

Multicenter Study of Long-Term Safety of Tolvaptan in Later-Stage Autosomal Dominant Polycystic Kidney Disease

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Abstract

Background and objectives Tolvaptan slows kidney function decline in patients with autosomal dominant polycystic kidney disease (ADPKD) at risk of rapid progression. In the 3-year Tolvaptan Efficacy and Safety in Management of ADPKD and Its Outcomes (TEMPO) 3:4, 2-year extension to TEMPO 3:4 (TEMPO 4:4), and 1-year Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in ADPKD (REPRISE) trials, aquaretic adverse events were common. Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevations occurred in all three studies. Three patients met Hy Law criteria (ALT or AST more than three times and total bilirubin more than two times the upper limit of normal) for severe drug-induced liver injury (two in TEMPO 3:4 and one in TEMPO 4:4). In REPRISE, liver enzyme monitoring frequency was increased to monthly, with no Hy Law cases. A long-term, phase 3 safety study has further characterized tolvaptan safety.

Design, setting, participants, & measurements Subjects who completed TEMPO 4:4, REPRISE, or other tolvaptan trials could enroll in this prospective, multinational, open-label safety study. Assessments included monthly liver enzyme testing during the first 18 months of tolvaptan exposure and every 3 months thereafter.

Results Among 1803 subjects, median tolvaptan exposure during the extension was 651 days (interquartile range, 538–924), and cumulative exposure (extension and previous trials) was ≤ 11 years. Subjects entering from REPRISE placebo experienced more aquaretic adverse events compared with subjects from TEMPO 4:4 or REPRISE tolvaptan (*i.e.*, patients with prior long-term tolvaptan exposure). Liver enzyme elevations also occurred more frequently in subjects from REPRISE placebo. Percentages experiencing ALT $\geq 3/ \geq 5/ \geq 10/ \geq 20$ times the upper limit of normal were 3.2%/2.1%/0.9%/0.7%, respectively, in subjects from REPRISE placebo and 0.6%–1.1%/0.0%–0.1%/0%/0%, respectively, in those from REPRISE tolvaptan and TEMPO 4:4. Percentages experiencing AST $\geq 3/ \geq 5/ \geq 10/ \geq 20$ times the upper limit of normal were 6.9%/3.8%/2.3%/0.8%, respectively, in subjects from REPRISE placebo and 0.9%–2.0%/0.0%–1.0%/0%/0%, respectively, in those from REPRISE tolvaptan and TEMPO 4:4. No Hy Law cases occurred.

Conclusions No new safety signals emerged during this long-term extension. Monthly liver function testing for the first 18 months of treatment appeared to enable effective detection and management of transaminase elevations.

Clinical Trial registry name and registration number: Open Label Extension of TEMPO 3:4, NCT02251275

CJASN 16: 48–58, 2021. doi: <https://doi.org/10.2215/CJN.10250620>

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the fourth leading cause of kidney failure, accounting for 5%–10% of cases globally (1,2). Tolvaptan, a selective antagonist of the arginine vasopressin receptor type 2, is the first approved treatment that targets a mechanism directly contributing to cyst development and growth (3,4). Tolvaptan slowed kidney function decline in patients at risk of rapid ADPKD progression in two pivotal trials, the 3-year Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and

Its Outcomes (TEMPO) 3:4 trial (NCT00428948) and the 1-year Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in Autosomal Dominant Polycystic Kidney Disease (REPRISE) trial (NCT02160145) (5,6).

TEMPO 3:4 completers could enroll in the open-label extension TEMPO 4:4 (NCT01214421), which provided at least 2 additional years of tolvaptan safety and efficacy data (7). As no hepatic safety signal had emerged previously for tolvaptan with use in other indications, liver enzyme monitoring was relatively infrequent in TEMPO 3:4 (every 4 months). An

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imbalance was seen in TEMPO 3:4 in the proportion of subjects with alanine aminotransferase (ALT) more than three times the upper limit of normal (4.4% tolvaptan versus 1.0% placebo) (8). In addition, two subjects in TEMPO 3:4 and one subject in TEMPO 4:4 developed potentially severe drug-induced liver injury (*i.e.*, met Hy Law criteria, defined as ALT or aspartate aminotransferase [AST] more than three times the upper limit of normal and total bilirubin more than two times the upper limit of normal in the absence of cholestasis [alkaline phosphatase less than two times the upper limit of normal]) (5,7,8). The transaminase elevations resolved in all subjects within approximately 4 months after tolvaptan discontinuation (8). Liver function testing frequency in TEMPO 4:4 was originally once every 6 months; it was subsequently increased to every 3 months and, finally, to monthly (8). In REPRISÉ, liver function testing was conducted monthly for the entirety of the study. The frequency of elevated liver function tests (5.6% tolvaptan versus 1.2% placebo) in REPRISÉ was similar to that in the TEMPO program, but no additional Hy Law cases were reported, likely due to more frequent monitoring and timely interruption of study medication in subjects experiencing liver enzyme elevations (6). Aquaretic adverse events (AEs; *e.g.*, thirst, polyuria, and nocturia) related to the mechanism of action of tolvaptan were common and well tolerated (9).

Subjects who completed earlier tolvaptan trials in ADPKD could enroll in an open-label, long-term extension (NCT02251275), the results of which are reported here. Liver function testing was monthly until 18 months of tolvaptan exposure accumulated, and then every 3 months. The primary objective was to describe the long-term safety and tolerability of tolvaptan in the treatment of ADPKD.

Materials and Methods

Participants

Subjects were eligible if they had completed REPRISÉ (on either tolvaptan or placebo), the TEMPO 4:4 open-label extension, or a prior tolvaptan ADPKD trial (TEMPO 3:4 or the phase 2 NOCTURNE trial [NCT01451827]). Additionally, subjects who interrupted or discontinued treatment in a prior tolvaptan trial for reasons other than elevated transaminases (hepatic safety) could enroll.

Other inclusion criteria were age ≥ 18 years, confirmed diagnosis of ADPKD by Pei–Ravine criteria (10,11), and eGFR (on the basis of the Chronic Kidney Disease Epidemiology Collaboration equation) ≥ 20 ml/min per 1.73 m² within 3 months of the baseline visit. Subjects with eGFR < 20 ml/min per 1.73 m² could enroll with medical monitor and sponsor approval and more frequent monitoring to ensure safety.

Exclusion criteria were chronic diuretic use, liver function abnormalities other than those expected for ADPKD, or medical history or findings inconsistent with safety or trial compliance.

Study Design

This trial was a phase 3, multicenter, open-label extension. Supplemental Material has the principal investigators and study sites. The study commenced in September 2014 and completed in December 2018.

The trial was planned to continue until the last subject enrolled from REPRISÉ completed 18 months of tolvaptan treatment in the extension. In the United Kingdom, subjects were permitted to complete 18 months of treatment; elsewhere, subjects entering from trials other than REPRISÉ could transition to commercially available tolvaptan (if available) prior to completing 18 months of the extension. Enrollment was extended by 6 weeks for subjects who entered from REPRISÉ, but the end date was not extended; therefore, subjects enrolled in the last 6 weeks may have not completed 18 months of tolvaptan treatment.

Treatments

Subjects from TEMPO 4:4 stayed at the last dose level in TEMPO 3:4 and started at the same dose in this extension. Subjects from REPRISÉ or prior tolvaptan trials were initiated on tolvaptan at a split dose of 45/15 mg with upward titration every 3–4 days to 60/30 or 90/30 mg/d according to tolerability. For all subjects, downward titrations to 30/15 and 15/15 mg were permitted at the discretion of the investigator according to subject tolerability and with medical monitor notification. Further downward titrations to 30 or 15 mg once daily were made in subjects taking moderate or potent cytochrome P450 3A4 inhibitors.

Split-dose regimens were taken twice daily, once upon awakening and another approximately 8–9 hours later. Subjects were encouraged to drink enough water to prevent thirst.

Assessments

Monthly liver function testing was required for all subjects during the first 18 months of cumulative tolvaptan exposure, with monitoring every 3 months thereafter. Nearly all subjects from TEMPO 4:4 met the 18-month requirement before enrolling in the long-term extension. All subjects rolling over from REPRISÉ were monitored monthly in the long-term extension, irrespective of previous treatment assignment, as the blind from REPRISÉ was still in effect. After REPRISÉ was unblinded, subjects who had been randomized to tolvaptan and fulfilled the 18-month cumulative exposure threshold could switch to testing every 3 months.

A blinded, independent Hepatic Adjudication Committee (HAC) reviewed reported liver abnormalities to determine the probable cause(s) (6,8). To qualify for adjudication, events had to meet any of the five hepatic standardized Medical Dictionary for Regulatory Activities (MedDRA) queries with any of the following liver-related investigations: ALT more than three times the upper limit of normal and total bilirubin more than two times the upper limit of normal, AST more than three times the upper limit of normal and total bilirubin more than two times the upper limit of normal, and either ALT or AST more than five times the upper limit of normal (lowered in March 2016 to a more stringent level of more than three times the upper limit of normal). Events of interest were allocated on the basis of expert opinion into causality groups for the potential relationship with study drug, as defined using the five-point US Drug Induced Liver Injury Network classification system (12,13): “definite,” “highly likely,” “probable,” “possible,” and “unlikely” (8). Subjects who met any

Table 1. Subject disposition, demographics, and baseline clinical characteristics

Parameter	Prior Trial Participation			Total
	From Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in Autosomal Dominant Polycystic Kidney Disease Tolvaptan	From Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in Autosomal Dominant Polycystic Kidney Disease Placebo	From Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes 4:4 Tolvaptan	
Disposition				
Enrolled	506	570	718 ^a	1803 ^b
Completed	434	423	624	1488
Discontinued	72	147	95	316
Demographics				
Age, yr				
Mean (SD)	49 (8)	49 (8)	46 (8)	47 (8)
Sex				
Men	272 (54%)	280 (49%)	375 (52%)	929 (52%)
Women	234 (46%)	290 (51%)	343 (48%)	874 (48%)
Height, cm				
Mean (SD)	174 (11)	173 (10)	175 (11)	174 (11)
Weight, kg				
Mean (SD)	86 (19)	84 (21)	82 (19)	84 (19)
Race				
White	461 (91%)	525 (92%)	694 (97%)	1689 (94%)
Baseline clinical characteristics				
CKD stage				
CKD 1	1 (0.2%)	0 (0.0%)	77 (11%)	81 (4%)
CKD 2	35 (7%)	33 (6%)	264 (37%)	334 (19%)
CKD 3a	131 (26%)	146 (26%)	156 (22%)	434 (24%)
CKD 3b	189 (37%)	230 (40%)	132 (18%)	554 (31%)
CKD 4	150 (30%)	158 (28%)	82 (11%)	390 (22%)
CKD 5	0 (0.0%)	3 (0.5%)	7 (1.0%)	10 (0.6%)
eGFR (CKD-EPI), ml/min per 1.73 m ²				
>45	167 (33%)	179 (31%)	497 (69%)	849 (47%)
≤45	339 (67%)	391 (69%)	221 (31%)	954 (53%)
≥25	429 (85%)	486 (85%)	662 (92%)	1586 (88%)
<25	77 (15%)	84 (15%)	56 (8%)	217 (12%)
<p>CKD stages were from the time of entry into this trial, and they were defined as follows: stage 1≥90 ml/min per 1.73 m², stage 2=60–89 ml/min per 1.73 m², stage 3a=45–59 ml/min per 1.73 m², stage 3b=30–44 ml/min per 1.73 m², stage 4=15–29 ml/min per 1.73 m², and stage 5<15 ml/min per 1.73 m². CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.</p> <p>^aThe number of subjects enrolling from the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) 4:4 (<i>n</i>=718) trial is one less than the number who completed or discontinued (<i>n</i>=719) due to one subject with missing data that resulted in exclusion from the enrolled population.</p> <p>^bThe table has no column for subjects who entered the extension directly from TEMPO 3:4 or NOCTURNE due to the small number of subjects (<i>n</i>=9; four from TEMPO 3:4 tolvaptan, two from NOCTURNE tolvaptan, and three from TEMPO 3:4 placebo) from those trials. Data from these subjects are included in the total column.</p>				

of the following liver enzyme elevation criteria were to permanently discontinue study drug: transaminase level more than eight times the upper limit of normal, transaminase level more than five times the upper limit of normal for >2 weeks, or either ALT or AST more than three times the upper limit of normal with total bilirubin more than two times the upper limit of normal.

Subjects were asked about AEs by investigators at monitoring visits. Clinical laboratory assessments generally followed the same schedule as liver function testing and included vital signs, directed physical examination, dietary review, self-assessed drug tolerability, serum creatinine, serum sodium, and review of concomitant medications. Treatment-emergent AEs were defined as AEs that

started after the initiation of study drug or AEs that were continuous from baseline and serious, study drug related, or resulted in death, discontinuation, interruption, or reduction of study therapy.

Statistical Analyses

As an objective of this study was to obtain data to detect potential safety signals, sample size was not determined by formal computation to achieve a target power. Two datasets were established: enrolled population (all subjects who enrolled in this open-label study) and safety population (all subjects in the enrolled sample who took one or more doses of tolvaptan). Safety variables were summarized by

descriptive statistics, with no inferential statistical analyses performed.

Ethical Conduct

This study was conducted in compliance with the protocol, the International Council for Harmonization Good Clinical Practice Consolidated Guideline (14), and applicable local laws and regulatory requirements. Copies of the protocol, any amendments, and the informed consent form were reviewed and approved by the governing institutional review board or independent ethics committee for each investigational site or country as appropriate.

Results

Subject Characteristics, Disposition, and Tolvaptan Exposure

Of 1814 screened subjects, 1803 enrolled in the extension, 1800 received greater than or equal to one dose of tolvaptan and were analyzed for safety, and 1488 (83%) completed the extension. The most common reasons for discontinuation were subject withdrawal of consent ($n=113$ subjects; 6%) and AEs ($n=111$ subjects; 6%). Among completers, 165 (11%) had <18 months of exposure to tolvaptan in the extension, and 1323 (89%) had ≥ 18 months. Nearly all subjects had previously participated in REPRISÉ (1076 [60%] subjects) or TEMPO 4:4 (718 [40%] subjects). Nine subjects came from other trials.

The sex distribution was approximately even; most subjects were White and non-Hispanic/non-Latino, with a mean age of 47 years (Table 1). CKD stage rates were stage 2: 19%; stage 3: 55% (3a: 24%; 3b: 31%); and stage 4: 22%. REPRISÉ enrolled subjects who were slightly older and had more advanced disease compared with those from TEMPO 3:4 and TEMPO 4:4. Statins were taken concomitantly by 546 (30%) subjects enrolled in the extension.

A range of previous tolvaptan exposures was represented (Figure 1). Subjects entering from REPRISÉ placebo, who were newly exposed to long-term tolvaptan, had the lowest completion rate (74%) versus those entering from REPRISÉ tolvaptan (86%) and from TEMPO 4:4 (87%) (Table 1).

During the long-term extension, the range of duration of tolvaptan exposure was 1–1435 days, with median exposure of 651 days (mean = 697; SD = 334; interquartile range, 538–924); 1311 of 1800 (73%) subjects had >18 months of tolvaptan exposure (Figure 2). Overall cumulative tolvaptan exposure (extension and previous trials) per the protocol allowed at least 78 months but was in some patients as long as approximately 134 months. Average doses were similar across the previous trial groups, with subjects overall taking a dose of 96 mg/d.

Adverse Events

Frequencies of AEs overall were similar across the three main subgroups by previous trial enrollment (Table 2). Subjects newly exposed to tolvaptan long term (*i.e.*, from REPRISÉ placebo) reported more treatment-emergent AEs (3678) than those from REPRISÉ tolvaptan (2965) and TEMPO 4:4 (3297). The most commonly occurring treatment-emergent AEs overall were generally associated

with ADPKD or the tolvaptan mechanism of action (Supplemental Table 1). The frequencies of these common AEs in subjects newly exposed to tolvaptan in the long-term extension were comparable with those seen in TEMPO 3:4 and REPRISÉ (5,6). Aquarectic AEs were more frequent in subjects from REPRISÉ placebo (Figure 3).

Overall, 17 (0.9%) patients, including two with malignant melanoma, had skin malignant tumor (four of 505 [0.8%] in the REPRISÉ tolvaptan, six of 569 [1%] in the REPRISÉ placebo, and seven of 717 [1.0%] in the TEMPO 4:4 groups), and four (0.2%) had skin tumors of unspecified malignancy (one of 505 [0.2%] in the REPRISÉ tolvaptan, one of 569 [0.2%] in the REPRISÉ placebo, and two of 717 [0.3%] in the TEMPO 4:4 groups), with no appreciable differences in frequency among the three main subgroups by previous trial participation. Four (0.2%) subjects had glaucoma-related treatment-emergent AEs. In a cross-trial comparison of subjects with the same length of tolvaptan exposure (12 months), subjects who entered the long-term extension from the REPRISÉ placebo group experienced skin malignancies and glaucoma at low rates similar to those observed in the previous REPRISÉ, TEMPO 4:4, and TEMPO 3:4 trials (Supplemental Table 2).

The frequency of serious treatment-emergent AEs was similar across the three main subgroups (Table 2), with kidney and urinary disorders among the most common, occurring in 76 (4%) subjects overall. The most frequently reported MedDRA preferred terms within this system organ class were consistent with events expected in ADPKD: AKI, 20 subjects (1%); kidney impairment, 11 (0.6%); ESKD, 11 (0.6%); kidney pain and kidney cyst hemorrhage, each eight (0.4%) (Supplemental Tables 3 and 4).

Treatment-emergent AEs leading to discontinuation of tolvaptan occurred more often in subjects from REPRISÉ placebo than those from REPRISÉ tolvaptan or TEMPO 4:4 (Table 2). In an analysis by cumulative tolvaptan exposure, discontinuations were most frequent in subjects during the first 18 months of tolvaptan exposure (Supplemental Table 5). The most frequent treatment-emergent AEs leading to discontinuation in the overall study population by preferred term were blood creatinine increased ($n=22$ subjects), kidney impairment ($n=14$), ESKD ($n=10$), ALT increased ($n=8$), and polyuria ($n=7$).

Liver Safety

Adverse Event Reporting. In AE reporting by MedDRA preferred term, 2.8% subjects had ALT increased, 0.6% had AST increased, and 1.1% had γ -glutamyltransferase increased (Table 3). These frequencies are on the basis of reports by investigators and not on predefined criteria.

Ten (0.6%) subjects had treatment-emergent AEs reported under the “hepatic failure, fibrosis and cirrhosis, and other liver-damage-related conditions” standardized MedDRA query, including four (0.8%) REPRISÉ tolvaptan subjects, one (0.2%) REPRISÉ placebo subject, and five (0.7%) TEMPO 4:4 subjects (Table 4). Of the events listed, treatment-emergent AEs in two (0.1%) subjects, both related to ascites, were considered serious by the investigator and not related to tolvaptan. The events were adjudicated by HAC, which determined causality by tolvaptan as

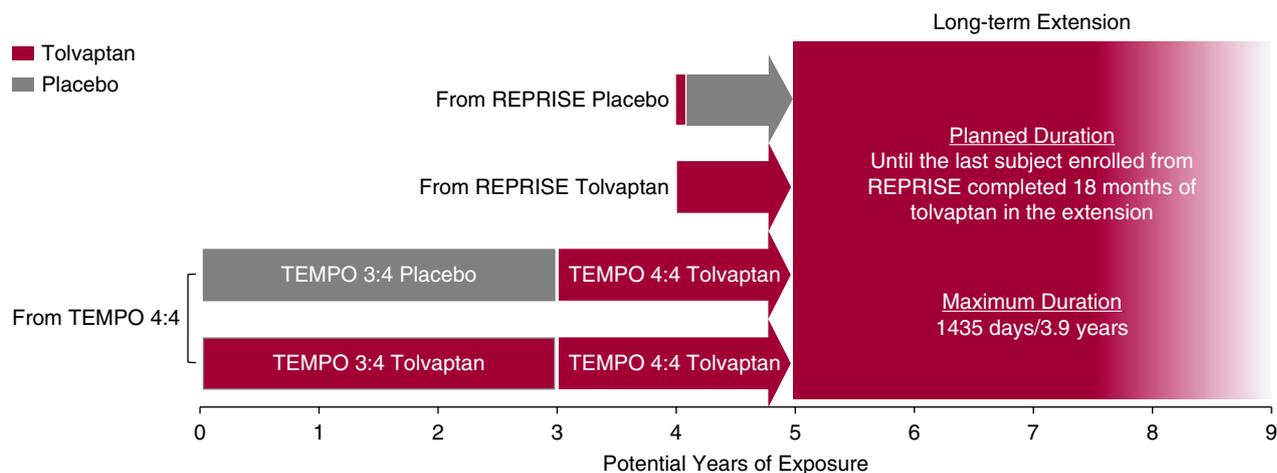


Figure 1. | Potential cumulative duration of tolvaptan exposure in subjects entering the long-term extension from the Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in Autosomal Dominant Polycystic Kidney Disease (REPRISE) and the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) 4:4 trials. All subjects in REPRISE had a brief (5-week) tolvaptan run-in period at the start of that study, and those randomized to the REPRISE placebo arm received placebo for 12 months and reinitiated tolvaptan in the long-term extension. Subjects from the tolvaptan arm of REPRISE had approximately 13 months of previous exposure, and those entering from TEMPO 3:4 (tolvaptan arm)/TEMPO 4:4 had up to 5 years of previous exposure.

“unlikely.” Another event (subject 7 in Table 4) was reported under the MedDRA preferred term “drug-induced liver injury.” Previously (trial day 247), the subject had experienced elevated ALT (more than four times the upper limit of normal) and elevated AST (more than three times the upper limit of normal) while taking tolvaptan 60/30 mg/d. No corrective treatments were administered,

but tolvaptan was interrupted on day 248. The event resolved on day 283, and on day 289, the subject was restarted on tolvaptan at 30/15 mg/d. On trial day 540, the subject experienced ALT more than two times the upper limit of normal, which was reported as “drug-induced liver injury,” and discontinued tolvaptan. The event resolved 26 days later. Bilirubin levels were normal for this subject

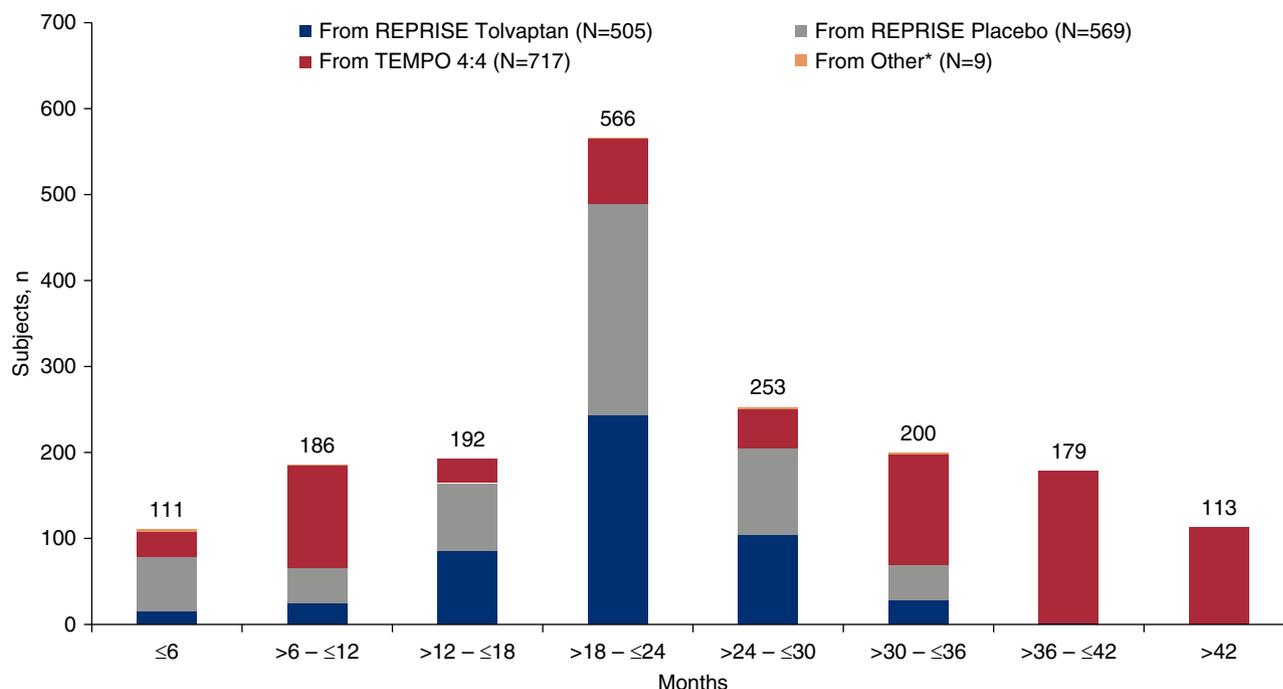


Figure 2. | Exposure to tolvaptan during the extension trial by previous trial participation. *Entered the long-term extension directly from TEMPO 3:4 or NOCTURNE (n=9; four from TEMPO 3:4 tolvaptan, two from NOCTURNE tolvaptan, and three from TEMPO 3:4 placebo).

Table 2. Overview of adverse events during tolvaptan treatment

Subjects and Adverse Events	Prior Trial Participation			Total, n=1800, n (%) ^a
	From Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in Autosomal Dominant Polycystic Kidney Disease Tolvaptan, n=505, n (%)	From Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in Autosomal Dominant Polycystic Kidney Disease Placebo, n=569, n (%)	From Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes 4:4 Tolvaptan, n=717, n (%)	
Subjects with AEs	473 (94)	531 (93)	643 (90)	1656 (92)
AEs	3567	4313	3963	11,932
Subjects with treatment-emergent AEs	473 (94)	531 (93)	640 (89)	1653 (92)
Treatment-emergent AEs	2965	3678	3297	10,019
Subjects with serious treatment-emergent AEs ^b	87 (17)	96 (17)	103 (14)	289 (16)
Subjects with severe treatment-emergent AEs ^c	74 (15)	78 (14)	83 (12)	238 (13)
Subjects with treatment-emergent AEs both serious and severe	43 (9)	40 (7)	44 (6)	128 (7)
Subjects discontinued trial drug due to AEs	33 (7)	65 (11)	38 (5)	137 (8)
Deaths ^d	1 (0.2)	5 (0.9)	3 (0.4)	9 (0.5)

AE, adverse event.
^aThe table has no column for subjects who entered the extension directly from the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) 3:4 or NOCTURNE trial due to the small number of subjects (n=9; four from TEMPO 3:4 tolvaptan, two from NOCTURNE tolvaptan, and three from TEMPO 3:4 placebo) from those trials. Data from these subjects are included in the total column.
^bSerious AEs were defined as those that resulted in any of the following outcomes: death; life-threatening risk in the opinion of the investigator; persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; requires inpatient hospitalization or prolongs hospitalization; congenital anomaly/birth defect; or other medically significant events that, on the basis of appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention.
^cAEs were graded as severe in cases resulting in an inability to work or perform normal daily activity.
^dCauses were tuberculosis in a subject from the Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in Autosomal Dominant Polycystic Kidney Disease (REPRISE) tolvaptan trial; aortic dissection/cardiogenic shock, CKD/septic shock, meningeal metastases, acute respiratory distress syndrome, and sudden death in subjects from REPRISE placebo; and cardiac arrest, subarachnoid hemorrhage, and ruptured cerebral aneurysm in subjects from TEMPO 4:4.

throughout the trial. The investigator considered the event to be related to tolvaptan, and HAC adjudicated the relationship with tolvaptan as “possible.”

Laboratory Values and Adjudication Results. The number of subjects with ALT three or more times the upper limit of normal among subjects with greater than or equal to one postbaseline measurement was 29 of 1792 (1.6%), and that for AST three or more times the upper limit of normal was 12 of 340 (3.5%). Frequencies of specific levels of ALT/AST elevation, obtained from laboratory testing independently of investigator AE reporting, are shown in Figure 4, with further description of elevations ten or more times the upper limit of normal in Supplemental Table 6. No subject met Hy Law criteria during the study.

A total of 53 cases of liver enzyme elevations met trigger criteria for HAC adjudication, occurring a mean of 316 days

(SD=285) after the first dose of tolvaptan in the extension. Adjudication results (probability of relationship with study drug) were “definite” (>95%), zero; “highly likely” (75%–95%), zero; “probable” (50%–74%), two; “possible” (25%–49%), 24; “unlikely” (<25%), 23; and “insufficient data,” four.

Five subjects had ALT or AST elevations more than three times the upper limit of normal at >18 months of tolvaptan therapy. One case with elevations in both ALT (4.7 times the upper limit of normal) and AST (3.1 times the upper limit of normal) occurred at month 21; the subject discontinued tolvaptan, and the elevation resolved 11 days later. The relationship with tolvaptan was adjudicated as “unlikely.” Another subject (subject 10 in Table 4) had ALT 3.0 times the upper limit of normal and AST 2.4 times the upper limit of normal on trial day 460 (month 15) and discontinued tolvaptan on day 467, after which the event

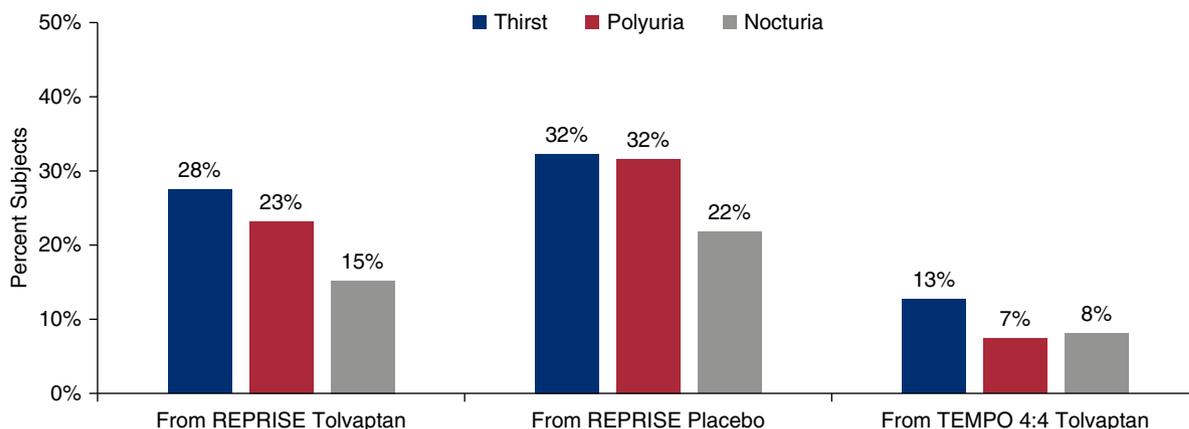


Figure 3. | Frequencies of common aquaretic adverse events by prior trial participation.

resolved by day 479. She did not resume tolvaptan. On day 536 (month 18), the subject had ALT 3.1 times the upper limit of normal and AST 2.9 times the upper limit of normal; she was diagnosed with nonalcoholic fatty liver disease. Her ALT level was elevated at day 628 (month 21) and had not normalized by the last trial follow-up visit on day 676 (month 22; ALT 3.3 times the upper limit of normal). The relationship with tolvaptan was adjudicated as “possible.” A case adjudicated as “unlikely” occurred at month 27 with elevated ALT (4.5 times the upper limit of normal)/AST (9.4 times the upper limit of normal), resulting in tolvaptan discontinuation and normalization of transaminases 55 days later. Two cases, both of which were in the range more than three to five times the upper limit of normal and adjudicated as “unlikely,” occurred at month 36. The first subject discontinued tolvaptan, and the event resolved 254 days later. The second subject, who had an underlying history of partial hepatectomy, hepatomegaly,

hepatic cysts, positive hepatitis A, and positive hepatitis B surface antibody, discontinued tolvaptan. The event did not resolve.

Deaths

Overall, nine subjects died (five from the REPRISE placebo group, one from the REPRISE tolvaptan group, and three from TEMPO 4:4) (Table 2). None of the deaths were considered related to study drug.

Discussion

In this multicenter, open-label extension study to evaluate the long-term safety of tolvaptan in subjects with ADPKD, tolvaptan was generally safe and well tolerated when administered twice daily in a split dose (*e.g.*, 45/15, 60/30, and 90/30 mg). Tolvaptan exposure was extensive, with 1311 subjects having >18 months of tolvaptan

Table 3. Hepatic enzyme elevations by prior trial participation on the basis of investigator adverse event reporting, Medical Dictionary for Regulatory Activities preferred term

Hepatic Enzyme Elevations	From Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in Autosomal Dominant Polycystic Kidney Disease Tolvaptan, n=505, n (%)	From Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in Autosomal Dominant Polycystic Kidney Disease Placebo, n=569, n (%)	From Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes 4:4 Tolvaptan, n=717, n (%)	Total, n=1800, n (%) ^a	Median Time to Elevation All Subjects, d (Interquartile Range)
ALT increased	10 (2.0)	23 (4.0)	17 (2.4)	51 (2.8)	245 (127–460)
Led to discontinuation	1 (0.2)	4 (0.7)	3 (0.4)	8 (0.4)	
AST increased	3 (0.6)	4 (0.7)	3 (0.4)	10 (0.6)	251 (129–460)
Led to discontinuation	0 (0.0)	1 (0.2)	1 (0.1)	2 (0.1)	
GGT increased	9 (1.8)	8 (1.4)	2 (0.3)	19 (1.1)	391 (116–653)
Led to discontinuation	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ -glutamyltransferase.

^aThe table has no column for subjects who entered the extension directly from the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes 3:4 or NOCTURNE trials due to the small number of subjects (n=9) from those trials. Data from these subjects were included in the total column and the calculation of median time to elevation.

Table 4. Investigator-reported treatment-emergent adverse events under the “hepatic failure, fibrosis and cirrhosis, and other liver-damage-related conditions” standardized Medical Dictionary for Regulatory Activities query by Medical Dictionary for Regulatory Activities preferred term

Subject	Preferred Term	Prior Treatment Subgroup	Serious (Yes/No), Relatedness to Study Drug per Investigator	Adjudicated Yes/No	Relatedness to Study Drug per Hepatic Adjudication Committee	Action Regarding Study Drug	Outcome
1	Ascites	REPRISE	No, not related	No		Continued	Not recovered/ not resolved
	Ascites	TOL	No, not related	No		Continued	Not recovered/ not resolved
2	Ascites ^a	REPRISE	Yes, not related	Yes	Unlikely	Continued	Recovered/ resolved
	Ascites ^a	TOL	Yes, not related	Yes	Unlikely	Discontinued	Recovered/ resolved
3	Ascites	REPRISE	No, not related	Yes	Unlikely	Continued	Not recovered/ not resolved
	Portal hypertension	TOL	No, not related	No		Continued	Not recovered/ not resolved
4	Ascites	REPRISE	Yes, not related	Yes	Unlikely	Discontinued	Recovered/ resolved
	Portal hypertensive gastropathy	PLC	Yes, not related	Yes	Unlikely	Discontinued	Recovered/ resolved
5	Portal hypertensive gastropathy	TEMPO	No, not related	No		Continued	Recovered/ resolved
	Varices esophageal	4:4 TOL	No, not related	No		Continued	Not recovered/ not resolved
	Portal hypertension	TEMPO	No, not related	No		Continued	Not recovered/ not resolved
7	Drug-induced liver injury	REPRISE	No, related	Yes	Possible	Discontinued	Recovered/ resolved
	Hepatic steatosis	TOL	No, not related	No		Continued	Not recovered/ not resolved
8	Hepatic steatosis	TEMPO	No, not related	No		Continued	Not recovered/ not resolved
	Liver injury	4:4 TOL	No, not related	Yes	Unlikely	Discontinued	Recovered/ resolved
9	Liver injury	TEMPO	No, not related	Yes	Unlikely	Discontinued	Recovered/ resolved
	Nonalcoholic fatty liver	4:4 TOL	No, not related	Yes	Possible	Not applicable ^b	Not recovered/ not resolved
	Nonalcoholic fatty liver	TEMPO	No, not related	Yes	Possible	Not applicable ^b	Not recovered/ not resolved

REPRISE, Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in Autosomal Dominant Polycystic Kidney Disease; TOL, tolvaptan; PLC, placebo; TEMPO, Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes.

^aTwo cases were recorded in the clinical database because the event severity changed from moderate to severe. The Hepatic Adjudication Committee adjudicated the two events together.

^bDrug had been withdrawn prior to the event of nonalcoholic fatty liver, due to an earlier event of alanine aminotransferase increasing.

exposure during the extension itself. Cumulative tolvaptan exposure in the extension and preceding trials was up to 11 years. The average dose of approximately 96 mg/d in this trial was consistent with TEMPO 3:4 and REPRISE, in which the majority of subjects tolerated doses 90–120 mg/d (5,6). Results in this study were comparable with the known safety profile from previous tolvaptan clinical trials (5,6).

Given the potential for serious liver-related events associated with tolvaptan use in ADPKD, hepatic AEs were of particular interest. Fifty-one subjects (2.8%) experienced ALT increased and ten (0.6%) experienced AST increased as MedDRA preferred terms reported by the investigators, of whom eight subjects and two subjects, respectively, discontinued treatment. The percentage of subjects with ALT three or more times the upper limit of normal by laboratory testing was 1.6%, and the percentage of subjects with AST three or more times the upper limit of normal was 3.5%. Among subjects entering the extension from the REPRISE placebo arm, AST elevations three or

more times the upper limit of normal were more frequent (6.9%), but the reason for this is unknown. Fifty-three subjects met adjudication criteria, with the likelihood as “probable” in two subjects and “possible” in 24. A total of ten of 1800 (0.6%) subjects experienced treatment-emergent AEs considered under the “hepatic failure, fibrosis and cirrhosis, and other liver-damage-related conditions” standardized MedDRA query; only one was thought by the investigator to be related to tolvaptan. No Hy Law cases were reported.

In this study, previous exposure to tolvaptan varied largely on the basis of earlier trial enrollment. Subjects who enrolled in REPRISE had to be tolvaptan naïve, so placebo-treated subjects in REPRISE had limited (5 weeks) exposure to tolvaptan, whereas tolvaptan-treated subjects in REPRISE could have approximately 13 months of exposure before enrollment in the extension. Subjects enrolling from TEMPO 4:4 could have had up to 5 years of tolvaptan treatment. Transaminase elevations three or more times the

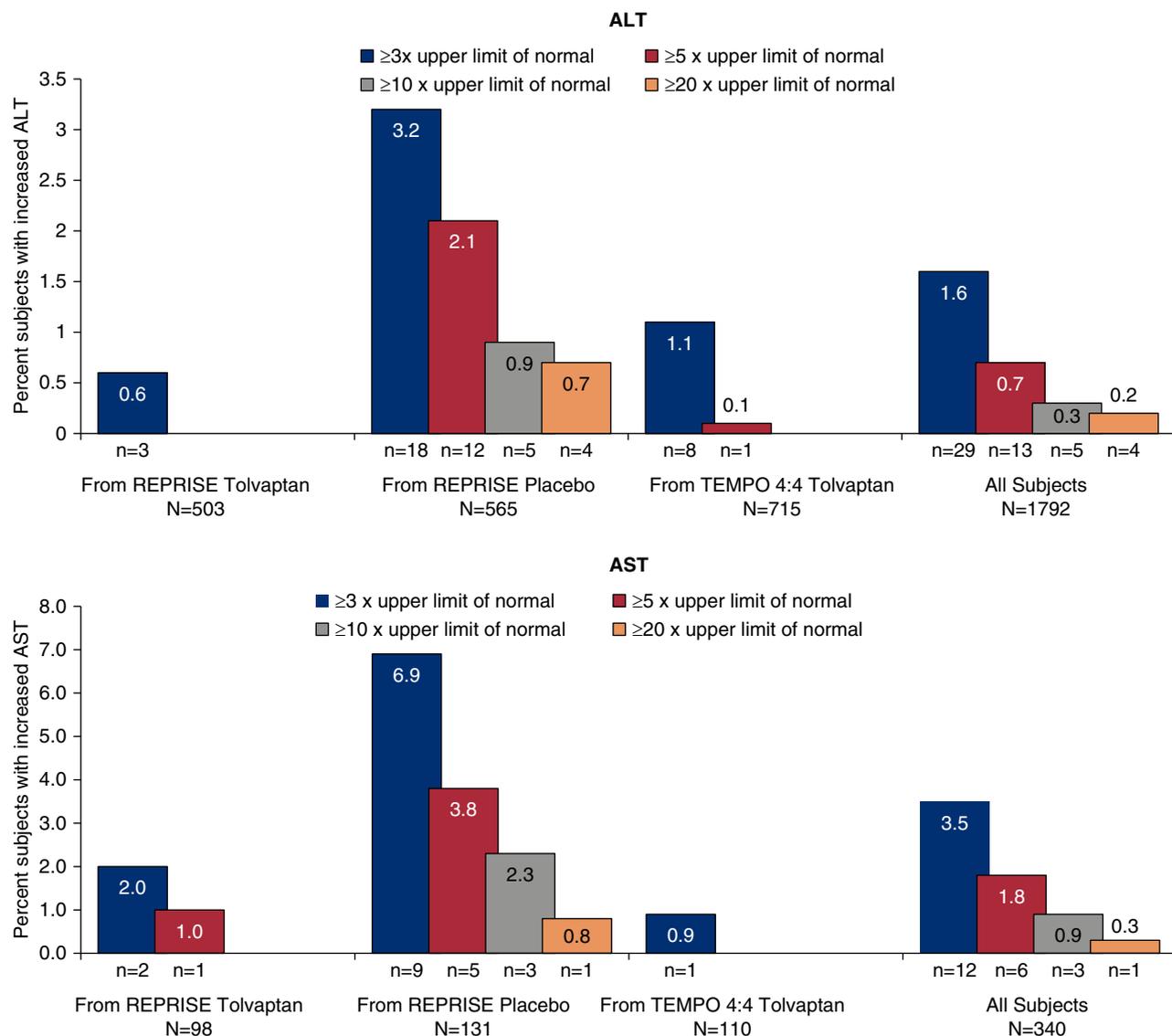


Figure 4. | Patients with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations by laboratory value threshold in the long-term extension, shown by prior trial participation. Denominators are the numbers of subjects with greater than or equal to one postbaseline measurement for the given laboratory test. Data from nine subjects entering from other trials are not shown. AST measurements were not required by protocol at the monthly visits, and as a result, the percentage of AST elevations might have been affected by selection bias.

upper limit of normal were notably less frequent in subjects entering from REPRISE tolvaptan and TEMPO 4:4 than in those entering from REPRISE placebo, which is consistent with a window of susceptibility, as previously described, within the first 18 months of tolvaptan therapy (8).

Similarly, aquaretic treatment-emergent AEs (*i.e.*, thirst, polyuria, and nocturia) were more frequent among subjects who had been receiving placebo in REPRISE (488 of 569; 86%) than in tolvaptan-treated subjects from REPRISE (333 of 505; 66%) and TEMPO 4:4 (202 of 717; 28%). Studies in patients without ADPKD have indicated that the aquaretic AEs of tolvaptan may diminish over time; alternatively, patients may get accustomed to them and may cease to report them as AEs (15,16).

Risk of skin malignancy may be elevated in ADPKD, particularly in patients with worsening kidney function (17). Skin malignant tumors (0.9%) and skin tumors of

unspecified malignancy (0.2%) occurred infrequently during this long-term extension. In TEMPO 3:4, AEs within the glaucoma standardized MedDRA query were seen in 20 of 961 (2%) patients receiving tolvaptan compared with five of 483 (1.0%) of those receiving placebo, whereas no glaucoma-related events were seen in REPRISE (data on file). Few subjects in this long-term extension (four of 1800; 0.2%) experienced glaucoma-related treatment-emergent AEs.

Limitations include the open-label trial design, with all subjects receiving tolvaptan. As there was no comparator arm, safety comparisons between tolvaptan and placebo over the long term cannot be assessed. At study sites outside the United Kingdom, subjects entering from studies other than REPRISE were permitted to transition to commercially available tolvaptan before completing 18 months of the extension, limiting the duration of study follow-up during the extension to <18 months for 11% of

subjects. Data on AEs in this study, including AKI and events related to liver injury, should be interpreted with caution, as the subjects consented to clinical trial participation and may not have experienced AEs at rates reflective of routine clinical practice.

In conclusion, safety results for tolvaptan in this study were consistent with the known safety profile on the basis of previous tolvaptan clinical trials. Monthly hepatic monitoring during the first 18 months of tolvaptan exposure and every 3 months thereafter enabled early detection of transaminase elevations and effective intervention (including drug interruption and discontinuation) during the period of greatest susceptibility to hepatic AEs. With this regimen, no new cases meeting Hy Law criteria were observed.

Disclosures

A.B. Chapman reports consultancy agreements with Janssen, Kadmon, Otsuka Pharmaceutical Development & Commercialization, Pfizer, Inc., Pfizer Pharmaceuticals, Reata, and Sanofi Pharmaceuticals; receiving research funding from the National Institutes of Health (NIH), Reata, and Sanofi Pharmaceuticals; receiving honoraria from Otsuka Pharmaceutical Development & Commercialization, Reata, and UpToDate; speakers bureau with Janssen and Otsuka Pharmaceutical Development & Commercialization; and serving on special emphasis and review panels for NIH/National Institute of Diabetes and Digestive and Kidney Diseases and Small Business Innovation Research. O. Devuyt reports consultancy agreements with Alnylam, Galapagos, Otsuka Pharmaceutical Development & Commercialization, and Sanofi Pharmaceuticals; receiving research funding from Otsuka Pharmaceutical Development & Commercialization and Roche; serving on the editorial boards for *CJASN*, *Kidney International*, *Nephrology Dialysis Transplantation*, *Orphanet Journal of Rare Diseases*, *Peritoneal Dialysis International*, and *Pfälters Archiv*; and serving on the steering committees for the Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in ADPKD (REPRISE) and Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) trials. A. Estilo reports employment with Otsuka Pharmaceutical Development & Commercialization. R.T. Gansevoort reports receiving several grants and consultancy fees from Galapagos, Ipsen, Ono Pharma, Otsuka Pharmaceutical Development & Commercialization, and Sanofi-Genzyme, all money was paid to the employing institution; consultancy agreements with AstraZeneca, Bayer, Galapagos, Otsuka Pharmaceutical Development & Commercialization, and Sanofi-Genzyme; receiving research funding from Bayer, Galapagos, Otsuka Pharmaceutical Development & Commercialization, and Sanofi-Genzyme; receiving honoraria from Bayer, Galapagos, Otsuka Pharmaceutical Development & Commercialization, and Sanofi-Genzyme; serving as a scientific advisor or member of *American Journal of Kidney Diseases*, *CJASN*, *Journal of Nephrology*, *Kidney360*, *Nephrology Dialysis Transplantation*, and *Nephron Clinical Practice*; and serving on the steering committees of the Developing Interventions to Halt Progression of ADPKD 1, REPRISE, STAGED-PKD, and TEMPO studies. M.E. Hoke reports employment with Otsuka Pharmaceutical Development & Commercialization, as well as serving as a member of the American Society of Nephrology and the National Kidney Foundation. J. Lee reports employment with Otsuka Pharmaceutical Development & Commercialization, as well as ownership interest in Apple Inc., Fidelity MSCI Energy Index ETF, and Wells Fargo & Co.

R.D. Perrone reports consultancy agreements with Goldfinch Bio, Otsuka Pharmaceutical Development & Commercialization, Palladiobio, Reata, Sanofi-Genzyme, and Vertex; receiving research funding from Kadmon, Otsuka Pharmaceutical Development & Commercialization, Reata, and Sanofi-Genzyme; receiving Department of Defense funding for the The Trial of Administration of Metformin to Tame PKD; receiving honoraria from Otsuka Pharmaceutical Development & Commercialization and Sanofi-Genzyme; serving as a scientific advisor or member of Otsuka Pharmaceutical Development & Commercialization, Sanofi-Genzyme, and UpToDate; other interests/relationships with UpToDate; and being a member of the steering committees for the REPRISE trial and the STAGED-PKD trial. O. Sergeyeva reports employment with Otsuka Pharmaceutical Development & Commercialization. V.E. Torres reports receiving grants from Blueprint Medicines, Mironid, Otsuka Pharmaceutical Development & Commercialization, Palladio Biosciences, and Sanofi-Genzyme, outside the submitted work, and receiving honoraria from UpToDate. All remaining authors have nothing to disclose.

Funding

This study was funded by Otsuka Pharmaceutical.

Acknowledgments

The authors thank Ms. Hui Li, Ms. Deborah Leung, Ms. Indra Agarwal, and Ms. Laurie Debuque (all Otsuka Pharmaceutical Development & Commercialization employees) for the support and expertise in development of the manuscript. Writing assistance, also funded by Otsuka Pharmaceutical Development & Commercialization, was provided by BioScience Communications, Inc. (New York).

Data Sharing Statement

To submit inquiries related to Otsuka Pharmaceutical Development & Commercialization clinical research or to request access to individual participant data (IPD) associated with any Otsuka Pharmaceutical Development & Commercialization clinical trial, please visit <https://clinical-trials.otsuka.com/>. For all approved IPD access requests, Otsuka Pharmaceutical Development & Commercialization will share anonymized IPD on a remotely accessible data sharing platform.

Supplemental Material

This article contains the following supplemental material online at <http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.10250620/-/DCSupplemental>.

Supplemental Material. List of principal investigators and study sites.

Supplemental Table 1. Incidence of treatment-emergent adverse events occurring in $\geq 2\%$ of subjects (safety sample).

Supplemental Table 2. Crosstrial comparison of treatment-emergent adverse events of skin malignancy and glaucoma over 12 months of tolvaptan exposure (long-term extension, REPRISE, TEMPO 4:4, and TEMPO 3:4 trials).

Supplemental Table 3. Serious treatment-emergent adverse events of AKI and kidney impairment.

Supplemental Table 4. Serious treatment-emergent adverse events of ESKD.

Supplemental Table 5. Overview of adverse events in the long-term extension by cumulative tolvaptan exposure (*i.e.*, exposure during prior trials and the long-term extension).

Supplemental Table 6. Subjects with elevations ten or more times the upper limit of normal in alanine aminotransferase or aspartate aminotransferase.

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Received: June 23, 2020 Accepted: October 29, 2020

Published online ahead of print. Publication date available at www.cjasn.org.

See related editorial, “Long-Term Safety of Tolvaptan in ADPKD: Where Do We Stand?” on pages 3–5.

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