

Pooled Data Analysis of the Long-Term Treatment Effects of Tolvaptan in ADPKD

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Introduction: In 1- and 3-year randomized trials, tolvaptan slowed kidney function decline in subjects with autosomal dominant polycystic kidney disease (ADPKD) at risk of rapid progression. The 3-year trial also evaluated effects on total kidney volume (TKV); slowing of TKV growth was demonstrated. Subjects were followed in open-label extension trials. To characterize longer-term effects of treatment, an analysis was conducted comparing tolvaptan-treated subjects with subjects from standard of care (SOC) ADPKD studies without tolvaptan.

Methods: This was a pooled, longitudinal analysis of data from 8 tolvaptan clinical trials and 5 studies without tolvaptan (natural history or SOC) in ADPKD. Data from subjects who participated in multiple studies were linked for longer follow-up. Outcomes were rates of change in estimated glomerular filtration rate (eGFR) and TKV over 5.5 years. To control for heterogeneity in disease characteristics between tolvaptan and SOC treatment groups, analysis populations matched for baseline demographic and disease characteristics were constructed.

Results: Matched analysis ($n = 1186$ in each treatment group) indicated that tolvaptan slowed annualized eGFR decline by 1.01 ml/min per 1.73 m² ($P < 0.001$) versus SOC over 5.5 years. An analysis conducted on the full, unmatched data set (tolvaptan: $n = 2928$; SOC: $n = 4189$) confirmed significant reduction in annual eGFR decline. Among subjects with TKV data, TKV was significantly reduced at years 1, 3, and 5 for tolvaptan versus SOC in both matched and full data sets.

Conclusion: Comparison of a pooled tolvaptan cohort to a pooled control cohort with ADPKD supports longer-term treatment effects of tolvaptan.

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KEYWORDS: autosomal dominant polycystic kidney disease (ADPKD); glomerular filtration rate; kidney function; longitudinal; tolvaptan; total kidney volume

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ADPKD is an inherited disorder in which the formation and expansion of fluid-filled cysts destroy adjacent renal parenchyma, leading to a gradual loss of kidney function and eventually end-stage kidney disease.¹ Mutations to the *PKD1* or *PKD2* genes cause ADPKD, but genetic determinants are complex, and the disease exhibits a highly variable interindividual rate of progression.¹ The disease typically progresses for decades before GFR starts to decline and chronic kidney disease (CKD) advances. Genetic studies estimate a median age for occurrence of end-stage kidney disease between 50 and 60 years of age in patients

with *PKD1* mutations and after age 70 years for those with *PKD2* mutations.²⁻⁴

Observation of outcomes in a clinical trial setting for ADPKD is challenging because of its lifelong, progressive nature and potentially long duration of time to outcomes of interest (e.g., kidney function decline, cardiovascular events, and mortality). In addition, it would be impracticable and unethical to conduct placebo-controlled trials over a span of decades to evaluate the effects of potential ADPKD therapies on renal outcomes. Randomized, controlled, phase 3 clinical trials of tolvaptan, the only currently approved treatment for ADPKD, assessed treatment effect by comparing eGFR decline between tolvaptan and placebo groups. Efficacy was evaluated over 3 years in the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes trial (TEMPO 3:4; NCT00428948) and over 1 year in the Replicating Evidence of Preserved Renal

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Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD trial (REPRISE; NCT02160145).^{5,6} The trials were enriched for subjects at risk of rapidly progressing disease to allow for detection of treatment effects during the trial. Eligibility criteria included variables such as age, TKV, baseline level of kidney function, and/or historical evidence of rapid GFR decline. TEMPO 3:4 ($N = 1445$) demonstrated the efficacy of tolvaptan in slowing deterioration in eGFR and rate of TKV growth in a relatively young study population (18–50 years) with large kidneys for age (TKV >750 ml) and relatively preserved kidney function (creatinine clearance ≥ 60 ml/min, mostly CKD stages 1–3).

The shorter REPRISE trial (1 year) was conducted in patients at later stages of CKD. REPRISE ($N = 1370$) demonstrated tolvaptan efficacy on kidney function decline in an older population (18–65 years) with more advanced disease (late CKD stage 2 to early CKD stage 4). Loss of kidney function in ADPKD accelerates over time, with patients advancing to later CKD stages more rapidly than earlier stages.⁷ Accordingly, treatment effects are more readily detectable in later-stage CKD patients.⁸ The tolvaptan pivotal trial data were supported by an additional 2-year follow-up in the open-label TEMPO 4:4 trial (NCT01214421), the first extension trial for subjects enrolled in TEMPO 3:4. Tolvaptan exhibited persistent effects in slowing eGFR decline and TKV growth.⁹ Given that all subjects in the extension received tolvaptan, no comparison was possible beyond early versus delayed tolvaptan treatment, that is, between subjects who were randomized to tolvaptan in TEMPO 3:4 and continued on tolvaptan in the extension and subjects who were randomized to placebo in TEMPO 3:4 and initiated tolvaptan in the extension. A phase 3b, long-term, open-label extension trial (156-13-211; NCT02251275) enrolled subjects from TEMPO 4:4, REPRISE, and other trials, but evaluated safety only.¹⁰

The use of control data from natural history studies or other trials where tolvaptan was not allowed provides a way to approximate tolvaptan treatment effect over the long term. In 2011, Higashihara *et al.*¹¹ reported 3 years of data on 51 tolvaptan-treated subjects who continued into extension trials from early phase tolvaptan trials, using for comparison matched subjects who participated in the Consortium of Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP; NCT01039987) cohort and the Modification of Diet in Renal Disease study.^{11–13} Significant effects on rates of TKV increase and eGFR decline were shown. More recently, Edwards *et al.*¹⁴ evaluated data from 108 subjects who had participated in tolvaptan clinical trials and open-label extensions at the Mayo Clinic.

Follow-up ranged from 1.1 to 11.2 years. Subjects were matched 1:2 to historical controls from the CRISP cohort and the HALT Progression of Polycystic Kidney Disease (HALT-PKD) Study B (NCT01885559)¹⁵ and compared for rate of eGFR decline, which was significantly slower with tolvaptan. The Mayo Clinic study provided a long duration of follow-up for tolvaptan-treated patients with ADPKD, with the limitation that relatively few subjects ($n = 36$) from this single-center cohort had follow-up for >5 years from baseline.¹⁴ Because large patient samples are needed for robust statistical analyses of treatment effects over time, a need still exists for large-scale comparisons with historical cohorts. Since these earlier studies, more data from tolvaptan-treated clinical trial subjects have become available, and the duration of follow-up has increased, with data available for many subjects across multiple trials. Similarly, long-term follow-up data from non-tolvaptan trials have accumulated in the databases of the National Institute of Diabetes and Digestive and Kidney Diseases. Accordingly, we conducted an analysis of pooled tolvaptan clinical trial data and control data from natural history studies and other trials to evaluate the longer-term treatment effects of tolvaptan versus SOC alone on eGFR and TKV.

METHODS

Design

This was a pooled data study in subjects with ADPKD that retrospectively compared tolvaptan with SOC. The primary objective was to assess the longer-term effects of tolvaptan on kidney function (measured by the rate of decline in eGFR) and kidney volume (TKV). Secondary objectives were to identify disease-associated factors that predict progression (as measured by eGFR and TKV) and assess the impact of tolvaptan treatment gaps on disease progression.

Analysis Population

This analysis included subjects with ADPKD with a broad range of age, kidney function (CKD1–CKD4), and TKV who were treated with tolvaptan or SOC. The tolvaptan cohort consisted of subjects who received at least 1 dose of tolvaptan in Otsuka-sponsored trials: TEMPO 2:4 (NCT00413777),¹¹ TEMPO 3:4,⁵ TEMPO 4:4,⁹ phase 1 trial 156-06-260, phase 2 trial 156-09-284 (NCT01336972),¹⁶ NOCTURNE (NCT01451827),¹⁷ and REPRISE.⁶ Some of these subjects continued to receive tolvaptan in the long-term, open-label, phase 3 safety study, which was also included in the analysis.¹⁰ The SOC was drawn in part from studies sponsored by the National Institutes of Health: CRISP, a long-term natural history study of ADPKD, and HALT-PKD studies A (NCT00283686) and B, which randomized subjects to

various antihypertensive regimens involving blockade of the renin-angiotensin-aldosterone system.^{15,18,19} The other SOC subjects were included from Otsuka-sponsored studies (the observational study OVERTURE [NCT01430494]²⁰ and subjects randomized to placebo in TEMPO 3:4 and NOCTURNE) (Figure 1). A brief description of each study with key eligibility criteria is shown for the Otsuka studies in Supplementary Table S1 and for CRISP and HALT-PKD in Supplementary Table S2. The data were obtained from Otsuka and the National Institutes of Health's National Institute of Diabetes and Digestive and Kidney Diseases Central Database Repository.

For subjects who participated in multiple studies, data were linked to achieve as longitudinal information as possible. Data collected in TEMPO 4:4, the long-term safety extension trial, and OVERTURE were linked, when possible, to the same subjects who participated in a prior tolvaptan trial. Data from HALT-PKD for subjects who previously participated in CRISP ($n = 61$ of 1044 [5.8%]) were linked in a similar manner. Unique subjects were identified, and new subject identification numbers were assigned in this analysis.

Follow-up started after the baseline date. For subjects in the tolvaptan cohort, the baseline date for eGFR and TKV outcomes was the date of their first dose of tolvaptan in the database. Subjects randomized to placebo in REPRIS received tolvaptan for 5 weeks before randomization and were therefore included in the tolvaptan group along with the subjects randomized to tolvaptan. For subjects in the SOC group, the

baseline date was the date of their first dose of placebo, the visit date for the start of investigational treatment in HALT-PKD, the enrollment date in OVERTURE, or baseline visit date in CRISP I. Subjects in the tolvaptan group could have had up to 2 treatment gaps between studies.

Outcomes

The primary outcomes were changes in eGFR and TKV. The eGFR was recalculated for this analysis based on serum creatinine, age, sex, and race using equations from the Chronic Kidney Disease Epidemiology Collaboration.²¹ TKV was calculated using the magnetic resonance imaging measurements reported in the studies.^{5,9,11,17,18,22,23}

Source data sets and case report forms were reviewed for other common variables of interest. Baseline covariates generally available and comparable from the source studies included the following: demographics, age at ADPKD diagnosis, CKD stage, eGFR, blood pressure (BP), age at onset of hypertension, history of complications (nephrolithiasis, hematuria, urinary tract infection [UTI]), TKV, and estimated TKV growth rate (calculated based on baseline TKV and age). Pain could not be included because of the lack of standardized assessment of pain across studies in ADPKD.²⁴

Statistical Analyses

No formal sample size calculation was performed for this study. The study size was restricted to individuals

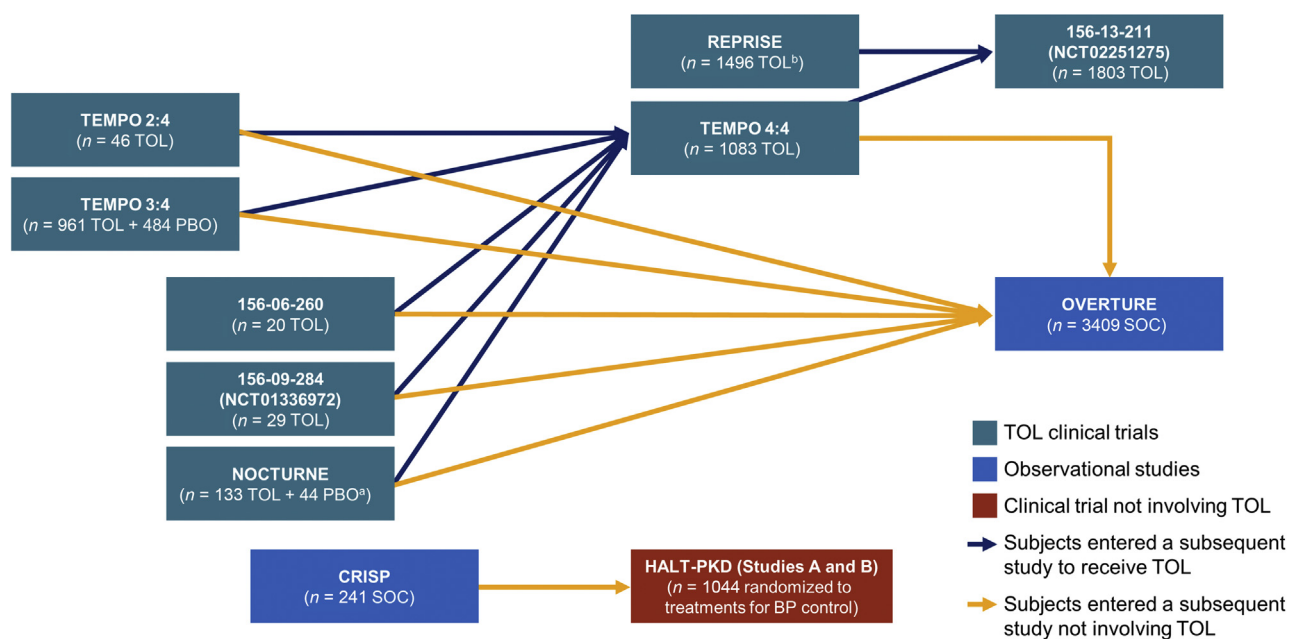


Figure 1. Source studies for the pooled analysis. ^aIncludes 1 subject who was randomized to TOL but did not receive TOL. ^bSubjects randomized to PBO in REPRIS received TOL for 5 wks before randomization and were therefore included in the TOL group. BP, blood pressure; PBO, placebo; SOC, standard of care; TOL, tolvaptan.

who were enrolled in the designated studies and who met the criteria for specific exploratory analyses.

To account for confounders, separate matched analysis sets were generated to assess treatment effects on eGFR and TKV. For the eGFR analysis, subjects randomized to tolvaptan in TEMPO 3:4 and REPRISE were matched at a 1:1 ratio to subjects on SOC from CRISP, HALT-PKD, and OVERTURE based on CKD stage, sex, age (± 2 years), baseline eGFR (± 5 ml/min per 1.73 m²), and baseline TKV (± 150 ml, if available). Eligibility and matching methods are specified in [Supplementary Table S3](#). Mixed models were used with fixed effects of treatment, time (as a continuous variable), treatment-by-time interaction, baseline eGFR, and squared time. The squared time term was added to account for the nonlinear relationship between eGFR and time.

For the matched TKV analyses, 2 different matched analysis sets were generated based on various eligibility and matching criteria ([Supplementary Table S4](#)). The tolvaptan cohorts included only subjects who were randomized to tolvaptan in TEMPO 3:4, as TKV was not assessed in REPRISE. The SOC cohort included only subjects enrolled in the 2 long-term (>5-year) studies with TKV assessment (CRISP and HALT-PKD Study A). The mixed models included treatment, time (as a continuous variable), treatment-by-time interaction, and the baseline TKV value (in logarithm) as fixed effects. The log transformation was applied to TKV.

Piecewise-mixed models were applied to the full analysis set (FAS) as an additional analysis to assess the treatment effect of tolvaptan on the rate of eGFR decline and TKV, identify factors that predict disease progression, and assess the impact of the tolvaptan treatment gap. All models included subject-specific intercept and slope (for time) as random effects with an unstructured variance-covariance matrix. Analyses were conducted using data up to 5.5 years. Because fewer subjects had data after 5.5 years, data after 5.5 years were excluded to reduce potential bias caused by informative missingness.

For the analysis of rate of eGFR decline, the estimates were adjusted for baseline eGFR, age, sex, race (White vs. other), height, systolic BP, diastolic BP, history of hematuria, history of UTI, history of nephrolithiasis, and time in the tolvaptan gap period. Baseline TKV was not adjusted for because it was not available in all included studies (e.g., HALT-PKD Study B and REPRISE). Because of the acute hemodynamic effect of tolvaptan (rapid reduction in eGFR after treatment initiation, which reverses after discontinuation),^{5,6,16,23,25} the following data in the tolvaptan cohort were excluded from analysis: observations made <7 days after tolvaptan initiation,

during the tolvaptan treatment gap, and after tolvaptan treatment termination. Additional details on the model can be found in the [Supplementary Methods](#).

For the analysis of treatment effect on TKV, the baseline variables TKV, CKD stage, age, sex, race (White vs. other), weight, body mass index (BMI), systolic BP, diastolic BP, history of hematuria, history of UTI, and history of nephrolithiasis were included as regression covariates (fixed effects) in the piecewise-mixed model. An immediate change at the beginning of each tolvaptan treatment period was built into the model to reflect the acute antisecretory effect of tolvaptan, whereby an initial rapid decrease in TKV growth occurs because of suppression of cyst fluid production.²⁵ Off-drug observations were included in the analysis to estimate the slope while patients were off treatment. The log transformation was applied to TKV (for additional details, see the [Supplementary Methods](#)).

RESULTS

Analysis Populations

A total of 7117 unique subjects (tolvaptan: 2928; without tolvaptan: 4189) comprised the FAS ([Figure 2](#)). Baseline demographics and disease characteristics in the FAS are summarized in [Table 1](#). The 2 cohorts had similar age and sex distribution, whereas compared with the SOC group, the tolvaptan group had a lower baseline mean eGFR (60 vs. 70 ml/min per 1.73 m²), more subjects in CKD stage 3 or worse (58.1% vs. 40.9%), larger TKV and height-adjusted TKV, and more frequent histories of signs of rapid disease progression (e.g., nephrolithiasis, hematuria, UTI). The matched eGFR analysis set, individually matched on key prognostic factors (age, sex, eGFR, CKD stage, and, if available, TKV) included 1186 subjects randomized to tolvaptan in TEMPO 3:4 and REPRISE matched to 1186 subjects from CRISP, HALT-PKD, and OVERTURE ([Table 1](#); [Supplementary Figure S1](#)). The matched eGFR analysis set was more comparable in terms of baseline disease characteristics between treatment groups and was different from the FAS. More than half of the matched subjects in each of the tolvaptan and SOC groups were in stage 3 or 4 CKD (stage 1, 16.3%; stage 2, 25.5%; stage 3, 47.4%; and stage 4, 10.9%), and both groups had baseline eGFR of 60 ml/min per 1.73 m² and similar baseline TKV (1468–1478 ml).

The subset of FAS subjects with TKV assessments ($n = 4917$; [Table 2](#); [Supplementary Figure S2](#)) was substantially smaller than the overall FAS because REPRISE and HALT-PKD Study B did not collect TKV data. The tolvaptan group had a higher mean baseline

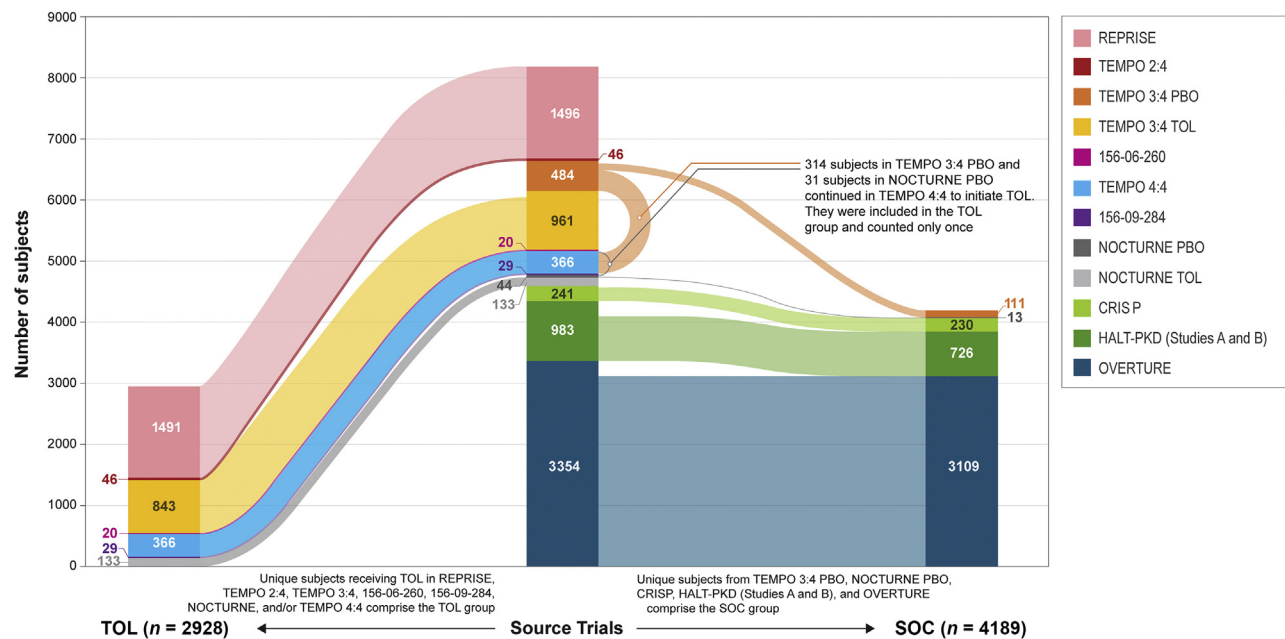


Figure 2. Subjects included in the full analysis set. Note: Some subjects were excluded from the full analysis set (total $n = 695$). Subjects enrolled in Japan (TEMPO 3:4 TOL, $n = 118$; TEMPO 3:4 PBO, $n = 59$; OVERTURE, $n = 245$) were excluded because previous trials showed a different response to TOL for Japanese subjects, and the reason was not clear. Subjects who received TOL in CRISP ($n = 11$) were also excluded, as were subjects randomized to low blood pressure control in HALT-PKD ($n = 257$), because low blood pressure control is not a standard practice. Finally, subjects were excluded who entered the TOL titration period in REPRIS but did not receive TOL ($n = 5$). HALT-PKD, HALT Progression of Polycystic Kidney Disease; PBO, placebo; SOC, standard of care; TOL, tolvaptan.

TKV (1817 ml vs. 1627 ml), a higher percentage with height-adjusted TKV ≥ 600 ml/m (78.9% vs. 60.0%), and a higher percentage of class 1D to 1E (53.9% vs. 33.0%) based on Mayo imaging classification.²⁶ The matched TKV analyses generated 102 matched subject pairs for set A and 182 for set B (Table 2). Different from the overall study population, subject baseline characteristics were more comparable on the key matched prognostic factors of baseline CKD stage, eGFR, and TKV.

Tolvaptan Exposure (Full Analysis Set)

The mean duration of tolvaptan treatment in the FAS was 3.7 (SD 3.0) years (Supplementary Table S5). The mean “compliance” rate (percentage of on-treatment days) was 87.6% (SD 18.8%), and 80.2% of subjects had a compliance rate of at least 70%. Off-treatment days were primarily attributable to the gap between the tolvaptan titration/run-in period for subjects randomized to placebo in REPRIS and resumption of tolvaptan at the start of the long-term safety trial. Most subjects in the tolvaptan group (97.7%) were tolvaptan naive at baseline. Furthermore, 69% of subjects received tolvaptan in multiple trials (or the extension within TEMPO 2:4), with a median total gap duration of 0.15 year (55 days). Figure 3a and b present a random sample of individual subject profiles for tolvaptan treatment duration and representative gaps in the treatment. The largest gaps appeared between trial

156-06-260 and TEMPO 4:4 ($n = 10$; mean: 865 days, min 324 days to max 1463 days).

Treatment Differences in Annual eGFR Decline and TKV Growth (Matched Sets)

In the matched eGFR analysis set over 5.5 years, the difference in the adjusted annual rate of eGFR decline (slope of eGFR with tolvaptan minus slope of eGFR with SOC) was 1.01 ml/min per 1.73 m² (95% CI 0.75–1.27) indicating a significant ($P < 0.001$) slowing in the rate of decline with tolvaptan of approximately 25% per year versus SOC (Figure 4). A confirmatory analysis that included only the linear time term yielded a result (difference of 1.05 ml/min per 1.73 m²; 95% CI 0.79–1.32; $P < 0.001$) similar to the result from the model that incorporated time squared. In the matched TKV analysis sets, estimated TKV at years 1, 3, and 5 was significantly smaller with tolvaptan than SOC (Table 3). The modeled time-by-treatment interaction for TKV during the follow-up period of 1 to 5.5 years was not statistically significant; however, it is likely because TKV diverged rapidly between tolvaptan and SOC in the first year and the rate of divergence decreased thereafter.

Treatment Differences in Annual eGFR Decline and TKV Growth (Full Analysis Set)

In the additional analyses conducted in the full analysis set, the difference in the adjusted annual rate of eGFR

Table 1. Baseline characteristics of subjects in the full analysis set and matched eGFR analysis set

| Characteristic | Full analysis set | | Matched eGFR analysis set | |
|--|----------------------|-----------------------------|---------------------------|-----------------------------|
| | Tolvaptan (n = 2928) | Standard of care (n = 4189) | Tolvaptan (n = 1186) | Standard of care (n = 1186) |
| Age in yr, mean (SD) | 43.6 (8.9) | 44.1 (12.7) | 44.2 (8.5) | 44.2 (8.6) |
| Female, n (%) | 1448 (49.5) | 2295 (54.8) | 604 (50.9) | 604 (50.9) |
| White, n (%) | 2649 (90.5) | 3376 (80.7) | 1072 (90.4) | 977 (82.6) |
| Height in m, mean (SD) | 1.74 (0.10) | 1.72 (0.10) | 1.74 (0.10) | 1.73 (0.10) |
| Weight in kg, mean (SD) | 82.5 (18.8) | 80.1 (18.6) | 82.4 (18.8) | 82.7 (18.8) |
| Body mass index, kg/m ² , mean (SD) | 27.2 (5.4) | 27.0 (5.5) | 27.2 (5.5) | 27.5 (5.7) |
| Age at ADPKD diagnosis in yr, mean (SD) | 28.8 (10.9) | 31.4 (13.5) | 29.3 (10.8) | 30.5 (11.0) |
| Chronic kidney disease stage, ml/min per 1.73 m ² , n | 2797 | 4095 | 1186 | 1186 |
| ≥90 (stage 1), n (%) | 472 (16.9) | 1222 (29.8) | 193 (16.3) | 193 (16.3) |
| 60 to <90 (stage 2), n (%) | 699 (25.0) | 1196 (29.2) | 302 (25.5) | 302 (25.5) |
| 45 to <60 (stage 3a), n (%) | 639 (22.8) | 652 (15.9) | 562 (47.4) ^a | 562 (47.4) ^a |
| 30 to <45 (stage 3b), n (%) | 693 (24.8) | 562 (13.7) | | |
| 15 to <30 (stage 4), n (%) | 294 (10.5) | 354 (8.6) | 129 (10.9) ^b | 129 (10.9) ^b |
| <15 (stage 5), n (%) | 0 | 109 (2.7) | | |
| Baseline eGFR, ml/min per 1.73 m ² , mean (SD) | 60.2 (26.6) | 70.1 (31.9) | 60.1 (26.4) | 60.1 (26.3) |
| Baseline systolic BP, mm Hg, mean (SD) | 129.5 (13.6) | 129.6 (15.8) | 130 (13.8) | 129.6 (15.0) |
| Baseline diastolic BP, mm Hg, mean (SD) | 82.4 (9.4) | 81.1 (10.8) | 82.7 (9.5) | 81.5 (10.3) |
| History of nephrolithiasis, n (%) | 573 (19.7) | 297 (7.1) | 249 (21.0) | 86 (7.3) |
| History of hematuria, n (%) | 906 (31.2) | 526 (12.6) | 365 (30.8) | 139 (11.7) |
| History of urinary tract infection, n (%) | 813 (28.0) | 427 (10.2) | 340 (28.7) | 103 (8.7) |
| With baseline TKV assessment, n | 1435 | 3482 | 537 | 537 |
| Baseline TKV in ml, mean (SD) | 1817 (1091.5) | 1627 (1293.8) | 1478 (702.4) | 1468 (706.0) |
| Baseline height-adjusted TKV, ml/m, n | 1434 | 3478 | 537 | 537 |
| <400, n (%) | 34 (2.4) | 698 (20.1) | 2 (0.4) | 7 (1.3) |
| 400 to <600, n (%) | 268 (18.7) | 692 (19.9) | 159 (29.6) | 153 (28.5) |
| ≥600, n (%) | 1132 (78.9) | 2088 (60.0) | 376 (70.0) | 377 (70.2) |
| Baseline estimated TKV growth rate, mean (SD) | 0.071 (0.023) | 0.056 (0.029) | 0.066 (0.018) | 0.065 (0.018) |
| Mayo imaging classification, n | 1434 | 3471 | 537 | 537 |
| Class 1A, n (%) | 6 (0.4) | 217 (6.3) | 0 | 0 |
| Class 1B, n (%) | 119 (8.3) | 873 (25.2) | 62 (11.5) | 64 (11.9) |
| Class 1C, n (%) | 537 (37.4) | 1,233 (35.5) | 252 (46.9) | 251 (46.7) |
| Class 1D, n (%) | 507 (35.4) | 734 (21.1) | 175 (32.6) | 182 (33.9) |
| Class 1E, n (%) | 265 (18.5) | 414 (11.9) | 48 (8.9) | 40 (7.4) |

ADPKD, autosomal dominant polycystic kidney disease; BP, blood pressure; eGFR, estimated glomerular filtration rate; TKV, total kidney volume.

^a30 to <60 ml/min per 1.73 m².

^bLess than 30 ml/min per 1.73 m².

decline between tolvaptan (-3.15 ml/min per 1.73 m²) and the SOC (-3.70 ml/min per 1.73 m²) was less than in the matched set but still statistically significant ($P < 0.001$) (Supplementary Table S6). Among full analysis set subjects with both baseline and postbaseline TKV assessments, the estimated ratio of TKV with tolvaptan compared with SOC was 0.97 at year 1 (i.e., 3% smaller with tolvaptan than in SOC). The ratio further declined to 0.89 at year 5 (i.e., 11% smaller with tolvaptan) (Supplementary Table S7). TKV growth was slower with tolvaptan (5.2% per year) compared with SOC (7.5% per year, $P < 0.001$).

Factors Predicting Disease Progression (Full Analysis Set)

The adjusted effects of factors on eGFR estimated from the piecewise-mixed model are shown in Table 4. Results indicated that lower baseline eGFR, older age, higher systolic BP, higher diastolic BP, and history of

hematuria were significantly associated with a lower (worse) postbaseline eGFR after adjusting for other factors in the model. In addition, the effect of history of nephrolithiasis was smaller but close to that of a history of hematuria. History of UTI, sex, and race were not associated with eGFR outcome. Special consideration was given to BMI, weight, and height. Because BMI is a function of weight and height, including all 3 of them in a model may cause collinearity (e.g., none is significant) or artificial effects (e.g., significant but in opposite directions). When assessing these 3 variables individually, only height was significant ($P = 0.016$) and therefore included in the final model; a higher height was associated with a lower eGFR.

The factors predicting TKV outcome (Table 4) were different from those predicting eGFR. A greater baseline TKV ($P < 0.001$), younger age ($P < 0.001$), male sex ($P < 0.001$), non-White race ($P = 0.003$), higher CKD stage ($P < 0.001$), and no history of UTI ($P <$

Table 2. Baseline characteristics of subjects with TKV data in the full analysis set and of subjects in the matched TKV analysis sets

| Characteristics | Full analysis set with TKV data | | Matched TKV analysis set A | | Matched TKV analysis set B | |
|--|---------------------------------|----------------|----------------------------|---------------|----------------------------|----------------------|
| | Tolvaptan (n = 1435) | SOC (n = 3482) | Tolvaptan (n = 102) | SOC (n = 102) | Tolvaptan (n = 182) | SOC (n = 182) |
| Age in yr, mean (SD) | 39.9 (8.0) | 43.3 (13.0) | 38.8 (6.6) | 38.7 (6.6) | 37.9 (6.9) | 37.7 (7.0) |
| Female, n (%) | 706 (49.2) | 1919 (55.1) | 50 (49.0) | 50 (49.0) | 93 (51.1) | 93 (51.1) |
| White, n (%) | 1359 (94.7) | 2782 (79.9) | 98 (96.1) | 91 (89.2) | 172 (94.5) | 165 (90.7) |
| Height in m, mean (SD) | 1.74 (0.10) | 1.72 (0.10) | 1.74 (0.10) | 1.74 (0.11) | 1.74 (0.10) | 1.74 (0.11) |
| Weight in kg, mean (SD) | 80.9 (17.9) | 79.4 (18.1) | 77.1 (19.4) | 81.7 (18.5) | 79.1 (18.9) | 82.5 (18.2) |
| Body mass index, kg/m ² , mean (SD) | 26.5 (5.0) | 26.8 (5.4) | 25.2 (5.0) | 26.9 (5.1) | 25.9 (5.3) | 27.2 (5.6) |
| Age at ADPKD diagnosis in yr, mean (SD) | 26.9 (9.7) | 31.0 (13.5) | 28.7 (8.4) | 28.3 (8.6) | 27.7 (8.7) | 27.8 (9.0) |
| Chronic kidney disease stage, ml/min per 1.73 m ² , n | 1428 | 3421 | 102 | 102 | 182 | 182 |
| ≥90 (stage 1), n (%) | 471 (33.0) | 1176 (34.4) | 42 (41.2) | 42 (41.2) | 76 (41.8) | 76 (41.8) |
| 60 to <90 (stage 2), n (%) | 619 (43.3) | 1050 (30.7) | 60 (58.8) | 60 (58.8) | 100 (54.9) | 100 (54.9) |
| 45 to <60 (stage 3a), n (%) | 230 (16.1) | 436 (12.7) | 0 | 0 | 6 (3.3) ^a | 6 (3.3) ^a |
| 30 to <45 (stage 3b), n (%) | 80 (5.6) | 361 (10.6) | 0 | 0 | | |
| 15 to <30 (stage 4), n (%) | 28 (2.0) | 304 (8.9) | 0 | 0 | | |
| <15 (stage 5), n (%) | 0 | 94 (2.7) | 0 | 0 | | |
| Baseline eGFR, ml/min per 1.73 m ² , mean (SD) | 78.6 (24.0) | 73.6 (32.4) | 88.4 (16.4) | 88.3 (16.3) | 88.0 (17.8) | 88.1 (17.6) |
| Baseline systolic BP, mm Hg, mean (SD) | 127.6 (13.0) | 129.5 (15.7) | 127.9 (15.0) | 127.7 (15.6) | 127.9 (14.3) | 126.7 (13.8) |
| Baseline diastolic BP, mm Hg, mean (SD) | 81.6 (9.3) | 81.3 (10.8) | 81.4 (9.8) | 80.7 (11.5) | 82.1 (10.1) | 80.7 (10.8) |
| History of nephrolithiasis, n (%) | 271 (19.1) | 255 (7.3) | 15 (14.7) | 13 (12.7) | 27 (14.8) | 25 (13.7) |
| History of hematuria, n (%) | 484 (34.2) | 459 (13.2) | 30 (29.4) | 11 (10.8) | 56 (30.8) | 34 (18.7) |
| History of urinary tract infection, n (%) | 454 (32.0) | 384 (11.0) | 26 (25.5) | 5 (4.9) | 54 (29.7) | 34 (18.7) |
| With baseline TKV assessment, n | 1,435 | 3,482 | 102 | 102 | 182 | 182 |
| Baseline TKV in ml, mean (SD) | 1817 (1091.5) | 1627 (1293.8) | 1245 (464.1) | 1235 (470.1) | 1283 (528.8) | 1271 (535.9) |
| Baseline height-adjusted TKV, ml/m, n | 1434 | 3478 | 102 | 102 | 182 | 182 |
| <400, n (%) | 34 (2.4) | 698 (20.1) | 1 (1.0) | 4 (3.9) | 2 (1.1) | 8 (4.4) |
| 400 to <600, n (%) | 268 (18.7) | 692 (19.9) | 41 (40.2) | 41 (40.2) | 75 (41.2) | 69 (37.9) |
| ≥600, n (%) | 1132 (78.9) | 2088 (60.0) | 60 (58.8) | 57 (55.9) | 105 (57.7) | 105 (57.7) |
| Baseline estimated TKV growth rate, mean (SD) | 0.07 (0.023) | 0.06 (0.029) | 0.06 (0.02) | 0.06 (0.02) | 0.06 (0.018) | 0.06 (0.019) |
| Mayo imaging classification, n | 1434 | 3471 | 102 | 102 | 182 | 182 |
| Class 1A, n (%) | 6 (0.4) | 217 (6.3) | 0 | 0 | 0 | 0 |
| Class 1B, n (%) | 119 (8.3) | 873 (25.2) | 21 (20.6) | 20 (19.6) | 29 (15.9) | 30 (16.5) |
| Class 1C, n (%) | 537 (37.4) | 1233 (35.5) | 44 (43.1) | 49 (48.0) | 80 (44.0) | 79 (43.4) |
| Class 1D, n (%) | 507 (35.4) | 734 (21.1) | 31 (30.4) | 27 (26.5) | 62 (34.1) | 62 (34.1) |
| Class 1E, n (%) | 265 (18.5) | 414 (11.9) | 6 (5.9) | 6 (5.9) | 11 (6.0) | 11 (6.0) |

ADPKD, autosomal dominant polycystic kidney disease; BP, blood pressure; eGFR, estimated glomerular filtration rate; SOC, standard of care; TKV, total kidney volume.

^aLess than 60 ml/min per 1.73 m².

0.001) were associated with a higher (worse) TKV outcome. Baseline systolic BP and diastolic BP were not associated with TKV. Baseline weight and BMI were both significantly associated with TKV (greater weight or BMI associated with a greater TKV) when assessed individually. When including both BMI and weight in the model, only BMI was significant. This suggests that BMI is a better predictor than weight. Baseline height was not associated with TKV outcome when assessed individually and therefore was not included in the final model.

Impact of the Tolvaptan Treatment Gap

The estimated rate of eGFR decline during the tolvaptan treatment gap was similar to the rate of decline while on SOC (−3.64 vs. −3.70 ml/min per 1.73 m² per year) (Table 4). The estimated rate of TKV growth during the tolvaptan treatment gap was larger than the growth rate while on treatment. This may reflect the

return of fluid to kidney cysts, in addition to continued growth after subjects interrupted tolvaptan.

DISCUSSION

The tolvaptan ADPKD clinical development program in adults demonstrated slowing of disease progression, indicating significant reductions in rates of eGFR decline and in TKV growth relative to placebo.^{5,6} These findings were supported by data from long-term extension trials.⁹ The lack of placebo control groups in the open-label extensions, however, limits conclusions about durability of the treatment effect. The present analysis was conducted to address this gap by pooling data from tolvaptan-treated trial subjects and comparing with data from SOC controls.

Consistent with the results of other studies that followed this methodological approach, the data reported here show statistically significant improvement in ADPKD outcomes over the long-term.^{11,14} Compared

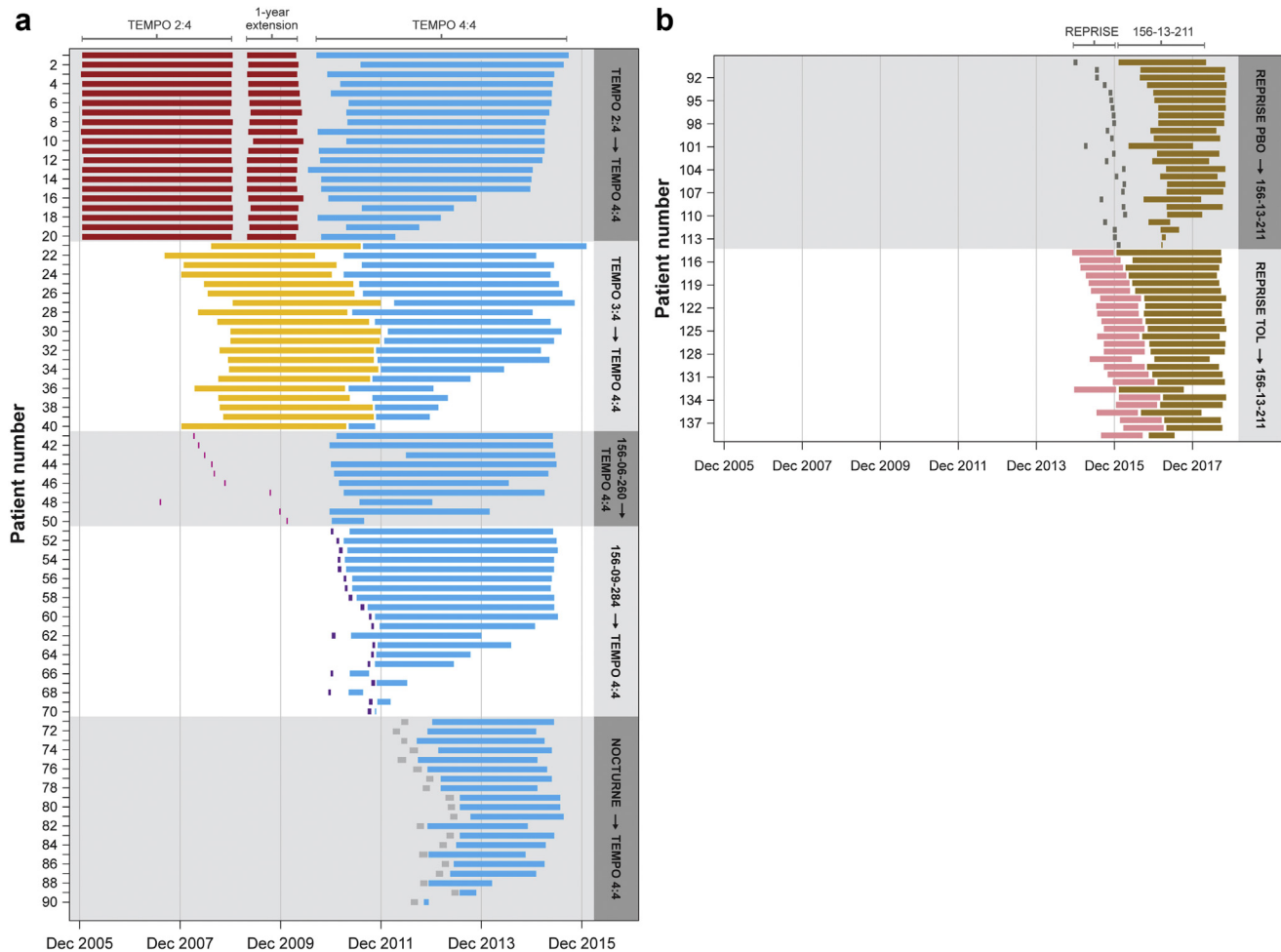


Figure 3. Sample subject profiles of tolvaptan treatment duration and gaps. (a) Subjects who continued into TEMPO 4:4. (b) Subjects from REPRISE who continued into long-term safety study 156-13-211. For TEMPO 2:4, TEMPO 3:4, 156-09-284, and NOCTURNE, a random sample of 20 subjects is presented. For REPRISE, a random sample of 25 subjects in each randomization arm is presented. Dec, December; PBO, placebo; TOL, tolvaptan.

with the earlier investigations, the current study drew on the greater amount of follow-up data now available from clinical trials of tolvaptan in ADPKD, comprising a tolvaptan-treated population of 2928 subjects, including 529 with at least 5 years of eGFR follow-up data. The present analyses excluded the off-treatment observations in the tolvaptan cohort to avoid potential overestimation of treatment effect because of the reversible acute hemodynamic effect of tolvaptan on eGFR. The large, pooled data set also enabled a robust analysis of patients matched for clinical characteristics at baseline, with 1186 subjects in each treatment group. In this matched analysis, the annual rate of eGFR decline with tolvaptan was significantly slowed by 1.01 ml/min per 1.73 m² versus SOC. This effect size is similar to the annual difference in eGFR of 1.01 to 1.20 ml/min per 1.73 m² reported in TEMPO 3:4 and REPRISE, suggesting the effects of tolvaptan are consistent and sustainable with long-term treatment.⁶ In the matched TKV analysis sets, estimated TKV at

year 1, 3, or 5 was significantly reduced with tolvaptan relative to SOC. Analyses conducted in the full data set confirmed that tolvaptan was associated with a significantly slower rate of eGFR decline and significantly reduced TKV.

During tolvaptan treatment gaps between studies, rates of eGFR decline and TKV growth increased versus treatment periods, supporting the benefits of consistent, long-term tolvaptan treatment. This analysis provides information of direct relevance to core concerns of patients and clinicians regarding kidney function trajectory, prognosis, and the potential effects of treatment.²⁴

This analysis also provided data about predictors of eGFR and TKV outcomes in ADPKD. Lower baseline eGFR, older age, higher systolic and diastolic BP, history of hematuria, and higher height were associated with a lower (worse) postbaseline eGFR outcome. Height and TKV are interdependent variables, as higher height means a lower height-adjusted TKV.

| Outcome/Time | Estimate (95% CI) | | | P Value |
|--|---------------------------|-----------------------------|---|---------|
| | Tolvaptan (n = 1186) | Standard of Care (n = 1186) | Difference (Tolvaptan - Standard of Care) | |
| eGFR | | | | |
| Year 1 | 54.85 (54.47–55.22) | 56.30 (55.91–56.70) | -1.46 (-2.00–-0.91) | <0.001 |
| Year 3 | 48.90 (48.33–49.46) | 48.33 (47.71–48.95) | 0.56 (-0.26–1.40) | 0.189 |
| Year 5 | 42.50 (41.61–43.38) | 39.91 (38.91–40.91) | 2.58 (1.29–3.88) | <0.001 |
| Change from theoretical baseline eGFR | | | | |
| Year 1 | -2.81 (-2.99–-2.63) | -3.82 (-4.06–-3.58) | 1.01 (0.75–1.27) | <0.001 |
| Year 3 | -8.76 (-9.24–-8.28) | -11.79 (-12.44–-11.14) | 3.03 (2.24–3.82) | <0.001 |
| Year 5 | -15.16 (-15.97–-14.35) | -20.21 (-21.26–-19.16) | 5.05 (3.73–6.37) | <0.001 |
| Annual Rate of Change | | | | |
| Year 1 | -2.81 (-2.99–-2.63) | -3.82 (-4.06–-3.58) | 1.01 (0.75–1.27) | <0.001 |
| Year 3 | -3.03 (-3.19–-2.87) | -4.04 (-4.25–-3.83) | 1.01 (0.75–1.27) | <0.001 |
| Year 5 | -3.26 (-3.49–-3.02) | -4.27 (-4.52–-4.01) | 1.01 (0.75–1.27) | <0.001 |

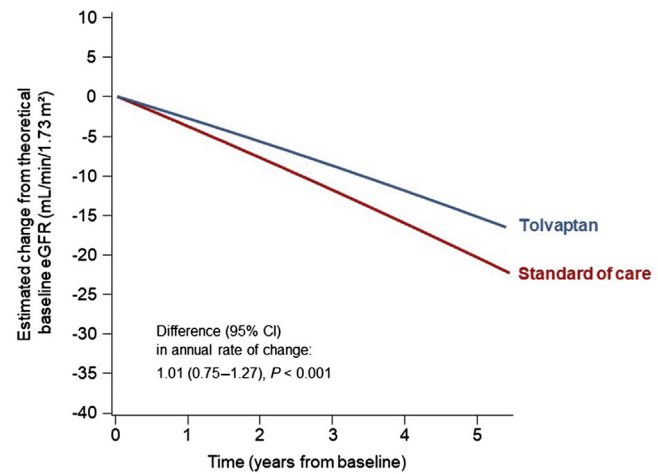


Figure 4. Decline in eGFR over time, by treatment cohort (matched analysis set). The estimated annual rate of decline varies by year, and accordingly, the curves shown are nonlinear (coefficient estimate for squared years from baseline is -0.056 [SE = 0.017, $P = 0.001$]). This reflects that the decline in eGFR over long term is nonlinear. Difference in annual rate of decline represents the slope (linear term of time) of tolvaptan minus the slope of SOC. This difference is constant over time (the treatment-by-time squared term was not significant and therefore removed for the final model). Mean eGFR change from theoretical baseline was estimated from the mixed model on the sample means/distributions of baseline characteristics. The mixed model included treatment, time on SOC, time, time-by-treatment interaction, time squared, and baseline eGFR as fixed effects and subject-specific intercept and slope (for time) as random effects. The random effects have an unstructured variance-covariance matrix. eGFR, estimated glomerular filtration rate; TOL, tolvaptan; SOC, standard of care.

Greater baseline TKV, younger age, male sex, non-White race, a higher CKD stage, no history of UTI, and greater BMI were associated with a greater (worse) TKV outcome. The results should be interpreted with caution, as the association of no UTI history with greater TKV is not in the direction that might be expected. The finding of a positive correlation between baseline BMI and growth in TKV is consistent with an earlier analysis of data from HALT-PKD Study A.²⁷

A limitation of the cohort control design is that differences between the treatment groups may have affected the outcomes. Use of matching and multiple regression adjustment for the relative comparison helped to reduce this source of bias, but the possibility of residual confounding still exists. Patient populations enrolled at different times and in different clinical studies may have had differences in clinical characteristics or lifestyle factors not reflected in the tables of baseline characteristics shown. In addition, it is likely that subjects who did not perform well dropped off earlier, especially among observational studies.

Therefore, we excluded observations after 5.5 years of follow-up to reduce potential bias caused by informative missingness. In the matched analysis of eGFR, duration of follow-up was matched for subjects from long-term studies. In analysis for TKV, matched sets with and without requirement for >3 years of data were conducted, and the results were very similar. Finally, the benefits of tolvaptan in reducing TKV growth rate may have been higher than in actuality, given that effects on TKV appear to be driven in part by an acute, early decrease in the secretion of cyst fluid after treatment initiation, followed by a more gradual, long-term decrease in cyst-cell proliferation.^{5,25}

In summary, the results of this longitudinal analysis conducted in the largest population reported to date support longer-term benefits of tolvaptan in inhibiting loss of kidney function and slowing the rate of kidney volume growth. The treatment effects of tolvaptan were consistent with findings from controlled clinical trials and substantiate the disease-modifying effects of tolvaptan.

Table 3. Estimated TKV (% of baseline) over time, by treatment cohort (matched analysis sets for TKV)

| Matched analysis set | Time | Tolvaptan | Standard of care | Ratio, tolvaptan/standard of care (95% CI) | P value |
|--|------|-----------|------------------|--|---------|
| Set A (102 subjects in each treatment group) | Yr 1 | 96.8 | 106.7 | 0.91 (0.89–0.93) | <0.001 |
| | Yr 3 | 109.7 | 121.2 | 0.91 (0.88–0.93) | <0.001 |
| | Yr 5 | 124.3 | 137.7 | 0.90 (0.86–0.95) | <0.001 |
| Set B (182 subjects in each treatment group) | Yr 1 | 97.3 | 106.9 | 0.91 (0.89–0.93) | <0.001 |
| | Yr 3 | 110.2 | 121.2 | 0.91 (0.89–0.93) | <0.001 |
| | Yr 5 | 124.8 | 137.4 | 0.91 (0.88–0.94) | <0.001 |

TKV, total kidney volume.

Results were estimated from mixed models, which included treatment, time, time-by-treatment interaction, and baseline TKV as fixed effects and subject-specific intercept and slope (for time) as random effects with an unstructured variance-covariance matrix.

Table 4. Adjusted effects of factors on eGFR and TKV up to 5.5 yr

| Fixed effect | Full analysis set eGFR (ml/min per 1.73 m ²) | | Full analysis set with TKV TKV (ratio) | |
|---|--|---------|--|---------|
| | Effect (95% CI) | P value | Relative effect (95% CI) | P value |
| Immediate treatment effect (tolvaptan vs. SOC) | -3.36 (-3.81 to -2.92) | <0.001 | 0.987 (0.983-0.992) | <0.001 |
| Years in SOC | -3.70 (-3.86 to -3.55) | <0.001 | 1.075 (1.071-1.078) | <0.001 |
| Years in tolvaptan | -3.15 (-3.28 to -3.02) | <0.001 | 1.052 (1.049-1.055) | <0.001 |
| Years in tolvaptan gap | -3.64 (-3.97 to -3.31) | <0.001 | 1.123 (1.113-1.134) | <0.001 |
| Baseline eGFR, ml/min per 1.73 m ² | 0.93 (0.92 to 0.94) | <0.001 | | |
| CKD stage (reference: stage 1) | | | | |
| Stage 4 or 5 | | | 1.038 (1.025-1.051) | <0.001 |
| Stage 3b | | | 1.036 (1.024-1.048) | <0.001 |
| Stage 3a | | | 1.019 (1.009-1.028) | <0.001 |
| Stage 2 | | | 1.002 (0.995-1.009) | 0.504 |
| Baseline log TKV | | | 2.727 (2.713-2.741) | <0.001 |
| Age, yr | -0.10 (-0.12 to -0.07) | <0.001 | 0.999 (0.999-0.999) | <0.001 |
| Sex (male vs. female) | 0.27 (-0.28 to 0.83) | 0.338 | 1.015 (1.008-1.023) | <0.001 |
| Race (White vs. other) | 0.30 (-0.27 to 0.86) | 0.303 | 0.989 (0.981-0.996) | 0.003 |
| Height, cm | -0.03 (-0.06 to -0.00) | 0.034 | | |
| Weight, kg | | | 1.000 (1.000-1.000) | 0.857 |
| BMI, kg/m ² | | | 1.001 (1.000-1.003) | 0.010 |
| Baseline systolic BP, mm Hg | -0.02 (-0.04 to -0.00) | 0.027 | 1.000 (1.000-1.000) | 0.636 |
| Baseline diastolic BP, mm Hg | -0.05 (-0.07 to -0.02) | <0.001 | 1.000 (0.999-1.000) | 0.326 |
| History of hematuria (yes vs. no) | -0.66 (-1.17 to -0.15) | 0.011 | 0.995 (0.988-1.002) | 0.128 |
| History of nephrolithiasis (yes vs. no) | -0.48 (-1.08 to 0.12) | 0.120 | 0.996 (0.988-1.005) | 0.365 |
| History of urinary tract infection (yes vs. no) | -0.18 (-0.73, 0.37) | 0.518 | 0.986 (0.979, 0.993) | <0.001 |

BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SOC, standard of care; TKV, total kidney volume. Estimated from the piecewise-mixed model, including intercepts and time slopes for tolvaptan and SOC, time slope for tolvaptan gap, and baseline characteristics.

DISCLOSURE

XZ, EKD, and DG are employees of RTI Health Solutions, which received funding from Otsuka. MH, IA, and DO are employees of Otsuka. JO and HBK are former employees of Otsuka.

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database of multiple autosomal dominant polycystic kidney disease clinical studies (abstract P0037).

SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#)

Supplementary Methods. Piecewise-mixed models were used to account for treatment gaps when assessing tolvaptan treatment effects on estimated glomerular filtration rate decline and on total kidney volume in the full analysis set.

Table S1. Otsuka-sponsored studies in autosomal dominant polycystic kidney disease.

Table S2. Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease and HALT Progression of Polycystic Kidney Disease studies.

Table S3. Eligibility criteria and matching methods for subjects in the matched analysis of treatment effect on estimated glomerular filtration rate.

Table S4. Eligibility criteria and matching methods for subjects in the matched analyses of treatment effect on total kidney volume.

Table S5. Tolvaptan treatment duration, compliance, and gap between studies (full analysis set).

Table S6. Annualized decline in estimated glomerular filtration rate (ml/min per 1.73 m²) in the full analysis set.

Table S7. Estimated total kidney volume (% of baseline) over time by treatment cohort in full analysis set subjects with total kidney volume data.

Figure S1. Selection of subjects for the matched eGFR analysis set.

Figure S2. Distribution of baseline total kidney volume (ml) and estimated glomerular filtration rate by Chronic Kidney Disease Epidemiology Collaboration equation (ml/min per 1.73 m²) in the tolvaptan and standard of care groups (full analysis set with total kidney volume data).

CONSORT Checklist (PDF).

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