Published in final edited form as:

Am J Nephrol. 2017 ; 45(3): 257–266. doi:10.1159/000456087.

Rationale and Design of a Clinical Trial Investigating Tolvaptan Safety and Efficacy in Autosomal Dominant Polycystic Kidney Disease

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Abstract

Background—In TEMPO 3:4, the vasopressin V2-receptor antagonist tolvaptan slowed kidney growth and resulted in function decline in autosomal dominant polycystic kidney disease (ADPKD) patients with relatively preserved kidney function.

Methods—Prospective, phase 3b, multi-center, randomized-withdrawal, placebo-controlled, double-blind trial of tolvaptan in ADPKD patients with late stage 2 to early stage 4 chronic kidney disease (CKD). The primary endpoint was estimated glomerular filtration rate (eGFR) change from pre-treatment baseline to post-treatment follow-up. Secondary endpoints included annualized eGFR slope, incidence of ADPKD complications, and overall and hepatic safety profiles. Participants were 18–55 year-old ADPKD patients with baseline eGFR ≥ 25 and ≤ 65 mL/min/1.73 m² or 56–65 year-old with eGFR ≥ 25 and ≤ 44 mL/min/1.73 m² and evidence of eGFR decline >2.0 mL/min/1.73 m² per year. Daily split doses of tolvaptan were titrated to tolerance (30/15, 45/15, 60/30, or 90/30 mg) and maintained for 12 months, after an 8-week pre-randomization period to screen out subjects unable to tolerate at least 60/30 mg for 3 weeks.

Results—Of 1,495 subjects who entered the tolvaptan titration period, 125 (8.4%) discontinued the study before randomization. One thousand three hundred seventy subjects (684 tolvaptan, 686 placebo) from 213 centers across 21 countries were randomized. Baseline demographics were well

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Disclosures

V.E.T., O.D., A.B.C., R.T.G., R.D.P., J.O., and F.S.C. are members of the Steering committee of the TEMPO 3:4 and TEMPO 4:4 trials. V.E.T., O.D., A.B.C., R.T.G., and R.D.P. have received research funding from Otsuka Pharmaceutical Development and Commercialization, Inc. (Princeton, NJ, USA); A.B.C. has received consultancy fees from Otsuka Pharmaceutical Development and Commercialization, Inc. J.O., J.D.B., F.S.C., and O.S. are employees of Otsuka Pharmaceutical Development and Commercialization Inc.

balanced across treatment arms. Information collected during the study included eGFR, survey scores (PKD history and outcome), adverse events, vital signs, hematology, urinalysis, and serum chemistry tests.

Conclusion—Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy (REPRISE) determines whether tolvaptan administered over 1 year exhibits disease-modifying properties in ADPKD patients with late stage 2 to early stage 4 CKD, which provides an important therapeutic advancement for this difficult-to-treat disease.

Keywords

Autosomal dominant polycystic kidney disease; Chronic kidney disease; Vasopressin; Vasopressin receptor antagonist; V2 receptor antagonist; Randomized clinical trial

Introduction

Autosomal dominant polycystic kidney disease (AD-PKD) is the most common inherited disorder of the kidney [1, 2]. The disease is typically caused by mutations in one of 2 proteins located in the primary cilium [3–5], a cell-surface organelle that coordinates various signaling pathways involved in development and tissue homeostasis [6–8]. In patients with ADPKD, dysregulation of the primary cilium causes localized and unregulated expansion of the renal tubule epithelium, resulting in the formation of fluid-filled cysts that grow and ultimately obstruct renal tubules, blood vessels, and lymphatics [9]. In general, progression of the disease, as measured by increasing kidney volume and decreasing kidney function, is inexorable, with an estimated 45–70% of patients developing end-stage renal disease (ESRD) by the age of 65 [10]. Twenty-eight thousand prevalent cases of ESRD were attributable to ADPKD in the United States in 2011, making it the fourth leading cause of ESRD next to diabetes, hypertension, and glomerulonephritis [11]. Other signs and symptoms of ADPKD include kidney/back pain, hypertension, gross hematuria, cyst infection, nephrolithiasis, mild albuminuria, and fatigue [1, 2].

Traditionally, therapy for ADPKD has focused on limiting the morbidity and mortality of the disease's complications [1, 2]. However, a recent randomized placebo-controlled trial – the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) 3:4 study – demonstrated that the modification of ADPKD progression was achievable following twice daily oral dosing with tolvaptan [12]. Tolvaptan is an oral selective vasopressin V2-receptor antagonist that has been demonstrated to correct clinically significant hypervolemic and euvolemic hyponatremia via promotion of free water clearance (aquaresis) [13]. Mechanistically, tolvaptan promotes aquaresis by inhibiting the binding of vasopressin to the V2-receptor, thereby lowering cAMP production in the distal nephron and collecting duct, which in turn decreases the expression and apical insertion of aquaporin-2 in the principal cells of collecting ducts. Importantly, lowering cAMP levels by vasopressin antagonism has also been shown to slow progression of established disease in animal models of ADPKD [14, 15]. This effect likely relates to the observation that elevated cAMP levels in renal tubular epithelial cells constitute the central mechanism responsible for unrestrained growth of cysts in ADPKD by promoting cystic

fibrosis transmembrane conductance regulator–mediated, chloride-driven fluid secretion and cell proliferation [16, 17].

Progressive ADPKD disease is ideally treated early by addressing its primary mechanism to halt or delay its morbid and mortal consequences. Thus, TEMPO 3:4 enrolled subjects with relatively early stage of ADPKD (creatinine clearance ≥ 60 mL/min and age <50 years) and a high likelihood of rapid disease progression (total kidney volume ≥ 750 mL) [18]. The primary endpoint of the trial was the earliest marker specific to ADPKD progression, that is, cyst growth measured by the total kidney volume. This choice of primary endpoint was made because estimated glomerular filtration rate (eGFR) was deemed to be a less reliable marker of disease progression during the early stages of the disease due to compensatory glomerular hyperfiltration. The tolvaptan group ($n = 961$) exhibited a significantly lower rate of growth in total kidney volume, a lower rate of worsening kidney pain, and a slower rate of decline in kidney function relative to the placebo group ($n = 484$) [12]. Tolvaptan may be the first disease-modifying therapy administered to ADPKD patients with the disease in its relatively early stages.

Contrary to an initial belief that progressive renal damage would prove more difficult to treat as the disease progressed, subjects who were already in chronic kidney disease (CKD) stage 3a or 3b at baseline in TEMPO 3:4 experienced similar treatment efficacy in post-hoc subgroup analyses [19]. However, only a small number of subjects who had the disease at its later stage was included in that study (14% with CKD stage 3a and 3% with CKD stage 3b). Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in ADPKD (REPRISE) is a new study that is seeking to confirm and expand upon this observation by specifically examining the efficacy and safety of tolvaptan over a 12-month period in a large population of patients with ADPKD who tolerate tolvaptan and are at late CKD stage 2 to early CKD stage 4. Here, we describe the rationale and design of REPRISE and present the enrollment information, demographic data, and baseline characteristics of the study population in this ongoing trial.

Methods

Patients

Eligible subjects are male or female between 18 and 65 years of age with a diagnosis of ADPKD per modified Pei-Ravine criteria [20, 21]. Subjects between 18 and 55 years are required to have an eGFR ≥ 25 and ≤ 65 mL/min/1.73 m². Those between 56 and 65 years are required to have an eGFR ≥ 25 and ≤ 44 mL/min/1.73 m² with evidence of ADPKD progression, that is, eGFR decline of >2.0 mL/min/1.73 m² per year based on historical eGFR data. A full list of inclusion and exclusion criteria is provided in Table 1.

Study Design

REPRISE (ClinicalTrials.gov Identifier: NCT02160145) is an ongoing phase 3b, multi-center, randomized-withdrawal, placebo-controlled, double-blind, parallel-group trial in tolvaptan-naïve subjects with late stage 2 to early stage 4 CKD as a result of ADPKD. Enrolling sites are located in North and South America, Europe, and Australia (Table 2).

The trial consists of an 8-week pre-randomization period, a 12-month treatment period, and a 3-week-follow-up period. A schematic of the overall trial design is shown in Figure 1. The pre-randomization period is divided into 4 sub-periods, a screening period (2 weeks), a single blind placebo run-in period (1 week), a single blind tolvaptan titration period (2 weeks), and a single blind tolvaptan run-in period (3 weeks). During the screening period, a subject's ADPKD diagnosis is confirmed based on historical imaging data and, if necessary, confirmatory imaging. Subjects fulfilling all eligibility requirements are entered into the placebo run-in period, where they receive a split dose of placebo every day for 1 week. Those that tolerate the placebo run-in enter a tolvaptan titration period, initially receive tolvaptan every day at a split dose of 30/15 mg, that is, 30 mg upon waking and 15 mg 8–9 h later. Over the next 2 weeks, the dose is titrated every 3–4 days to 45/15 mg, 60/30 mg, and finally 90/30 mg based on subject reported tolerability. Subjects who tolerate tolvaptan at doses of 60/30 or 90/30 mg continue for a 3-week tolvaptan run-in period to confirm tolerability. Those unable to tolerate tolvaptan at 60/30 or 90/30 mg during the titration or run-in period are discontinued from the study and considered run-in failures. This strategy was designed to ensure that enrolled and randomized patients were able to tolerate the doses of tolvaptan used in the TEMPO 3:4 trial, thus minimizing patient withdrawal in the active arm of the trial.

Subjects who successfully complete the pre-randomization period are randomized 1:1 in a double-blind fashion to continue receiving split-dose tolvaptan or matching placebo tablets every day for 12 months. Randomization is stratified according to baseline eGFR (<45 or >45 mL/min/1.73 m²), age (<55 or >55 years), and total kidney volume ($<2,000$, $>2,000$ mL, or unknown). The maximally tolerated dose of tolvaptan established during the run-in period, or the equivalent as matching placebo, is dispensed according to the subject's randomization outcome. Down-titration to 45/15 mg (or 30/15 mg with medical monitor approval) or temporary interruption from treatment are permitted during the long-term treatment period if tolerability becomes an issue, with permission to return to higher doses if possible. Subjects have monthly laboratory testing and report to their study sites every 3 months throughout the entire 12-month treatment phase. A 3-week follow-up period starts immediately after the last dose of study medication and consists of 3 laboratory blood draw visits between follow-up days 8 and 21 (Fig. 1).

Given the aquaretic effect of tolvaptan, and to help with blinding, all subjects are recommended to ingest at least 2–3 liters of fluid per day throughout the study unless otherwise directed by their study doctor. Additionally, subjects are prohibited from using diuretics and are asked to ingest 1–2 cups of water before bedtime, regardless of perceived thirst, and to replenish fluids overnight with each episode of nocturia. Finally, all subjects are instructed to ingest fluids in anticipation or at the first sign of thirst. Possible dehydration is monitored by the subjects themselves by self-assessment of changes in body weight and reporting of symptoms. Acute changes of $>3\%$ body weight (increase or decrease) over any 7-day period are noted. Restrictions on dietary sodium chloride (<5 g/day), protein (<1 g/kg/day) and caffeinated drinks and foods (no more than 2 coffee-equivalents per day) are also recommended due to the possible benefits of such measures in patients with a history of, or predisposition for, hypertension or kidney disease [2].

Objectives

Primary Objective—The primary objective of REPRISE is to compare the efficacy of tolvaptan relative to placebo in patients with stage 2 to early stage 4 CKD (eGFR ≥ 25 and < 65 mL/min/1.73 m²) attributable to ADPKD, as assessed by change in eGFR from pre-treatment baseline to post-treatment follow-up.

Secondary Objectives—The secondary objectives of REPRISE include the following:

- To compare the efficacy of tolvaptan relative to placebo, as assessed by change in annualized eGFR slope,
- To compare the overall and hepatic safety profiles of tolvaptan and placebo,
- To compare the incidence of ADPKD complications (e.g., hypertension, kidney pain, gross hematuria, nephrolithiasis, urinary tract infection and others), including the assessment of medical, social, and economic consequences of new and ongoing PKD-related morbidities, medical resource utilization (office/emergency room healthcare visits, hospital admissions, procedures and therapies) and productive days lost due to PKD outcomes in the tolvaptan and placebo groups,
- To assess changes in urinary osmolality and urine specific gravity in the tolvaptan and placebo groups.

Efficacy Assessments

Two aliquots of blood are collected at every trial visit, stored frozen, and used to determine serum creatinine levels by a central laboratory. While one blood sample is analyzed immediately upon receipt for safety reasons, the formal efficacy analysis is based on duplicate samples collected contemporaneously. Batched analysis using the enzymatic method is conducted for each subject upon his/her individual completion of all study assessments to eliminate inter-day variability of the assay.

The eGFR values are calculated using the Chronic Kidney Disease Epidemiology (CKD-EPI) formula [22], with the first 2 assessments at screening used to calculate a mean eGFR value in order to determine if the inclusion criteria are all fulfilled. As alterations in metabolism could impact serum creatinine concentration and renal function estimations, subjects are requested to maintain stable dietary protein and water intake, to maintain a stable exercise routine, and to avoid changes in medications, if possible.

Patients also complete Polycystic Kidney Disease History and Outcomes Surveys at screening, at the end of the tolvaptan run-in, and during the treatment period either monthly (over the phone or in person) or during quarterly clinic visits (in person). The surveys collect information relevant to the medical, social, and economic consequences of new and ongoing PKD-related morbidities.

Safety Assessments

Safety is assessed by adverse events (including causality and severity, as per the Common Terminology Criteria for Adverse Events, version 4.03 [23]). Adverse events are collected at each patient contact and analyzed on a regular basis by the trial's Medical Monitor and the sponsor's Safety group. As ADPKD is a progressive disorder involving the kidney, liver, and occasionally other organ systems, a number of adverse events are expected to be associated with the disease, including urine concentration defects, hypertension, renal pain, renal infection, nephrolithiasis, hematuria, and ESRD. In addition to adverse events, safety is assessed by checking the vital signs, by direct physical examination, self-assessed tolerability, adverse events, hematology, urinalysis and serum chemistry tests, including serum sodium and osmolality.

In TEMPO 3:4 and its open-label extension (TEMPO 4:4), subjects on tolvaptan experienced aminotransferase elevations more frequently than those on placebo, and 3 of the tolvaptan subjects fulfilled the definition of Hy's Law cases (see Discussion for more detail) [24]. Consequently, subjects in REPRISE undergo hepatic transaminase, alkaline phosphatase and total bilirubin assessments during the pre-randomization period and at each monthly visit during the treatment period. The appearance of any suspicious symptoms or signs, or any transaminase or bilirubin elevations reaching or exceeding $2 \times$ upper level of normal, prompt immediate retesting (i.e., within 72 h) and an increased frequency of subsequent monitoring. In cases where transaminases and bilirubin are both elevating with an uncertain or rapidly increasing trajectory, temporary interruption of study medication is mandated. Study medications are not resumed until monitoring indicates that the abnormalities have resolved, are stable or are not rapidly increasing, and then only with an increased frequency of monitoring. In addition, re-challenge with study medication occurs only if the abnormalities are adjudicated as having a $<50\%$ likelihood of being related to treatment (per drug-induced liver injury [DILI] network probability criteria [25]) by an independent expert hepatic adjudication committee. Subjects were asked to provide consent to both the extra monitoring measures and to the re-challenge.

Statistics

Sample Size—Based on a mixed model repeated measurements (MMRM) analysis of the non-Japanese stage 3 CKD subjects from the TEMPO 3:4 trial, the treatment difference in renal function during the 12th month was estimated to be $1.07 \text{ mL/min/1.73 m}^2$. It was expected that the corresponding intra-subject variance was $14.2 \text{ mL/min/1.73 m}^2$ and inter-subject variance was $28.05 \text{ mL/min/1.73 m}^2$ at month 12. With 3 repeated measures at pre-treatment baseline and at post-treatment follow-up, respectively, the power calculation estimated that, for a 2-sided alpha set at 0.05 for a power of 90%, and with an assumption of 10% dropout rate in the trial, a total sample size of approximately 1,300 subjects was needed.

Primary Endpoint—The primary endpoint of the trial is defined as change in eGFR from pre-treatment baseline (average of 2 samples taken over the screening period and 1 sample taken during the placebo run-in period) to post-treatment follow-up (average of 3 samples taken during the 3-week follow-up period), annualized (divided) by each subject's treatment

duration. The annualized change in eGFR is analyzed by a weighted analysis of covariance, with treatment and randomization stratification factors as factor and covariate baselines. The weight used in the analysis is equal to the reciprocal of the estimated variance of this annualized change from baseline for each subject.

Key Secondary Endpoints—The key secondary endpoint of the trial is the annualized rate (slope) of eGFR change, which is derived from each individual subject eGFR slope using the CKD-EPI equation. The analysis of the key secondary endpoint will be formally conducted, once the primary endpoint is significant at a 2-sided alpha of 0.05. In this analysis, all eGFR observations from placebo run-in, tolvaptan run-in (not including tolvaptan titration), double blind treatment, and post-treatment follow-up (not including data collected in the first week after the last dose) periods will be included, with the data of tolvaptan run-in and tolvaptan subjects in the double blind treatment period being flagged (yes = 1 and no = 0) with a tolvaptan acute hemodynamic effect. The linear mixed effect model with effects of time (as a continuous variable), treatment, time-treatment interaction, acute hemodynamic effect, pre-treatment baseline (of the primary endpoint), and randomization stratification factors will be used to fit the GFR estimates, in which the intercept and time are both a fixed effect and a random effect. An un-structured variance covariance matrix is assumed for the random intercept and time. The time variable used in the model may start from the first observation of eGFR obtained from placebo run-in period. The covariate “acute hemodynamic effect” in the model is the flag variable with value of 0 and 1 specified earlier in this section for the data observed during tolvaptan run-in and the data observed for tolvaptan subjects during the double blind treatment period. The starting point of this eGFR slope analysis is the eGFR observation during the placebo run-in period.

Ensuring Complete Follow-Up Information

The intent of REPRISE is to obtain follow-up data that are as complete as possible. Thus, subjects who discontinue study drug, or who discontinue study drug and replaced it with marketed tolvaptan (which is now available in several regions conducting the trial), continue with scheduled visits and assessments through month 12.

Ethical Considerations

Institutional review boards/independent Ethics Committees are required to approve the protocol and informed consent forms are completed 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 it adheres to the ethical principles that have their origin in the Declaration of Helsinki. Participant privacy is ensured by deidentifying all submitted data and by 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 monitors study safety and efficacy.

Study Organization

The design and conduct of the study are overseen by a steering committee with the study sponsors. An independent data monitoring committee, managed by an independent statistical

data analysis center, is established to monitor the safety and efficacy of the trial. An expert hepatic adjudication committee independently adjudicates probable causality of liver-associated safety findings. All study committees are guided by charters defining their roles and responsibilities and methods specific to the committee. The study sponsor is responsible for the analysis of trial data and dissemination of trial results.

Results

The first screening visit occurred on May 21, 2014. In total, 2,283 subjects were screened, of whom 1,519 (66.5%) proceeded to the placebo run-in period, 1,495 (65.5%) entered the tolvaptan titration period, and 1,428 (62.5%) entered the tolvaptan run-in period (Fig. 2). Reasons for screen failures are listed in Table 3. After the tolvaptan run-in period, 1,370 subjects (60.0%) entered the double-blind placebo-controlled arm of the trial and were randomized in a 1:1 ratio to tolvaptan ($n = 684$) or placebo ($n = 686$), with the first patient, first visit occurring on July 14, 2014. The last patient randomized to the study occurred on March 30, 2016 and the last visit is targeted for April 18, 2017.

The purpose of the tolvaptan titration (2 weeks) and run-in periods (3 weeks) is to enrich subjects who can tolerate tolvaptan treatment in order to minimize the number of early aquaretic-related discontinuations. Of the 1,495 subjects who entered the tolvaptan titration period, 125 (8.4%) discontinued the study prior to randomization. This finding was consistent with results from TEMPO 3:4, which reported an 8.3% rate of discontinuation due to aquaresis-related symptoms [12] and justified the study design.

Baseline demographics were well balanced between treatment arms (Table 4) with 49.6% male subjects (49.7 vs. 49.6%, in tolvaptan- and placebo-treated subjects, respectively), a mean age of 47.3 ± 8.2 years (47.2 ± 8.0 vs. 47.3 ± 8.3 years), and a baseline eGFR of 43.0 ± 11.6 mL/min/1.73 m² (43.0 ± 11.7 vs. 42.9 ± 11.5 mL/min/1.73 m²).

Discussion

The REPRISE trial is designed to confirm the beneficial effects of tolvaptan on renal function in subjects with late stage 2 to early stage 4 CKD attributable to ADPKD. Eligible subjects are between 18 and 65 years of age, with acceptable eGFRs set per specific age cohort. Specifically, at baseline, subjects between 18 and 55 years are required to have an eGFR ≥ 25 and ≥ 65 mL/min/1.73 m², whereas those between 56 and 65 years are required to have an eGFR ≥ 25 and ≥ 44 mL/min/1.73 m² with evidence of ADPKD progression. These cutoffs were chosen based on prior studies indicating that AD-PKD patients with an eGFR <60 mL/min/1.73 m² (CKD stage 2) by 55 years or an eGFR <45 mL/min/1.73 m² (CKD stage 3b) by 65 years are at a high risk of progression to ESRD [26]. To date, randomization is complete, with the final subject scheduled to complete the trial on April 18, 2017.

The primary endpoint in REPRISE is the change in eGFR from pre-treatment baseline to post-treatment follow-up, which differs from the TEMPO 3:4 trial, where the change in total kidney volume from pre-treatment baseline to on-treatment at year 3 was the primary endpoint. The simpler and less costly primary endpoint in REPRISE is tenable because

eGFR correlates well with disease severity during the later stages of disease, while it correlates less well at an early stage of the disease [9]. The key secondary endpoint – annualized rate of change in eGFR – was chosen because it represents a practical and clinically meaningful description of disease progression in ADPKD patients. Moreover, this clinical endpoint was designed to account for the 5–10% acute drop in GFR that is observed upon drug initiation; a hemodynamic effect that is fully reversed upon drug withdrawal. The REPRISE secondary endpoint – change in annualized slope of eGFR – was designed to account for this effect.

A split dosing regimen is used to maintain 24-h inhibition of the V2-receptor. A higher dose is used early in the day, while a lower dose is used 8–9 h later, in order to produce a maximal inhibition on waking and a gradual fall-off of effect during the night when frequent urination could lead to interruption of sleep. Subjects in REPRISE receive tolvaptan at a daily split dose of 30/15, 45/15, 60/30, or 90/30 mg during the 12-month double-blind treatment phase (following dose adjustment per tolerability as needed). In TEMPO 3:4, 8.3% of tolvaptan subjects withdrew from the study due to aquaretic symptoms [12]. In a subsequent analysis, 42% of those who discontinued due to aquaretic symptoms did so by the end of titration visit (week 3) [27]. This contributed to an imbalanced withdrawal of tolvaptan subjects and missing follow-up data. Thus, one of the predefined operational goals of REPRISE is to limit the number of subjects discontinuing early due to a lack of tolerability to tolvaptan. The trial therefore includes an extensive pre-randomization phase, consisting of a screening period, placebo run-in period, tolvaptan titration period, and tolvaptan run-in period, designed to screen out subjects at a high potential of early withdrawal due to tolvaptan intolerance. Of the 1,495 subjects who entered the tolvaptan titration period, 125 were unable to tolerate tolvaptan through the run-in period, thereby minimizing the potential leading to early discontinuation due to poor tolerability to study drug by 8.3%, a rate similar to that observed in TEMPO 3:4 [12].

The most notable safety issue associated with chronic tolvaptan use is the potential for idiosyncratic hepatic toxicity [24]. With a once every 4-month monitoring scheme, 2 subjects on tolvaptan in TEMPO 3:4 and one subject on tolvaptan in its open-label extension study (TEMPO 4:4; frequency of approximately 1:400) had laboratory and clinical evidence of potentially serious DILI [24]. Of note, no imbalance in hepatic events was observed between tolvaptan and placebo in lower-dose clinical trials of patients with hyponatremia, heart failure, or cirrhosis [24]. The onset of hepatocellular injury occurred between 3 and 18 months after starting tolvaptan, with gradual resolution over the subsequent 1–4 months. None of the events were associated with liver failure, chronic liver injury/dysfunction, or death. In light of these data, subjects in REPRISE are tested for hepatic transaminase, alkaline phosphatase, and total bilirubin during screening and at each monthly visit, and evidence of liver damage is assessed by the trial's sponsor and the independent hepatic adjudication committee. A previous analysis noted that since liver chemistry monitoring was relatively infrequent in TEMPO 3:4 and its open-label extension, it might be reasonable to assume that the risk of DILI could be mitigated with more frequent monitoring and earlier treatment discontinuation [24]. Consequently, the sponsor and hepatic adjudication committee in REPRISE have been set up to ensure the assessment of adverse hepatic signals.

Like any clinical study, REPRISE has some potential limitations resulting from its design. First, the randomized-withdrawal design may lead to a perception on the part of the subject of his or her treatment assignment. The prescription of additional fluids to subjects may serve to confound this effect. The primary outcome based on eGFR measurement is objective and expected to be unaffected by the participant's perceptions; however, the increased water intake in placebo subjects might be expected to slow renal function decline because of AVP suppression, which could lead to an underestimation of the treatment effect. Second, the study pre-selects for subjects with high tolerability of vasopressin antagonists and may therefore overestimate the effectiveness of tolvaptan in a general ADPKD population, where treatment withdrawal could occur at higher rates. On the other hand, this design has the benefit of providing an estimate of the percentage of subjects who can tolerate the drug and is fully consistent with guidance from the US FDA on enrichment strategies [28]. Third, the short duration of the trial may reduce the likelihood of finding a significant difference between tolvaptan and placebo in the primary endpoint (absolute change in eGFR from pre-treatment to post-treatment, normalized by the subject's duration of treatment). MMRM analyses of the non-Japanese CKD-3 subjects from TEMPO 3:4 indicated that the REPRISE sample size should be sufficiently powered to detect a 1.07 mL/min/1.73 m² difference in renal function, which is 25% less than that observed in TEMPO 3:4 at 12 months (1.43 mL/min/1.73 m²). Furthermore, 3 serum creatinine measurements are taken both pre- and post-treatment for each subject, and measured as a batch upon study completion to minimize interday variation in laboratory measurement. Bearing in mind the above caveats, REPRISE is expected to provide valuable information on the safety and efficacy of tolvaptan in patients with more advanced ADPKD.

Acknowledgments

Support

Funded by Otsuka Pharmaceuticals Co., Ltd. Tokyo, Japan and Otsuka Pharmaceutical Development and Commercialization, Inc., Rockville, Maryland.

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Fig. 1.
REPRISE study schematic. F/U, follow-up. * Can be extended up to an additional 8 weeks for subjects needing stabilization after changing other treatments.

Fig. 2.
Subject disposition.

Table 1**Eligibility requirements for REPRISE**

<i>Inclusion criteria</i>	
Male and female subjects age 18–55 years of age (inclusive) with eGFR between 25 and 65 mL/min/1.73 m ² or	
Male and female subjects 56 to <66 years of age with eGFR between 25 and 44 mL/min/1.73 m ² with evidence of ADPKD progression, that is, eGFR decline of >2.0 mL/min/1.73 m ² per year, based on historical eGFR data and medical monitor discretion	
Male and female subjects who are tolvaptan naive	
Diagnosis of ADPKD by modified Pei-Ravine criteria	
<ul style="list-style-type: none"> • • 	With family history: several cysts per kidney (3 if by sonography; 5 if by CT or MRI)
	Without family history: 10 cysts per kidney (by any radiologic method, above) and exclusion of other cystic kidney diseases. Conditions to be excluded include: multiple simple renal cysts, renal tubular acidosis, cystic dysplasia of the kidney, multicystic kidney, multilocular cysts of the kidney, medullary cystic kidney and acquired cystic disease of the kidney
<i>Exclusion criteria</i>	
Women of childbearing potential who do not agree to practice 2 different methods of birth control or remain abstinent during the trial and for 30 day after the last dose of study medication. If employing birth control, 2 of the following precautions must be used: vasectomy of partner, tubal ligation, vaginal diaphragm, intrauterine device, birth control pill, birth control implant, birth control depot injection, condom, or sponge with spermicide	
Women who are breast-feeding and/or who have a positive pregnancy test result prior to receiving study medication	
Need for chronic diuretic use	
Hepatic impairment or liver function abnormalities other than that expected for ADPKD with typical cystic liver disease during the pre-randomization period	
Subjects with advanced diabetes (e.g., glycosylated hemoglobin >7.5%, and/or glycosuria by dipstick, significant proteinuria, retinopathy), evidence of additional significant renal disease(s) (i.e., currently active glomerular nephritides), renal cancer, single kidney, or recent (within last 6 months) renal surgery or acute kidney injury	
Subjects with contraindications to required trial assessments	
Subjects who, in the opinion of the trial investigator or medical monitor, have a medical history or medical findings inconsistent with safety or compliance with trial assessments	

Table 2

Study sites and number randomized

Country	Sites, <i>n</i>	Total randomized, <i>n</i>
Argentina	10	20
Australia	10	34
Belgium	8	64
Canada	6	46
Czech Republic	9	30
Denmark	4	24
France	10	59
Germany	9	99
Hungary	3	14
Israel	6	38
Italy	10	75
Netherlands	2	24
Norway	2	4
Poland	8	36
Romania	3	17
Russia	4	4
South Africa	3	23
Spain	5	59
Sweden	6	23
United Kingdom	16	89
United States	79	588
Total	213	1,370

Table 3

Reasons for screen failures

Reasons for screen failures	Number of subjects (<i>n</i> = 765)*
Subject did not meet inclusion/exclusion criteria	688
Subject was withdrawn by investigator	9
Subject withdrew consent	44
Other reason	42

* 16 subjects had 2 reasons and 1 subject had 3 reasons for screen failure.

Table 4

Demographics and baseline characteristics

Characteristics, mean (SD)	Tolvaptan (n = 684)	Placebo (n = 686)	Total (n = 1,370)
Male, %	49.7	49.6	49.6
Age, years	47.2 (8.0)	47.3 (8.3)	47.3 (8.2)
Race, %			
Caucasian	91	93	92
Asian	4	3	3
Other	5	4	5
Height, cm, mean (SD)	173 (10)	174 (10)	173 (10)
Weight, kg, mean (SD)	83.5 (18.7)	84.3 (20.5)	83.9 (19.6)
BMI, kg/m ² , mean (SD)	27.9 (5.6)	27.9 (5.9)	27.9 (5.7)
eGFR, mL/min/1.73 m ² , mean (SD), n (%)	43.1 (11.6) [†]	42.9 (11.5) [‡]	43.0 (11.6) [§]
CKD 2 (45–65)	22 (6.8)	23 (7.1)	45 (6.9)
CKD 3a (30–45)	100 (30.9)	104 (31.9)	204 (31.4)
CKD 3b (15–30)	138 (42.6)	145 (44.5)	283 (43.5)
CKD 4 (<15)	64 (19.8)	54 (16.6)	118 (18.2)
Blood pressure, mm Hg			
Systolic	129.5 (14.4)	130.1 (14.0)	129.8 (14.2)
Diastolic	82.3 (9.7)	82.4 (9.8)	82.4 (9.8)

[†]n = 649,

[‡]n = 659,

[§]n = 1,308.