In a large cohort of patients with ADPKD, mean annual total kidney volume growth rate was ~5%.[5] Growth rate in the TEMPO 3-4 Study is expected to be higher because only patients with large kidneys (baseline total kidney volume ≥750 mL) are included. Assuming an average untreated growth rate of 7%, an average 20% decrease in growth rate deemed clinically significant, 85% power to detect this difference, and a 2-sided α of 0.045, ~504 patients (split 2:1, tolvaptan to placebo) are needed. This sample-size calculation uses the sample-size formula for longitudinal trial provided by Lefante[25] and assumes (in log scale) the total noise standard deviation and standard deviation of the slope across patients to be 0.017 and 0.0184, respectively. Assuming a 20% withdrawal rate for the trial, ~600 patients need to be enrolled in the trial. By doubling this, enrollment of 1,200-1,500 patients was targeted so the study was powered to provide a higher than usual degree of statistical significance for the primary end point and a reasonable ability to evaluate the secondary composite end point.

Statistical Analyses

Analysis will take place after completion of the study. The analysis of the primary end point is to fit the log-transformed total kidney volume data to a linear mixed-effect Laird-Ware model, with a *P* value derived by applying the "sandwich" estimator of the covariance matrix to the Wald test of the treatment-time interaction of the model, using observed cases of all intent-to-treat patients. In addition to the primary analysis as provided, mixed-model repeated-measures analysis will be applied to the repeated measures of change from baseline in total kidney volume (based on logarithm transformed data) as a sensitivity analysis. This analysis has been implemented as a means of handling incomplete data due to early study withdrawal. The mean difference in the 2 treatment groups at year 3 under the mixed-model repeated measures will be used to estimate the treatment effect at year 3. Mixed-model repeated measures include stratification factors (hypertensive status, kidney volume status, and creatinine clearance status at baseline and geographic region), visit, treatment, and treatment-visit interaction as class variables and baseline total kidney volume as covariate. An observed cases data set will be used in this mixed-model repeated-measures analysis.

Secondary composite efficacy will be analyzed using the Andersen-Gill approach of the extended Cox model for analysis of time to multiple events with *P* value provided using the robust Wald test using sandwich estimate for the covariance matrix.[26,27] No adjustment for missing data will be made; however, patients discontinuing study medication are asked to continue reporting outcomes of ADPKD on a regular basis. Additionally, several sensitivity analyses, including independent adjudication of events and differing observation periods (pre- and on-treatment baseline to on- and post-treatment follow-up), will be performed to explore potential confounders and confirm findings.

Analysis of the safety data set, defined as all patients who consume at least 1 dose of investigational product, will include

comparisons of trends in clinical laboratory test results, vital signs, electrocardiograms, and adverse events. Tolerance and adherence to treatment with study medication also will be described. No interim efficacy analysis will be performed for this study.

Ethical Considerations

Institutional review boards/independent ethics committees approved the protocol and informed consent forms in all participating centers according to regional requirements. The trial is conducted according to the International Conference of Harmonisation Good Clinical Practice Guidelines and all other applicable regulatory requirements and adheres to the ethical principles that have their origin in the Declaration of Helsinki. Participant privacy is ensured by deidentifying all submitted data and using a participant identification code. All patients have the right to withdraw from the study at any time during the trial. An independent data monitoring committee will monitor study safety and efficacy.

Study Organization

The design and conduct of the study are overseen by a steering committee. An independent data monitoring committee, managed by an independent statistical data analysis center, has been established to monitor the safety and efficacy of the trial. A clinical events committee was formed to independently adjudicate events contributing to the secondary composite end point for inclusion in a sensitivity analysis. All study committees are guided by charters defining their roles and responsibilities and methods specific to the committee.

RESULTS

This study includes 1,445 adult men and women (aged 18-50 years) in a relatively early stage of ADPKD who were recruited from January 2007 to January 2009. Patients were screened and enrolled at 132 sites worldwide; 38 sites in the Americas, 56 in Europe, 30 in Japan, and 8 in Australia. The final patient is expected to complete the trial in February 2012.

Baseline characteristics of the study population are listed in Table 2 for the group as a whole and for women and men separately. These preliminary data have been quality-control audited, but will not be formally locked until the final participant completes the study. In total, 1,445 patients are randomly assigned in the TEMPO 3-4 Study (52% men aged 39 ± 7 years). Median total kidney volume is almost 1.5 L, approximately twice the minimum total kidney volume needed to meet the inclusion criteria. Estimated kidney function is on average relatively well preserved at baseline (eCCr, 105 mL/min), with ~30% of patients having eCCr of 60-80 mL/min. More than 75% of patients use at least 1 antihypertensive drug to control blood pressure. Median urinary albumin-creatinine ratio is 3 mg/mmol for the entire group, with >50% of patients having microalbuminuria (defined as 2.8-28 mg/mmol for women and 2.0-20 mg/mmol for men) and 5% having overt proteinuria (>28 or 20 mg/mmol, respectively). Medication interfering with the renin-angiotensin-aldosterone system is used by nearly half the patients. The percentage of men treated with antihypertensive drugs is slightly higher than in women. Men have larger kidneys and a significantly higher eCCr (all $P < 0.001$), although estimated GFR (calculated using the MDRD [Modifi-

Table 2. Baseline Characteristics of Participating Patients

	All (N = 1,445)	Women (n = 699)	Men (n = 746)
Age (y)	39 ± 7	39 ± 7	38 ± 7
Body mass index (kg/m^2)	26 ± 5	26 ± 6	27 ± 5
Systolic blood pressure (mm Hg)	126 ± 14	126 ± 13	131 ± 14
Diastolic blood pressure (mm Hg)	82 ± 10	81 ± 9	84 ± 10
MAP (mm Hg)	98 ± 11	96 ± 10	99 ± 11
Patients using ≥1 antihypertensive	1,108 (77)	495 (71)	613 (82)
Patients using ACEi and/or ARB	696 (48)	313 (45)	383 (51)
Total kidney volume (L)	1.46 (1.07, 2.01)	1.30 (0.98, 1.73)	1.64 (1.19, 2.23)
Serum creatinine (mg/dL)	1.0 ± 0.3	0.9 ± 0.2	1.2 ± 0.3
Urinary osmolarity (mOsm/kg H_2O)	502 ± 179	477 ± 177	525 ± 177
Urinary ACR (mg/mmol)	3.2 (1.7, 7.0)	3.5 (2.0, 7.1)	2.8 (1.5, 6.7)
Overt proteinuria	75 (5.5)	50 (7.0)	25 (3.8)
eGFR (mL/min/1.73 m^2)	79 ± 23	79 ± 21	78 ± 24
eCCr (mL/min)	105 ± 34	99 ± 31	110 ± 35

Note: Categorical variables are given as number (percentage); continuous variables are given as mean ± standard deviation or median (25th, 75th percentile) in case of skewed distribution. Overt proteinuria is defined as ACR >28 mg/mmol for women and >20 mg/mmol for men. eGFR was calculated using the Modification of Diet in Renal Disease Study equation. eCCr was calculated using the Cockcroft-Gault formula. Conversion factors for units: serum creatinine in mg/dL to μmol/L, ×88.4; eGFR in mL/min/1.73 m^2 to mL/s/1.73 m^2 and eCCr in mL/min and mL/s, ×0.01667.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-creatinine ratio; ARB, angiotensin receptor blocker; eCCr, estimated creatinine clearance; eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure.

cation of Diet in Renal Disease] Study equation) is approximately the same, which is explained by a higher body surface area for men.

A blinded sample size re-estimation was prespecified to be conducted after either 1,000 patients enrolled or at least 200 patients completed their 12-month visit, whichever came first. The blinded sample size re-estimation was conducted on October 20, 2008, when more than 1,000 patients were enrolled and suggested that a sample size of 1,400 patients would be expected to provide at least 80% power to the key composite secondary end point of the study. No adjustment to the original sample size of the trial was required, and enrollment was stopped to ensure at least 1,400 patients were enrolled.

DISCUSSION

The TEMPO 3-4 Study seeks to determine whether tolvaptan inhibits total kidney volume growth in patients with ADPKD and such changes meaningfully affect the clinical course of the disease.

The primary end point of the trial is change in total kidney volume. The CRISP showed that kidney enlargement results from expansion of cysts. This growth is continuous and quantifiable and associated with a decrease in kidney function. Higher rates of kidney enlargement are associated with a more rapid decrease in kidney function.[4,5] In a large number of animal studies, treatments that inhibited kidney enlargement also protected kidney function.[4] Furthermore, several studies show that the rate of increase in kidney volume can be measured reliably.[28-30] These data provide support for the assumption that change in rate of kidney volume is a valid end point to assess the efficacy of study drugs to attenuate disease progression.

Patients selected for this study are 50 years or younger with ADPKD, eCCr $\geq$60 mL/min, and total kidney volume $\geq$750 mL. These criteria were formulated to include patients at a relatively early stage of disease, but with a high likelihood of rapid disease progression. This was done for several reasons. First, tolvaptan is believed likely to delay disease progression, not restore kidney function. Second, given that ADPKD is a progressive condition, intervention as early in life as possible to delay or prevent long-term consequences (including kidney failure) seems most appropriate. Third, young patients with high total kidney volume are likely to have a more difficult course than patients of the same age with smaller kidneys because larger kidneys appear to be associated with hypertension, pain, hematuria, albuminuria, and kidney function decrease.[5] Assessment of a treatment effect on the secondary outcomes as defined in the TEMPO 3-4 Study therefore will be feasible. Fourth, these patients, who have at baseline reasonably preserved kidney function, but already have a large kidney volume, are likely to be rapid progressors and prone to develop kidney failure.[5] This specific subgroup would benefit most from a potential effective treatment. Compared with 2 recent studies assessing mTOR (mammalian target of rapamycin) inhibitor effects on ADPKD progression, our study population has earlier and/or milder disease compared with the population of the everolimus trial[31] (mean age, 39 years; mean estimated GFR, 79 mL/min/1.73 m^2; and median total kidney volume, 1.46 L compared with 45 years, 55 mL/min/1.73 m^2, and 1.65 L, respectively), but later and/or more severe disease compared with the population in the sirolimus trial[32] (31 years, 92 mL/min/1.73 m^2, and 0.90 L, respectively). Neither of these studies showed a clear benefit for either total kidney volume or estimated GFR.

The key secondary composite events of hypertension, decreasing kidney function, renal pain, and albuminuria will be analyzed as noted. Additionally, sensitivity analyses will be performed. Events beginning from the date of first dose of study medication or beginning after the end of titration, both to the end of the double-blind treatment period and end of a post-treatment, off-drug period of 14-42 days will be compared. These sensitivity analyses will evaluate the potential for short-term hemodynamic effects of study treatment or protocol-mandated withdrawal of diuretic therapy on these clinical outcomes. A number of additional secondary end points also have been specified, including examining decreasing kidney function as a "slope," proportions of and time to nonhypertensive patients becoming hypertensive, proportions of hypertensive patients decreasing use of antihypertensive therapy, and changes in renal pain scores.

Study limitations include the currently uncertain clinical relevance of the primary outcome of kidney volume, an uncertain power for the key secondary composite end point of disease progression events, and possibly inadequate power to show a definitive effect on currently accepted measures of kidney function. Ultimately, the power of the study will depend on the relative effects of vasopressin V2 receptor inhibition on the disease's natural course.

In conclusion, the TEMPO 3-4 Study is the first clinical study investigating the efficacy of a selective vasopressin V2 receptor antagonist in patients with ADPKD. Baseline data show that we were able to include a large number of patients with ADPKD relatively early in their disease, with a high likelihood of disease progression. Blinded sample size recalculation performed after 1,000 patients were enrolled confirms that the trial has appropriate

power to address the primary and secondary outcomes of this study. We hypothesize that tolvaptan will be able to inhibit or decrease kidney volume growth, improve clinical outcomes, and be an effective therapeutic option for patients with ADPKD in a relatively early phase of the disease.

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