Delaying Progression of Renal Complications of Autosomal Dominant Polycystic Kidney Disease by Tolvaptan Inhibition of Arginine Vasopressin

Briefing Document

for

5 August 2013 Advisory Committee Meeting of the Cardiovascular and Renal Drugs Division of the US Food and Drug Administration

Otsuka Pharmaceutical Development & Commercialization, Inc.
2440 Research Boulevard
Rockville, Maryland 20850

Issued 3 July 2013

THIS DOCUMENT IS AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Executive Summary

Tolvaptan is a selective vasopressin V_2 receptor antagonist proposed to slow kidney disease in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD). This document provides information on tolvaptan relevant to the Center for Drug Evaluation and Research Cardiovascular and Renal Drugs Advisory Committee Meeting on Monday, 05 August 2013. The sponsor has been asked to provide information to support informed decisions and recommendations on the following:

- Evidence supporting the efficacy of tolvaptan in the chronic treatment of ADPKD.
- Evidence supporting the safe-use of tolvaptan for chronic treatment of ADPKD.
- Basis for believing the observed and expected benefits of tolvaptan may reasonably outweigh the potential for observed or expected harm when given chronically to patients with ADPKD.

Autosomal Dominant Polycystic Kidney Disease is a Progressive Syndrome with No Existing Therapy

Autosomal dominant polycystic kidney disease leads to progressive destruction of normal kidney structure leading to end-stage renal disease (ESRD). The disease affects the structure of the kidneys through proliferation and growth of numerous fluid-filled cysts. The expanding cysts compress normal tissue and blood vessels resulting in ischemia, inflammation and fibrosis leading to progressive nephron loss. The remaining nephrons are initially able to compensate through glomerular hyperfiltration up to a point when nephron loss is so great that compensatory hyperfiltration of remaining nephrons is no longer adequate and renal function begins to decline. Clinical manifestations of kidney disease may be sporadic (hematuria, infections, pain) or chronic (hypertension, albuminuria, renal insufficiency) and indicate ongoing and cumulative damage to the kidney.

There are currently no therapies which can slow the deterioration of kidney function in ADPKD. Current management focuses on ameliorating symptoms of pain, control of blood pressure, and treatment of infections with antibiotics. None of these treatments target the underlying cause of the disease.

Parents with ADPKD have a 50% chance of passing a mutated PKD1 or PKD2 gene to their children. Development of cysts appears to require a second mutation in the paired normal allele (second hit hypothesis). Patients carrying the mutated PKD1 gene have

more cysts than those with PKD2 mutations which accounts for their progression to ESRD at an earlier age.

The number of diagnosed ADPKD cases was estimated at 116,228 in the US in 2009 which qualified tolvaptan for an orphan designation. Though a rare genetic disease, it ranks as the sixth leading cause of ESRD in the US (2.3% of the new ESRD cases).[1] An estimated 45% to 70% of patients with ADPKD progress to ESRD by age 65.[8] Over the past 30 years, the age of onset for ESRD among ADPKD patients has remained the same (median age of 54). In contrast, effective therapy has delayed the onset of ESRD in patients with nephropathy due to hypertension, diabetes and glomerulonephritis.

Autosomal dominant polycystic kidney disease patients fear the physical and emotional burdens of dialysis while holding out hope for receiving a kidney transplantation. This disease has a devastating physical, emotional, and financial toll on patients and their families (Section 1).

Arginine Vasopressin Promotes Structural Damage in ADPKD

Arginine vasopressin (AVP) promotes ADPKD structural damage by increasing the rate of cyst growth (Section 1.2). AVP stimulates the V_2 vasopressin receptor, thereby increasing cAMP intracellular signaling; increased cAMP leads to fluid secretion into the cysts and cyst cell proliferation.[9] Cyst formation and expansion disrupts normal kidney structure, impacting hemodynamic flow, leading to ischemia, fibrosis and decreased nephron number and function.

Inhibition of AVP binding at the V_2 receptor decreases adenylyl cyclase activity, resulting in a decrease in intracellular cAMP in the kidney.[10,11] In animal models of ADPKD, eliminating, lowering or blocking AVP leads to decreased kidney weight, cyst volume, and fibrotic volume.[12] Rats with no endogenous production of AVP (Brattleboro rats [$AVP^{-/-}$/$Pkhd1^{+/+}$]) and rats with a PKD phenotype (PCK rats [$AVP^{+/+}$/$Pkhd1^{-/-}$]) were crossed to generate rats with a PKD phenotype and varying levels of AVP. At 10 and 20 weeks of age, PCK [$Pkhd1^{-/-}$/$AVP^{-/-}$] rats had lower renal cAMP and almost complete inhibition of cystogenesis compared with PCK [$Pkhd1^{-/-}$/$AVP^{+/+}$] and PCK [$Pkhd1^{-/-}$/$AVP^{+/-}$] rats. The eventual appearance of cysts in the PCK [$Pkhd1^{-/-}$/$AVP^{-/-}$] rats indicated that other redundant factors contribute to cyst formation and expansion. When given the V_2 vasopressin agonist, 1-deamino-8-D-arginine vasopressin, PCK [$Pkhd1^{-/-}$/$AVP^{-/-}$] rats showed an increase in renal cAMP and developed explosive renal

cystic disease surpassing that seen in PCK [Pkhd1$^{-/-}$/AVP$^{+/+}$] rats. These data convincingly support that AVP activation of the kidney V_2 receptor is a key promoter of the production, growth and proliferation of cysts and suggest that V_2 receptor antagonists may provide the first opportunity to interrupt the pathophysiology of the disease in humans.

Tolvaptan's Mechanism of Action Slows ADPKD Progression and Causes Aquaresis

Tolvaptan blocks the kidney V_2 receptor, thereby reducing intracellular cAMP. This results in two physiologic consequences. The first is to prevent the insertion of aquaporin channels into the apical membrane of the distal tubules and collecting ducts, resulting in decreased reabsorption of water. This effect, referred to as aquaresis, is the physiologic basis of tolvaptan's therapeutic effects for the treatment of hyponatremia. The second is unique to the dysregulated cells of ADPKD. Here, lowering cAMP production slows cyst cell proliferation and secretion, resulting in decreased cyst growth and fibrosis (Section 2.1).

The animal model discussed above and other animal models where tolvaptan was administered in food or via gavage (twice daily) suggest that tolvaptan treatment is most effective when initiated at an early stage in disease progression and given chronically. This provides the greatest benefit in reducing cyst growth before it begins to adversely affect renal function.

These animal data supported early phase clinical trials. Dose-ranging clinical phase 2 PK/PD trials indicated that a split-dose regimen of tolvaptan administered as 45/15 mg, 60/30 mg or 90/30 mg would be effective in continuously blocking AVP (as measured by suppressed urine osmolality; Section 3.3) in a majority of patients with ADPKD, therefore affording the greatest potential to slow the progression of the disease.

Endpoint Selection for the Pivotal ADPKD Trial

The tolvaptan program in ADPKD focuses on important aspects of the progression of ADPKD:

- kidney structure
- kidney events of ADPKD progression
- kidney function

Experts provided the best, available scientific and clinical evidence at the time, which in concert with regulatory advice, contributed to the design of the pivotal tolvaptan ADPKD trial. This, added to extensive clinical experience with tolvaptan from other indications, guided the design, dosing regimen, population, and endpoint selection of the pivotal tolvaptan ADPKD trial (Section 3.2). Clinical researchers working with the National Institutes of Health (NIH) proposed total kidney volume (TKV) as a practical endpoint for measuring ADPKD renal cyst burden and progression (when measured with magnetic resonance imaging [MRI]). Trial 156-04-251 was therefore designed to measure change in total kidney volume (TKV) as the primary endpoint for kidney structure Section 5.5.1.

To assess clinically significant events marking the progression of ADPKD kidney damage, a key secondary composite endpoint focused on events of progression of ADPKD (significantly (30%) worsening renal function, renal pain, hypertension, and albuminuria) Section 5.6.1. An exploratory measure of all subject-reported ADPKD outcomes supported this endpoint (Section 5.9.1).

Given the importance of understanding how tolvaptan could preserve kidney function, the rate of loss of glomerular filtration (1/serum creatinine or eGFR slope) served as the next, hierarchically ordered secondary endpoint (Section 5.7.1). Evaluation of renal function as a continuous change (in contrast to a threshold-event) allowed interpretation of efficacy across the range of all enrolled subjects. This included those whose function was relatively preserved due to hyperfiltration, and were unlikely to reach a threshold event in a span of 3 years.

Other secondary, exploratory and pharmacodynamic endpoints were prespecified to further the understanding of tolvaptan's effects on the primary endpoint of TKV and the key secondary composite endpoint and its components. These also provided a broader picture of the overall clinical impact of ADPKD progression.

Current collaborations between FDA and the PKD Outcomes and CKD Progression Consortia have led to a better appreciation of how TKV and eGFR thresholds (eg, 30%) can be used to predict risk of progression to ESRD. These efforts support the choice of ADPKD clinical trial endpoints, particularly when targeting subjects with early disease. The population studied in the tolvaptan pivotal trial included those at risk of rapidly progressing ADPKD (TKV at least 750 mL), but whose renal function was largely preserved (eCrCL $\geq$ 60 mL/min). The hypothesis was that this population of patients would have measurable and clinically-relevant progression of ADPKD in a reasonable timeframe.

Regulatory Communications Regarding Endpoints and Design of Pivotal Trial

For the efficacy endpoints, there were extensive communications between the FDA and Otsuka. The FDA consistently stated that the Agency would not currently accept changes in kidney volume as a surrogate endpoint and thus would place emphasis on the findings for the key secondary composite endpoint at Pre-Investigational New Drug Meeting (16 Mar 2005), Special Protocol Assessment (SPA) meeting (15 Nov 2005), Statistical meeting (10 June 2009) and pre-NDA meeting (19 July 2012).

The Agency and Otsuka both agreed on the study endpoint structure: total kidney volume for the primary endpoint and a composite for the key secondary endpoint. The FDA indicated that the key secondary composite endpoint must provide evidence of effectiveness. There was agreement that if the primary endpoint and the composite endpoint are both statistically significant with other endpoints supportive, the single phase 3 trial would be sufficient to support a New Drug Application (NDA) approval (SPA meeting, 15 Nov 2005). In order to provide convincing evidence of treatment benefit, the key secondary composite endpoint would need a p-value of < 0.01 (Statistical meeting, 10 Jun 2009). Based on the trial findings, the Agency reiterated at the pre-NDA meeting that the single, pivotal 156-04-251 trial was adequate to support a filing; and that they do not currently accept changes in kidney volume as a surrogate endpoint and thus will place [review] emphasis on the findings for the key secondary composite endpoint.

For the trial design, it was agreed that the best use of available subjects would be to titrate them to the highest dose.

Pivotal Trial 156-04-251

Trial 156-04-251 was a 3-year, multinational, randomized (2:1), double-blind, placebo-controlled trial in 1445 subjects (tolvaptan n = 961, placebo n = 484 [1 randomized placebo subject was not dosed]) assessing the long-term efficacy and safety of tolvaptan with oral split-dose regimens (titrated between 60 mg/day [45/15 mg], 90 mg/day [60/30 mg], and 120 mg/day [90/30 mg] with the first dose to be taken upon awakening and the second to be taken 8 hours later).

Primary Efficacy Endpoint: Tolvaptan Reduced TKV Growth

Tolvaptan reduced the rate of TKV growth (primary trial endpoint) over 3 years in comparison with placebo, with an absolute difference of 2.71%/year ($p < 0.0001$)

(Section 5.5.2). This reduction represented a 49.2% decrease in the growth rate of kidneys (Table 1).

Table 1 Primary Endpoint (Random Effect Intercept) in Trial 156-04-251: Total Kidney Volume Rate of Growth (%/year), ITT, Within Treatment Period

Parameter	Tolvaptan	Placebo
Rate of percent growth per year		
Number of subjects	819	458
Mean	2.777	5.608
Median	2.265	5.585
SD	5.659	5.330
Minimum	−23.129	−20.634
Maximum	64.270	43.948
Estimated slope	0.0280	0.0551
Treatment effect		
Difference (%)	−2.708	
95% CI	−3.269, −2.147	
Slope reduction (%)	49.2	
Ratio of geometric mean	0.974	
95% CI	0.969, 0.980	
p-value	< 0.0001	

CI = confidence interval; IMP = investigational medicinal product; ITT = intent-to-treat; MRI = magnetic resonance imaging; SD = standard deviation; TKV = total kidney volume.
For additional details of analysis, see Table 5.5.2-1.

A mixed-model repeated measures (MMRM) analysis showed the treatment effect for TKV in Trial 156-04-251 to be greatest in the first year, but the beneficial effects of tolvaptan were clearly evident in the second and third year, indicating continued incremental separation from treatment with placebo (see Figure 1) at approximately 30% per year. These findings were confirmed by additional sensitivity and supportive analyses (Section 10.4.1). Analyses addressing potential bias due to missing data are addressed in Section 5.11. All confirmed the primary endpoint result with a statistically significant difference between groups favoring tolvaptan.

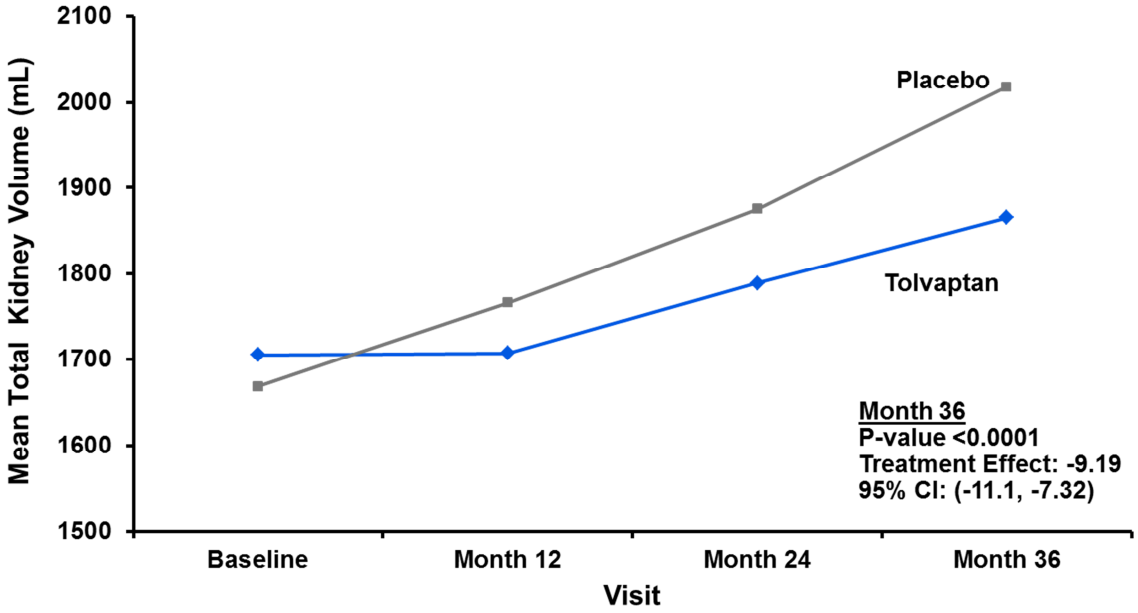


Figure 1 MMRM Analysis of Percent Change from Baseline in TKV in Trial 156-04-251

These effects resulted in a cumulative increase in TKV of 9.6% in tolvaptan treated patients over the course of the 3-year pivotal trial, compared to a cumulative increase of 18.6% in patients receiving placebo (MMRM analysis, p<0.0001). Integration of on-treatment data from the 3-year Trial 156-04-251 with short-term data suggests a reduction of TKV growth by approximately 6% in year one and an additional 2% per year thereafter in tolvaptan subjects, versus an average growth rate of 6% per year in placebo subjects (Section 10.4.1.1). This represents a nearly 50% reduction in the rate of increase of TKV over the first three years. A long-term clinical benefit in TKV would reasonably be expected given a 30% (ie, 4% versus 6%) reduction of kidney growth in each subsequent year of trial treatment. This effect size is clinically relevant and similar to that seen for the rate of renal function decline (Section 5.7.2).

Key Composite Secondary Endpoint: Tolvaptan Reduced the Rate of the Events Associated with Clinical Progression of ADPKD (Including Incidence of Worsening Renal Function and Incidence of Clinically Relevant Renal Pain)

The findings of the key secondary composite endpoint from Trial 156-04-251 were consistent with the results of the primary endpoint (Section 5.6.2). The key secondary composite endpoint measured tolvaptan's effects on 4 clinically relevant complications important to ADPKD patients and their physicians (worsening of renal function, renal pain, hypertension, and albuminuria). Tolvaptan reduced the time to multiple events of the pooled composite endpoints by 13.5%. These findings were robust (p = 0.0095, see

Figure 2), a result that was replicated when using outcomes that were independently adjudicated (p = 0.0044) by a Clinical Events Committee. Additional sensitivity and supportive analyses were performed to test the robustness of the results of the key secondary composite endpoint (Section 10.4.2) and individual components (Section 10.4.3). Analyses addressing potential bias due to missing data are addressed in Section 5.11. Each of these analyses produced results consistent with the primary analysis.

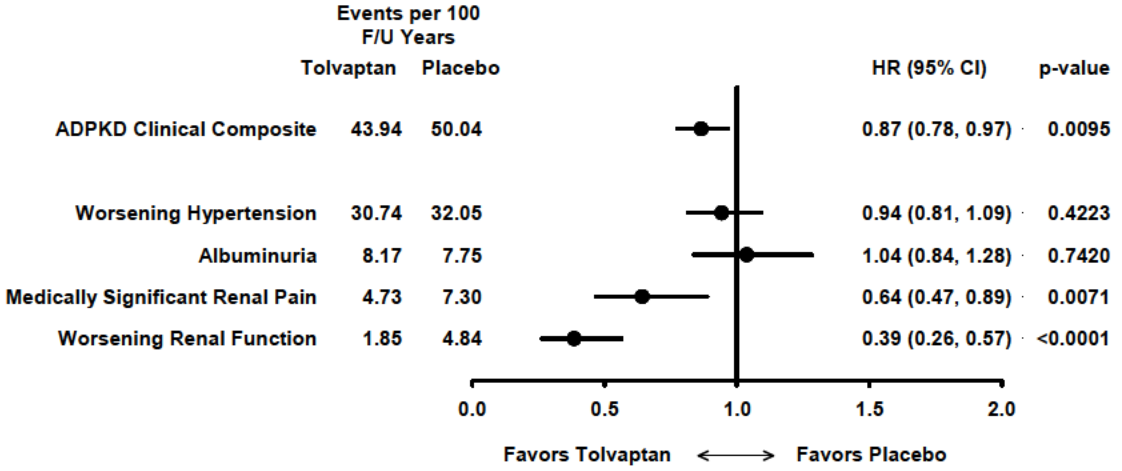


Figure 2 **Forest Plot of the Secondary Key Composite Endpoint and Components in Trial 156-04-251; ITT, Within the Treatment Period**

CI = confidence interval; F/U = follow up.

Prospectively planned exploration of the components of the key secondary composite endpoint in Trial 156-04-251 revealed that favorable effects of tolvaptan treatment were evident in the worsening of renal function (ie, the incidence of a 30% decrease in kidney function) and renal pain components, while no effects were apparent for hypertension or albuminuria (Figure 2). The impact on worsening of renal function was clinically and statistically significant with a 61% effect size, p < 0.0001. Renal pain events were also reduced to a clinically and statistically relevant degree (effect size = 36%, p < 0.001).

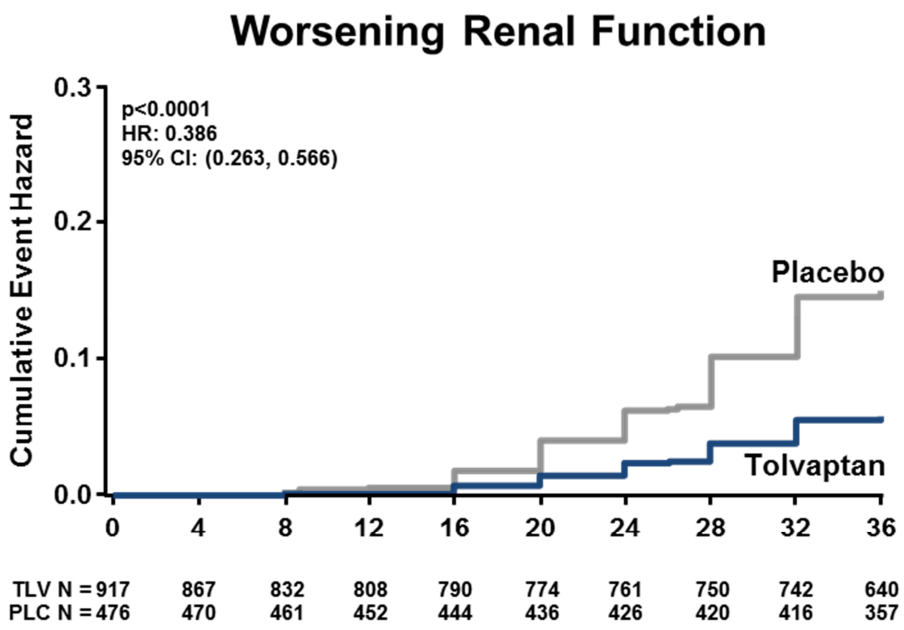


Figure 3 **Cumulative Intensity Plot of Time to Multiple Events of Worsening Renal Function in Trial 156-04-251**

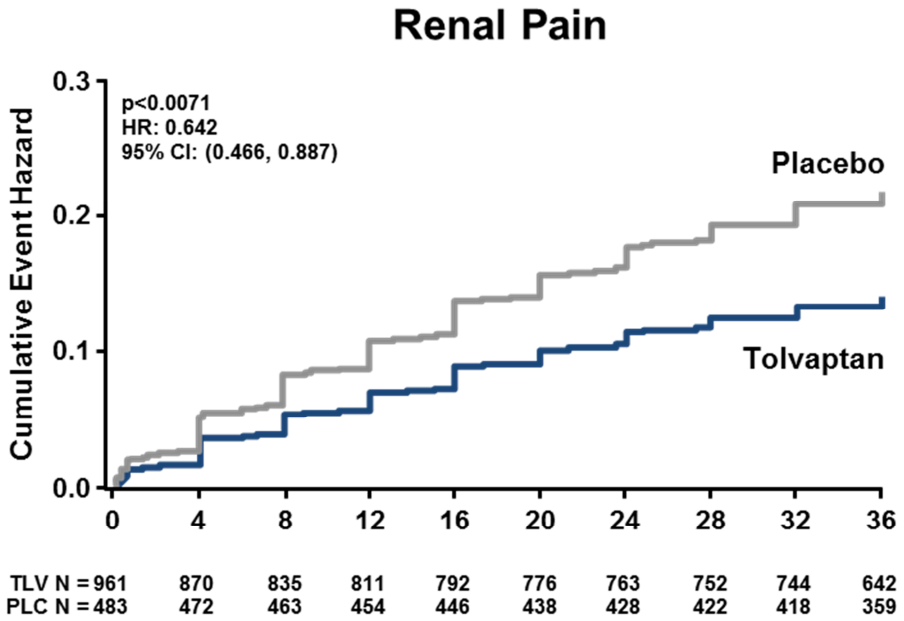


Figure 4 **Cumulative Intensity Plot of Time to Multiple Events of Renal Pain in Trial 156-04-251**

Comparing the temporal incidence of worsening renal function (Figure 3) and renal pain events (Figure 4), the beneficial separation in renal function required at least 16 months of tolvaptan therapy, whereas a reduced number of medically significant renal pain

events were apparent earlier than the Month 4 visit. Separation from placebo grew over the course of the trial for both of these component measures.

Supporting these results, analyses of subject-reported outcomes indicated that renal pain was the most frequent event leading to hospitalizations. Tolvaptan led to nominally significant reduction in hospitalizations for renal pain odds Ratio = 0.23, 95% CI 0.09 to 0.54, p = 0.0004, demonstrating the importance of this key secondary composite component (Section 5.9.2).

First Hierarchically Ordered Secondary Endpoint: Tolvaptan Slowed Renal Function Decline by Approximately 30%

The key secondary composite component of events of worsening renal function is better suited to capture progression of subjects with rapidly progressing disease who already have a lowered eGFR. The slope of renal function decline assesses the effects of therapy in all subjects. This endpoint (using 1/serum creatinine) favored tolvaptan treatment with a slope of −2.609 versus a slope for placebo of −3.812 for a treatment effect of +1.203 $(mg/mL)^{-1}$ $year^{-1}$ (95% CI 0.622 to 1.783, p < 0.0001) (Section 5.7). This equates to a 32% treatment effect and is supportive of the 61% hazard reduction for worsening renal function events.

Renal function slope analyses in subgroups of subjects with CKD Stage 1, CKD Stage 2 or CKD Stage 3 at baseline showed consistent effects favoring tolvaptan, with a 30-33%. reduction in rate of change. This observation demonstrates a consistent benefit of tolvaptan across the earlier phases of ADPKD and is consistent with our understanding of the progression of the illness.

Another sensitivity analysis was aimed at understanding the impact of hemodynamic responses of GFR before, during, and after tolvaptan treatment. Tolvaptan results in an acute and reversible decrease in GFR which produces an acute increase in serum creatinine (Section 4.2.2.1, Figure 5). Therefore, sensitivity analyses calculating slopes incorporating all pretreatment and post-treatment data points (Analysis 1 in Table 2) or using only pretreatment and post-treatment data points (Analysis 2 in Table 2) were performed. Both of these analyses were highly statistically significant (p <0.0001) and in close agreement with the prespecified on-treatment analysis.

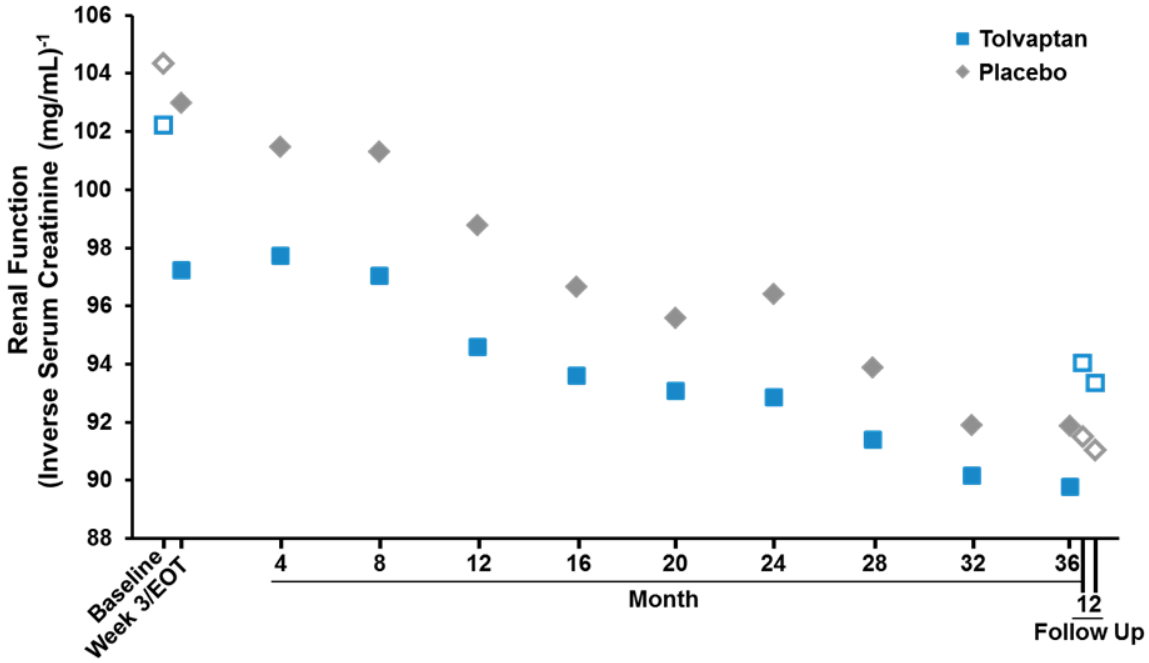


Figure 5 **Mean Change in Renal Function by Reciprocal of Serum Creatinine in Trial 156-04-251**

EOT = end of treatment; GFR = glomerular filtration rate. Filled symbols = on treatment, Empty symbols = pre- or post-treatment.

Table 2 **Analyses of Slope of Reciprocal of Serum Creatinine in Trial 156-04-251**

Analysis	Slope (mg/mL) $^{-1}$ year^{-1}			p-value
	Placebo Group	Tolvaptan Group	Treatment Effect (95% CI)	
Pre-specified on-treatment analysis: Week 3/EOT to Month 36	-3.81	-2.61	1.20 (0.622-1.783)	<0.0001
Sensitivity Analysis 1: All data, Baseline to Last Follow-up	-3.98	-2.43	1.55 (1.034-2.067)	<0.0001
Sensitivity Analysis 2: Off -drug data points only, Baseline and Follow-up Visits	-4.32	-2.70	1.61 (0.789-2.433)	0.0001

CI = confidence interval; EOT = end of titration.

The primary analysis used change from a post-titration, on-treatment, steady-state value (Week 3/EOT). There are precedents for use of this approach to account for acute,

reversible changes in serum creatinine when evaluating long-term trends for renal function (refer to Section 5.15).[6,13,14,15,16,17]

Additional sensitivity and supportive analyses were performed to test the robustness of the renal function slope results (Section 10.4.4). Analyses addressing potential bias due to missing data are addressed in Section 5.11. Each of these analyses produced results consistent with the primary analysis.

Among the sensitivity analyses, correlation analyses demonstrated an association between TKV growth and renal function decline and TKV growth and renal pain events (Section 5.10). This supports the hypothesis that preservation of renal function by tolvaptan may be related to its reduction of cyst growth.

The Pivotal Trial Results are Consistent and Convincing

Tolvaptan slowed the progression of both TKV growth and renal function decline across the 3-year duration of the pivotal trial. Effects on continuous variables (TKV and eGFR) were associated with parallel effects on discrete clinical outcomes of ADPKD (worsening renal function and renal pain events). These clinical outcomes are relevant as indicative of the current risk of hospitalization (due to renal pain) and the future risk of ESRD (30% decrease in eGFR).

Total kidney volume data from patients whose treatment with tolvaptan was interrupted and then re-initiated suggest that the benefits of tolvaptan accumulate only during treatment (Section 5.13). Treatment interruptions reduce the opportunity for maximizing clinical benefit over a patient's lifetime.

Sensitivity analyses (Section 10.4) and the impact of missing data (Section 5.11) on the results of the first 3 trial endpoints (rate of change in TKV, key secondary composite, and renal function rate of change) was investigated. Results for sensitivity analyses were consistent with the endpoints' primary analysis. Missing data from subjects withdrawing from Trial 156-04-251 (23% tolvaptan versus 14% placebo) was treated as missing at random (MAR) since the imbalance was entirely accounted for by adverse events related to aquaresis or hepatic enzyme abnormalities and not due to disease progression. Additional analyses accounting for data missing not at random (MNAR) collectively suggest the preservation of a significant effect and demonstrated that missing data did not lead to false positive conclusions.

Consistent results of subgroup analyses (Section 5.14) across the first 3 trial endpoints support applicability of these efficacy results to entirety of the population studied.

Explorations of ADPKD-related outcomes (Section 5.9) showed that subjects receiving tolvaptan reported less renal pain, nephrolithiasis, hematuria, UTI, and anemia compared with subjects on placebo. Tolvaptan reduced medical resource utilization and lost productivity due to these complications.

Overall, observed benefits for ADPKD subjects are consistent with tolvaptan's expected mechanism of action, are clinically relevant and are robustly significant. Benefits for patients are expected to accrue with long-term therapy. Tolvaptan is the first therapy to be shown in a well-controlled, randomized, clinical trial to alter the course of ADPKD, potentially leading to a delay in the onset of ESRD.

SAFETY

Extensive Safety Database

As of February 1, 2013, the safety profile of tolvaptan in the ADPKD program is based on clinical experience in 1682 subjects, nearly half of whom were exposed for at least 3 years. To date, 7551 adult subjects worldwide have been exposed to oral tolvaptan in single- and multiple-dose clinical trials in ADPKD and other indications (Section 6.1).

Common AEs are Primarily Aquaretic-related

The most commonly occurring AEs in Trial 156-04-251 were related to the mechanism of action and did not often lead to discontinuation (Section 6.5). Despite these effects, approximately 75% of subjects receiving tolvaptan were able to maintain on therapy for 3 years, with approximately 50% of those who completed the trial maintaining the highest dose of 120 mg/day.

Tolvaptan is a potent, specific AVP V_2 receptor antagonist that produces free water clearance (aquaresis), an ideal treatment effect for conditions such as hyponatremia and fluid overload. In subjects with ADPKD, tolvaptan's aquaretic action was associated with expected treatment-emergent adverse events (TEAEs) of thirst, dry mouth, pollakiuria, and polyuria. Discontinuations in the tolvaptan treatment group were higher due to these side effects, which presented no grave risk or persistent injury.

The most frequently reported TEAEs in tolvaptan subjects in Trial 156-04-251 (ie, reported at an incidence > 10% and at least twice that of placebo subjects) were Thirst (55.3% vs 20.5%), Polyuria (38.3% vs 17.2%), Nocturia (29.1% vs 13.0%), Pollakiuria (23.2% vs 5.4%), and Polydipsia (10.4% vs 3.5%)

Adverse Events of Special Interest

Using data from the 3-year pivotal trial, 3 new safety signals were identified and recognized in the proposed tolvaptan label: risk for hepatic injury is listed as a "Boxed Warning"; and risks for skin neoplasm (esp. basal cell carcinoma) and glaucoma are described in "Warnings and Precautions". These risks are important patient management issues for a disease that requires life-long treatment and are discussed in greater detail below.

Increased incidence of elevation of transaminases was observed in tolvaptan-treated subjects. Elevation (>3 x upper limit of normal [ULN]) of ALT (alanine transaminase) was observed in 4.4% (42/958) of patients on tolvaptan and 1.0% (5/484) of patients on placebo, while elevation (>3xULN) of AST (aspartate transaminase) was observed in 3.1% (30/958) of patients on tolvaptan and 0.8% (4/484) patients on placebo.

An independent, expert, adjudication committee conducted a blinded review of all subjects who experienced significant elevations after tolvaptan exposure was conducted. Significant elevations were present only in ADPKD subjects, and a number of cases were adjudicated as highly likely or probable in their relationship to tolvaptan therapy. The committee identified a period of susceptibility to elevated transaminases ranging from 3 to 14 months from the beginning of treatment, suggesting the potential for mitigation in the signal through early identification with frequent monitoring. Withdrawal from treatment led to resolution of transaminase elevations to below 3xULN within 1 to 4 months.

Among those identified, 2 subjects from Study 156-04-251 met Hy's laboratory criteria (ie ALT > 3xULN and total bilirubin > 2xULN for drug-induced liver injury; a third such subject was identified from an open-label extension trial 156-08-271. All three subjects were adjudicated as probable or highly likely due to tolvaptan, all returned to below 1xULN, and none experienced fulminant liver failure or permanent livery injury or dysfunction.

Liver enzyme abnormalities were not found to be related to baseline characteristics, tolvaptan dose, or total exposure. Their pattern points to an idiosyncratic mechanism rather than direct toxicity (Section 6.8.2). Based on these findings, a theoretical estimate of the risk of observing drug-induced liver failure in patients with ADPKD is 1:3000.

The committee also evaluated subjects with elevations in liver enzymes from studies in other indications with tolvaptan (eg, hyponatremia and congestive heart failure). No cases were identified that were causally related to tolvaptan suggesting that the signal for liver injury was specific to the ADPKD population.

Based on these findings, Otsuka has proposed warning of the risk of potential liver injury in labeling. In addition, Otsuka has proposed a REMS (risk evaluation mitigation strategy) that would mandate that physicians regularly attest that their patients are completing monthly liver monitoring for the first 18 months of therapy and periodically thereafter. If patients do not comply with monthly liver monitoring, they will not receive continued distribution of tolvaptan (Table 3).

Table 3 Proposed Risk Evaluation and Mitigation Strategy

REMS Elements		Description
Certification	Physician	Physicians are required to demonstrate their knowledge of safe use to prescribe Tolvaptan
	Patients	Patients are educated for the safe use of Tolvaptan with the medication guide and product labeling
	Information communicated	• The risk of hepatotoxicity of Tolvaptan • Requirements of LFTs, prior to initiation and thereafter every month for the first 18 months (then at regular 3-6 month intervals)
Specialty Pharmacy		Only certified specialty pharmacy can dispense Tolvaptan directly to the patient
Patient Registry		All patients and their information are entered into the privacy-protected database (eg, frequency of LFT)
Assurance of regular liver function tests		• Physicians are required to attest every 2 months that they have ordered and reviewed the completed LFTs, and that the patient is still an appropriate candidate to continue Tolvaptan therapy • The attestation is required for Tolvaptan to be shipped to patient

LFT=liver function test.

Malignant tumors were also reported more frequently in tolvaptan-treated subjects than in placebo-treated patients (1.7% versus 0.4%) (Section 6.8.1.1). This imbalance was primarily driven by skin neoplasms, in particular basal cell carcinomas; a finding that had not been observed in prior placebo-controlled, non-ADPKD trials. While skin cancers were not clearly attributable to treatment, a causal relationship could not be excluded. Therefore, Otsuka has proposed that a new Warning and Precaution be included in product labeling for ADPKD.

Finally, an imbalance was also noted in the incidence of glaucoma for tolvaptan vs. placebo treated patients in Trial 156-04-251 (0.8% vs 0.4%, respectively). Glaucoma was observed as a very rare event in earlier clinical studies, but was not previously included in labeling. While these AEs were not clearly attributable to treatment, and a causal relationship could not be ruled out, Otsuka has again recommended that a new Warning and Precaution be included in product labeling for ADPKD.

BENEFIT-RISK

In subjects with ADPKD, tolvaptan treatment was shown to significantly slow cyst growth (TKV) and the associated decline in renal function (eGFR), as well as to provide significant reductions in the incidence of events of worsening kidney function and renal pain. Observed benefits of treatment included a nearly 50% reduction in the rate of kidney growth over 3 years, a significant delay in renal function decline across CKD stages 1-3, and a significant reduction in renal pain events leading to fewer hospitalizations. When taken together, these data suggest that tolvaptan will substantially delay the time to onset of ESRD (ie the need for dialysis and/or transplantation).

Observed risks include aquaretic side-effects and the potential for liver injury, indicating the need to monitor clinical laboratory results. The potential risk for irreversible liver damage indicates careful monitoring to identify and mitigate potential harm. Otsuka is committed to working with FDA, physicians and patients to develop a REMS to address the risk of hepatic injury, including monthly monitoring of hepatic transaminases (Section 7).

Tolvaptan has a favorable benefit-risk profile. ADPKD's unmet medical needs are benefited by robust efficacy on meaningful clinical endpoints. These benefits, combined with strategies to address tolvaptan's observed and expected risks, support the approval of tolvaptan for the treatment of rapidly progressing ADPKD.

Table of Contents

List of In-text Tables

List of In-text Figures

List of Abbreviations

ADPKD	Autosomal dominant polycystic kidney disease
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUCss	Area under the concentration-time curve from 0 to 24 hours at steady state
AUCτ	Area under the concentration-time curve t steady state
AVP	Arginine vasopressin
BP	Blood pressure
BT	Bilirubin, total
BUN	Blood urea nitrogen
cAMP	3'-5'-cyclic adenosine monophosphate
CEC	Clinical Events Committee
CI	Confidence interval
CKD	Chronic kidney disease
CL/F	Apparent total body clearance following extravascular administration
C_{max}	Maximum plasma concentration
$C_{min,ss}$	Minimum plasma concentration from 0 to 24 hours at steady state
CMQ	Custom MedDRA query
CrCL	Creatinine clearance
CRISP	Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease
CSR	Clinical study report
CYP	Cytochrome P-450 enzyme
dBP	Diastolic blood pressure
DILI	Drug induced liver injury
eCrCL	Estimated creatinine clearance
$eCrCL_{CG}$	Estimated creatinine clearance determined using the Cockcroft-Gault formula
eGFR	Estimated glomerular filtration rate
$eGFR_{CKD-EPI}$	Estimated glomerular filtration rate by the Chronic Kidney Disease Epidemiology Collaboration
$eGFR_{MDRD}$	Estimated glomerular filtration rate by the Modification of Diet in Renal Disease formula
ETASU	Elements to Assure Safe Use
ESHD	End stage hepatic disease
ESRD	End stage renal disease
EOT	End of titration
ET	Early termination

EU	European Union
FDA	Food and Drug Administration
FWC	Free water clearance
GFR	Glomerular filtration rate
HFM	High fat meal
HR	Hazard ratio
HTN	Hypertension
ICH	International Conference on Harmonisation
IM	Intramuscular
IR	Immediate release
IV	Intravenous
IVRS	Interactive voice response system
ITT	Intent-to-treat
LS	Least squares
MAP	Mean arterial pressure
MAR	Missing at random
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
mGFR	Measured glomerular filtration rate
Min	Minimum
MMRM	Mixed model repeated measures
MNAR	Missing not at random
MRI	Magnetic resonance imaging
NDA	New drug application
NIH	National Institutes of Health
OC	Observed cases
OPC	Otsuka Pharmaceutical Company, Ltd
OPDC	Otsuka Pharmaceutical Development & Commercialization, Inc
OTC	Over-the-counter
PD	Pharmacodynamic
PK	Pharmacokinetic
PKD	Polycystic kidney disease
PMDA	Pharmaceuticals and Medical Devices Agency
QTc	Corrected QT (interval)
REMS	Risk Evaluation and Mitigations Strategy
SAE	Serious Adverse Event
sBP	Systolic blood pressure
SD	Standard deviation
SOC	System organ class
SPA	Special protocol assessment
$t_{1/2,z}$	Elimination half-life during the terminal elimination phase
TEAE	Treatment-emergent adverse event
TKV	Total kidney volume
US	United States
UTI	Urinary tract infection

1 Autosomal Dominant Polycystic Kidney Disease: An Unmet Medical Need

1.1 Background on Autosomal Dominant Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease (ADPKD) is a rare, hereditary, systemic disease characterized by progressive development of cysts that impinge on and ultimately disrupt normal kidney architecture. It is the leading monogenic cause of heritable chronic renal failure and demonstrates considerable phenotypic variability. The PKD1 and PKD2 genetic variants of ADPKD appear to differ primarily in the relative number of renal cysts formed at any given age, not in the rate of their growth.[18,19,20,21,22,23]

ADPKD gene defects disrupt the normal differentiated phenotype of renal tubular epithelium. The mutations lead to increases in intracellular 3'-5'-cyclic adenosine monophosphate (cAMP) leading to a loss of mitotic polarity, increased cellular proliferation and apoptosis, and fluid secretion into cysts.[11,24,25,26]

Cyst growth displaces and destroys normal kidney tissue, culminating in fibrosis, renal architectural derangement, and ultimately kidney failure.[11,24] An estimated 45% to 70% of patients with ADPKD progress to ESRD by age 65.[8] A cyst-filled kidney can eventually weigh up to 20 pounds or more.[20] This burden may result in intermittent episodes of acute pain, as cysts rupture or hemorrhage. At least one quarter of adults with ADPKD are asymptomatic; however, diagnostic testing for the disease in patients with a family history of the disease may have unintended negative impacts, as denial of health and life insurance for individuals with ADPKD is not uncommon.[27]

Studies of ADPKD have shown that it progresses at varying rates, but typically does not manifest as detectable loss of renal function until quite late in the course of the disease, when parenchymal deterioration has reached a point where serious therapeutic interventions are necessary.[28] The number, distribution, and growth rate of cysts determine the timing and severity of related clinical outcomes.[18,27,29] Negative clinical outcomes begin years to decades before declining renal function can be detected, leading to kidney failure for many but not all patients.[3,21,10] Most ADPKD patients present with symptoms such as hypertension, flank pain, urinary tract infection (UTI), nephrolithiasis, gross hematuria or a palpable abdominal mass.[27,30,31] In the later stages of the disease, multiple organs become involved and can manifest as a broad spectrum of complications, as shown in Table 1.1-1.

Table 1.1-1 Manifestations of ADPKD

Symptoms Observed in Early Stages Often Leading to Diagnosis	Outcomes and Consequence of Long-term ADPKD
• Hypertension • Hematuria • Polyuria • Nocturia • Palpable Kidneys • Kidney Stones • Abdominal/Flank Pain • Hernia • Diverticulosis • Recurrent Urinary Tract Infections	• Aneurysms • Seminal Vesicle, Dura, and Arachnoid Cysts • Vascular Dissections • Valvular Heart Disease • Dilated Cardiomyopathy • Pericardial Effusion • Renal Artery/Vein Occlusions • Bile Duct Dilation • Hepatic Cysts • Pancreatic Cysts • Intraductal Papillary Mucinosis • Neoplasms • Male Infertility

1.2 Role of Arginine Vasopressin as a Promoter of ADPKD

Arginine vasopressin (AVP) is a neuropeptide hormone released from the posterior pituitary. Arginine vasopressin causes vasoconstriction via vascular V_{1a} receptors and promotes water reabsorption in the kidneys via V_2 receptors, both of which are G protein-coupled transmembrane receptors. A decrease in blood pressure (BP), or an increase in plasma osmolality, leads to an increase in blood AVP concentrations.

The cells forming early cysts appear to arise from the collecting duct, a tissue where AVP is a principle stimulator of cAMP, which appears to stimulate cyst development and growth through proliferation and secretion.[23]

Arginine vasopressin, by increasing cAMP intracellular signaling, leads to chloride transport- mediated fluid secretion into the cysts and, separately, promotes proliferation of the lining cells.[9,21] Cyst formation and expansion disrupts normal kidney structure, impacting hemodynamic flow, leading to ischemia, fibrosis and decreased nephron number and function. As shown in Figure 1.2-1, cysts grow from nephrons, separate from the nephrons, and then continue to enlarge, causing the kidneys to enlarge as well.

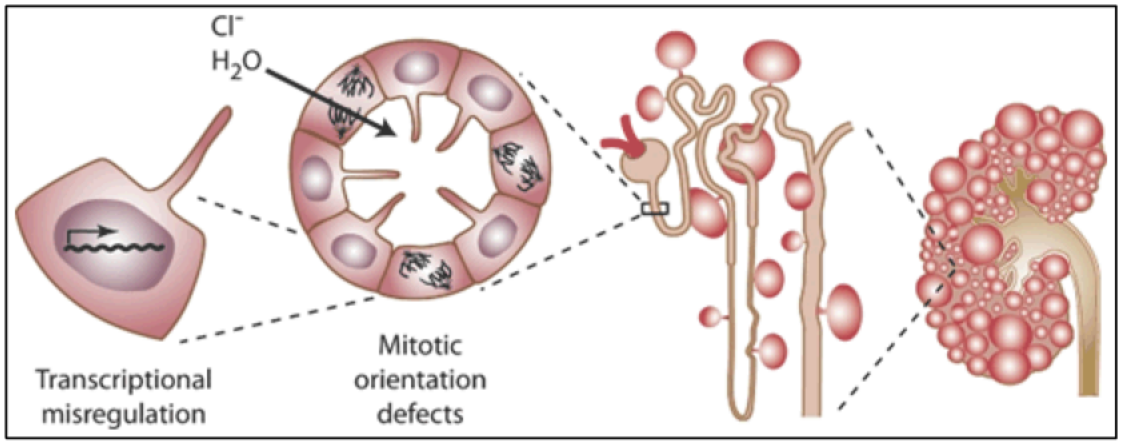


Figure 1.2-1 ADPKD Effects Begin at the Nephron - the Vital Basic Functional and Structural Unit of the Kidney

From Chapin HC, Caplan MJ. The cell biology of polycystic kidney disease. J Cell Biol 2010; 191: 701–10. Reproduced with permission.

Inhibition of AVP binding at the V_2 receptor decreases adenylyl cyclase activity, resulting in a decrease in intracellular cAMP in the kidney.[10,11] In animal models of ADPKD, eliminating, lowering or blocking AVP leads to decreased kidney weight, cyst volume, and fibrotic volume.[12] Rats with no endogenous production of AVP (Brattleboro rats [$AVP^{-/-}$/$Pkhd1^{+/+}$]) and rats with a PKD phenotype (PCK rats [$AVP^{+/+}$/$Pkhd1^{-/-}$]) were crossed to generate rats with a PKD phenotype and varying levels of AVP. At 10 and 20 weeks of age, PCK [$Pkhd1^{-/-}$/$AVP^{-/-}$] rats had lower renal cAMP and almost complete inhibition of cystogenesis compared with PCK [$Pkhd1^{-/-}$/$AVP^{+/+}$] and PCK [$Pkhd1^{-/-}$/$AVP^{+/-}$] rats. The eventual appearance of cysts in the PCK [$Pkhd1^{-/-}$/$AVP^{-/-}$] rats indicated that other redundant factors contribute to cyst formation and expansion. When given the V_2 vasopressin agonist, 1-deamino-8-D-arginine vasopressin, PCK [$Pkhd1^{-/-}$/$AVP^{-/-}$] rats showed an increase in renal cAMP and developed explosive renal cystic disease surpassing that seen in PCK [$Pkhd1^{-/-}$/$AVP^{+/+}$] rats. These data convincingly support that AVP activation of the kidney V_2 receptor is a key promoter of the production, growth and proliferation of cysts and suggest that V_2 receptor antagonists may provide the first opportunity to interrupt the pathophysiology of the disease in humans.

1.3 Epidemiology

The worldwide prevalence of ADPKD varies between less than 1:2000 to 1:4000. In the United States (US), ADPKD is the fourth leading cause of kidney failure, affecting all races and genders equally. The number of diagnosed ADPKD cases in the US in 2009 was estimated at 116,228, which supported tolvaptan's orphan designation.[29,32,33,34,35]

1.4 Unmet Medical Need

Currently there is no available pharmacologic therapy that targets the underlying pathophysiology of ADPKD. Existing therapies are palliative, targeting pain, infection, and hypertension. Dialysis, surgical intervention, and transplantation may be necessary. Often, the only definitive intervention for renal complications in ADPKD is kidney transplantation, which typically occurs after years of peritoneal or hemodialysis and complications associated with them. These chronic complications contribute to early and ever increasing life-long morbidity and mortality. ADPKD is the fourth highest cause leading to ESRD.[8]

Medical research has made little progress in delaying the time to development of ESRD in the current patient generation versus the previous one.[36] Moreover, once kidney function is compromised beyond an estimated glomerular filtration rate (eGFR) < 30 mL/min, healthcare utilization costs incurred by ADPKD patients rise steeply,[8] further underscoring the importance for patients, their families, and society at large for an intervention that slows the progression of ADPKD and delays initiation of renal replacement therapy.

2 Tolvaptan as a Treatment for ADPKD

2.1 Mechanism of Action

In 1999, the mechanisms of pathologic response to AVP in PKD animal models were first reported, leading to the initiation of the tolvaptan ADPKD development program. In animal models of ADPKD, endogenous AVP is elevated and elevates renal cAMP, which leads to increased cyst fluid accumulation and epithelial cell growth.[10,11] In human subjects with ADPKD, elevated plasma AVP concentrations, and/or exaggerated response of AVP to fluid deprivation or a sodium challenge, have been observed.[18,19,23]

Tolvaptan is a highly selective AVP V_2 receptor antagonist with an affinity for the human V_2 receptor that is 1.8 times that of native AVP.[37] Tolvaptan affinity for the V_2 receptor

is 29 times greater than for the V_{1a} receptor. When taken orally, tolvaptan prevents the binding of AVP at the V_2 receptor in the kidney. The decreased binding of AVP to the V_2 receptor lowers adenylate cyclase activity, resulting in a decrease in intracellular cAMP concentrations.[11,24] Inhibition of AVP binding at the V_2 receptor was shown to delay development of renal cysts in several models of PKD including human nephronophthisis (pcy mouse),[38] autosomal recessive polycystic kidney disease (ARPKD; PCK rat),[25,39] and ADPKD ($PKd2^{WS25/-}$ mouse).[40,41] Other models of AVP reduction[12,42] also provided substantive evidence of the critical importance of the role of AVP in the pathogenesis of ADPKD.

In human ADPKD cyst epithelial cells, tolvaptan inhibited AVP-stimulated in vitro cyst growth and isosmotic transepithelial secretion of chloride into cysts.[43] As a selective V_2 receptor inhibitor, tolvaptan would act on those cells from which ADPKD cysts appear to arise. As shown in Figure 2.1-1, cAMP increases secretion and proliferation, which leads to cyst formation and increase in total kidney volume.[18,43] By modulating cyst cell proliferation and secretion of fluids into cysts, tolvaptan was hypothesized to have a beneficial effect on the downstream clinical consequences of ADPKD, ie, eGFR, renal pain, hypertension, and albuminuria.

Inhibition of the V_2 receptor in the kidney epithelial cells also prevents aquaporin 2 containing vesicles from fusing with the plasma membrane, which, in turn, causes an increase in urine water excretion that results in an increase in free water clearance (aquaresis) and a decrease in urine osmolality. In Figure 2.1-1, aquaresis is shown as a mechanism by which V_2 receptor blockade might increase the incidence of adverse events (AEs) such as polyuria and thirst. V_2 receptor blockade in non-cystic cells, however, produces a physiologic response which can be used to monitor effective AVP blockade, ie, decreases in urine osmolality.

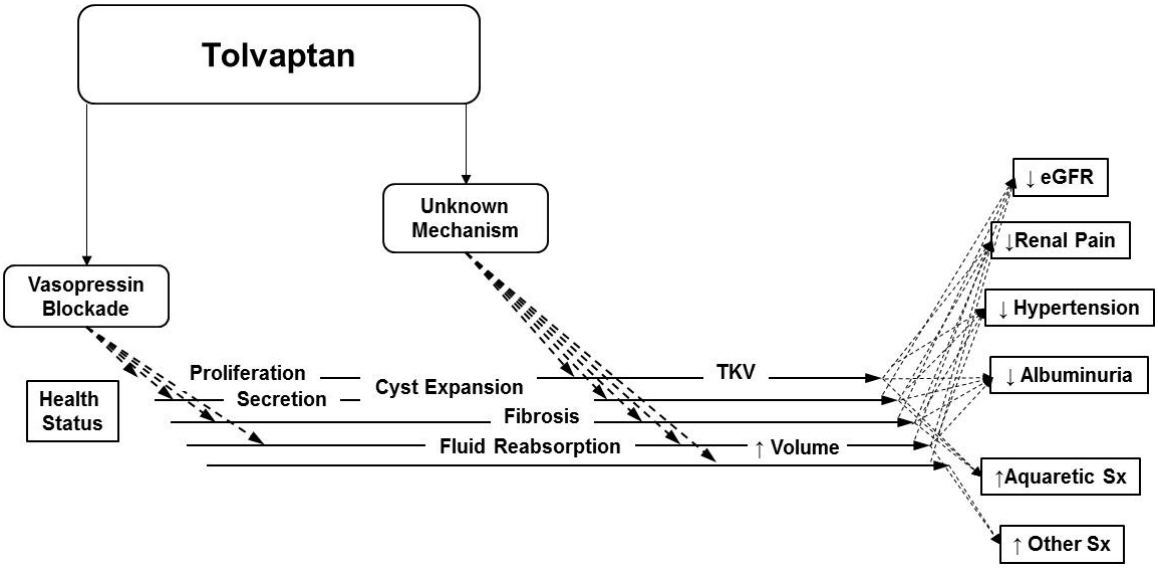


Figure 2.1-1 Proposed Mechanistic Action of Tolvaptan in ADPKD Outcomes

eGFR = estimated glomerular filtration rate; TKV = total kidney volume; Sx = symptoms.

Reprinted (with adaptation) with permission from "Evaluation of biomarkers and surrogate endpoints in chronic disease," 2010,[44] by the National Academy of Sciences, Courtesy of the National Academies Press, Washington, D.C.

Reduction or blockade of AVP can be assured when the concentration of urine falls below that of plasma (roughly 285-300 mOsm/kg). Continuous inhibition of the V_2 receptor, as evidenced by continuous suppression of urine osmolality, was shown in animal PKD models to be more efficacious in decreasing the rate of TKV.

Because tolvaptan acts through blockade of AVP activation of the V_2 receptor, there is no expectation that tolvaptan would confer a benefit in tissues where V_2 receptors are not present, eg, hepatic cholangiocytes.

2.2 Efforts Toward Development of a Treatment for ADPKD

Over 30 years of research and collaboration among a broad and diverse group of organizations has culminated in tolvaptan being the first intervention to provide convincing evidence of a favorable impact on the progression of ADPKD. This evidence exists in the demonstration of inhibiting kidney cyst growth, reducing events relating to kidney pain, and slowing the decay of kidney function. Starting in 1982, when the Polycystic Kidney Disease Foundation was established with the goal of finding a treatment, there have been significant advances by organizations including National Institutes of Health (NIH), PKD Foundation, the Food and Drug Administration (FDA;

the Agency), the PKD Outcomes Consortium/Critical Path Institute, and industry, including companies like Otsuka. Progress has included the identification of the PKD1/PKD2 genes, the identification of the vasopressin receptors as therapeutic targets, the identification of meaningful clinical endpoints for interventional trials, and the execution of the largest clinical program (tolvaptan) for study of an intervention for this disease.

2.3 Regulatory Milestones in the ADPKD Development Program

The tolvaptan ADPKD clinical development program began in 2004 concurrent with ongoing hyponatremia and congestive heart failure programs. The ADPKD program is global in scope, with 17 ongoing or completed trials conducted in the 3 major International Conference on Harmonisation (ICH) regions. The trial details are summarized in Section 10.1.

Otsuka held scientific advice meetings regarding the ADPKD development program with the US FDA (March and November 2005), European Medicines Agency (24 Oct 2005), and the Japan Pharmaceuticals and Medical Devices Agency (22 Nov 2005). In the US, the development program for tolvaptan for ADPKD was granted Fast Track designation on 20 Jan 2006 and Orphan Drug designation on 06 Apr 2012. In Japan, the program was granted Orphan Drug status on 11 Aug 2006.

Regulatory input sought and obtained from the US FDA contributed to the design and analysis of the pivotal trial, 156-04-251. Certain key aspects of this feedback and how it shaped the development program are described below.

- A Pre-investigational New Drug Meeting was held on 16 Mar 2005; key points included:
  - Alternative endpoints were suggested, including those that could be “measured in a reasonable time,” including hypertension, renal function decline, and hematuria.
  - Non-clinical and clinical pharmacology studies are adequate.
  - Dose selection approaches were discussed.
- A special protocol assessment (SPA) for trial 156-04-251 was submitted on 18 Aug 2005, to which the FDA responded on 29 Sept 2005 and discussed in a meeting on 15 Nov 2005. Specific protocol recommendations included:
  - Target population in the protocol is reasonable.
  - Titration approach for dosing accepted as “the best use of available patients is to titrate them to the highest dose. The design is therefore acceptable.”
  - “If the hypothesis that early treatment is necessary to affect outcome is correct, we recognize the difficulty in demonstrating the effects in renal function, a late consequence. On the other hand, there is no intervention to alter renal volume that is known to affect renal function, so it is hard to accept renal volume as a

surrogate. Even if one thought it 'reasonably likely' to predict favorable changes in renal function many years later, patients seem unlikely to remain on placebo for long after the drug is available. It will therefore be possible only to observe the placebo-treated and tolvaptan-treated patients on long-term tolvaptan. It is possible, of course, that the 3-year delay in treatment in the placebo group will lead, years later to earlier development of renal dysfunction."

- "... keeping volume as the primary endpoint and the suggested composite as a needed endpoint that would be reviewed if the volume effect were favorable."
- "We suggest you craft a composite end-point including the various serious manifestations of the disease - pain requiring surgical decompression, hematuria, infection, nephrolithiasis, and perhaps others. This could be assessed as a time-to-first event or as a measure of total burden of disease over time."
- "Consider a sequential analysis, with the first endpoint rate of renal volume changes as proposed. The second, tested at p=0.05 if the first is successful, would be the [composite] endpoint..." "You would need to choose others [endpoints]. Certainly, rate of GFR change would be important."
- A key secondary composite endpoint must be favorable to provide evidence of effectiveness.
- "Subjects withdrawn for any reason should be followed for outcomes until the end of the study."
- "The analysis of the primary endpoint will need a conservative plan for handling excess withdrawals from the tolvaptan treatment arm."
- The Agency expressed a willingness to consider different methods for imputing various types of missing data.
- The Agency agreed if the primary endpoint and composite endpoint are both statistically significant, with other endpoints supportive, the single phase 3 trial would be sufficient to support New Drug Application (NDA) approval.

- The protocol with detailed statistical methodology was submitted in March 2006 to the FDA.
- On 10 June 2009, a Statistical Meeting was held with FDA.
  - FDA stated that "we do not currently accept changes in kidney volume as a surrogate endpoint" and thus will place emphasis on the findings for your key secondary composite endpoint.
  - FDA noted it "did not consider changes in renal volume as an irrelevant endpoint and commented that showing an effect of tolvaptan on renal volume provides supportive data."
  - The Agency indicated that were they to consider the primary endpoint of change in TKV as anything more than a "gatekeeper," they would agree to a proposed use of mixed-measures repeat model (MMRM) sensitivity analysis.
  - The FDA stated, "A p-value < 0.05 from a single trial is acceptable for your primary efficacy endpoint because we do not consider this endpoint a surrogate of benefit. In order to provide convincing evidence of treatment benefit, the composite key secondary endpoint will need a p-value < 0.01."

  - The Agency noted that it is important to establish whether or not tolvaptan's effect on these endpoints (serum creatinine, urinary albumin, blood pressure) persists off treatment. "If these benefits persist, it would be easier to believe that tolvaptan therapy led to a change in the underlying renal anatomy/disease process." To help address this issue, the sponsor proposed measuring key endpoints at a follow-up visit 14 days after study subjects have completed therapy.
  - The sponsor agreed to adjudication of the key secondary composite events.
- Notable correspondence with the Agency dated 23 Mar 2012, prior to trial unblinding, related that the potential consideration of TKV as a surrogate marker, which could lead to a pathway for approval (eg, for Trial 156-04-251) via the Subpart H regulations, was declined by FDA.
- A Pre-NDA Meeting was held on 19 Jul 2012. Therein, the Agency agreed that the efficacy and safety results of the single, pivotal 156-04-251 trial were adequate to support a filing. The Agency reiterated that they do not currently accept changes in kidney volume as a surrogate endpoint and thus will place (review) emphasis on the findings for the key secondary composite endpoint. Otsuka discussed with FDA the new findings for DILI and Otsuka's proposed risk management strategy, including plans for adjudication of suspect cases of liver injury.
- In November 2012, a meeting was held with FDA to discuss the hepatic adjudication report and the proposed risk mitigation plan. At this point, actions taken to monitor subjects in ongoing clinical trials and methods to disseminate information to patients currently taking Samsca® (tolvaptan) were discussed. This culminated in the distribution of Dear Healthcare Provider letters on 22 January 2012 and 01 May 2013.

Tolvaptan was approved initially in 2009 by the FDA and the European Union (EU) for the treatment of specific forms of hyponatremia and in 2010 by Japan for the adjunct treatment of volume overload in heart failure. It has since been approved in 10 markets (US, EU, Hong Kong, Japan, Taiwan, Canada, Republic of Korea, China, Indonesia, and Australia) for various forms of hyponatremia and also volume overload in heart failure (Japan). With dose ranges of 7.5 to 15 mg/day approved in Japan and 15 to 60 mg/day approved in all other regions, a comprehensive assessment of safety has been submitted in support of prior regulatory approvals. This assessment identified the most common AEs associated with tolvaptan as being related to its mechanism of action (eg, thirst, polyuria). Additionally, a mortality trial in over 4000 acutely decompensated heart failure patients given 30 mg once daily demonstrated that in a best standard of care setting, adjunctive tolvaptan was noninferior to adjunctive placebo for mortality or cardiovascular morbidity.

3 Tolvaptan Clinical Development Program in ADPKD

3.1 Overview of Clinical Development Program

Tolvaptan's clinical development extended from prior programs in other indications to the ADPKD population and its particular needs. The pivotal trial of the ADPKD program consists of a 3-year, multinational, randomized, double-blind, placebo-controlled trial in 1445 subjects (Trial 156-04-251; also known as the "TEMPO 3:4" trial)[45] (see Section 3.2). This trial was developed based on phase 2 confirmation of effective dose range and is supported by trials addressing key safety, efficacy, pharmacokinetic (PK), and pharmacodynamic (PD) questions. The ADPKD clinical program comprises 17 completed or ongoing trials, as shown in Figure 3.1-1 (see also Section 10.1). Note that, while a modified-release (MR) formulation of tolvaptan is being studied in ADPKD subjects, the focus of the current marketing application is the immediate-release (IR) formulation.

In addition to the pivotal Trial 156-04-251, five phase 2 and 3 open-label extension trials (Trials 156-04-250, 156-05-002, 156-08-271, 156-09-003, and 156-10-003) in ADPKD subjects were designed to evaluate safety and long-term efficacy outcomes (TKV, eGFR) with tolvaptan, including (in Trial 156-04-250) the effects of interrupted treatment. Combined data from the 2 completed trials, 156-04-250 and 156-05-002 (N = 63 subjects), were analyzed in comparison with a matched cohort of untreated ADPKD subjects receiving standard of care (analysis designated as Study 156-09-283). The natural history matched-control data were derived from 2 NIH studies: Modification of Diet in Renal Disease (MDRD)[13] and CRISP I.[3] Refer to Section 10.3 for by-trial summaries of the 2 completed open-label extension trials 156-04-250 and 156-05-002, as well as for the matched-control comparison Study 156-09-283.

In addition to the long-term trials, data on the PK/PD of tolvaptan, including urine osmolality, TKV and/or GFR, are available from 6 clinical pharmacology trials in ADPKD subjects with varying degrees of renal function.

In total, 1682 subjects have been exposed to the proposed IR formulation of tolvaptan used in the ADPKD program. Clinical data in other indications (7551 adult subjects worldwide) and marketing experience were also considered in the safety evaluation for use of tolvaptan in patients with ADPKD.

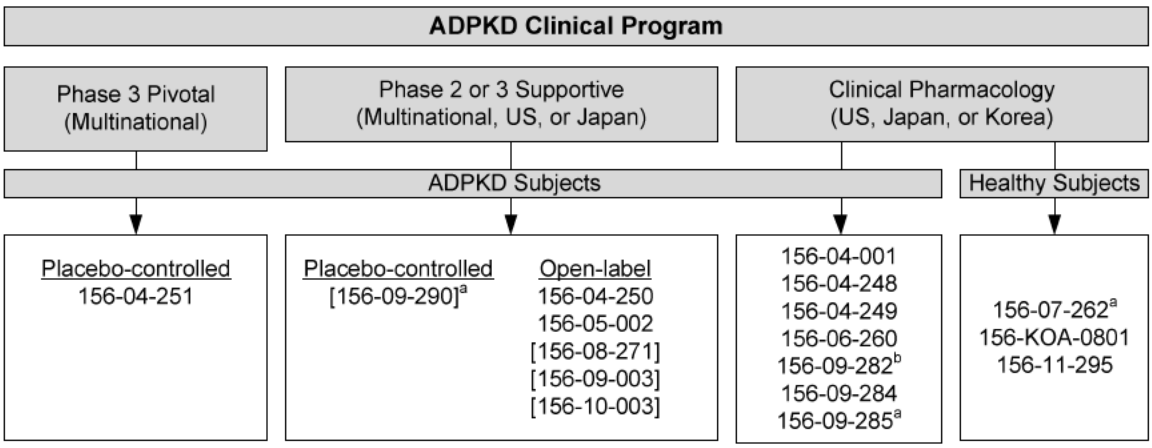


Figure 3.1-1 Tolvaptan ADPKD Clinical Program

[ ] Represents ongoing trial.
ADPKD = autosomal dominant polycystic kidney disease; US = United States.
[a] Modified release capsule tested in addition to immediate release tablet.
[b] Included healthy subjects and renally impaired subjects. Subjects with ADPKD were eligible for participation; however, none was enrolled.

3.2 Pivotal Trial Design, Trial 156-04-251

Trial 156-04-251 was a long-term safety and efficacy of tolvaptan in which oral split-dose regimens (titrated between 60 mg/day and 120 mg/day) were compared with placebo over 3 years. The 3-year trial duration was selected to provide an adequate period to detect clinically relevant differences in the selected efficacy endpoints. This trial was conducted from January 2007 to January 2012 and included subjects from 129 enrolling centers in the Americas, Japan, Europe, and Australia. The primary objective of this trial was to evaluate the long-term efficacy of tolvaptan in ADPKD subjects through rate of TKV change and clinical outcomes of progression as a composite endpoint (consisting of events related to progression of renal pain, worsening renal function, hypertension, and albuminuria) for tolvaptan compared with placebo subjects. The trial was designed to enroll between 1200 and 1500 subjects who were randomized in a 2:1 ratio to tolvaptan or placebo groups.

Subjects aged 18 to 50 years with ADPKD (meeting modified Ravine criteria) were recruited with relatively preserved renal function (estimated creatinine clearance by Cockcroft-Gault [$eCrCL_{CG}$] ≥ 60 mL/min [CKD Stages 1 to 3; see Section 10.2])[46,47,48] and total kidney volume consistent with rapid cystic growth (≥ 750 mL by MRI). These thresholds were chosen to enrich the trial population for those whose cystic disease was more rapidly progressing. These selection criteria obviate the need for genetic

classification (PKD1, PKD2), as the phenotypic expression is more predictive of disease outcome.

The trial began with a screening period for baseline evaluation, and proceeded to a treatment period that included an initial titration phase of up to 3 weeks followed by a long-term maintenance phase up to 36 months, and 2 follow up visits after discontinuation of trial medication. Subjects were evaluated weekly during the titration phase and every 4 months (monthly for subjects at Japanese sites) starting from Month 4 through Month 36. Follow up Visit 1 occurred 7 to 21 days after the Month 36 visit, and Follow up Visit 2 occurred 7 to 21 days after Follow up Visit 1. The trial design schematic is shown in Figure 3.2-1.

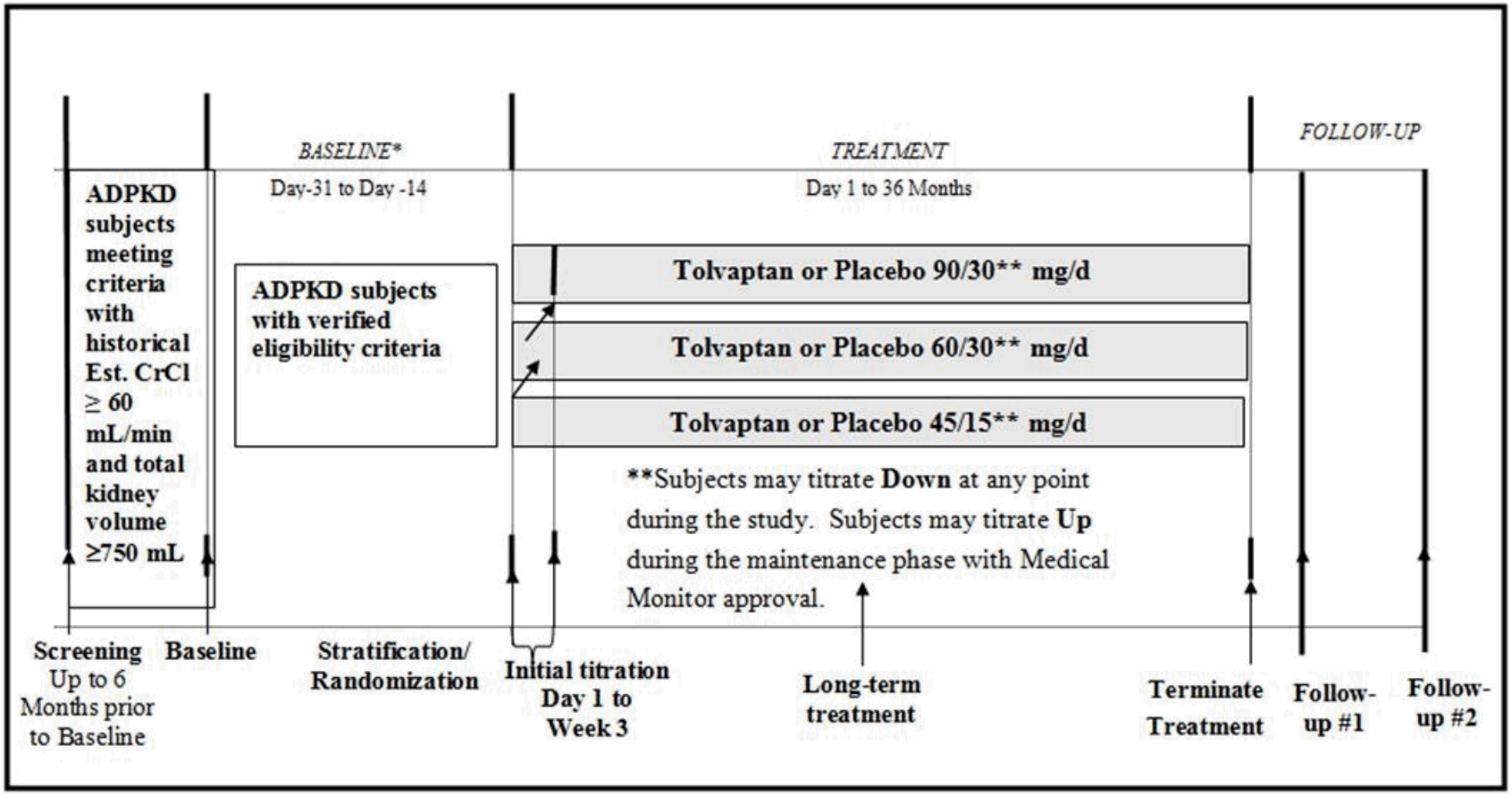


Figure 3.2-1 Trial 156-04-251 Design Schematic

The schedule of assessments is provided in Table 3.2-1. Assessments at post-titration and following end of treatment were conducted to assess the anticipated acute effects of tolvaptan on urine osmolality and serum creatinine, and their response to treatment initiation and withdrawal. MRI assessments for evaluation of TKV were performed annually, and assessments of renal function, PKD Outcomes, and safety were performed every 4 months, or at early termination (ET). MRI assessments were performed at ET only if the preceding assessment was performed no less than 6 months earlier, based on an expectation that minimal differences in TKV would require at least 6 months to be detectable.[49]

Table 3.2-1 Schedule of Assessments for Pivotal Trial 156-04-251

Assessment	Screening	Baseline Day -31 to Day -14	Randomization Day 1	Titration Wk 1, 2	Wk 3/ EOT	Mo 4, 8, 16, 20, 28, 32	Mo 12, 24	Mo 36/ET[a]	FU Visits (7-21 days after Mo 36/ET and 7-21 days after FU #1)
Informed Consent	X	X							
Inclusion/Exclusion	X	X	X						
Medical/ADPKD History	X	X	X	X	X	X	X	X	X
Concomitant meds	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X
Tolerability				X	X	X	X	X	
Physical Exam[b,c]	D	X	D	D	D	D	D	X	D
VS/weight[c]	X	X	X	X	X	X	X	X	X
ECG		X	X		X			X	
Blood/urine: PK		X			X		X	X	
Blood/urine: PD		X			X		X	X	
Blood/urine: Safety[c]	X	X	X	X	X	X	X	X	X
Urine Pregnancy	X	X	X	X	X	X	X		X
1° Endpoint MRI		X					X	X[d]	
Composite 2° Efficacy Endpoints Labs/Pain/BP[e]	X	X			X	X	X	X	X
PKD Outcomes	X	X	X		X	X	X	X	X
Nonfasting spot urine osmolality					X		X	X[f]	
Fasting spot urine osmolality			X						X[g]
Stratify/Randomize			X						

D = directed; EOT = end of titration; ET = early termination; FU = follow-up; Mo = month; Wk = week.

[a]Telephone contact (for outcomes only) occurred through Follow up Visit 2 for randomized subjects who discontinued from investigational product administration.

[b] A complete exam was required at Baseline and Month 36/ET. For all other visits, a directed exam should be conducted at the investigators discretion if deemed necessary to assess changes in Medical History, AEs or other medically indicated parameters (D=directed).

[c] In Japan subjects visited study sites monthly (±2 weeks) to undergo physical examinations, safety laboratory assessments, and measurement of vital signs (heart rate, BP, and body weight).

[d] MRI was performed at, or as near to, a clinical ET visit as was practical. MRI was done only if >6 months had elapsed since the last MRI and was not repeated beyond the ET visit.

[e] Blood required for renal function included serum creatinine; urine for renal function included spot albumin/creatinine ratio; clinic exam for BP; standardized renal pain score to be assessed in conjunction with confirmation of renal origin of pain by exam and/or history.

[f] Nonfasting spot urine osmolality was not done at ET visit.

[g] Performed only at Follow-up Visit 2.

If a subject wished to withdraw from the trial or trial medication, they were first asked to give their permission for additional follow up. Follow up minimally consisted of investigators contacting subjects by telephone at trial-specified visit intervals for collection of self-reported PKD Outcomes (ie, clinical outcomes associated with ADPKD disease progression) through Month 36 and the 2 trial follow-up visits. If subjects did not give permission for follow up, they were not followed further.

Eligible subjects were randomized to receive either tolvaptan or placebo in a 2:1 ratio. Subjects were stratified by presence of HTN at baseline (systolic BP [sBP] > 139 mmHg and/or diastolic BP [dBP] > 89 mmHg or antihypertensive treatment), baseline eCrCL (< 80 mL/min), and baseline TKV (< 1000 mL). In addition, centralized randomizations were performed in each region independently (the Americas, Japan, and Europe plus Australia) so that there were 24 strata in this trial. Blocks (in size of 3) of randomization code generated by computer were assigned to each of the strata at the beginning of the trial.

Subjects were ineligible if they were allergic to tolvaptan or related compounds, were unaware of thirst, had conditions (eg, recent kidney surgery) or therapies (eg, chronic diuretics, experimental therapies) likely to limit successful completion or confound assessments, or had contraindications to MRI imaging. All subjects remained on standard concomitant medications. Concomitant use of potent cytochrome P450 (CYP) 3A4 inhibitors was avoided.

In this trial, 3 split-dose regimens of tolvaptan (45/15 mg, 60/30 mg, and 90/30 mg) were selected to provide as constant and complete an inhibition of the AVP V_2 receptor as would likely be tolerated by individuals taking tolvaptan chronically (refer to Section 3.4).

An IDMC periodically reviewed unblinded trial results provided by a sponsor-independent data analysis center to evaluate the treatments for excess AEs, determine whether the basic trial assumptions remained valid, and judge whether the overall integrity and conduct of the trial remained acceptable. This committee made recommendations to the Steering Committee for the trial, which had the responsibility to accept, reject, or to modify the IDMC's recommendations. Additionally, an independent Clinical Events Committee (CEC) adjudicated data for disease progression events contributing to the key secondary composite endpoint to confirm that they were consistent with clinically relevant levels of progression, providing independent verification of events for sensitivity analysis.

3.3 Pivotal Trial Endpoints

A list of the Trial 156-04-251 endpoints is provided in Table 3.3-1. The endpoints for this trial were selected on the basis of their representing clinically meaningful outcomes that lie on the continuum to ESRD. They were selected as being specific for ADPKD based on available literature and current scientific research.

Table 3.3-1 Trial 156-04-251 Endpoints (and Testing Hierarchy)

Primary (first)	• Rate of kidney volume (total, both kidneys) change (normalized as percentage) from baseline for tolvaptan (combining all doses) relative to placebo
Key secondary (second)	• Time to multiple investigator-reported ADPKD clinical progression events for tolvaptan (combining all doses) relative to placebo while on treatment, including: – Onset or progression of HTN (BP measurement, need for HTN treatment), – Severe renal pain (requiring medical intervention), – Worsening albuminuria (by category), and – Worsening renal function (25% decrease in 1/serum creatinine [ie, 33% increase in serum creatinine] between the Week 3/end of titration [EOT] and Month 36 visits)
Other secondary (3rd through 7th)	• Rate of renal function change from the Week 3/EOT to the last on-drug trial visit. The primary measure was reciprocal of serum creatinine. Additional analyses using other methods of estimating renal function were performed. • For subjects who were nonhypertensive at baseline, change from baseline for resting mean arterial pressure (MAP) at scheduled clinic visits until taking antihypertensives. • Change from baseline in renal pain as assessed by a 0 to 10 pain scale as average area under the concentration-time curve (AUC) between baseline and the last trial visit or the last visit prior to initiating medical (eg, narcotic or antinociceptives [eg, tricyclic antidepressants]) or surgical therapy for pain. • For subjects who were nonhypertensive at baseline, time to progress to a) high-pre-HTN (sBP > 129 mmHg and/or dBP > 84 mmHg), b) HTN (sBP > 139 mmHg and/or dBP > 89 mmHg), or c) requiring antihypertensive therapy. • For subjects who were taking antihypertensive therapy at baseline, percentage with clinically sustained decreases of BP leading to a sustained reduction in antihypertensive therapy compared with baseline (while taking trial medication) at visits on Months 12, 24, and 36 for hypertensive subjects.

Table 3.3-1	Trial 156-04-251 Endpoints (and Testing Hierarchy)
Explora-tory (not ordered)	• Change from pretreatment baseline to post-treatment Follow-up Visit 2 in the components of the key secondary composite endpoint to demonstrate the clinical well-being of the subjects randomized to the trial. • Changes from the Month 36/Early Termination (ET) visit to Follow-up Visit 2 in the components of the key secondary composite endpoint to determine the maintenance of clinical benefit and to exclude acute effects of tolvaptan. • Change from pretreatment baseline to post-treatment Follow-up Visit 2 in urine concentrations of trough osmolality and fasting osmolality • Time to events that were considered by the subject and/or physician to be clinically significant and potentially related to the progression or manifestations of the disease. Events in this analysis were those checked in the PKD Outcomes (Part 2) case report form (CRF). Only the events starting from the Month 4 visit were included in the analysis, and only subjects who had follow-up to Month 4 were included in the analysis. Two analyses were provided: the first included all 13 PKD-related outcomes as potential events; the second included only the PKD-related outcomes that were more closely related to kidney enlargement as potential events. • ADPKD outcomes and medical resource utilization. Analysis of additional events attributed to ADPKD for tolvaptan subjects were to be compared with placebo subjects, including their health-economic outcomes.

A detailed discussion of the statistical approach for these clinical efficacy measures is provided in Section 5.5.1 for rate of TKV growth, Section 5.6 for key secondary composite (see also Section 5.6.1 for the components of the key secondary composite endpoint), and Section 5.7.1 for rate of renal function decline.

3.3.1 Total Kidney Volume

Total kidney volume change had been shown to accurately represent the evolution of cyst growth and therefore structural derangement of renal parenchyma. Tolvaptan had been shown in animal models to reduce the development of cystic burden and fibrosis through effect on proliferation and secretion, thereby preserving normal renal architecture. Because cystogenesis is the direct cause of kidney damage, tolvaptan would necessarily have to reduce the rate of TKV growth to provide a benefit in human ADPKD patients. We hypothesized that a reduction in rate of TKV growth would be required to confer measurable clinical benefits and therefore placed TKV growth as our first endpoint.

3.3.2 Composite Endpoint

Given the slowly progressive nature of ADPKD and the episodic nature of clinical manifestations during its progression, the FDA recommended we construct a composite endpoint to capture the effects of treatment. The composite endpoint was constructed to represent clinically meaningful changes in physiologic parameters and symptoms

reasonably expected to develop or worsen with progressive ADPKD. The components included

1) Events of worsening renal function: in a trial population where renal function is relatively preserved (CKD Stages 1 to 3), cyst growth leads to a deterioration of renal function. Events were counted when a sustained on-treatment increase in serum creatinine of 33.3% was met (inverse serum creatinine decline of 25%), which represents a clinically meaningful change in kidney function at this stage of disease.
2) Events of renal pain: patients experience renal pain when increasing cyst growth stretches the renal capsule and because of kidney-specific ADPKD complications including cyst infection, cyst rupture, cyst hemorrhage, pyelonephritis, and kidney stones. This component included events deemed serious enough by the patient for him/her to bring it to medical attention and by the physician to prescribe varying intensity of medical intervention.
3) Events of worsening blood pressure or hypertension: cyst growth and kidney ischemia lead to hypertension in early ADPKD. Events were considered to have occurred if a prehypertensive subject's blood pressure reproducibly increased or if a hypertensive subject required more intensive therapy.
4) Events of worsening albuminuria: cystic destruction of nephrons leads to compensatory hyperfiltration and glomerular stress. This results in increasing proteinuria in later stages of ADPKD. Events were counted as sustained proteinuria in categorical thresholds from normal to micro- to macro-proteinuria.

3.3.3 Other Endpoints

The remaining secondary and exploratory endpoints represented further approaches to assess the clinical outcomes associated with tolvaptan therapy.

3.4 Pivotal Trial Dose Selection and Administration

As AVP regulates concentration of urine, reduction or blockade of AVP can be assured when the concentration of urine falls below that of plasma (roughly 285-300 mOsm/kg). Effective AVP blockade should reduce stimulation of cAMP and therefore decrease cellular proliferation and fluid secretion into cysts in subjects with ADPKD. Animal models suggested that early intervention and continuous blockade of AVP, as measured by suppression of urine osmolality, would be more efficacious in decreasing the rate of cystic growth.[8,10,32,36] Therefore the objective of tolvaptan therapy in ADPKD is to continuously inhibit AVP binding at the V_2 receptor. During the trial, spot urine osmolality was measured at expected trough levels of tolvaptan, but not reported to investigators, to maintain their blind. At the end of the trial, maintenance of urine osmolality suppression was confirmed through exploratory PK/PD analyses.

In phase 2 trials, the dose response of urine osmolality in ADPKD subjects was evaluated. Panel B of Figure 3.4-1 is a plot of mean urine osmolality in urine samples collected from 0-4, 4-8, 8-12, 12-16, 16-24, and 24-28 hours at baseline and after single ascending doses of 15, 30, 60, and 120 mg administered 72 hours apart to 8 subjects with ADPKD and well preserved renal function. Panel A of Figure 3.4-1 is a plot of corresponding mean tolvaptan concentrations. The lower edge of the gray box in Panel A indicates the minimally effective concentration of tolvaptan and the upper edge indicates the concentration where a maximal increase in urine output is achieved; concentrations above the gray box produce the same rate of urine output. Increasing doses of tolvaptan above 15 mg do not significantly increase the maximal suppression of urine osmolality but extend the duration of time that such suppression occurs.

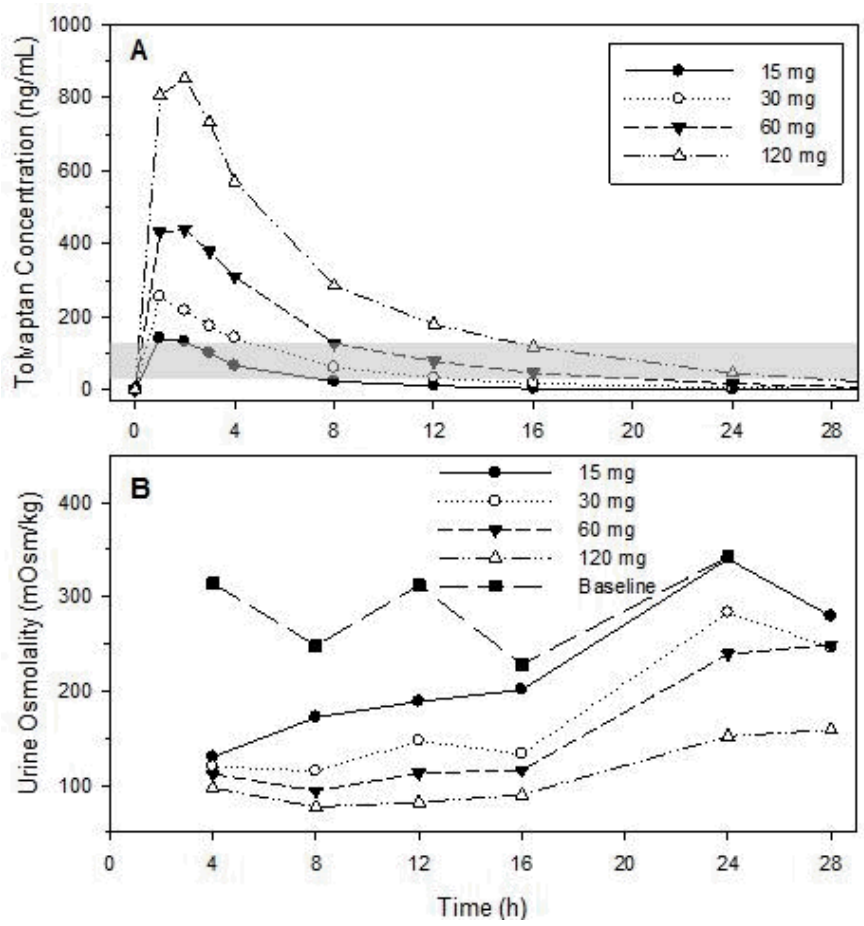


Figure 3.4-1 Mean Tolvaptan Plasma Concentrations (A) and Mean Urine Osmolality Plotted at the End-time of the Collection Interval (B) Following Ascending Single Oral Doses of Tolvaptan in Eight Subjects with ADPKD; Trial 156-04-248

Note: The lower edge of the gray box in Panel A indicates the minimally effective concentration of tolvaptan and the upper edge indicates the concentration where a maximal increase in urine output is achieved.

These data also show that there is a rapid rate of offset in AVP inhibition once tolvaptan plasma concentrations drop below the lower threshold of about 25 ng/mL. It would require single daily doses of >120 mg to suppress urine osmolality for 24 hours, ie, produce a trough spot urine osmolality of < 300 mOsm/kg. Split-dose regimens (second dose 8 to 9 hours after first dose, rather than the more common every 12 hours regimen) were tested with the goal of prolonging tolvaptan action throughout the night without increasing night-time urine excretion so much that nocturia would be a significant clinical problem.

In a clinical trial exploring ascending split-dose regimens (Trial 156-04-250), ADPKD subjects were titrated weekly from a daily regimen of 30/15 mg to 45/15 mg, 60/30 mg and then 90/30 mg. Each week subjects were asked "Could you tolerate taking this dose of tolvaptan for the rest of your life, please answer only yes or no?" If subjects answered no, they were down-titrated to the previous dose. Subjects who answered yes were up-titrated to a maximum dose level of 90/30 mg. Urine osmolality was measured in spot samples taken just prior to the first dose (expected trough tolvaptan blood level), prior to the second dose, and prior to bedtime. Table 3.4-1 summarizes the percent of subjects with urine osmolality < 300 mOsm/kg by sampling time point. As tolvaptan doses increased, urine osmolality prior to the second dose and prior to bedtime were most easily suppressed. The 45/15 mg dose was the lowest dose at which at least 90% of subjects had urine osmolality values < 300 mOsm/kg for both the prior to the second dose and prior to bedtime samples, indicating that urine osmolality would be suppressed (AVP would be inhibited) for at least 16 hours per day in a large majority of subjects.

Table 3.4-1 Percent of Subjects with Urine Osmolality Less Than 300 mOsm/kg Following Split-dose Regimens of Tolvaptan; Trial 156-04-250

Time of Day	Week of Treatment and Dose					
	Day 0	Week 1	Week 2	Week 3	Week 4[a]	
	Baseline n=45[b]	30+15 mg n=45	45+15 mg n=43	60+30 mg n=43	45+15 mg n=14	90+30 mg n=27
Prior to First Dose	24	64	70	77	42	85
Prior to Second Dose	33	84	98	98	93	100
Prior to Bedtime	38	91	93	98	92	100

Note: Values of n reflect number of subjects with at least 1 osmolality value for the dose.

[a]After Week 3, 27 subjects up-titrated, 15 subjects down-titrated and 1 remained at 60+30 mg.

[b]Subject 2025 excluded as the subject had no urine osmolality samples at the prescribed doses.

Following the 60/30 mg regimen at Week 3, 77% of subjects had urine osmolality values < 300 mOsm/kg at prior to the first dose, the expected nadir of tolvaptan effect. For the subjects that up titrated to the 90/30 mg regimen, 85% were suppressed. Therefore, if the hypothesis that the best efficacy would be observed if AVP was maximally inhibited for the entire 24-hour day, ie, urine osmolality suppressed to its maximal extent, and always below 300 mOsm/kg is correct, then a 60/30 mg regimen may be suitable for many subjects but the 90/30 mg regimen would produce additional inhibitory activity in some subjects who would not experience optimal inhibition at lower doses.

As an example of tolvaptan concentrations and urine osmolality following multiple dosing with 90/30 mg, Figure 3.4-2 presents a plot of mean tolvaptan concentrations following 7 days of dosing at 90/30 mg in 12 subjects with ADPKD and $eGFR_{CKD-EPI}$ > 60 mL/min/1.73 m^2. Additionally shown are plots of median urine osmolality at baseline and following treatment along with individual spot trough urine osmolality values at baseline and on Day 8 presented in the insert to the right.

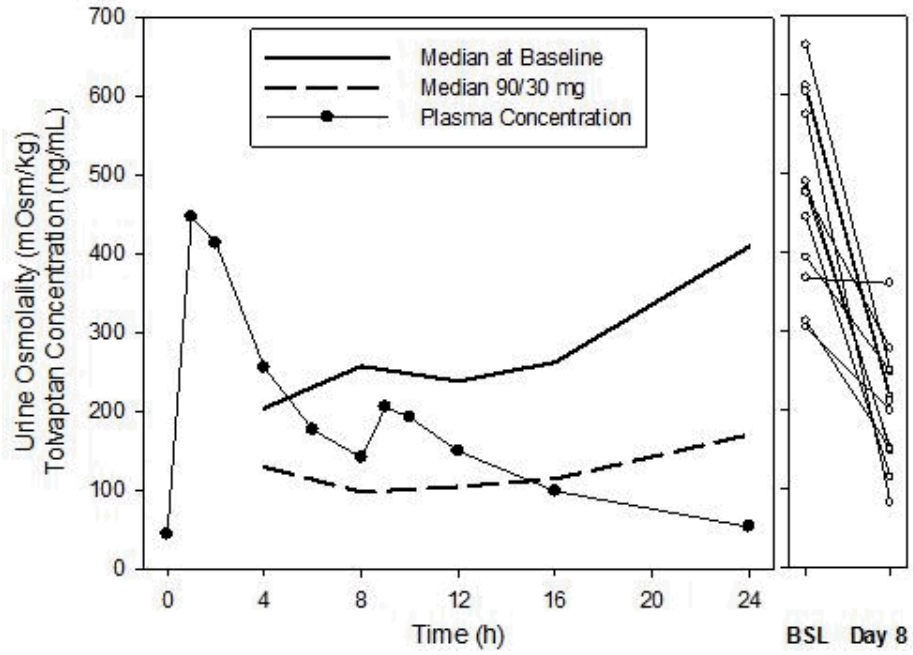


Figure 3.4-2 Mean Tolvaptan Plasma Concentrations, Median Urine Osmolality and Individual Trough Spot Urine Osmolality at Baseline and Following 90/30 mg Tolvaptan Administered for 7 Days to 12 Subjects with ADPKD; Trial 156-09-285

Note: Median urine osmolality values plotted at the end-time of the collection interval. BSL=Baseline. Day 8 is 24 hours after 90 mg dose on Day 7 of treatment regimen.

For the pivotal 156-04-251 trial, split-dose regimens of 45 mg AM/15 mg PM (45/15 mg), 60 mg AM /30 mg PM (60/30 mg) and 90 mg AM /30 mg PM (90/30 mg) were selected based on the titration scheme developed in Trial 156-04-250. The twice-daily regimen, with a higher morning dose and a lower dose approximately 9 hours later, produces maximal inhibition during daytime hours with a gradual fall-off of effect to prevent excess urine production during the sleep period. Forced titration to an individual's maximally tolerated dose was required in order to produce a maximal suppression in urine osmolality (inhibition of AVP binding) in an effort to maximize clinical efficacy.

A sample titration schedule is presented in Table 3.4-2. Subjects began treatment with the lowest dose and on the day following each 1-week safety assessment, doses were titrated to the next higher dose treatment group until either a level of intolerability or the highest dose was reached. If a subject could not tolerate a given dose, the titration phase was over for that subject, and the maintenance phase began at the dose level tolerated and lasted to Month 36. All subjects were encouraged to progress to the highest dose as this was likely to be the most effective. Subjects were to maintain the highest tolerated dose for 3 years, but could interrupt, down- and/or re-uptitrate as clinical circumstances warranted. Drug interruptions were also allowed as needed for intervening illness, with resumption of therapy either at the highest tolerated dose or at lower doses with titration as tolerated.

Table 3.4-2 Example Dosing Schedule in Trial 156-04-251

Trial Day	Nominal Time	Dose
Week 1 (Days 1-7)	8 AM & 5 PM	45/15 mg taken as three 15 mg tablets every AM and one 15 mg tablet every PM or matching placebo
Week 2[a] (Days 8-14)	8 AM & 5 PM	60/30 mg taken as two 30 mg tablets every AM and one 30 mg tablet every PM or matching placebo
Week 3[a] (Days 15-21)	8 AM & 5 PM	90/30 mg taken as three 30 mg tablets every AM and one 30 mg tablet every PM or matching placebo
Week 3 to Month 36[a]	8 AM & 5 PM	Highest tolerated regimen

[a]Actual time may have varied depending on sleep cycle.

3.5 Statistical Analysis Methods for Trial 156-04-251

3.5.1 Sample Size Calculation

The original sample size calculation for Trial 156-04-251 was based on data and/or methodology adapted from the NIH-CRISP and HALT studies.[28,50] With prognostic enrichment, a kidney growth rate of 7%/year was predicted for the placebo arm. A target of one-fifth reduction, equating to a growth rate of 5.6%/year for the tolvaptan group, was regarded as clinically relevant. The total noise standard deviation and the standard deviation of the slope across subjects were respectively assumed to be 0.017 and 0.0184 (in log10 scale). Using the sample size calculation formula for longitudinal trials provided by J. Lefante,[51] with 85% power and 2:1 randomization, the calculated sample size was 504. With an assumption of 20% withdrawal rate for the trial, about 600 subjects would need to be enrolled. By doubling this number, we effectively attained a power equivalent to two independent studies, while enhancing the ability to evaluate the key secondary composite endpoint, which was expected to require an unknown but higher number of subjects to achieve reasonable power over a period of 3 years.

Because the sample size needed for the key secondary composite endpoint was unknown at the planning stage of this protocol, a blinded sample size recalculation was discussed with the Agency.

3.5.2 Blinded Sample Size Re-calculation

The Agency agreed that a blinded sample size recalculation could be performed without statistical penalty. This was conducted on 20 October 2008 based on the available, preliminary data, when 1000 subjects had been enrolled, as prespecified in the protocol. This sample size recalculation suggested that a total sample size of 1400 would be an appropriate for this study. This sample size falls into the sample size range of 1200 to 1500 originally specified in the protocol.

Power projection of the key secondary composite endpoint against an alpha of 0.01 was performed in response to guidance received from a Type C Meeting with the FDA on 10 June 2009, after closing of the enrollment in which 1445 subjects were randomized. It was projected that this 3-year trial would have 2074 events; among them, 975 would be first events. Assuming a 20% reduction in the key secondary composite endpoint and following a method provided in Therneau and Grambsch (2000),[52] with an assumption the three non-first recurrent events were equivalent to one first event, it was projected that the trial would have 90% power to detect a treatment difference in the key secondary composite endpoint. The final power of the endpoint would depend on the final number

of events (as well as first events) in the trial and the conversion ratio of non-first recurrent events to first events.

3.5.3 Analysis Datasets

The SAP-specified primary and sensitivity analyses adhered to the intent-to-treat (ITT) principle. Two datasets were constructed. The first including all data from baseline visit (Day −14 to Day 0) up to 14 days after the last dose of trial medication was designated as the "Within Treatment Period" dataset. This dataset was prespecified in the SAP and was agreed to by the Agency The second including all data from baseline (Day −14 to Day 0) to Month 36 regardless of last dose of trial medication was designated as the "Regardless of Treatment Period" dataset (and would include any subject who was randomized but did not receive treatment). This dataset was used for sensitivity analysis. Unless otherwise specified, no imputation of missing data was performed for either dataset.

3.5.4 Prespecified Hierarchical Test Procedure

Statistical test was conducted based on the hierarchical order given in Table 3.3-1 with an alpha of 0.05.

The statistical tests on the components of the key secondary composite endpoint were considered as exploratory analyses, with no requirement for adjustment for multiplicity.

The composite PKD Outcome endpoints were also exploratory endpoints. No adjustments for multiplicity were set for these or other exploratory analyses.

3.5.5 Analysis of the Slope of Total Kidney Volume Growth

The primary analysis of the first (primary) endpoint used each subject's log-transformed TKV for each time point to estimate their slope of TKV growth. For each treatment group, individual slopes were used to obtain an overall slope estimate. The overall slope estimates were compared between treatments to derive a treatment effect described as a ratio of geometric means.

Since the above analysis assumes linearity, a sensitivity analysis of TKV using mixed model repeated measurements (MMRM) was also performed, with treatment, visit, treatment visit interaction, and randomization stratification factors as factors, and baseline and baseline visit interaction as covariates.

3.5.6 Analysis of the Key Secondary Composite Endpoint and Its Components

The primary analysis of the second (key secondary composite) endpoint was an on-treatment analysis of time to multiple events. Time to multiple event analysis was used

to measure progression of disease and not a single, ultimate outcome. Composite components were treated with equal weight. However, sandwich covariance matrix estimates were used to account for the correlation between multiple events in an individual subject. Time to first event analysis was also provided as a sensitivity analysis for the analysis of time to multiple events.

Analyses on the components of the key secondary composite endpoint were identical to the analysis of the endpoint.

3.5.7 Analysis of the Slope of Renal Function (Reciprocal of Serum Creatinine)

Analysis of the third endpoint, renal function slope, as a continuous variable was similar to the analysis of the primary TKV endpoint, except that no log transformation was applied. The primary measure of renal function was reciprocal of serum creatinine.

As described in Section 4.2.2.1, an acute and reversible increase in serum creatinine attributable an acute and fully reversible decrease in GFR was anticipated. This effect is similar to that observed with ACE inhibition and requires analyses which account for these effects (either on-treatment or pre- to post-treatment comparisons). The primary analysis of this endpoint was performed within the treatment period using data between Week 3/EOT and Month 36/ET. Sensitivity analyses included analysis regardless of the treatment period and analyses incorporating pre-titration and post-treatment data points.

3.5.8 Other Sequentially Ordered Secondary Endpoints

The fourth sequential endpoint tested was change in MAP for subjects who had not yet reached hypertensive status or treatment with antihypertensive therapies. The analysis followed that of the primary TKV analysis except that log transformation was not applied, and data were censored once a subject began antihypertensive therapy.

The fifth sequential endpoint tested was a time-averaged AUC change in renal pain (0 to 10 Likert scale) between baseline and Month 36 or the last visit prior to initiating medical or surgical therapy. This was analyzed by analysis of covariance (ANCOVA). An MMRM analysis was also applied to this efficacy variable (change in pain scale, not AUC) as a sensitivity analysis.

The sixth sequential endpoint tested was a time to multiple event analysis for including nonhypertensive subjects and analyzing their progression to the next prehypertensive or hypertensive state. Analysis was similar to that used for the key secondary composite endpoint.

The seventh sequential endpoint tested the percentage of hypertensive subjects taking antihypertensive therapy at baseline who had clinically sustained decreases of BP leading to a sustained reduction in antihypertensive therapy compared with baseline. The last observation carried forward dataset was used for this analysis.

3.5.9 Analysis of the Composite PKD Outcomes Endpoint

The analyses of the composite PKD Outcomes endpoint were similar to the analysis of the key secondary composite endpoint. Two analyses were prospectively defined prior to unblinding the treatment codes: the first was a 13-item composite event analysis using all individual recorded PKD-related outcomes as potential ADPKD disease progression events; the second was a 9-item PKD-related outcomes composite of events that were more plausibly related to kidney enlargement. The events having the highest frequency in the blinded population were also analyzed as individual components. These analyses are further described in Section 5.9.1. Risk of hospitalization was assessed using the Exact Test to derive the odds ratio and confidence intervals.

4 Biopharmaceutics and Clinical Pharmacology

4.1 Biopharmaceutics and Bioavailability

As submitted to the hyponatremia NDA, the oral bioavailability of tolvaptan following administration as the 30-mg clinical tablet was 56% (42% to 80%). Dose strength equivalence of 15 mg, 30 mg, and 60 mg clinical tablets was determined in healthy subjects. The 30-mg clinical tablet was considered equivalent to the 30-mg approved tablet on the basis of dissolution testing. The dose strength equivalence of the 30-mg approved tablet to the 90-mg proposed commercial tablet was determined in healthy subjects.

Tolvaptan plasma concentrations following the high-fat meal (HFM) or fasting for 60 and 90 mg doses showed higher initial plasma concentrations in the HFM subjects, but by 6 hours postdose, mean tolvaptan concentrations were similar for both states. In the single ascending dose trials, tolvaptan doses from 60 to 480 mg produced similar mean urine volumes for the first 12 hours postdose as plasma concentrations across this range of doses produced a maximal rate of urine output. Therefore, the increased tolvaptan concentrations observed in the ‘fed’ state would not be expected to have any additional effect on urine output in the first 6 hours postdose when compared to the fasted state.

Otsuka proposes to market tolvaptan tablets of 15-, 30-, 45-, 60- and 90-mg strengths for the ADPKD indication. Tablets of 15-, 30- and 60-mg strengths were previously

approved for the treatment of hyponatremia. The 45-mg tablet will be approved on the basis of dissolution testing. Dose strength equivalence of the 30-mg approved tablet to the 90-mg proposed commercial tablet was established in a clinical trial.

4.2 Clinical Pharmacology

4.2.1 Pharmacokinetics

Clinical pharmacology (pharmacokinetic/pharmacodynamic [PK/PD]) trials in healthy subjects using tolvaptan tablets have included single dose trials (2 ascending dose, Japanese-Caucasian bridging), multiple dose trials (age/gender, thorough QTc), food-drug and drug-drug interaction trials (grapefruit juice, ketoconazole, rifampin, lovastatin, warfarin, amiodarone, furosemide, hydrochlorothiazide, and digoxin), 4 trials in subjects with heart failure and 1 special population trial in subjects with hepatic impairment (multiple ascending doses). Additionally, the sponsor has performed 1 special population trial in subjects without ADPKD but with renal impairment and 6 trials involving subjects with ADPKD with chronic kidney disease (CKD) Stage 1 to 4 (refer to Section 10.2). Trials included a single ascending dose trial, 15 to 120 mg, multiple once daily dosing of 15 or 30 mg and multiple split-dose regimens with comparison of PK and PD in Japan and US subjects, multiple split-dosing trial at 90/30 mg and renal function testing following 7 or 21 days of dosing in subjects with varying degrees of renal function.

Tolvaptan is eliminated primarily by metabolism as only about 19% of a tolvaptan dose is excreted unchanged in feces and less than 1% is excreted unchanged in urine. None of the 14 metabolites detected in human plasma have pharmacologic activity at concentrations measured at proposed clinical doses.

Tolvaptan is a sensitive cytochrome P450 (CYP) 3A4 (CYP3A4) substrate; concentrations increase 4-fold when administered with strong CYP3A4 inhibitors. A dose reduction to 15 mg or 30 mg once daily is recommended for 45/15mg and 90/30mg regimens, respectively, when tolvaptan is given with strong CYP3A inhibitors. Tolvaptan has no inhibitory activity at CYP3A4 or CYP2C9 and is a P-glycoprotein substrate and inhibitor with no clinically significant inhibitory activity.

Following intravenous (IV) administration, the elimination half-life ($t_{1/2,z}$) of tolvaptan is about 3 hours. Following multiple once daily oral doses of 30, 60, and 300 mg or multiple split-dose regimens (second dose 8 to 9 hours after first dose) ranging from 15 mg AM/15 mg PM (15/15mg) to 90 mg AM/30mg PM (90/30mg), accumulation of tolvaptan concentrations was minimal.

Following single oral doses, maximum plasma concentrations (C_{max}) show less than dose proportional increases from 30 to 240 mg and then a plateau at doses from 240 to 480 mg. Values of $t_{1/2,z}$ increase from 3 hours for a 15 mg dose to 12 hours for 120 mg and higher doses. Following 300 mg once daily doses, a reduction in bioavailability was observed as C_{max} and AUC during the dosing interval at steady state (AUC_{τ}) were only 4.2- and 6.4-fold higher, respectively, when compared with the 30-mg dose.

The plateau in C_{max} with increasing dose and decrease in bioavailability following multiple dosing at 300 mg may be due to saturation of absorption in the upper small intestine and/or dissolution rate-limited absorption as tolvaptan solubility in water is very low, 0.00005 %w/v or 0.0005 mg/L. The increasing values of $t_{1/2,z}$ are thought to be due to low but continued absorption of tolvaptan from the lower gastrointestinal tract.

The human plasma protein binding of tolvaptan is 98% or higher to albumin and α_1-acid glycoprotein; binding is not affected by cardiac function, renal or hepatic impairment.

Tolvaptan PK is not significantly affected by age, sex, race, and mild or moderate hepatic impairment. Plasma concentrations in subjects with heart failure are 2-fold higher when compared to healthy subjects. The impact of renal impairment on tolvaptan concentrations was relatively small until creatinine clearance (CrCL) fell below 30 mL/min. In the population PK analysis of subjects with ADPKD, it was determined that as eGFR decreases from 72.2 to 9.79 (mL/min/1.73 m^2), there is an associated 32% reduction in apparent clearance (CL/F). In subjects with ADPKD and relatively intact renal function, ie, serum creatinine ≤ 1.4 mg/dL (males) or ≤ 1.2 mg/dL (females) or eGFR > 60 mL/min/1.73 m^2, tolvaptan pharmacokinetics are similar to healthy subjects.

4.2.2 Pharmacodynamics

Pharmacodynamics, including the effect on renal function, kidney volume, free water clearance, urine excretion rate, urine osmolality (see Section 3.4), urine volume, fluid balance, serum sodium and uric acid, and hemodynamic parameters, were assessed in a number of clinical trials in subjects with ADPKD and in subjects without ADPKD but with impaired renal function. When matched for renal function, tolvaptan treatment produced similar PD responses in healthy subjects/subjects without ADPKD and impaired renal function and subjects with ADPKD. Pharmacodynamic responses were also similar in US and Japanese ADPKD subjects with relatively intact renal function.

In addition to assessment of renal pharmacodynamic parameters, a thorough QTc trial was conducted in healthy male and female subjects given 30 mg or 300 mg tolvaptan once daily for 5 days. Individually corrected QT intervals were unchanged by tolvaptan.

4.2.2.1 Acute Effect on Renal Function

The acute effect of tolvaptan on renal function (GFR) was assessed in 2 clinical trials in the same subjects who were assessed for changes in TKV (Section 4.2.2.2). Results from the 2 trials were similar. Modest (approximately 6% to 10%), but statistically significant, reductions in mean measured GFR (mGFR by iothalamate clearance) were seen in subjects with well preserved (GFR > 60 mL/min) and moderately impaired (GFR 30 to 60 mL/min) renal function; a nonsignificant decrease (−2.1%) was seen in subjects with poor renal function, GFR < 30 mL/min. Mean creatinine and uric acid clearances were decreased about 12% to16% and 20% to 25%, respectively, and the percent decreases were independent of baseline renal function.

As the mGFR results were similar irrespective of duration of tolvaptan exposure (8 days compared to 21 days), it appears that changes in response to tolvaptan administration occur within days after the start of dosing. At 21 days posttreatment, mGFR values were not significantly different from baseline.

Although mean mGFR was not significantly decreased in subjects with eGFR < 30 mL/min/1.37m^2 (CKD Stage 4), slight nonsignificant decreases were also observed in CrCL, urea clearance and uric acid clearance and the percent decreases were larger than for mGFR at around 8 to 10%. Overall, this indicates that tolvaptan is most likely decreasing GFR in these subjects, but not to the same extent as subjects with better (ie, GFR > 30 mL/min) renal function. Decreased creatinine and uric acid clearances lead to increases in serum creatinine and uric acid.

Tolvaptan administered as 60/30 mg or 90/30 mg regimens has a small negative effect on urea nitrogen clearance that is not clinically significant and has no effect on sodium or potassium clearance at any level of renal function.

In summary, tolvaptan, at dose regimens of 45/15 mg to 90/30 mg, decreases mGFR 6% to 10% in subjects with CKD Stage 1 to 3 (eGFR > 30 mL/min) and changes are reversible after the end of tolvaptan treatment. As discussed by Irazabal et al[53] and hypothesized by Bankir and colleagues,[54,55] GFR is decreased following V_2 inhibition due to the hemodynamic changes that occur in response to the decrease in urine osmolality. As the offset of tolvaptan's action on urine osmolality after discontinuation of treatment is rapid, it would be expected that the decreases observed in GFR would be quickly reversible as well.

4.2.2.2 Acute Effects on Total Kidney Volume

In a phase 2 trial, 156-04-250, which was started just prior to the pivotal trial, 156-04-251, it was observed that tolvaptan produces an acute and reversible reduction in TKV. In Trial 156-04-250, an acute effect was noted: following 8 weeks on tolvaptan at a split-dose regimen ranging from 15/15 mg to 90/30 mg, the mean percent change in TKV was −1.11%. Three years later, subjects had a treatment interruption of 3-6 months in duration, the increase in TKV observed from treatment withdrawal to just prior to restarting tolvaptan appeared to show an increase in volume consistent with the reversal of this acute effect (see Section 5.13).

Subsequently, a post-hoc analysis of Trial 156-06-260 TKV data demonstrated that after only 8 days of treatment with 45/15 mg tolvaptan, a statistically significant decrease from baseline in TKV could be observed (mean [SD] change from baseline of −1.9 [2.4]%, p = 0.0040).

An acute decrease in TKV following initiation of tolvaptan treatment was prospectively confirmed in Trial 156-09-284, where, after 3 weeks of treatment with weekly uptitrated doses of tolvaptan to 90/30 mg, a statistically significant decrease from baseline in TKV was observed (mean [SD] change from baseline of −3.7 [3.0]%, p <0.0001). The reversible nature of this was confirmed when, at 21 days post-treatment, TKV returned toward baseline, but the difference was still significantly lower than baseline: mean (SD) value of −1.7 (2.9)%, p = 0.0063.

4.2.2.3 Effect on Pharmacodynamic Serum and Plasma Concentration Endpoints

Serum creatinine concentrations are considered a marker of GFR as creatinine is extensively filtered (cleared) by the kidney. As the result of tolvaptan treatment, GFR is slightly decreased (Section 4.2.2.1) and, consequently, creatinine clearance is reduced and increases are observed in serum creatinine. Table 4.2.2.3-1 summarizes changes in serum creatinine concentrations that were observed during renal function testing following multiple doses of tolvaptan in ADPKD subjects with well-preserved renal function. Values were also obtained during renal function testing at 21 days after the last dose of tolvaptan for subjects treated for 21 days.

Similar changes were also observed in cystatin C concentrations, another endogenous compound considered a marker of GFR.

Table 4.2.2.3-1 Serum Creatinine Concentrations During Renal Function Testing Following Tolvaptan Administration to Subjects with ADPKD and Well-preserved Renal Function; Trial 156-06-260 and Trial 156-09-284

Trial	ADPKD Population (n)	Regimen	Time Point	Serum Creatinine Mean (SD) (mg/dL)	Change (SD) From Baseline
Trial 156-06-260	$eCrCL_{CG}$ >60 mL/min, No Hypertension (6)	45/15 mg, 7 days	Baseline	0.80 (0.25)	-
			Day 7	0.88 (0.30)	0.08 (0.06)
	$eCrCL_{CG}$ >60 mL/min, Hypertension treated with ACEi or ARB (6)	45/15 mg, 7 days	Baseline	0.95 (0.16)	-
			Day 7	1.04 (0.23)	0.09 (0.11)
Trial 156-09-284	$eGFR_{MDRD}$ >60 mL/min/1.73 m^2 Hypertension treated with ACEi or ARB (9)	45/15 mg, 7 days; 60/30 mg, 7 days; 90/30 mg, 7 days. 21 days of total treatment	Baseline	0.78 (0.14)	-
			Day 21	0.86 (0.13)	0.05 (0.05)
	$eGFR_{MDRD}$ >60 mL/min/1.73 m^2 Hypertension treated with ACEi or ARB (9)	21 days after treatment withdrawal	Day 21	0.81 (0.13)	0.00 (0.04)

$eCrCL_{CG}$ = estimated creatinine clearance by Cockcroft-Gault, $eGFR_{MDRD}$ = estimated glomerular filtration rate by MDRD, ACEi =angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker

Tolvaptan blockade of V_2 receptors produces an increase in free water clearance (aquaresis), a negative shift in fluid balance and increases serum sodium and osmolality. It is known that uric acid secretion is decreased and AVP concentrations are increased as volume status decreases and serum osmolality increases. Therefore, the increases also observed in uric acid, AVP concentrations, and its peptide precursors AVP-neurophysin and copeptin, following tolvaptan administration are consistent with expected physiological changes. Mean AVP concentration increases ranged from 2 to 9 pg/mL (and upper limit of normal being 5 pg/mL), and were not dose dependent; the increases in AVP did not cause measurable increases in V_1-mediated effects such as blood pressure.

Increases in serum sodium and osmolality can be minimized if subjects maintain a neutral fluid balance (Section 4.2.2.5). Subjects in the pivotal 156-04-251 trial were encouraged to drink water and minimal, 1-2 mmol/L, mean increases in serum sodium were observed.

Concentrations of serum sodium, osmolality, creatinine, cystatin C, uric acid, AVP, AVP-neurophysin, and copeptin returned to baseline after discontinuation of tolvaptan, demonstrating the reversible nature of the changes.

Tolvaptan treatment does not meaningfully change urea nitrogen, potassium, albumin, aldosterone, renin, cAMP, calcium, or parathyroid hormone concentrations.

4.2.2.4 Effect on Free Water Clearance and Urine Volume

Tolvaptan administration increases free water clearance (FWC) and consequently increases urine excretion rates, ie, changes in FWC are paralleled by changes in urine excretion rate. Maximal increases in urine excretion rates, 3 to 5 times baseline, were observed as tolvaptan concentrations reached 100 to 125 ng/mL; following a 45-mg dose, tolvaptan concentrations reach this level at about 1 hour postdose. Marked elevations of tolvaptan plasma concentrations produced a sustained, but not greater, magnitude of response, as active concentrations of tolvaptan were present for longer periods of time. The offset of tolvaptan action is rapid, and no increase in excretion rate is observed when tolvaptan concentrations decrease to below 25 ng/mL.

The 90/30 mg regimen was the highest daily dose used in the pivotal Trial 156-04-251; in 2 clinical pharmacology trials (Trial 156-09-285 and Trial 156-09-284) in subjects with ADPKD and estimated glomerular filtration rate by the Modification of Diet in Renal Disease formula ($eGFR_{MDRD}$) > 60 mL/min/1.73 m^2 administered a 90/30 mg dose regimen for at least 7 days, mean (SD) 24-hour urine volumes for each respective trial were 7464 (2103) mL (compared to baseline 3644 [1467] mL) and 6532 (2036) mL (compared to baseline 1982 [553] mL).

4.2.2.5 Fluid Balance/Serum Sodium

Fluid balance was studied extensively in phase 2 trials that were conducted under carefully controlled conditions. These studies suggested that a new set-point for fluid balance is established after the first days of treatment. By treatment Day 5, subjects are mildly fluid contracted relative to baseline but typically adapt to a stable balance of intake/output. This is readily monitored by serum sodium concentration. While fluid balance was not measured in the pivotal trial, serum sodium reflected rapid equilibrium with modest increases in serum sodium in most subjects and with few transient excursions into the hypernatremic range. In some cases, persistent hypernatremia can indicate when a subject cannot manage the prescribed dose of tolvaptan and should lead to down-titration or treatment discontinuation.

Based on the known mechanism of action of tolvaptan and consistency with previous data, the observed changes in sodium concentration (ie, hypernatremia) are attributable to

tolvaptan and should be managed clinically through appropriate guidance to a patient regarding fluid intake.

4.2.2.6 Mean Arterial Pressure

In ADPKD subjects with varying degrees of renal function, mean arterial pressure (MAP) was unchanged after 3 weeks of tolvaptan treatment. Hypertension was evaluated as part of the key secondary composite endpoint in the pivotal Trial 156-04-251, and BP was collected as a vital sign safety measure. Section 5.7.1 provides additional detail on results showing that tolvaptan treatment had no significant effect on BP compared to placebo.

5 Clinical Efficacy of Tolvaptan

5.1 Subject Disposition in Trial 156-04-251

In the pivotal trial, 2122 subjects were screened, and 1445 subjects were randomized to receive trial medication: 961 to tolvaptan and 484 to placebo. All but 1 subject (randomized to placebo) received at least 1 dose of trial medication. Seventy-seven percent (740/961; 77.0%) of tolvaptan subjects and 86.2% (417/484) of placebo subjects completed scheduled visits in the trial through Month 36 (Table 5.1-1), a relatively high rate of completion for a 3-year trial.

PKD Outcomes data were used in sensitivity analyses to account for potentially missing data from early-withdrawing subjects in Trial 156-04-251: 102/961 (10.6%) tolvaptan subjects and 27/484 (5.6%) placebo subjects agreed to further follow-up of PKD Outcomes via telephone after withdrawing from study medication. In contrast, 119/961 (12.4%) tolvaptan subjects and 40/484 (8.3%) placebo subjects refused any additional follow-up after terminating from the trial. Cumulatively, 87.6% (842/961) of tolvaptan subjects and 91.7% (444/484) of placebo subjects were followed for PKD Outcomes.

Table 5.1-1 Subject Disposition in Trial 156-04-251

Subjects	Tolvaptan N = 961 n (%)	Placebo N = 484 n (%)
Randomized	961 (100.0)	484 (100.0)
Treated	961 (100.0)	483 (99.8)
Completed to Month 36	740 (77.0)	417 (86.2)
Discontinued study medication early	221 (23.0)	67 (13.8)
Discontinued and followed for PKD Outcomes	102 (10.6)	27 (5.6)
Discontinued and refused follow-up for PKD Outcomes	119 (12.4)	40 (8.3)
Reasons for Discontinuation		
Lost to follow up	15 (1.6)	8 (1.7)
Adverse experience	148 (15.4)	24 (5.0)
Subject met withdrawal criteria[a]	4 (0.4)	0 (0.0)
Investigator withdrew subject	3 (0.3)	4 (0.8)
Subject withdrew consent	50 (5.2)	30 (6.2)
Protocol deviation	1 (0.1)[b]	1 (0.2)[b]
Time Course of Discontinuation		
Discontinued subjects, up to Month 4	99 (10.3)	11 (2.3)
Discontinued subjects, up to Week 3/EOT	47 (4.9)	6 (1.2)
Discontinued subjects, beyond Month 4	122 (12.6)	56 (11.5)

EOT = end of titration; PKD = polycystic kidney disease.

[a]Withdrawal criteria included pregnancy (n=3) and "inability to adhere to trial proceeding" (n=1).

[b]Required chronic use of diuretics.

For illustration of the subject withdrawal rate in Trial 156-04-251, Figure 5.1-1 indicates the percentage of subjects receiving a dose of study medication at a given daily dose regimen (blue = 90/30 mg; orange = 60/30 mg; green = 45/15 mg) and who withdrew from taking study medication but continued follow up for PKD Outcomes (grey) or deferred further follow up (black). The percentages at the far right represent the proportion of subjects in each category at the Month 36 visit/telephone call.

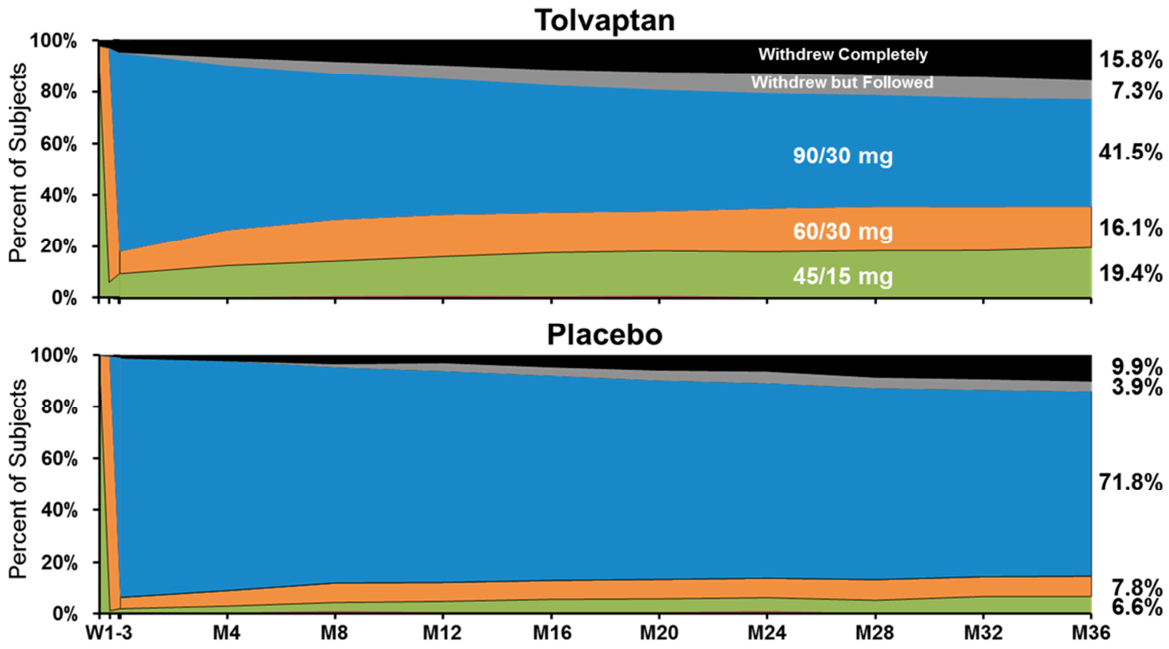


Figure 5.1-1 Time Course of Dose Titration by Treatment Group in Trial 156-04-251

M = month; W = Week.
The percentages at the far right represent the proportion of subjects in each category at the Month 36 visit/telephone call.

In the tolvaptan group, 23.0% of subjects withdrew from study medication early, compared with 13.8% of subjects in the placebo group. The imbalance was driven by a greater number of withdrawals due to AEs in the tolvaptan versus placebo group (148/961 [15.4%] subjects versus 24/484 [5.0%] subjects, respectively), entirely due to aquaretic AEs related to tolvaptan's mechanism of action and hepatic AEs potentially related to off-target effects, as discussed in Section 6.5.

In contrast to the placebo group, approximately half of the withdrawals in the tolvaptan group occurred before Month 4 (10.3% tolvaptan, 2.3% placebo withdrawals up to Month 4). This affected the numbers of subjects having both a baseline and postbaseline MRI assessment for the primary efficacy analysis, as MRIs were performed at early termination visits only if at least 6 months had elapsed since the last MRI. For tolvaptan, 842/961 (87.6%) subjects and for placebo 465/484 (96.1%) subjects were analyzed for the primary efficacy sensitivity analysis (regardless of treatment period). All 1445/1445 (100%) subjects were included in the secondary efficacy analyses. However, the average duration of follow up at visits where secondary efficacy evaluations could be completed was 2.51 years for tolvaptan and 2.77 years for placebo. Analyses to determine if missing data affected the study conclusions are described in Section 5.11.

All subjects receiving at least 1 dose of trial medication (1444/1445 [99.9%]) were included in the safety analyses. One subject randomized to placebo did not receive trial medication and therefore was excluded from safety analyses.

A total of 87 subjects withdrew consent to participate further in the trial (80/1445; 5.5%) or were withdrawn by the investigator (7/1445; 0.5%). An independent physician reviewed and classified the reasons for discontinuation.

- Of the 7 subjects withdrawn by the investigator, 3 (3/961; 0.3%) subjects in the tolvaptan treatment group and 4 (4/484; 0.8%) in the placebo treatment group were removed for noncompliance or inability to comply with the visit schedule.
- Of the 80 subjects who withdrew consent, 50 (50/961; 5.2%) subjects were in the tolvaptan treatment group and 30 (30/484; 6.2%) subjects were in the placebo group. The type of reasons given by the subjects for withdrawing were:
  - Personal/family reason not otherwise specified (eg, "personal reason," "at his will," "at his request," "did not want to continue," "unwilling to return to clinic") for a total of 30 (30/1445; 2.1%) subjects, including 21 (21/961; 2.2%) subjects in the tolvaptan group and 9 (9/484; 1.9%) subjects in the placebo group
  - Trial burden/logistical issues (eg, "too long driving distance," "too time consuming," "interference with job") for a total of 24 (24/1445; 1.7%) subjects, including 16 (16/961; 1.7%) subjects in the tolvaptan treatment group and 8 (8/484; 1.7%) in the placebo treatment group
  - Transfer/relocation (6/961; 0.6% tolvaptan; 4/484; 0.8% placebo)
  - Planning pregnancy (4/961; 0.4% tolvaptan; 3/484; 0.6% placebo)
  - Various others for a total of 3 (3/961; 0.3%) subjects in the tolvaptan treatment group (eg, "incarceration," "to avoid an eventual asthenia," "AEs interfering with work") and 6 (6/484; 1.2%) subjects in the placebo group ("not motivated anymore," "wants second opinion," "concerned about new consent form mentioning heart clots," "forgetting to take pills too often," "after stopping study drug for surgery," "due to worsening kidney function")

Out of the 80 subjects above who discontinued due to withdrawal of consent, 4 subjects are further described below because the specified reason for withdrawal of consent could be interpreted as an AE:

- Subject 04251-705-2703 in the tolvaptan treatment group experienced moderate Thirst (onset on Day 1) and severe Pollakiuria (onset on Day 2) that prompted a dose reduction. However, the events did not immediately resolve, and the subject withdrew consent due to "AEs interfering with work." The last dose of trial medication was taken on Day 21, both events resolved on Day 41, and both events were assessed as definitely related to the use of trial medication.
- Subject 04251-104-0728 in the placebo treatment group withdrew consent "after stopping trial medication for surgery." The site recorded an AE of "surgery elective

brain aneurysm," with onset on Day 105. The last dose of trial medication was taken on Day 102, the event resolved on Day 108, and was assessed as unrelated to the use of trial medication.

- Subject 04251-126-0304 in the placebo treatment group withdrew consent "due to worsening of kidney function." The site recorded AEs of mild "hyperuricemia" with onset on Day 842 and mild "kidney pain" with onset on Day 858. The last dose of trial medication was taken on Day 860. The event of hyperuricemia was continuing at the time the subject withdrew from the trial (Day 977); the event of "kidney pain" resolved on day of trial termination. Both events were considered unrelated to trial medication.
- Subject 04251-552-4221 in the tolvaptan treatment group withdrew consent due to personal reasons. The site recorded a serious AE of severe new-onset glaucoma on Day 521. Visual field tests were done on Day 562, Day 604, and Day 637, which revealed highly reproducible glaucomatous damage in the right eye and no or very mild damage in the left eye. The subject was treated with bimatoprost drops. Tolvaptan was interrupted due to the event starting on Day 606 and was not restarted. As of Day 1278, the investigator reported that the subject's intraocular pressures (IOPs) were still elevated and he was still receiving treatment (not specified). The investigator assessed the event of glaucoma as possibly related to tolvaptan.

5.2 Demographics, Baseline Characteristics, and Medical History in Trial 156-04-251

Demographics, baseline characteristics, and medical history were well balanced between treatment groups in Trial 156-04-251.

The mean age was 38.7 years and ranged from 18 to 51 years. The majority of subjects were Caucasian (84.3%), and approximately half were male (51.6%). Relative to the US population, there was disproportionate over-representation of Asian (Japanese) subjects and under-representation of African-American and Hispanic-American subjects (Table 5.2-1).

Table 5.2-1 Demographic Characteristics in Trial 156-04-251: Age, Height, Weight, and Race by Sex

Demographic Characteristic	Tolvaptan			Placebo			Total		
	Male (N = 495)	Female (N = 466)	Total (N = 961)	Male (N = 251)	Female (N = 233)	Total (N = 484)	Male (N = 746)	Female (N = 699)	Total (N = 1445)
Age (years)									
Number of subjects	495	466	961	251	233	484	746	699	1445
Mean	38.2	38.9	38.6	38.3	39.4	38.8	38.3	39.1	38.7
SD	7.1	7.1	7.1	7.3	7.0	7.1	7.1	7.1	7.1
Median	39.0	40.0	39.0	39.0	40.0	39.0	39.0	40.0	39.0
Minimum	18	19	18	18	18	18	18	18	18
Maximum	51	50	51	50	50	50	51	50	51
Height (cm)									
Number of subjects	495	465	960	251	232	483	746	697	1443
Mean	180.4	166.2	173.5	180.0	166.6	173.6	180.3	166.4	173.6
SD	7.9	7.3	10.4	7.4	6.5	9.7	7.8	7.0	10.2
Median	180.0	166.0	173.0	180.0	167.0	173.0	180.0	167.0	173.0
Minimum	150	143	143	159	150	150	150	143	143
Maximum	210	192	210	201	188	201	210	192	210
Weight (kg)									
Number of subjects	495	466	961	251	233	484	746	699	1445
Mean	87.68	70.74	79.47	86.13	70.30	78.51	87.16	70.59	79.15
SD	15.80	16.59	18.27	16.96	16.04	18.31	16.21	16.4	18.28
Median	86.00	66.50	78.20	82.70	66.90	75.50	85.00	66.70	77.50
Minimum	50.6	40.6	40.6	54.7	46.0	46.0	50.6	40.6	40.6
Maximum	160.6	133.6	160.6	151.8	135.2	151.8	160.6	135.2	160.6
Race,[a] n (%)									
Caucasian	418 (84.4)	392 (84.1)	810 (84.3)	204 (81.3)	204 (87.6)	408 (84.3)	622 (83.4)	596 (85.3)	1218 (84.3)
Black	7 (1.4)	9 (1.9)	16 (1.7)	3 (1.2)	0	3 (0.6)	10 (1.3)	9 (1.3)	19 (1.3)
Hispanic	8 (1.6)	5 (1.1)	13 (1.4)	6 (2.4)	3 (1.3)	9 (1.9)	14 (1.9)	8 (1.1)	22 (1.5)
Asian	61 (12.3)	60 (12.9)	121 (12.6)	37 (14.7)	25 (10.7)	62 (12.8)	98 (13.1)	85 (12.2)	183 (12.7)
Other	1 (0.2)	0	1 (0.1)	1 (0.4)	1 (0.4)	2 (0.4)	2 (0.3)	1 (0.1)	3 (0.2)

[a]Percentages are based on the number of male, female, or total randomized subjects.

The pivotal Trial 156-04-251 population represents subjects in the mid-range of ADPKD disease who were enriched based on prognosis for rapid progression. At baseline, approximately 34% of subjects were CKD Stage 1, 49% CKD Stage 2, and 17% CKD Stage 3 based on eGFR calculated using the CKD-EPI formula (refer to Figure 5.2-1). These subjects were expected to represent the core of a population appropriate for therapy. Prognostic indicators based on risk of future progression to ESRD (hypertension, renal function, and renal volume) guided appropriate patient selection, were also used as stratification factors in the trial, and were designated as prespecified subgroups for further analysis.

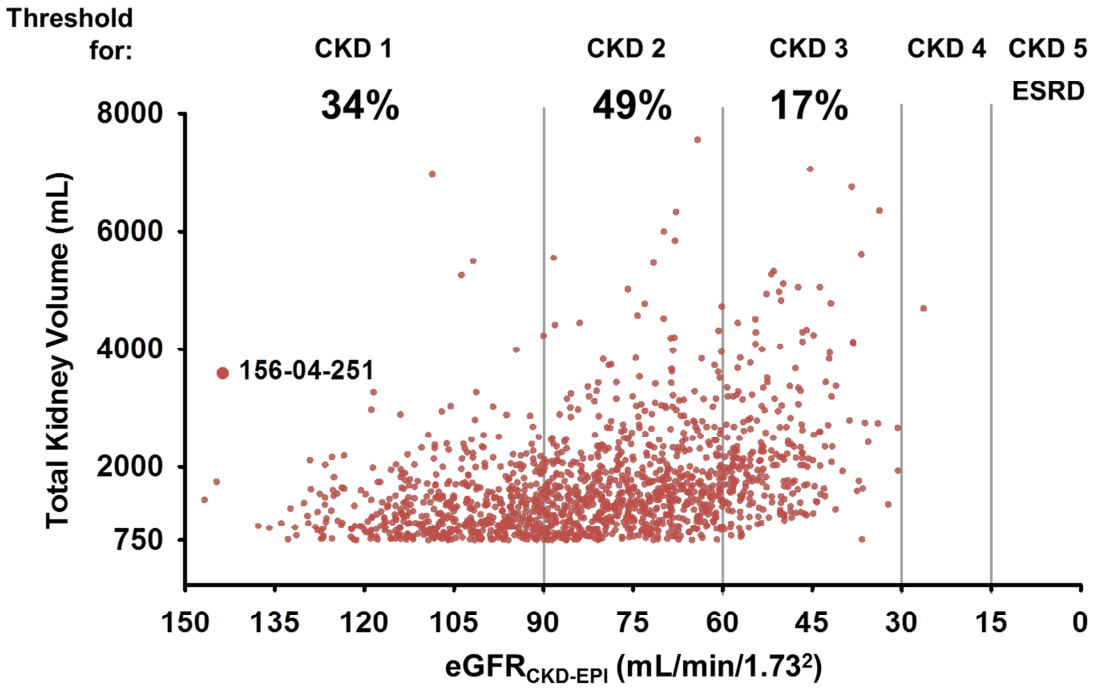


Figure 5.2-1 **Distribution of Trial 156-04-251 Trial Population by Baseline CKD Stage Classification (Renal Function Estimated by CKD-EPI Formula)**

CKD-EPI = Chronic Kidney Disease-Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; ESRD = end=stage renal disease; TKV = total kidney volume.

The mean age at first diagnosis of ADPKD was 27.4 years (range = 0 to 50 years; Table 5.2-2). The presenting symptoms leading to the ADPKD diagnosis were high BP (334/1445, 23.1%), renal pain (218/1445, 15.1%), blood in urine (143/1445, 9.9%), and UTI (109/1445, 7.5%); for the remainder of subjects, the reason for diagnosis was other

(839/1445, 58.1%) or unknown (60/1445, 4.2%). Due to limitations of the CRFs in Trial 156-04-251, the "other" reasons for diagnosis were not collected. An independent examination of data from subjects from Trial 156-04-251 who enrolled in Trial 156-08-271 with "other" reasons for their ADPKD diagnosis (as of 17 Jul 2012; 289 subjects) found that:

- 59.5% were asymptomatic at screening but had a family history of ADPKD,
- 23.5% experienced signs and symptoms that were related to ADPKD,
- 14.5% were asymptomatic with an incidental finding of ADPKD identified during routine care,
- 2.4% experienced signs and symptoms that were unrelated to ADPKD.

History of hypertension and hematuria, which are known indicators of rapid progression of ADPKD, were well balanced between treatment groups.

The mean (SD) baseline $eGFR_{CKD-EPI}$ was 81.61 (21.60) mL/min/1.73 m^2. Mean (SD) TVK was 1692.3 (905.31) mL (Table 5.2-3). At baseline, a total of 1157 (1157/1445, 80.1%) subjects had a history of hypertension and 735 (735/1445, 50.9%) subjects had a history of renal pain. Additionally, 53.3% (770/1445) and 5.3% (76/1445) of subjects had microalbuminuria and overt proteinuria, respectively, in their baseline labs.

An identical proportion (76.9%) of subjects in both treatment groups used hypertension medications before the start of trial medication. The proportion of subjects taking medications for renal pain was similar at the start of the trial (5.1% for the tolvaptan group vs 5.8% for the placebo group). Overall, 10.2% (148/1445) of subjects were taking analgesics (including an additional 4.8% [69/1445] specifically for kidney pain).

At baseline, 23.1% of subjects were taking no antihypertensive medications while 71.3% (1031/1445) were taking agents acting on the renin-angiotensin system, 19.9% (287/1445) were taking calcium channel blockers, and 18.1% (262/1445) were taking beta blockers. The overall use of other concomitant medications (medications not for HTN or renal pain) was comparable between the tolvaptan group (58.8%) and the placebo group (53.3%) prior to the trial.

Table 5.2-2 ADPKD History in Trial 156-04-251

Parameter	Tolvaptan (N = 961)	Placebo (N = 484)	Total (N = 1445)
Age of diagnosis (years)			
Number of subjects	958	484	1442
Mean	27.3	27.6	27.4
SD	9.5	9.3	9.4
Median	27.0	28.0	27.5
Minimum	0	1	0
Maximum	50	50	50
Diagnosis due to, n (%):			
High blood pressure	228 (23.7)	106 (21.9)	334 (23.1)
Blood in urine	96 (10.0)	47 (9.7)	143 (9.9)
UTI	76 (7.9)	33 (6.8)	109 (7.5)
Renal pain	141 (14.7)	77 (15.9)	218 (15.1)
Unknown	37 (3.9)	23 (4.8)	60 (4.2)
Other	553 (57.5)	286 (59.1)	839 (58.1)
History of, n(%):			
Hepatic cysts	571 (59.4)	291 (60.1)	862 (59.7)
Non-hepato-renal cysts	121 (12.6)	50 (10.3)	171 (11.8)
Hematuria	338 (35.2)	164 (33.9)	502 (34.7)
Proteinuria	233 (24.2)	116 (24.0)	349 (24.2)
Nephrolithiasis	187 (19.5)	109 (22.5)	296 (20.5)
Upper urinary tract infection	290 (30.2)	164 (33.9)	454 (31.4)
Anemia	105 (10.9)	48 (9.9)	153 (10.6)
Colonic diverticuli	23 (2.4)	7 (1.4)	30 (2.1)
Vascular/cardiac abnormalities	116 (12.1)	51 (10.5)	167 (11.6)
Abdominal hernia	107 (11.1)	43 (8.9)	150 (10.4)

ADPKD = autosomal dominant polycystic kidney disease; SD = standard deviation; UTI = urinary tract infection.

Table 5.2-3 Pretitration Baseline Renal Function and Total Kidney Volume in Trial 156-04-251

Parameter	Tolvaptan (N = 961)	Placebo (N = 484)	Total (N = 1445)
1/serum creatinine ($[mg/mL]^{-1}$)			
Number of subjects	958	482	1440
Mean	102.27	104.30	102.95
SD	27.21	33.87	29.61
Median	100.00	100.00	100.00
Minimum	43.7	35.5	35.5
Maximum	263.2	500.0	500.0
$eGFR_{CKD-EPI}$ (mL/min/1.73 m^2)			
Number of subjects	958	482	1440
Mean	81.35	82.14	81.61
SD	21.02	22.73	21.60
Median	80.76	80.40	80.74
Minimum	32.3	26.4	26.4
Maximum	132.8	186.7	186.7

Table 5.2-3 Pretitration Baseline Renal Function and Total Kidney Volume in Trial 156-04-251

Parameter	Tolvaptan (N = 961)	Placebo (N = 484)	Total (N = 1445)
TKV (mL)			
Number of subjects	961	483	1444
Mean	1704.8	1667.5	1692.3
SD	921.27	873.11	905.31
Median	1456.7	1468.5	1458.8
Minimum	750.0	751.1	750.0
Maximum	7555.4	6751.1	7555.4
Height-adjusted TKV (mL/m)			
Number of subjects	960	482	1442
Mean	978.56	958.18	971.75
SD	514.84	483.27	504.43
Median	858.70	849.30	857.00
Minimum	394.7	408.7	394.7
Maximum	4317.4	3750.6	4317.4

CKD-EPI = Chronic Kidney Disease-Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; SD = standard deviation; TKV = total kidney volume.

5.3 Dose Titration Pattern in Trial 156-04-251

Modal analysis was used in Trial 156-04-251 to identify the pattern of dosing over the trial course, as illustrated in Figure 5.3-1. Modal dose reflects the dose taken most frequently within the specified time period. At the Week 3/EOT visit, the majority of subjects in the tolvaptan and placebo groups (80.9% [752/929] and 93.8% [450/480], respectively) had titrated to the highest 90/30 mg dose. Dose reduction was more common in the tolvaptan group, primarily during the initial 12 months, when approximately 20% and 6% of tolvaptan and placebo subjects, respectively, down-titrated from the 90/30 mg dose (since Week 3/EOT). By Month 36, the proportion of tolvaptan subjects receiving the highest dose was 54.4% (404/742), while 21.2% (157/742) were receiving a 60/30 mg dose, and 24.1% (179/742) were receiving a 45/15 mg dose. The proportion of placebo subjects at the highest dose by Month 36 was 83.3% (348/418), at 60/30 mg was 9.1% (38/418), and at 45/15 mg was 7.7% (32/418). At Month 36, the average daily doses in the tolvaptan and placebo groups, respectively, were 96.5 mg and 110.6 mg. These data, coupled with the subject discontinuation data, indicate tolerability of the higher doses is maintained over the long-term for subjects who persist beyond the first 4 to 12 months of therapy.

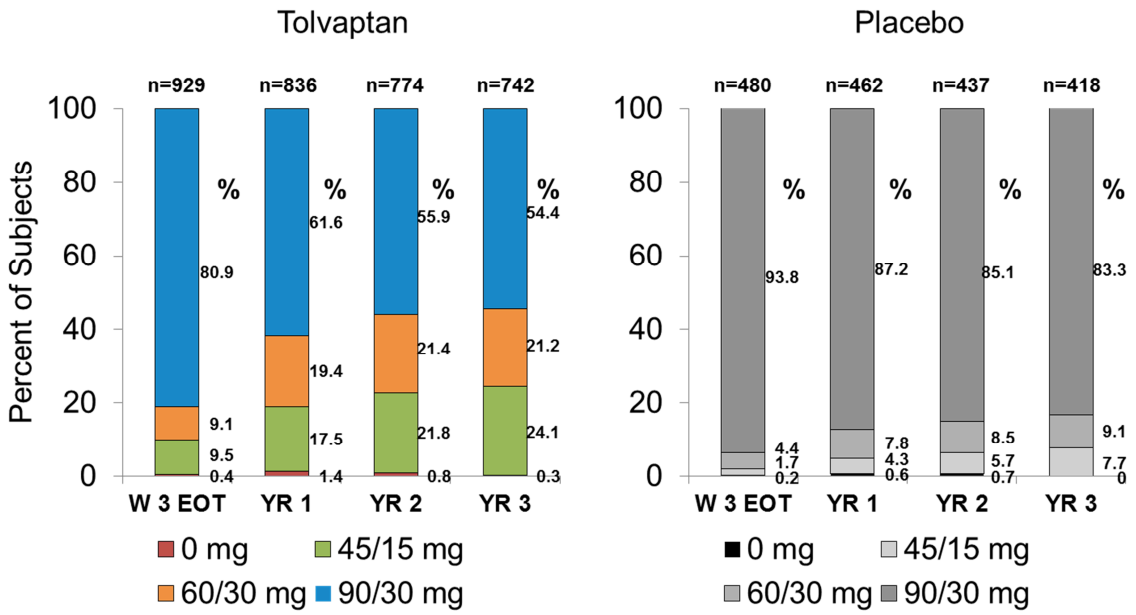


Figure 5.3-1 Titration Pattern Over Time in Trial 156-04-251

EOT = end of titration; W = week.
Represents modal dose since prior visit.

5.4 Datasets Analyzed for Efficacy in Trial 156-04-251

Table 5.4-1 summarizes the datasets used for the prospectively defined primary (TKV slope), key secondary composite endpoint, and third (renal function slope) endpoint analyses. Analyses followed ITT principles for the primary and secondary endpoints. Based on the nature of the analyses to be performed, subjects having both baseline and postbaseline data were evaluated for efficacy during the treatment period (from start of the first dose to 14 days following last dose of trial medication). Results of the sensitivity analyses are described in Section 10.4.

Table 5.4-1 Efficacy Datasets Analyzed (First Three Endpoints) in Trial 156-04-251

Number of Subjects	Tolvaptan (N = 961) n (%)	Placebo (N = 484) n (%)	Total (N = 1445) n (%)
Randomized (ITT)	961 (100.0)	484 (100.0)	1445 (100.0)
Analyzed for primary efficacy: TKV[a]			
ITT, within the treatment period (primary analysis)	819 (85.2)	458 (94.6)	1277 (88.4)
ITT, regardless of the treatment period	842 (87.6)	465 (96.1)	1307 (90.4)
Analyzed for key secondary efficacy: composite[b]			
ITT, within the treatment period (primary analysis)	961 (100.0)	483 (99.8)	1444 (99.9)
ITT, within the treatment period using Week 3/EOT as baseline	922 (95.9)	478 (98.8)	1400 (96.9)
ITT, regardless of the treatment period	961 (100.0)	484 (100.0)	1445 (100.0)
Analyzed for secondary efficacy: renal function using reciprocal of serum creatinine			
ITT, subjects with at least 4 months of follow-up, within treatment period using Week 3/EOT as baseline and excluding observations deemed unreliable by the investigator (primary analysis)	842 (87.6)	464 (95.9)	1306 (90.4)
ITT, subjects with at least 4 months of follow-up, within treatment period using Wk 3/EOT as baseline	870 (90.5)	472 (97.5)	1342 (92.9)
ITT, regardless of the treatment period	909 (94.6)	476 (98.3)	1385 (95.8)

EOT = end of titration; ET = early termination; ITT = intent-to-treat;TKV = total kidney volume; MRI = magnetic resonance imaging.

Note: "Within the treatment period" was defined as the period starting from the first dosing day to 14 days after the last dose of trial medication.

[a]Subjects were analyzed for the primary efficacy endpoint if they were randomized and had baseline and postbaseline observations on TKV. Subjects withdrawing from the trial early would have an MRI during the ET visit only if the subject's most recent MRI was greater than 6 months prior to withdrawal.

[b]Subjects were analyzed for the key secondary composite endpoint if they were randomized.

5.5 Primary Endpoint: Total Kidney Volume Slope

5.5.1 Description of the First (Primary) Endpoint - Total Kidney Volume Slope

At the initiation of the pivotal trial, the only completed interventional trials in ADPKD had involved fewer than 200 subjects treated for a period of 2 to 3 years.[48] Little had been published on the disease's characteristic progression and no interventions had been successful. Total kidney volume was selected as an endpoint most directly tied to tolvaptan's anticipated effects on cyst proliferation and expansion. Total kidney volume had also been evaluated and found to be a uniquely valuable measure of the disease's progression. Its ability to detect changes over a relatively short (3-year) period of the disease's slow course of progression permitted estimation of power for what would be a clinically relevant degree of change (20% reduction). While the sponsor acknowledges

that TKV is an unvalidated surrogate, TKV was chosen as the primary endpoint for this trial because if no effect were seen in TKV, it was believed no other clinical benefits would be conveyed to patients.

The TKV endpoint methodology established in the NIH CRISP program was adapted for the pivotal study and validated.[5] Total kidney volume also served as a mechanism for prognostic enrichment: data available during protocol design supported an association of larger TKV with more rapid progression of TKV growth and possibly the advance of renal dysfunction. Therefore, a minimum TKV of 750 mL was selected to enrich the population. Because ADPKD has no definitive therapy that can demonstrate an effect on disease progression or outcome, finding a concordance between an effect on TKV and other clinically accepted endpoints was considered the most practical way of developing support of tolvaptan's mechanism of action in this disease. Additionally, enrichment of the population was anticipated to be useful in evaluating the endpoints over a 3-year period in subjects with early ADPKD (defined as having an estimated creatinine clearance of at least 60 mL/min using Cockcroft-Gault equation).

The prospectively defined primary endpoint in this trial was the rate of TKV (both kidneys) change (normalized as percentage) from baseline. In order to derive the primary endpoint, MRI was performed to evaluate TKV at baseline (31 to approximately 14 days prior to randomization) and at Month 12, 24, and 36/ET visits. Contemporary reports suggested TKV rate of change was slow and would require as much as 6 months to detect a change.[49] Therefore, a minimum of 6 months between ET and the previous MRI assessment was required. For the purpose of statistical modeling, time to MRI from randomization was treated as a continuous variable, expressed as years from the date of the Baseline MRI visit to the date of the MRI visit, ie, (date of MRI visit – date of MRI visit at Baseline)/365.25, instead of a class variable with values of 0, 1, 2, or 3. In addition, to reduce heterogeneity in variance and achieve linearity over time, $\log_{10}$ transformation was applied to the TKV data.

5.5.2 Results of the Primary Endpoint

In the pivotal Trial 156-04-251, tolvaptan reduced the rate of TKV growth (primary trial endpoint), and by extension cystogenesis, by approximately half in comparison with placebo (2.78% vs 5.61%/year), for a difference of 2.71%/year ($p < 0.0001$). This represented a 49.2% reduction of growth rate (Table 5.5.2-1, Figure 5.5.2-1). These data are displayed graphically in Panel A as a scatter plot of individual subject TKV percent change from baseline values, at actual time from first dose, overlaid with lines

representing the slopes for each treatment group. Panel B is a box and whisker plot of the same values grouped by trial visit.

Table 5.5.2-1 Primary Endpoint (Random Effect Intercept) in Trial 156-04-251: Total Kidney Volume Rate of Growth (%/year), ITT, Within Treatment Period

Parameter	Tolvaptan	Placebo
Rate of percent growth per year[a]		
Number of subjects	819	458
Mean	2.777	5.608
Median	2.265	5.585
SD	5.659	5.330
Minimum	−23.129	−20.634
Maximum	64.270	43.948
Estimated slope[b]	0.0280	0.0551
Treatment effect		
Difference (%)	−2.708	
95% CI[c]	−3.269, −2.147	
Slope reduction (%)	49.2	
Ratio of geometric mean[d]	0.974	
95% CI	0.969, 0.980	
p-value[e]	< 0.0001	

CI = confidence interval; ITT = intent-to-treat; MRI = magnetic resonance imaging; SD = standard deviation.

Note - Subjects with baseline and postbaseline MRI results are included in the primary analysis. "Within treatment period" is defined as the period starting from the first dosing day to 14 days after the last dose of trial medication.

[a] Summary statistics are derived by regressing logarithm-transformed kidney volume data against time, then displaying regression-slope exponentials. Time variable used in the regression is equal to (MRI date - baseline MRI date)/365.25.

[b] Slope is estimated by subtracting 1 from the geometric mean of annualized growth rate.

[c] Derived from delta method assuming independence between the estimates of the slope between the 2 treatments. Difference in slope produced post-hoc to facilitate clinical interpretation.

[d] An estimate of the ratio of geometric mean of annualized growth rate of tolvaptan and placebo.

[e] Derived from testing the time treatment interaction using linear mixed model in which both intercept and slope are fixed and random effects.

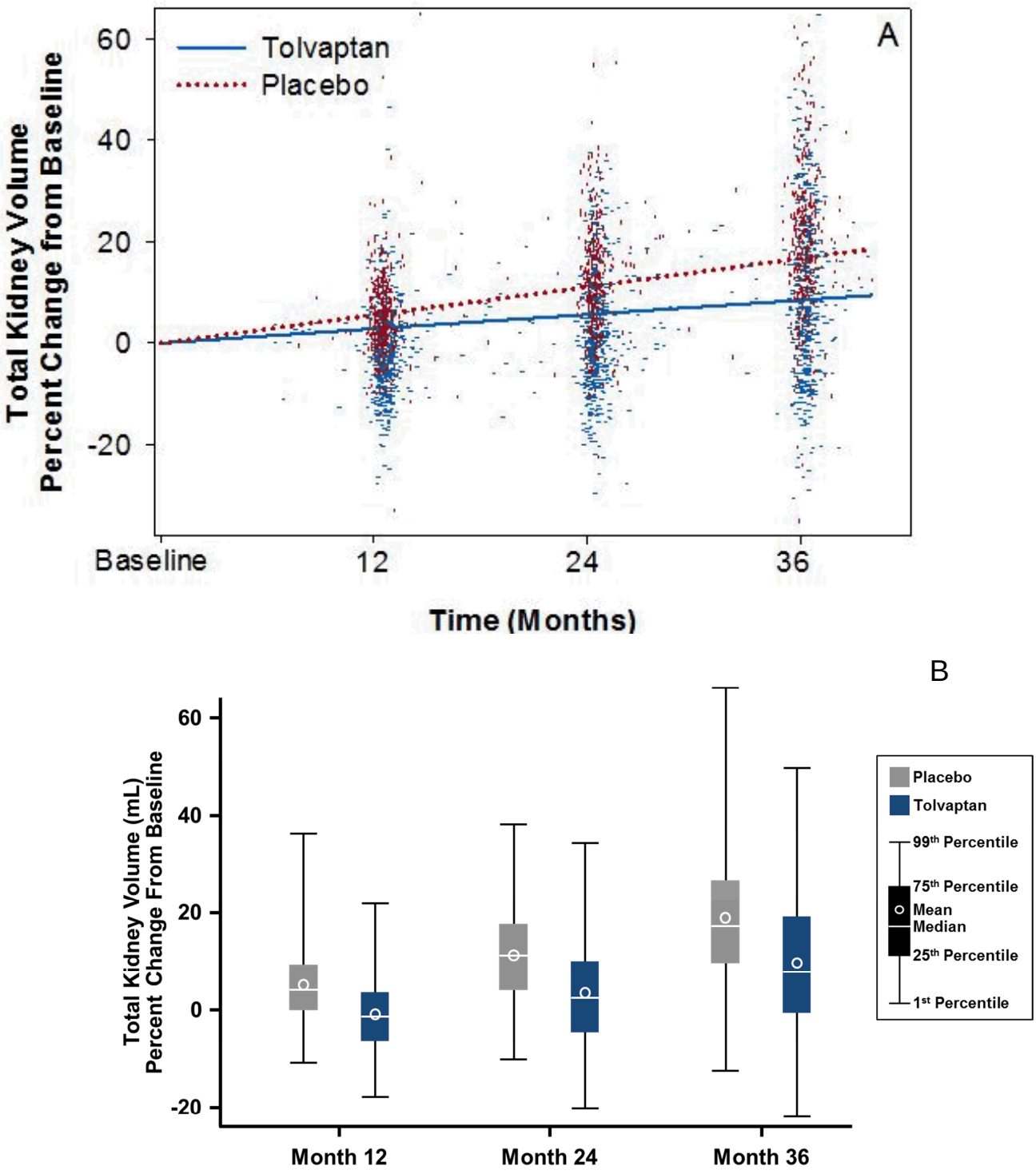


Figure 5.5.2-1 Percent Change from Baseline in Total Kidney Volume in Trial 156-04-251 - ITT, Within Treatment Period

Effect of tolvaptan on annual slope of kidney volume Slopes of total kidney volume growth (% change from baseline), ITT within treatment period and individual patient data included in slope calculations;

6 of 1315 placebo and 3 of 2370 tolvaptan outlier data points are not shown in the figure; Ratio of geometric mean = 0.97 (95% CI = 0.97-0.98); P <0.001 (Panel A). Box and whisker plot of the same data grouped by visit, showing mean, median, and percentiles by treatment group (1st, 25th, 75th, 99th; Panel B).

Panel A from: NEJM. Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. 367 (25): 2407-18. Copyright © (2012) Massachusetts Medical Society. Reprinted with permission.

The above analysis was prespecified in the protocol with both intercept and slope as random effects; however, the variance of the random effect intercept was zero, resulting in a non-positive definite variance-covariance matrix for the random effects. Therefore, a post-hoc analysis of the primary endpoint was performed using a linear mixed model in which the intercept was a fixed effect and the slope was fixed and random effect. The results of the revised analysis were consistent with the SAP-specified analysis, with a 49.9% reduction in TKV growth rate in the tolvaptan group compared with the placebo group (estimated slope of 2.75% and 5.49% per year, respectively). The inference statistics of these 2 analyses were similar, and both of them had a p-value < 0.0001.

5.5.3 Sensitivity Analyses of the Primary Endpoint

Measurement of total kidney volume is a unique and novel endpoint for clinical trials. Relatively little information was available regarding the potential for an intervention's effects on TKV. As an example, acute effects which might lead to a non-linear time course were not anticipated when the protocol was written; however, advice led us to include a number of sensitivity and exploratory analyses which are important in a fuller understanding of this endpoint and tolvapan's actions on it. These sensitivity and exploratory analyses are presented in Section 10.4.1 while analyses focusing on specific approaches to missing data are discussed in Section 5.11.

While all sensitivity analyses were consistent with the primary analyses, the prospectively defined MMRM analysis which can handle non-linearity revealed that the effect of tolvaptan was greatest in the first year with smaller and similar, but still statistically significant, effects for Year 2 and Year 3 (Section 10.4.1.1). A by-center analysis showed tolvaptan was favored for a majority of centers (Section 10.4.1.6). A by-country analysis favored tolvaptan in all countries.

5.6 Key Secondary Composite Endpoint

5.6.1 Description of the Second (Key Secondary Composite) Endpoint and its Components

The concept of a key secondary composite endpoint was recommended by the FDA as a measure of time to multiple ADPKD clinically relevant, investigator-reported progression events for tolvaptan (combining all doses) relative to placebo while on treatment. This endpoint was designed to measure outcomes which are clinically relevant to the patient, and provide evidence of the effects of events related to the ongoing destruction of kidney tissue and progression of kidney disease. Components of the composite are not definitive outcomes (eg, albuminuria); they each represent measures of new, ongoing or worsening pathophysiological processes in the kidney. The four composite components selected were measures of the disease which were believed to be likely related to cyst expansion and which might be measurable over a 3-year period.

5.6.1.1 Worsening Renal Function Event Component

Cyst growth gradually decreases renal function through physical destruction of nephrons. Ongoing, progressive and irreversible reduction in eGFR, creatinine clearance, or GFR, was considered reliable evidence of meaningful disease progression. In previous trials of therapies for diabetic nephropathy a 100% increase in serum creatinine was used as an acceptable threshold. Since FDA agreed that this degree of change was not likely to be reached in early ADPKD within a reasonable time, a 25% decline in the reciprocal of serum creatinine (1/serum creatinine), which is equivalent to a 33% increase in serum creatinine, was used. A worsening renal function event was defined as a reduction of renal function of at least 25% reduction in the reciprocal serum creatinine from baseline, and each subsequent further 25% reduction based on the reciprocal serum creatinine observed at the previous event. A 25% reduction in the reciprocal serum creatinine had to be confirmed by a second visit which was at least 14 days apart to be considered as a worsening renal function event. If a second visit was less than 14 days apart, the visit would be discarded and the next visit which was at least 14 days apart would be used for confirmation. If confirmed, the first visit of 25% reduction was the date at which the event occurred, and the reciprocal serum creatinine of the event was defined as the reciprocal serum creatinine which was less severe between these two visits.

Serum creatinine measurements for calculation of renal function were taken at Screening, Baseline, Week 3 (or EOT), Months 4, 8, 12, 16, 20, 24, 28, 32, 36/ET, Follow-up Visit 1, and Follow-up Visit 2. For the consideration of the renal function component,

the baseline was defined as Week 3/EOT due to the known acute and reversible hemodynamic effects on GFR and serum creatinine (see Section 4.2.2.1).

5.6.1.2 Renal Pain Event Component

Cyst expansion could lead to pain due to stretching of the renal capsule, cyst rupture, cyst hemorrhage, infection, etc. All these underlying processes are themselves events which represent acute-on-chronic injury to the kidney. Therefore the frequency of intermittent acute kidney pain can be a reliable sign of meaningful disease progression. Since no accepted patient-reported outcomes for ADPKD pain existed, an event defined by a subject complaint which on assessment led to a prescription for medical intervention for pain relief was used (eg, nerve block, use of narcotic or other prescription and non-prescription nociceptive agents, or requirement for medical leave). This is much less sensitive than a typical pain scale, but since the pain events were likely to be intermittent, it was felt to be more specific. Interventions at 3 levels were included such that a lower level intervention could not be an event once a higher level intervention had occurred.

The component of renal pain counted events arising from all causes of renal pain associated with ADPKD (infection, cyst rupture, hemorrhage, nephrolithiasis, etc) but was limited to interventions specifically aimed at reducing pain, eg, not including lithotripsy or antibiotics. To meet this endpoint, pain was required to satisfy 2 criteria:

1) in the judgment of the principal investigator (PI), the pain had to originate from the kidney or upper urinary tract
2) in the judgment of the PI, the pain had to be significant enough to require a medical intervention.

In the construction and analysis of this endpoint, the level of intervention used was further categorized based on 3 levels of intervention (listed below in decreasing order of intensity).

1) use of invasive surgical or radiological procedures
2) use of prescription narcotic or antinociceptive agents which are centrally acting (eg, tricyclic antidepressants)
3) use of prescription or non-prescription non-narcotic analgesics or antinociceptive agents or the prescription of medical leave or limitations on activities.

Investigators learned of pain events via subject self-report during scheduled or unscheduled trial visits, or through a report from the subject's primary care physician. The occurrence of such events was recorded on special case report forms (CRFs). The investigator was to document whether a medication or intervention was used in management of renal pain. The date of the event was the date the intervention was

prescribed. If the prescription date was missing or partially reported on the CRF for medication-related events, the medication start date was utilized as the event date.

5.6.1.3 Hypertension Event Component

Presence or degree of hypertension has been accepted as a validated surrogate of cardiovascular risk. Progression of BP increase or difficulty in management of hypertension represent a novel and untested method for assessing the progress of CKD, however these characteristics are theoretically reasonable surrogates of progressive renal ischemia due to cyst growth. In untreated, pre-hypertensive patients, BP itself could serve as an endpoint with various thresholds leading to categorical changes. There were two kinds of events for worsening hypertension: events based on BP for non-hypertensive subjects not taking hypertensive medication, and events based on increased doses or new medications for worsening hypertension in hypertensive subjects already taking hypertensive medication. Once treated, the intensity of treatment was used as a measure of progression of hypertension. Subjects who became hypertensive during the trial could have both kinds of hypertensive events.

Blood pressures were grouped into four categories (in increasing order of significance):

- normotensive (sBP < 120 and dBP < 80 mmHg and off therapy)
- low-pre-hypertensive (sBP ≤ 129 and dBP ≤ 84 mmHg but not normotensive and off therapy)
- high-pre-hypertensive (sBP ≤ 139 and dBP ≤ 89 mmHg but not normotensive/low-pre-hypertensive and off therapy)
- hypertensive (sBP >139 and/or dBP > 89 mmHg or on anti-hypertensive therapy).

Subjects whose BP shifted to a higher category in two consecutive visits compared to baseline category (or the category of their most recent previous BP events) were considered to have a BP event. In this case, the first of the two consecutive visits was considered as the visit of the event, and the less severe category among the two consecutive visits was considered as the category of the event. Based on these BP event categories, a subject could have at most three BP events.

A subject could have as many hypertensive medication events as possible, if each of them was an introduction or dose increase of hypertensive medication, as compared to their most recent previous hypertensive medication events. An IV and intramuscular (IM) route of hypertensive medication for treating worsening hypertension was always considered as a hypertensive medication event.

Blood pressure measurements were taken at Screening, Baseline, Day 1, Weeks 1, 2, and 3 (or End of Titration [EOT]), Months 4, 8, 12, 16, 20, 24, 28, 32, 36/ET, Follow-up Visit 1, and Follow-up Visit 2.

5.6.1.4 Albuminuria Event Component

Although not typically associated with ADPKD, as cysts grow and renal function continues to deteriorate, stress on the remaining normal nephrons (due to hyperfiltration, fibrosis and hemodynamic changes) are believed to be associated with progressively higher levels of proteinuria. The endpoint counted an event defined by persistent clinically relevant shifts in thresholds (no proteinuria, micro-, macro-albuminuria) defined by central laboratory thresholds for each gender.

Categories of albuminuria based on urine albumin/creatinine ratio were grouped in the following in increasing order of significance (see below). At most, 2 events could occur.

- “normal” (urine albumin/ creatinine of < 2.8 mg/mmol female or < 2.0 mg/mmol male)
- “microalbuminuria” (urine albumin/ creatinine of 2.8-28 mg/mmol female or 2.0-20 mg/mmol male)
- “overt proteinuria” (urine albumin/ creatinine of >28 mg/mmol female or >20 mg/mmol male)

Albuminuria was assessed using spot urine albumin/creatinine ratio measurements determined for urine samples collected at the clinic during visits at Screening, Baseline, Week 3 (or EOT), Months, 4, 8, 12, 20, 24, 28, 32, 36/ET, Follow-up Visit 1, and Follow-up Visit 2. Urine samples were collected using second morning urine after awaking, collected using "clean-catch, mid-stream" technique.

5.6.1.5 Analysis Method for the Key Secondary Composite Endpoint

Because tolvaptan was believed to act through reduction of cyst expansion and its consequences, the key secondary composite endpoint was placed after the primary TKV endpoint. This order was selected since the hypothesis requires cyst growth as an earlier step in disease progression. Success in the key secondary composite endpoint was presumed to be dependent of the success of the TKV endpoint.

For the primary analysis of the key secondary composite endpoint, all the clinical ADPKD progression events occurring during the double-blind treatment period from a) the date of the first dose of trial medication (for HTN, proteinuria, and renal pain) or b) the completion of the titration phase (for renal function) to the date of trial completion/ET were included in the analysis for all ITT subjects.

By agreement with the FDA, this primary analysis did not include data from visits for subjects who had withdrawn from trial medication administration but continued to have telephone contact on PKD Outcomes. These data were added to sensitivity analyses for exploratory purposes.

The double-blind treatment period was typically defined as a period from the first dose of trial medication to the end of a 14-day window of the last dose of trial medication. For this endpoint, events occurring within the first 2 days of trial medication initiation were excluded from analysis, because they were considered to be due to baseline conditions. Analysis of time to multiple (recurrent) events using proportional rate and mean model was used for the analysis of the key secondary composite endpoint to provide a point estimate of the hazard ratio (which for time to multiple event analyses may be more appropriately considered to be an "intensity ratio") and its p-value. This analysis of rate and mean model was identical to the analysis of the intensity model (Andersen-Gill model) using the sandwich covariance matrix estimate to derive standard errors for the Wald test.

Two analyses of the key secondary composite endpoint were conducted:

1) The first analysis included all events observed during the double-blind treatment period as defined in the previous paragraph, using Day 1 as the baseline value for all components other than worsening renal function. This analysis was the primary analysis of the key secondary composite endpoint.
2) The second analysis included a sensitivity analysis of all events observed during the double-blind treatment period from Week 3/EOT to the end of the double blind treatment period, using Week 3/EOT as the new baseline value for all components. This sensitivity analysis was proposed to reduce the possible noise from BP measures taken during a period of acclimation to the trial, the trial medication, and while other antihypertensive medications were being stabilized or titrated, as diuretics were discontinued as required per protocol in the screening and titration period.

A significance level of 0.05 (two-sided) was used to declare statistical significance for the key secondary composite endpoint, for the purpose of subsequent sequential analysis.

Additional considerations for these analyses included the following:

- Follow-up Visit 1 was used to confirm events whose first occurrence was reported as Month 36.
- if an event was first reported at the ET visit, no confirmation was required.
- dates of events were mapped to the next scheduled or unscheduled visit.
- multiple events mapping to a single visit were collapsed to a single event.

- subjects reaching their Month 36/ET visit without having an event at that visit were censored at that point.

5.6.2 Results of the Key Secondary Composite Analysis

For the primary analysis of the key secondary composite endpoint, all the clinical ADPKD progression events occurring during the double-blind treatment period from the date of first dose (Day1) of study medication for all ITT subjects were included in the "within treatment period" analysis. In this analysis, tolvaptan reduced the rate of the pooled composite events by 13.5% (p = 0.0095), meeting the FDA-prescribed level of significance (Figure 5.6.2-1).

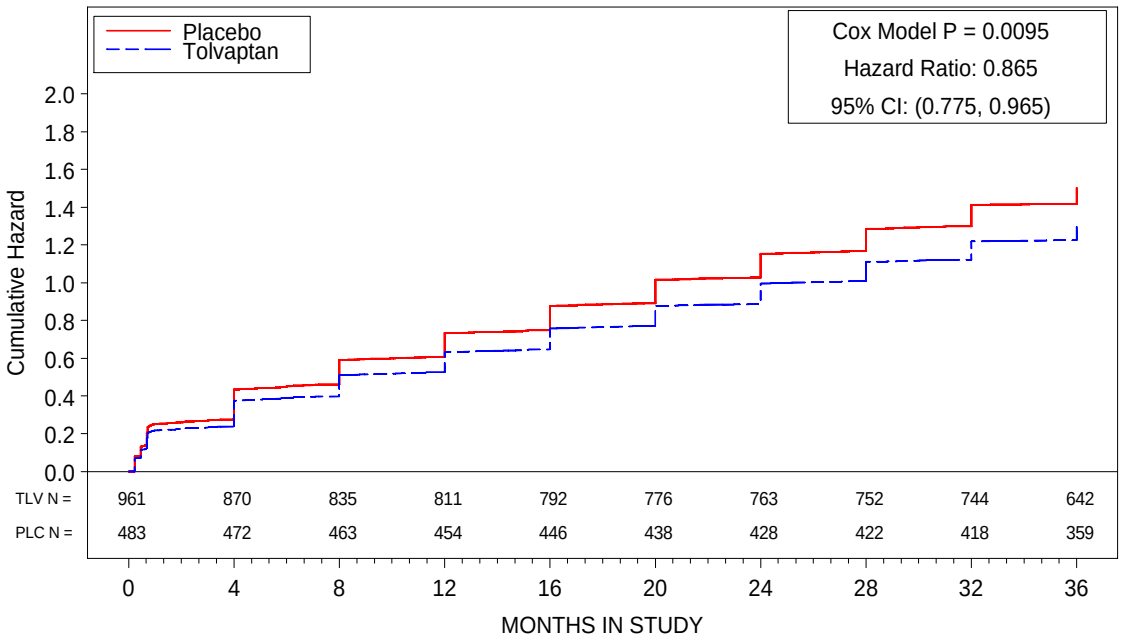


Figure 5.6.2-1 Cumulative Hazard Functions of Time to Multiple Events for the Key Secondary Composite Endpoint in Trial 156-04-251; ITT, Within Treatment Period

PLC = placebo; TLV = tolvaptan.

The second analysis using Week 3/EOT visit as baseline was also significant (HR 0.877, 95% CI 0.785 - 0.980, p = 0.0203).

5.6.3 Sensitivity Analyses of the Key Secondary Composite Endpoint

The key secondary composite endpoint was a composite of unique and novel events representing ADPKD disease progression. Relatively little information was available regarding the frequency of these events in early ADPKD patients. To gain a better

understanding of this endpoint and its components, a variety of sensitivity and exploratory analyses were conducted for each. These analyses for the overall key secondary composite endpoint are presented in Section 10.4.2 while analyses focusing on specific approaches to missing data are discussed in Section 5.11.

While all sensitivity analyses, including an analysis using events considered clinically meaningful for disease progression by a clinical events committee (CEC), were consistent with primary analysis (Section 10.4.2.1), the by-center analysis of the key secondary composite endpoint demonstrated that treatment effect came from most of the centers, not just from a few large centers (Section 10.4.2.6). The by-country analysis showed 9 out of 15 countries demonstrated a treatment effect in favor of tolvaptan with the US result nominally favorable for tolvaptan and consistent with the overall result.

5.6.4 Analyses of the Individual Components of the Key Secondary Composite Endpoint

The key secondary composite endpoint was constructed to provide adequate power to detect an effect on measures related to clinically important disease progression. If an overall effect on the composite was shown, it would be important to evaluate tolvaptan's effects on each of its components. If the effect was driven by a single component of uncertain clinical significance (eg, albuminuria), FDA might consider the composite to have little clinical value. These components were analyzed prospectively without need for adjustment for multiplicity, as agreed by the FDA.

The component analysis revealed that the positive composite result was driven by worsening renal function events and renal pain events (Table 5.6.4-1).

Table 5.6.4-1 Supplemental Analysis in Trial 156-04-251: Time to Multiple Events for Components of the Key Secondary Composite Endpoint; ITT, Within Treatment Period

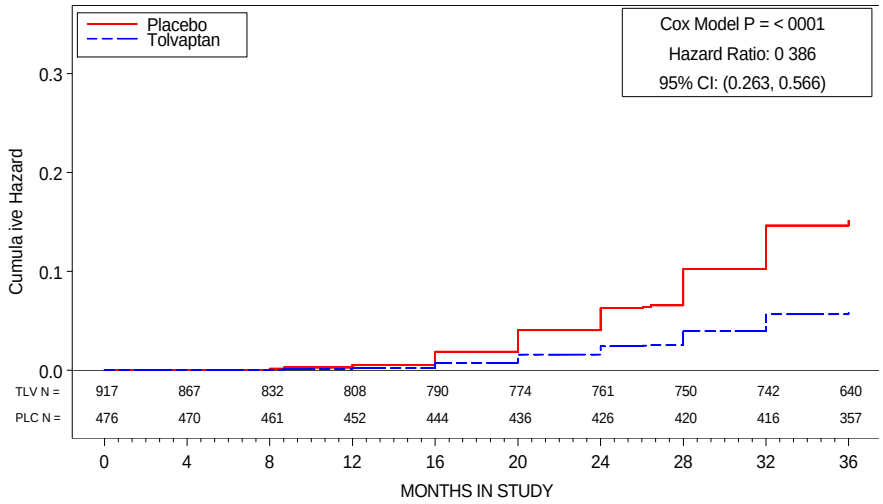
Parameter	Worsening Renal Function		Renal Pain		Worsening Hypertension		Worsening Albuminuria	
	Tolvaptan (N = 961)	Placebo (N = 483)	Tolvaptan (N = 961)	Placebo (N = 483)	Tolvaptan (N = 961)	Placebo (N = 483)	Tolvaptan (N = 961)	Placebo (N = 483)
Number of subjects	917	476	961	483	961	483	961	483
Number of events	44	64	113	97	734	426	195	103
Total follow-up years	2378	1323	2387	1329	2387	1329	2387	1329
E/100 follow-up years	1.85	4.84	4.73	7.30	30.74	32.05	8.17	7.75
Mean follow-up years	2.59	2.78	2.48	2.75	2.48	2.75	2.48	2.75
HR[a]	0.386		0.642		0.942		1.037	
95% CI[a]	0.263, 0.566		0.466, 0.887		0.814, 1.090		0.837, 1.284	
p-value[a]	< 0.0001		0.0071		0.4223		0.7420	

CI = confidence interval; E = event; EOT = end of titration; HR = hazard ratio; ITT = intent-to-treat.

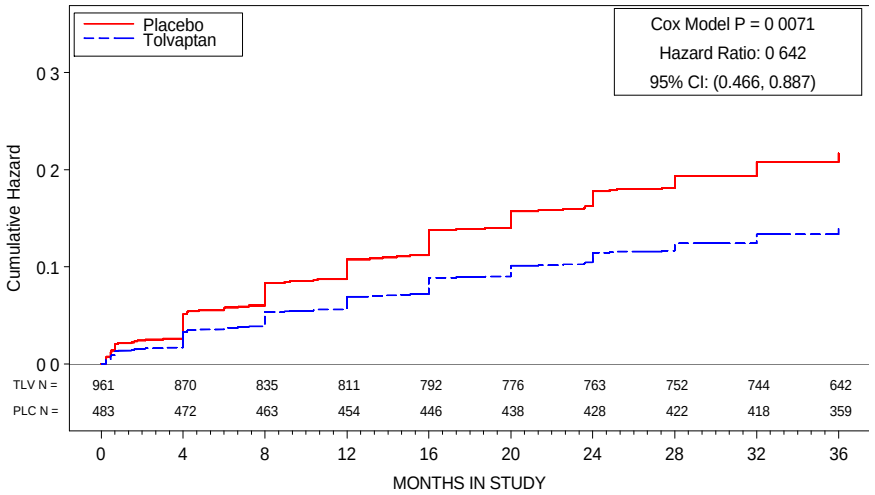
[a]Derived from rate and mean model of time to recurrent event analysis with factor treatment. All endpoints are assessed from pretreatment baseline except for Worsening Renal Function, which uses the Week 3/EOT as baseline.

These results reflect a relative improvement of 61.4% for events of worsening renal function and 35.8% for renal pain events. Treatment did not impact worsening hypertension or albuminuria events (at bottom of Figure 5.6.4-1).

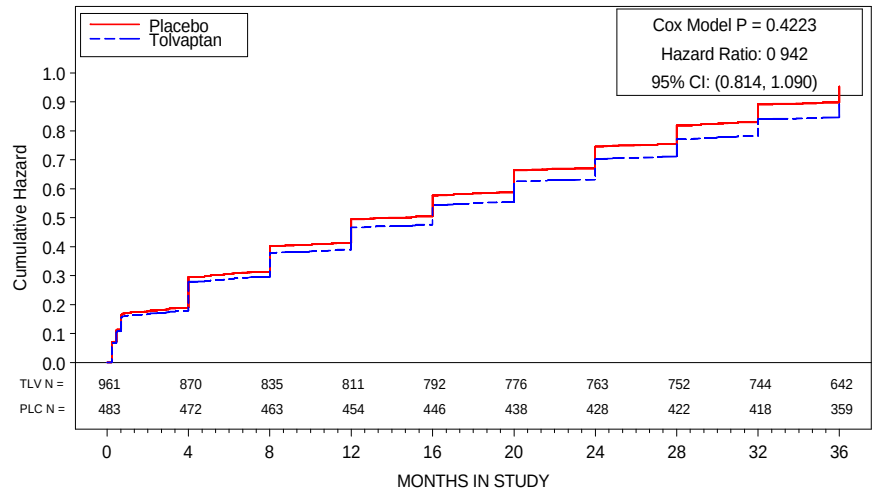
The beneficial reduction in worsening renal function events was evident after the first year of tolvaptan therapy, whereas separation between treatment groups for the reduction in renal pain events was observed early in the treatment period. This difference in pattern was likely due to the relatively slow rate of renal function decline required to produce a reproducible increase in serum creatinine of 33%. The observed rate of worsening renal function events in the placebo group is consistent with the relative risk for a 30% decline in renal function for ADPKD when matched to baseline kidney volume. This risk estimate was derived from a model using retrospective data from ADPKD patients which was recently presented to FDA by the PKD Outcomes Consortium (28 Jun 2013). This degree of change is associated with a clinically and statistically meaningful increased risk of progression to ESRD in a dataset consisting of non-ADPKD patients with chronic kidney disease (CKD Progression Consortium meeting on 3 Dec 2012, Baltimore, MD).



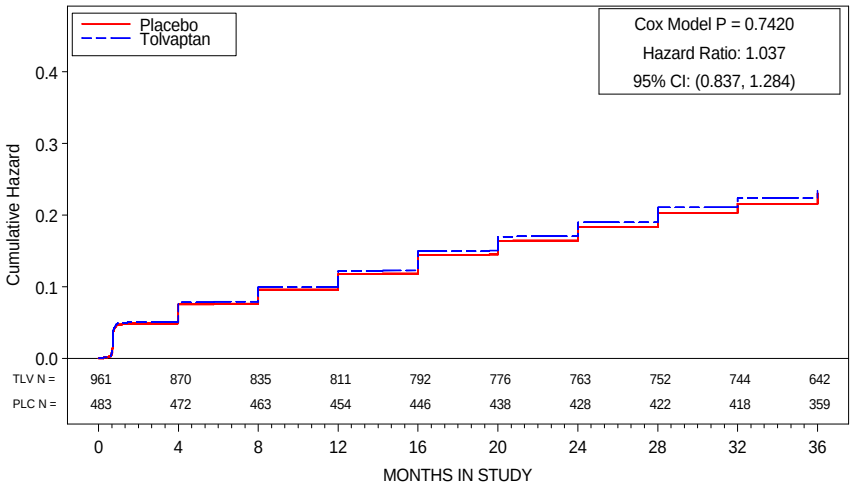
Worsening Renal Function



Renal Pain



Worsening Hypertension



Worsening Albuminuria

Figure 5.6.4-1 Cumulative Hazard Function of Time to Multiple Events for Components of the Key Secondary Composite Endpoint in Trial 156-04-251

CI = confidence interval; PLC = placebo; TLV = tolvaptan.

5.6.5 Sensitivity Analyses of Components of the Key Secondary Composite Endpoint

Further sensitivity analyses of all components of the key secondary composite were performed to test the robustness of results. The sensitivity analyses for events of worsening renal function and renal pain are described in Section 10.4.3. Where appropriate, results for worsening hypertension and albuminuria event components are also described. The analyses assessing the impact of missing data on the conclusions of the key secondary endpoint component analyses for renal pain and worsening renal function events are provided in Section 5.11. Related analyses are available from patient-reported renal pain intensity (0 to 10 Likert scale) and PKD Outcomes, reported in Section 5.8.2 and Section 5.9, respectively.

Consistent with the key secondary composite endpoint sensitivity analysis using adjudicated events, the sensitivity analysis using adjudicated events of only renal pain and worsening renal function were consistent with primary analysis (Section 10.4.3.1). A by-country analysis of time to multiple renal pain events and worsening of renal function events revealed that 12 countries favored tolvaptan numerically, one country had no event in either treatment group, and 2 countries favored placebo numerically (Section 10.4.3.9). In the US, renal pain events trended toward significance. There were not enough events for a by-center analysis to be performed.

5.7 Third Endpoint: Renal Function Slope

5.7.1 Description of the Third (Renal Function Slope) Endpoint

The change in the slope of renal function, the third sequentially tested endpoint in Trial 156-04-251, points to the entire population's trend for kidney disease progression. Use of estimated GFR slope assesses the continuous overall effects of an intervention on function in contrast to the composite component of worsening renal function events which is driven by those subjects whose disease is progressing most rapidly. The reciprocal of serum creatinine has a linear relationship with GFR, unlike the serum creatinine level that has a curvilinear relationship, and approximates GFR values when expressed as $(mg/mL)^{-1}$.

Since acute, consistent and reversible increases in serum creatinine concentration are produced by tolvaptan through a known hemodynamic effect (refer to Section 4.2.2.3), the change from a post-titration, on-treatment, steady-state value (Week 3/EOT) was prospectively defined to be used for renal function change assessments. Additional details are presented in Section 5.7.3.

To be consistent with the key secondary composite endpoint, GFR estimates based on serum creatinine data that were considered unreliable by the investigators were excluded from the primary analysis of the eGFR endpoint. Sensitivity analysis using all available was also provided.

5.7.2 Results of the Slope of Renal Function

The renal function decline (using 1/serum creatinine slope) was slowed by tolvaptan treatment by approximately 32%: estimated slope of −2.609 $(mg/mL)^{-1}$ $year^{-1}$ versus placebo −3.812 $(mg/mL)^{-1}$ $year^{-1}$ for a treatment effect of +1.203 $(mg/mL)^{-1}$ $year^{-1}$ (95% CI 0.622 to 1.783, $p < 0.0001$) (see Table 5.7.2-1). These data are displayed graphically in Figure 5.7.2-1 as a scatter plot of the individual subject change from Week 3/EOT in 1/serum creatinine, at actual time after first dose, overlaid with lines representing the slopes for each treatment group.

Table 5.7.2-1 Secondary Endpoint: Rate of Change in Renal Function in Trial 156-04-251; ITT Subjects With at Least 4-month Follow-up, Excluding Observations Deemed Unreliable by Investigators, Within Treatment Period

Endpoint	Tolvaptan	Placebo
1/serum creatinine ($[mg/mL]^{-1}$)		
Number of subjects	842	464
Mean rate of change per year[a]	−2.555	−3.682
Estimated slope[b]	−2.609	−3.812
Treatment effect[c]	1.203	
95% CI	0.622, 1.783	
p-value[b]	< 0.0001	
$eGFR_{CKD-EPI}$ ($mL/min/1.73\ m^2$)		
Number of subjects	842	464
Mean rate of change per year[a]	−2.680	−3.568
Estimated slope[b]	−2.723	−3.700
Treatment effect[c]	0.977	
95% CI	0.597, 1.357	
p-value[b]	< 0.0001	

CI = confidence interval; EOT = end of titration; ITT = intent-to-treat;

[a] Summary statistics were based on slope of change, obtained by regressing renal function data (Week 3/EOT and beyond) against time by subject. Time variable used in the regression was equal to (observation date - Week 3/EOT date)/365.25.

[b] Derived from testing the time treatment interaction using linear mixed model in which both intercept and slope are fixed and random effects.

[c] An estimate of the difference between the slopes of tolvaptan and placebo.

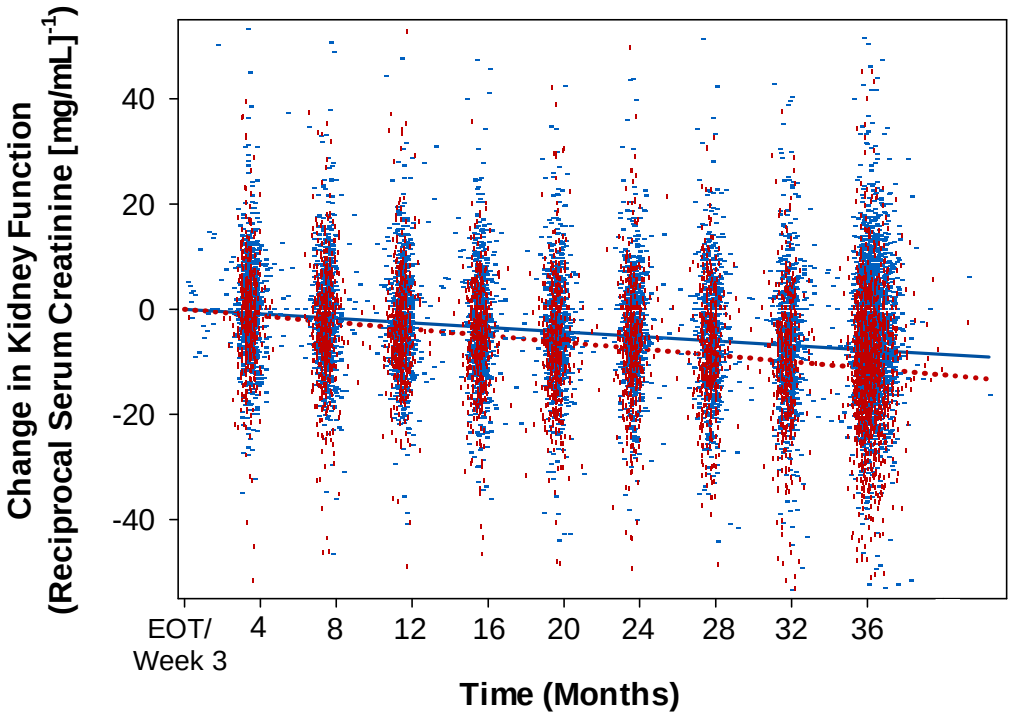


Figure 5.7.2-1 **Rate of Change in Renal Function in Trial 156-04-251 - ITT Subjects With at Least 4-month Follow-up, Excluding Observations Deemed Unreliable by Investigators, Within Treatment Period**

Effect of tolvaptan on annual slope of kidney function. Solid line represents tolvaptan; dotted line represents placebo.

Slopes of kidney function estimated by reciprocal serum creatinine $(mg/mL)^{-1}$, ITT, within treatment period using on-treatment baseline (Week 3/end of titration) and individual patient data included in slope calculations; 19 of 4759 placebo and 16 of 8564 tolvaptan outlier data points are not shown in the Figure; annual difference in slope= 1.202 $(mg/mL)^{-1}$/year (95% CI = 0.62-1.78); P <0.001.

From: NEJM. Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. 367 (25): 2407-18. Copyright © (2012) Massachusetts Medical Society. Reprinted with permission.

The 32% effect size in the 156-04-251 trial for tolvaptan in ADPKD doubles that seen in the RENAAL trial for losartan in diabetic nephropathy, which produced a relative treatment effect of 16% (−4.2 versus −5.0 mL/min/1.73m^2/year) (Section 5.7.3).[17]

5.7.3 Sensitivity Analyses of the Slope of Renal Function

The most important sensitivity analysis for renal function slope was aimed at understanding the impact of hemodynamic responses of GFR before, during, and after tolvaptan treatment. Tolvaptan results in an acute and reversible decrease in GFR which produces an acute increase in serum creatinine (Section 4.2.2.1,Figure 5.7.3-1). Therefore, sensitivity analyses calculating slopes incorporating all pretreatment and

posttreatment data points (Analysis 1 in Table 5.7.3-1) or using only pretreatment and posttreatment data points (Analysis 2 in Table 5.7.3-1) were performed. Both of these analyses were highly statistically significant (p <0.0001) and in close agreement with the prespecified on-treatment analysis.

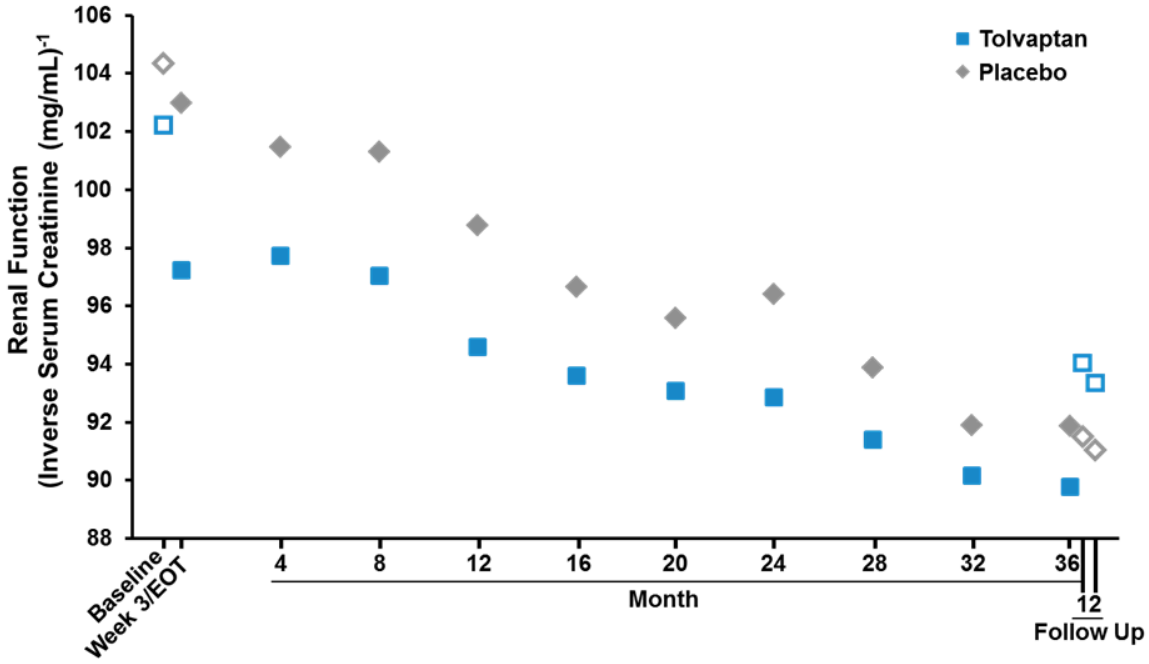


Figure 5.7.3-1 Mean Change in Renal Function by Reciprocal of Serum Creatinine in Trial 156-04-251

EOT = end of treatment; GFR = glomerular filtration rate. Filled symbols = on treatment, Empty symbols = pre- or post-treatment.

Table 5.7.3-1 Analyses of Slope of Reciprocal of Serum Creatinine

Analysis	Slope (mg/mL) $^{-1}$ year^{-1}			p-value
	Placebo Group	Tolvaptan Group	Treatment Effect (95% CI)	
Pre-specified on-treatment analysis: Week 3/EOT to Month 36	-3.81	-2.61	1.20 (0.622-1.783)	<0.0001
Sensitivity Analysis 1: All data, Baseline to Last Follow-up	-3.98	-2.43	1.55 (1.034-2.067)	<0.0001
Sensitivity Analysis 2: Off -drug data points only, Baseline and Follow-up Visits	-4.32	-2.70	1.61 (0.789-2.433)	0.0001

CI = confidence interval; EOT = end of titration.

The primary analysis used change from a post-titration, on-treatment, steady-state value (Week 3/EOT). There are precedents for use of this approach to account for acute, reversible changes in serum creatinine when evaluating long-term trends for renal function (refer to Section 5.15).[6,13,14,15,16,17]

Other sensitivity analyses were performed to evaluate the robustness of this endpoint and to further examine the effects of applying the analyses using various alternative formulas for estimating renal function ($eGFR_{CKD-EPI}$, $eGFR_{MDRD}$, and $eCrCL_{CG}$), various tests for non-linearity, non-normality, and to test the effects of including additional data (eg, serum creatinine measures deemed unreliable by the investigator) or data points (pre- and post-treatment values). The results of these sensitivity analyses are described in Section 10.4.4. Analyses employing various methodologies to explore the impact of missing data are described in Section 5.10.

All sensitivity analyses were consistent with the primary analysis but two analyses were of particular interest. The first was the analysis using the CKD-EPI formula for estimation of GFR. The CKD-EPI formula was not available at the time of protocol initiation but is now considered the most accurate formula for estimation of GFR from serum creatinine, as it does not systematically underestimate measured GFR at higher values[56] (Section 10.4.4.1).

A by-center analysis of the rate of decline for $eGFR_{CKD-EPI}$ demonstrated that the treatment effects of the rate of renal function change favored tolvaptan for the majority of the trial centers. A by-country analysis of the rate of $eGFR_{CKD-EPI}$ change showed that in 12 out of 14 countries tolvaptan demonstrated a favorable treatment effect (not evaluable in 1 country, Denmark) with the US result nominally favorable for tolvaptan and consistent with the overall result (Section 10.4.4.8).

5.8 Other Secondary Trial Endpoints

Control of potential error due to multiplicity was managed through pre-specified hierarchical testing of endpoints (Section 3.5.4). Beyond the third endpoint above, the 4th through 7th secondary endpoints each failed to reach the $p < 0.05$ level of significance required for formal inferential statistical testing. Any subsequent sensitivity, exploratory, subgroup and PK/PD endpoints were subjected to inferential analyses, even if pre-specified, only to provide nominal descriptions of variances of estimates of difference between treatment groups.

5.8.1 Fourth Endpoint: Blood Pressure in Non-hypertensive Subjects

The potential effects of tolvaptan on MAP were evaluated in subjects not receiving antihypertensive therapy. The primary analysis included subjects who had completed at least 4 months of follow up prior to receiving antihypertensive medication to mitigate the effects of early withdrawal and improve accuracy of annualized slope estimates. Results of this analysis were not statistically different between groups. The estimated slope of MAP increased by 0.837 mmHg/year for tolvaptan and 1.084 mmHg/year for placebo, for an estimated treatment effect of −0.246 (95% CI −1.059 to +0.566, p = 0.5520).

Additional sensitivity analyses were performed, including analyses of subjects using all available observations, MMRM by-visit analyses and analyses of each component of MAP (sBP and dBP). None of these analyses yielded significantly different overall results, but each suggested an overall trend for decreased slope of BP increase in the tolvaptan group.

The lack of significant difference in this endpoint may be attributed to the slow progression of MAP (3.7 mmHg over 3 years for placebo), modest treatment effect on BP (0.5 mmHg over 3 years) and the relatively small number (around 200) of subjects available for un-confounded BP assessment. Additionally, subjects in both treatment groups trended towards a slight improvement in sBP during the trial (mean change ranging from −0.9 to −2.9 mmHg for tolvaptan and −0.6 to −2.2 mmHg for placebo) likely reflecting better overall clinical management of hypertension during the trial. The relatively high prevalence of treated hypertension seen in the population at baseline may have limited the power to assess effects on MAP progression.

5.8.2 Fifth Endpoint: Renal Pain Score in Subjects Untreated for Pain at Baseline

The potential effects of tolvaptan on renal pain were examined using the secondary endpoint of time-averaged AUC of renal pain score (Lickert scale from 0-10 for no to worst pain) for subjects not taking pain medications at baseline. The primary pre-specified analysis included all subjects not taking pain medications and included all scores received during treatment up to the initiation of medication or therapy for pain. The results of this analysis were not different between groups (least squares mean AUC of −0.00 for tolvaptan and 0.08 for placebo, difference of −0.08, 95% CI −0.20 to +0.03, p = 0.1604).

Additional sensitivity analyses included a by-visit MMRM analysis and analyses restricted to those with baseline pain (a pain score > 0). Neither analysis reached significance. Results of the MMRM analysis varied widely by visit, typically favoring

tolvaptan, but rarely trending or reaching nominal significance. Analyses of subjects with baseline pain were limited by the relatively small number (less than 350) of subjects who were not taking pain medications at baseline. Both sets of analyses were hampered by the fact that in most subjects, pain appeared to be reported intermittently, and this instrument had an unusually long recall period of 4 months, which was likely insensitive to scoring intermittent pain. Nevertheless, these results generally support the key composite component results for renal pain.

In response to an FDA request relating to the key secondary composite renal pain event component, additional analyses of the renal pain scale were generated to understand the nature of pain leading to these events. An alternative post-hoc analysis which measures the maximum change in pain for these intermittent events is provided below.

Data presented in Table 5.8.2-1 indicate that the tolvaptan group of subjects reported a nominally lower average "maximum change" in pain score.

Table 5.8.2-1 Maximum Change from Baseline in Renal Pain Scale (0-10) in Trial 156-04-251; ITT Subjects with Post-baseline Renal Pain Scale Observations, Within Treatment Period

Baseline	N	Mean	SD	Min	Max	Diff (95% CI)	P-value
Tolvaptan	951	0.81	1.75	0	10	-	-
Placebo	481	0.92	1.88	0	10		
Maximum Change from Baseline							
Tolvaptan	951	1.59	2.69	-9	10	-0.47 (-0.77 - -0.17)	0.0019
Placebo	481	2.04	2.90	-6	10		

CI = confidence interval; Diff = difference; ITT = intent-to-treat; SD = standard deviation.

The difference in results between the maximum change analysis and the AUC analysis was believed to be due to the nature (acute intensity versus chronicity) of pain being reported. We next evaluated whether this shift was attributable to the subgroup who reported renal pain events to the key secondary composite component of renal pain events (Table 5.8.2-2). Subjects without renal pain events had a lower baseline and lower maximum change in score for both treatment groups. Similarly, when comparing scores between those without renal pain events and those with events, the latter group's higher baseline and maximum change in renal pain scores were no different between tolvaptan and placebo subjects. Therefore subjects who reported renal pain events differed from those without events.

Table 5.8.2-2 Maximum Change from Baseline in Renal Pain Scale (0-10) by Subjects with or without Renal Pain Events in Trial 156-04-251; ITT Subjects with Post-baseline Renal Pain Scale Observations, Within Treatment Period

Subjects without Renal Pain Events					
Baseline	**N**	**Mean**	**SD**	**Min**	**Max**
Tolvaptan	857	0.69	1.58	0	9
Placebo	403	0.77	1.72	0	10
Maximum Change from Baseline					
Tolvaptan	857	1.19	2.31	-9	10
Placebo	403	1.43	2.43	-6	10
Subjects with Renal Pain Events					
Baseline	**N**	**Mean**	**SD**	**Min**	**Max**
Tolvaptan	94	1.93	2.63	0	10
Placebo	78	1.72	2.41	0	8
Maximum Change from Baseline					
Tolvaptan	94	5.24	3.11	-2	10
Placebo	78	5.18	3.11	-1	10

ITT = intent-to-treat; SD = standard deviation; max = maximum; min = minimum.

Results of this patient-reported pain intensity scale are concordant with the results of the key secondary composite component of renal pain. They also provide insight into the subjects' perceived level of pain which was associated with triggering events of renal pain. In order to capture a pain event, as was done in the key secondary composite endpoint, a significant difference in patient-reported pain appears to be required. Tolvaptan treatment did not lower the maximum pain score as an anti-nociceptive; it reduced the incidence of renal pain adequate to trigger an event necessitating medical intervention. The reduction by tolvaptan in the relative frequency of these events is described in Section 5.6.4. The medical significance of this reduction is also discussed in Section 5.9.2.4 where renal pain captured as a clinically relevant PKD Outcome contributed to lower overall rates of hospitalization and other patient outcomes.

5.8.3 Sixth Endpoint: Time to Multiple Hypertension Progression Events in Non-hypertensive Subjects

It was possible that hypertension progression events (defined by categorical BP change or prescription of a new antihypertensive treatment) would more sensitively discriminate an effect of tolvaptan in patients who were not yet hypertensive. For this analysis, hypertension progression was evaluated on a time to multiple event basis in subjects non-hypertensive at baseline. Neither this analysis nor a sensitivity analysis for time to first event revealed a significant effect of tolvaptan (HR 0.996, 95% CI 0.805 to 1.233, p = 0.9704 and HR 0.941, 95% CI 0.678 to 1.306, p = 0.7177, respectively). As noted previously, analysis was limited by the small numbers within the non-hypertensive subpopulation (around 250 subjects).

5.8.4 Seventh Endpoint: Percentage of Subjects with Sustained Reductions in Antihypertensive Therapy

Effects on blood pressure control were also evaluated in subjects who were already hypertensive and taking antihypertensive medications. This analysis measured the frequency of subjects who were already receiving antihypertensives and achieved a sustained reduction of anti-hypertensive therapy attributable to lowered MAP. Reductions meeting these criteria were infrequent (< 10% of eligible subjects). The results of a last observation carried forward (LOCF) analysis and an observed case (OC) analysis were nominally in favor of tolvaptan at every visit tested (Months 12, 24, and 36, or Follow-up Visits 1 or 2), yet neither analysis reached statistical significance nor a trend at any time during treatment or post-treatment. One explanation for the lack of statistical significance could be the small number of subjects achieving such a response.

5.9 PKD Outcomes Exploratory Endpoint

5.9.1 Description of PKD Outcomes

A prespecified, exploratory endpoint, PKD Outcomes, in Trial 156-04-251 addressed relevant medical, social, and economic consequences of new and ongoing ADPKD-related morbidities. In addition to outcomes related to the 4 component events of the key secondary composite endpoint, other outcomes that may or may not be related to renal cystogenesis were examined. Complications of ADPKD were assessed by subjects and investigators at each trial visit (or by telephone contact for those subjects who withdrew from treatment, but agreed to be followed), and were recorded when they rose to a clinically significant level. Additionally, important health care consequences (time off work, clinic or emergency room visits, hospitalizations and procedures) which resulted from these events were recorded.

Prior to unblinding, the FDA had communicated that it would be important to identify any additional outcomes which might support efficacy. Therefore, the pooled data were evaluated while still blinded, and the SAP was modified to include analyses of 1) the overall 13-item ADPKD Outcomes composite (13 items: renal pain, hematuria, albuminuria, nephrolithiasis, upper urinary tract infection [UTI], anemia, abdominal/inguinal hernia, significant drop in renal function [eg, dialysis], hypertension, colonic diverticuli, vascular/cardiac abnormalities, hepatic cysts, and cysts in other organs), 2) subset composite of 9 items reasonably related to kidney enlargement (9 items: renal pain, hematuria, albuminuria, nephrolithiasis, UTI, significant drop in renal function, hypertension, anemia, abdominal/inguinal hernia), and 3) individual event rates

for the 4 prespecified most frequent components of PKD Outcomes (hypertension, renal pain, UTI, and hematuria).

PKD Outcomes data were requested from subjects who withdrew from treatment, as a means of obtaining more complete data for analysis. The subjects who agreed to have at least these telephone calls increased overall follow up from 77.0% to 87.6% for tolvaptan subjects (mean follow up of 2.66 years) and from 86.2% to 91.8% for placebo (mean follow up of 2.80 years).

5.9.2 Results of PKD Outcomes

While exploratory, the PKD Outcomes analyses support findings of the key secondary composite endpoint and the effect of tolvaptan on ADPKD physiology.

5.9.2.1 Overall PKD Outcome Frequency

The frequency of these ADPKD outcomes were consistent with the pattern of results observed in the key secondary composite endpoint (eg, while outcomes relating to renal pain were significantly reduced, those for hypertension were not) and suggest tolvaptan favorably delays ADPKD kidney progression in a number of ways meaningful to patients and their physicians. Overall event frequency is depicted in Table 5.9.2.1-1.

Table 5.9.2.1-1 PKD Outcomes Exploratory Endpoint in Trial 156-04-251: Summary of Number of Subjects with Clinically Significant Outcomes; All Subjects Followed to Trial Medication Discontinuation or Trial Completion

Clinically Significant Event	Tolvaptan (N=961)[a] n[b] (%)	Placebo (N=484)[a] n[b] (%)
Hypertension	336 (34.9)	173 (35.7)
Renal pain	252 (26.2)	184 (38.0)
Urinary tract infection	95 (9.8)	71 (14.6)
Hematuria	73 (7.5)	67 (13.8)
Anemia	22 (2.2)	22 (4.5)
Abdominal or inguinal hernia	30 (3.1)	18 (3.7)
Nephrolithiasis	17 (1.7)	17 (3.5)
Significant drop in renal function	9 (0.9)	5 (1.0)
Albuminuria	5 (0.5)	7 (1.4)
Vascular/cardiac abnormality[c]	42 (4.3)	22 (4.5)
Hepatic cysts[c]	17 (1.7)	8 (1.6)
Other organ cysts[c]	13 (1.3)	9 (1.8)
Colonic diverticuli[c]	4 (0.4)	0

PKD = polycystic kidney disease.

[a]Total number of subjects who answered the outcome survey.

[b] Total number of subjects with a clinically significant outcome.

[c] Outcomes pre-specified as unlikely to be related to ADPKD renal progression (size/function) which were excluded from the 9-item composite.

5.9.2.2 Time to Event Analyses of Common PKD Outcomes

Prior to unblinding, but after the overall event rates were known and based on knowledge of all events with a rate of approximately 5% or greater, analyses of time to multiple events and time to first event of renal pain, UTI, hematuria, and HTN were pre-specified. The analyses of the time to multiple events and to first events of renal pain, UTI, and hematuria were individually nominally significantly different (fewer events on tolvaptan; time to multiple event data shown):

- Renal pain outcomes: 13.63 versus 20.47 events per 100 follow-up years
  - Hazard ratio = 0.666, 95% CI 0.538 to 0.825, p = 0.0002
- Upper UTI outcomes: 4.21 versus 6.62 events per 100 follow-up years
  - Hazard ratio = 0.636, 95% CI 0.441 to 0.917, p = 0.0153
- Hematuria Outcomes: 2.69 versus 4.97 events per 100 follow-up years
  - Hazard ratio = 0.542, 95% CI 0.369 to 0.797, p = 0.0018

No differences were observed in the analysis of time to multiple and first events of HTN (time to multiple event data shown):

- Hypertension outcomes: 15.52 versus 16.78 Events per 100 follow-up years
  - Hazard ratio = 0.925, 95% CI 0.762 to 1.124, p = 0.4345

5.9.2.3 Time to Event Analyses for PKD Outcome Composites

For each of the 13 individual PKD Outcomes components, the proportion of subjects in the tolvaptan group that experienced each outcome was either less than or similar to the proportion of subjects in the placebo group that experienced that outcome (Table 5.9.2.1-1), consistent with the primary and secondary endpoints.

Notably, in analysis of the 13-item composite of complications related to ADPKD progression, tolvaptan reduced the rate of complications by 20.8% on a time-to-multiple-event basis, a significant difference between groups (p = 0.0003) (Figure 5.9.2.3-1). Results were consistent and nominally significant for time to first event.

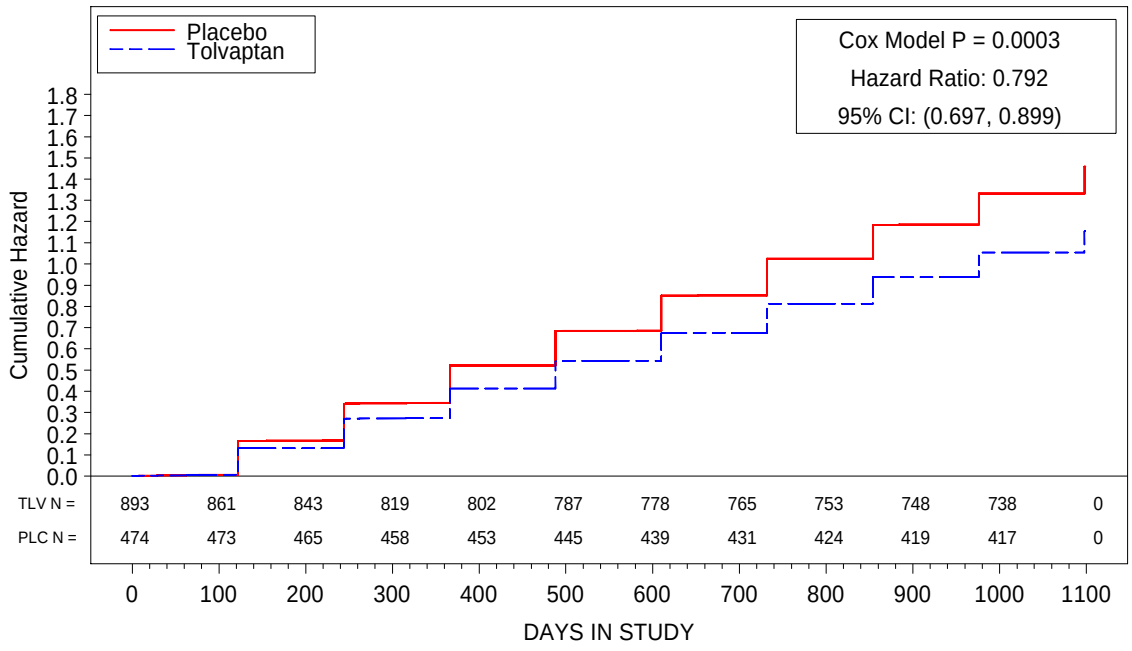


Figure 5.9.2.3-1 Cumulative Hazard Functions of Time to Multiple ADPKD Outcomes (All Thirteen Items)

PLC = placebo; TLV = tolvaptan.
Note: Within treatment period and subjects followed at least to Month 4.

Time-to-multiple-event analysis of the 9-item composite of complications believed to be related to kidney enlargement supported the hypothesized relationship between the primary and key secondary composite endpoints, with a reduced events rate of 23.0% (p = 0.0001) (Figure 5.9.2.3-2.). Results were consistent and nominally significant for time to first event.

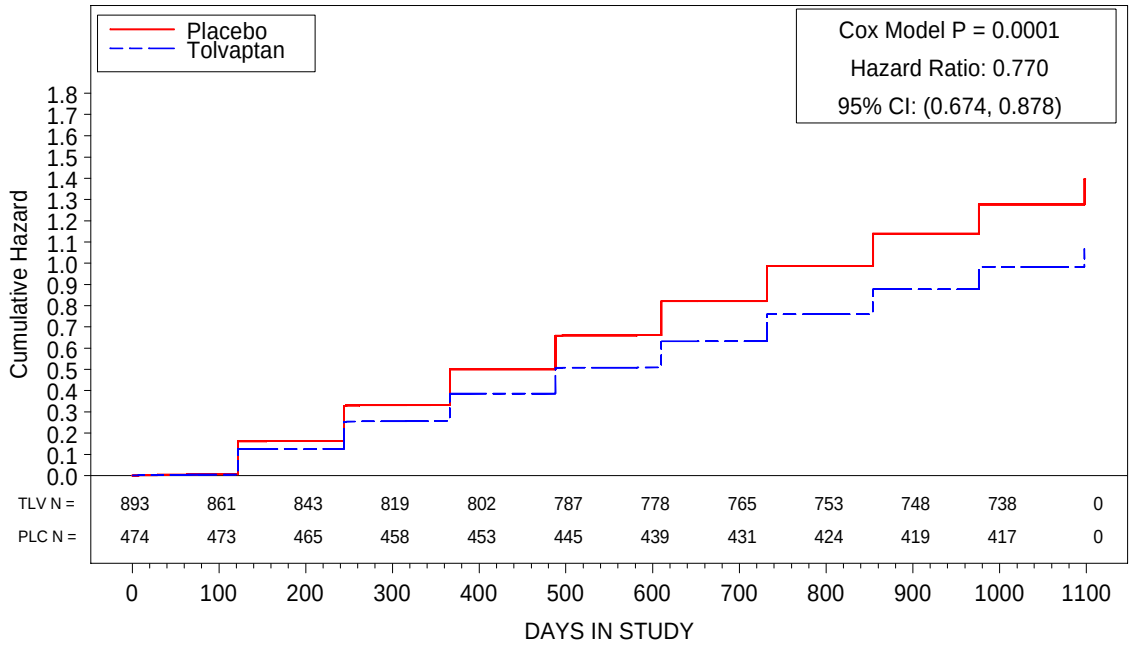


Figure 5.9.2.3-2 Cumulative Hazard Functions of Time to Multiple ADPKD Outcomes (Nine Items)

PLC = placebo; TLV = tolvaptan.
Note: Within treatment period and subjects followed at least to Month 4.

5.9.2.4 Clinical Relevance of PKD Outcomes

5.9.2.4.1 Frequency of Socioeconomic Impact for PKD Outcomes

Tolvaptan subjects were found to have experienced fewer socioeconomic outcomes (lost productivity) and decreased resource utilization (healthcare visits, medical procedures), most notably in relation to kidney pain, hematuria, and urinary tract infection (Table 5.9.2.4.1-1). A smaller reduction in healthcare visits was seen for hypertension, consistent with the frequency of these outcome events. The frequency of health care visits reported was highest for kidney pain and other outcomes which are directly attributable to the cystic pathophysiology of ADPKD (upper UTI, hematuria, nephrolithiasis, and abdominal/inguinal hernia). The impact of tolvaptan was apparent for those events which occur intermittently, but less so for events which take years to manifest (like hernia and hypertension).

Table 5.9.2.4.1-1 Percent of Subjects in Trial 156-04-251 with Socioeconomic Outcomes of ADPKD Related Morbidity (Ordered by Decreasing Frequency for Placebo Group Healthcare Visits)

	Healthcare Visit (Office, ER, Hospital)		Medical Procedure		Lost Productivity	
Event Type (At any Visit)	Tolvaptan	Placebo	Tolvaptan	Placebo	Tolvaptan	Placebo
Kidney pain	8.8	13.8	3.2	7.0	5.5	10.9
Upper UTI	7.8	11.3	1.4	3.3	2.7	3.7
Hypertension	9.6	10.9	1.7	1.4	0.6	1.0
Hematuria	2.7	4.5	1.0	1.6	1.3	2.0
Vascular/cardiac abnormalities*	3.0	3.5	1.9	1.6	1.1	1.4
Nephrolithiasis	1.6	2.4	0.9	1.4	1.0	0.6
Abdominal/inguinal hernia	2.1	2.2	1.7	1.6	1.4	1.6
Anemia	0.9	1.8	0.5	0.6	0.2	0.2
Other organ cysts*	0.9	1.0	0.5	0.4	0.4	0.2
Renal function event (eg, dialysis)	0.3	0.6	0	0.4	0.1	0.4
Hepatic cysts*	0.9	0.6	0.7	0.4	0.5	0.6
Albuminuria	0.1	0.4	0	0	0	0
Colonic diverticuli*	0.5	0	0.3	0	0.5	0

ADPKD = autosomal dominant polycystic kidney disease; ER = emergency room; UTI = urinary tract infection.
*Excluded in 9-item ADPKD Outcomes Composite.

5.9.2.4.2 Hospitalizations Due to PKD Outcomes

FDA had also indicated that reductions in health care utilization, specifically hospitalizations, would lend support to a clinical benefit for an intervention. We therefore examined the frequency of these events in a post-hoc analysis using Fisher's Exact Test.

The likelihood of being hospitalized for the 13-item PKD Outcomes was lower for tolvaptan treatment (odds ratio = 0.56, 95% CI 0.36 to 0.88, p = 0.0114). This appeared to be driven largely by tolvaptan's reduction in the odds of being hospitalized for renal pain (odds ratio = 0.23, 95% CI 0.09 to 0.54, p = 0.0004).

These post-hoc results support the clinical importance of findings related to renal pain events and outcomes as collected by this trial. Tolvaptan has generated a clinically significant reduction in one of the more important early outcomes of ADPKD.

5.10 Correlation of Total Kidney Volume with Other Clinical Outcomes

The tolvaptan clinical program's design is based on the hypothesis that renal cystogenesis is a proximate cause of most of the renal consequences of the disease. The relationship of cyst growth to renal function and other clinical complications (renal pain, hematuria, infection, hypertension and proteinuria) was described in a white paper published by Grantham, Chapman and Torres.[18] In addition to demonstrating the correlation between

total kidney volume and renal function in humans, this article also summarized then available evidence in more than a dozen animal models for interventions slowing both kidney growth and deterioration of kidney function. Included among those interventions effective in animal models were vasopressin antagonists.

The earliest evidence for a clinical intervention favorably affecting both cystogenesis and renal function arose from tolvaptan's initial phase 2 trials. Subjects contributing to these early clinical pharmacology trials were offered participation in 3-year open-label extension trials in the USA (156-04-250) and Japan (156-05-002) conducted in parallel with the global pivotal 156-04-251 trial. Historical control data for renal function (eGFR) and/or TKV were available from two NIH studies, permitting a matched-control comparison between the effect of tolvaptan therapy and the disease's natural course. Tolvaptan subjects' TKV changed an average of 1.7%/year compared with a 5.8%/year change for matched controls ($p < 0.01$). Tolvaptan subjects change in renal function, as assessed by $eGFR_{MDRD}$, was similarly reduced −0.7 versus −2.1 mL/min/1.73m^2/year ($p < 0.02$).

The results of this comparison are displayed graphically in Figure 5.10-1.[57] The correlation of change in annualized % change in TKV and change in eGFR was observed ($r = -0.21$, $p < 0.01$). The natural tendency of most untreated subjects with ADPKD is rightward and downward progression. This trajectory was disrupted for both by tolvaptan therapy where subjects remained clustered nearer the intersection of lines indicating zero change.

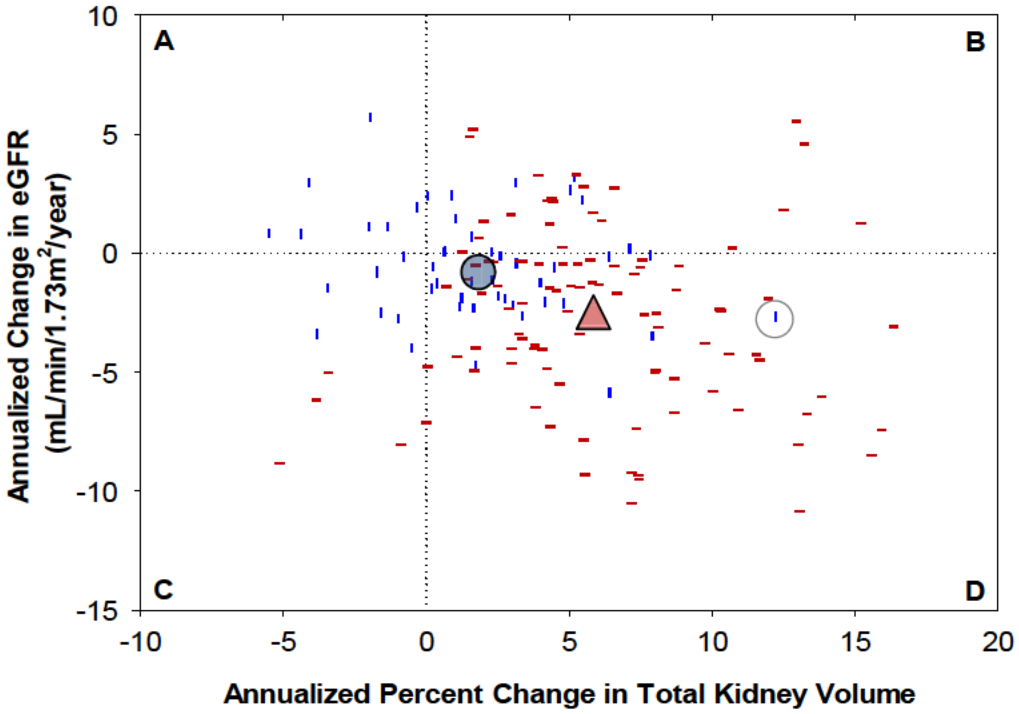


Figure 5.10-1 **Correlation of Annualized Percent Change in Total Kidney Volume and Change in Kidney Function; Combined Data from Trial 156-04-250 and Trial 156-05-002 In Comparison with Natural History Data from Two NIH Studies**

Small blue horizontal dashes = tolvaptan subjects; small red vertical dashes = matched ADPKD controls; large blue circle = mean change for tolvaptan subjects; large red triangle = mean change for placebo subjects. Vertical and horizontal dashed lines represent zero change for TKV and eGFR. The tolvaptan subject circled provided 3 years of data but was non-compliant with therapy.

Correlations between changes in TKV and changes in renal function were also examined in the 156-04-251 pivotal trial. The percent change in TKV and last-visit renal function was moderately correlated (correlation coefficients ranging between −0.29 for $eGFR_{MDRD}$ and −0.23 for $eCrCL_{CG}$; all p-values < 0.0001) when analyzed for all subjects. Correlations were stronger for the placebo subject subgroup and slightly weaker for tolvaptan subjects, yet always significant with all p-values < 0.0001. The slope of TKV and the slope of renal function had a similar correlation to the percent change when analyzed for all subjects, all subjects excluding tolvaptan baseline TKV, tolvaptan subjects, tolvaptan subjects excluding baseline TKV, and placebo subjects. As for the 156-04-250 trial, the tolvaptan group mean for Trial 156-04-251 remained closer to the point of zero change for both TKV and renal function, supporting a proportionate benefit for both in most subjects (Figure 5.10-2).

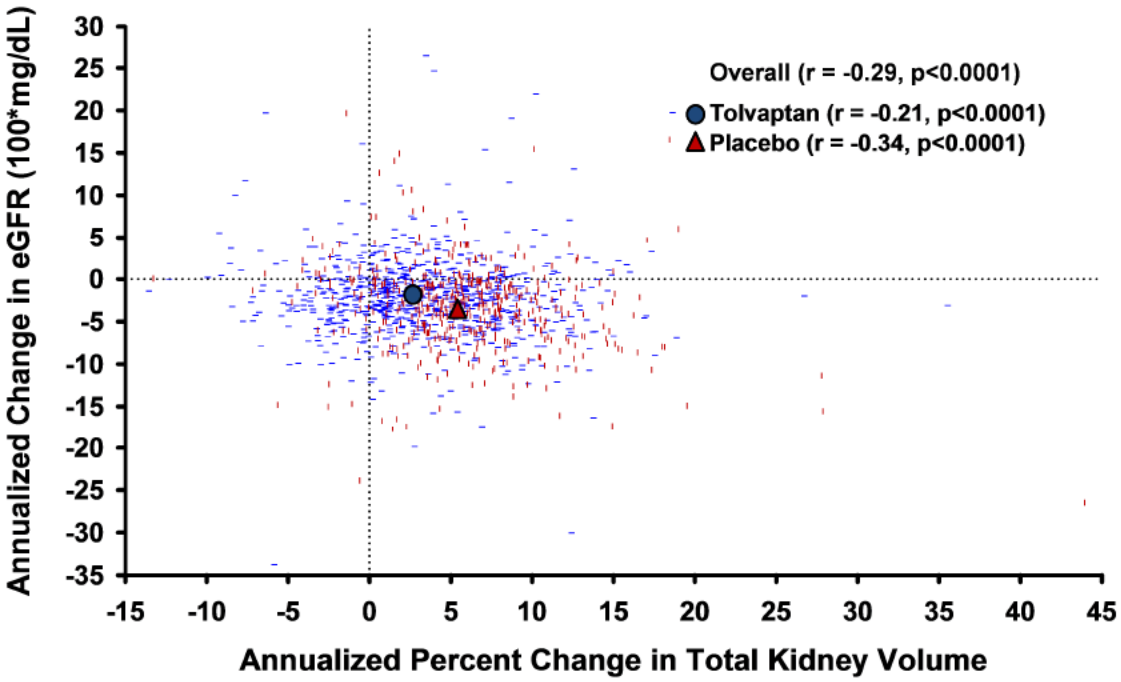


Figure 5.10-2 Correlation of Annualized Percent Change in Total Kidney Volume and Change in Kidney Function in Trial 156-04-251

Small blue horizontal dashes = tolvaptan subjects; small red vertical dashes = placebo subjects; large blue circle = mean change for tolvaptan subjects; large red triangle = mean change for placebo subjects. Vertical and horizontal dotted lines represent zero change for TKV and eGFR.

Correlation analyses between height-adjusted TKV and renal function (estimated by CKD-EPI) were performed post-hoc. In the overall population, and tolvaptan and placebo treatment groups, height-adjusted TKV at baseline and Month 36 showed increasingly improved correlations with each yearly assessment of eGFR. This is consistent with recently published data for the CRISP II cohort.[58] Again, correlations at baseline, and at years 1, 2 and 3 were generally stronger for placebo subjects ($r = -0.396$, -0.433, -0.426, -0.439, respectively) than tolvaptan subjects ($r = -0.370$, -0.426, -0.420, -0.434, respectively).

Associations between changes in TKV and worsening renal function events and renal pain events were examined as post-hoc exploratory analyses. Worsening renal function events were correlated with percent change in TKV and TKV slope ($p < 0.0001$). For the placebo group, every 1% increase in TKV slope was associated with a further 12% increase in HR for worsening renal function events. The association between baseline height-adjusted TKV and worsened renal function events was also evident (Figure 5.10-3).

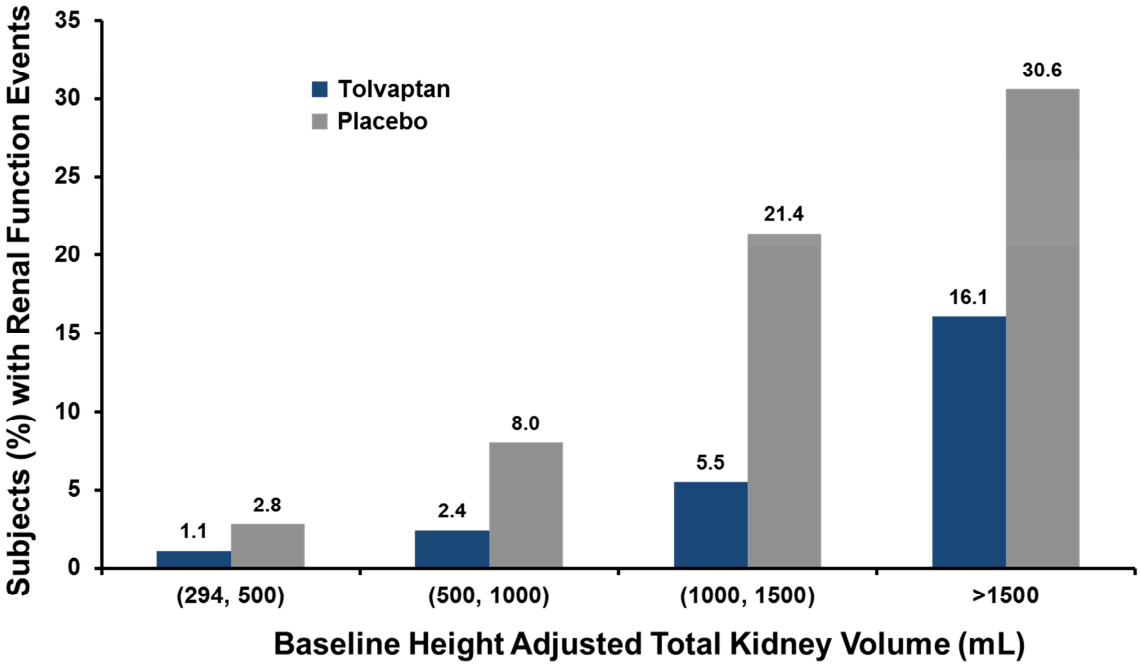


Figure 5.10-3 Worsening Renal Function Component Events by Height Adjusted Total Kidney Volume in Trial 156-04-251

Correlation of renal pain events with the percent change in TKV and TKV slope showed that while the correlation with TKV slope was nominally statistically significant for the placebo group (p = 0.0440), the slope correlation within the tolvaptan group (p = 0.5790) was not. Neither correlation with TKV percent change (p = 0.3446 and 0.6755) was significant. For the placebo group, every 1% increase in TKV slope was associated with a further 4% increase in HR for renal pain events. The association between baseline height-adjusted TKV and renal pain events was less evident and seemed to follow more of a threshold pattern for the placebo group (Figure 5.10-4).

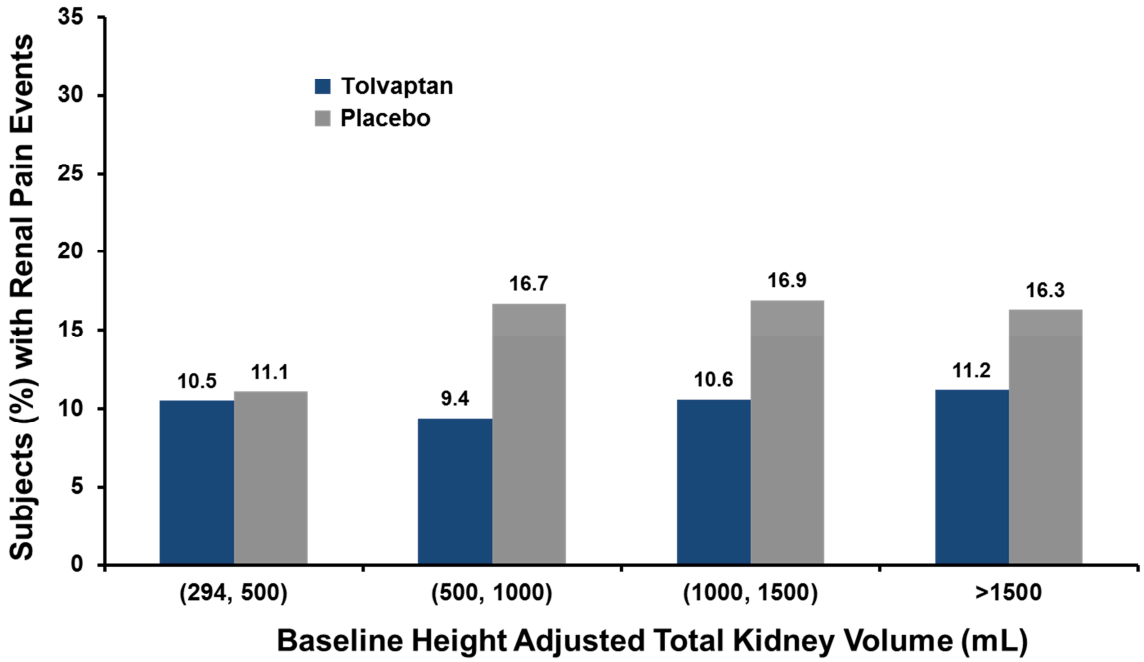


Figure 5.10-4 Renal Pain Component Events by Height Adjusted Total Kidney Volume in Trial 156-04-251

These preliminary correlation analyses support a relationship between TKV and other ADPKD outcomes. Further, while the continued increase of TKV in subjects treated with placebo is more strongly correlated with progression of renal dysfunction and renal pain outcomes, this association is diminished in the group treated with tolvaptan. Such disassociation would be expected for an intervention having an effect on the progression of both outcomes.

Tolvaptan's proposed mechanism of action involves slowed cyst cell proliferation and fluid secretion, which are directly linked to TKV growth, and local destruction of nephrons. Alternate mechanisms for improvement in renal function through other means could exist, but would not explain the correlations with cystogenesis and TKV.

5.11 Missing Data

This section addresses the potential for missing data to influence the trial conclusions. In general, 2 types of statistical analyses were performed in Trial 156-04-251:
1) likelihood-based analyses such as slope analysis and MMRM analysis conducted for endpoints of TKV and renal function, and 2) analyses based on a semi-parametric approach such as (extended) Cox model for time to (multiple) event analysis for the key secondary composite endpoint and its components.

As likelihood-based analyses, slope analysis and MMRM analysis are still valid if the data are missing at random (MAR), ie, if missing data only depend on the previous observation. However, an assumption of MAR cannot be taken for granted, especially for the TKV variable, in which about 10% of subjects who did not have post-baseline TKV observations due to early discontinuation, and the renal function slope variable, in which there were a smaller number of subjects who discontinued before reaching the post-treatment baseline Week 3/EOT and hence excluded from the analysis.

Since baseline characteristics were not included in the model of slope analysis for the TKV and renal function slope endpoints and it's well established that certain baseline ADPKD characteristics are predictive of more rapid disease progression, the impact of missing data deserved a further review. For the time to multiple event analyses, censoring a subject who dropped out of the trial provided a natural way to handle missing data. However, because of the difference in dropout rates (23.0% [221/961] in the tolvaptan group versus 13.8% [67/484] in the placebo group), missing data remained an issue. Because baseline-adjusted analyses are performed under the assumption of data MAR, sensitivity analyses under the assumption of data missing not at random (MNAR) were necessary and were additionally performed.

Various analytical approaches to address the issue of data MNAR were employed in Trial 156-04-251. These approaches comprised

1) responder analyses that classified withdrawn subjects as non-responders in the analysis, with response defined as at least a 20% improvement in rates of both TKV growth and renal function decline over the placebo response;
2) multiple imputation and placebo imputation of MMRM change from baseline analyses where placebo response and worse-than-placebo response were imputed for TKV and renal function slope missing data;
3) multiple imputation of time to event analyses where placebo response was imputed for missing data in the key secondary composite and its two positive components;
4) sensitivity analyses of the key secondary composite endpoint and its two positive components where events of AE withdrawal additionally contributed as events in the analysis;
5) renal pain event analyses that incorporated data, where possible, collected from subjects terminating trial medication early who were followed for PKD Outcomes;
6) in addition, baseline inference characteristics were evaluated in two approaches:

a. analyses adjusting for demographic and baseline characteristics as covariates in the model; and
b. review of the baseline characteristics predictive of ADPKD disease progression for subjects completing the trial to infer how results may have been impacted for tolvaptan subjects withdrawing from the trial early.

The results of these analyses are described in Section 10.5. The most sensitive analysis accounting for data MNAR, the responder analysis (Section 10.5.1), which treated withdrawn subjects as non-responders, demonstrated a near doubling of the responder rate in the tolvaptan group for subjects showing at least 20% improvement in both TKV growth and renal function decline slopes in comparison to the placebo response (31.4% tolvaptan, 18.6% placebo; odds ratio 2.006; 95% CI 1.537-2.619; $p < 0.0001$). This effect size as well as statistical significance were maintained as progressively restrictive responder criteria were applied, ie, no events in the key secondary composite components of renal pain or worsening renal function added to the original responder definition ($p < 0.0001$), or no events in any of the 4 components of the key secondary composite added to the original responder definition ($p = 0.0003$).

In a more stringent analysis that penalized as non-responders any withdrawn subjects in the tolvaptan group but not in the placebo group, results on tolvaptan remained statistically favorable (31.4% tolvaptan, 19.8% placebo; odds ratio 1.852; 95% CI 1.426-2.406; $p < 0.0001$), including on application of the more restrictive responder definitions (no renal pain or worsening renal function events, $p < 0.0001$; or no events in the key secondary composite, $p = 0.0007$).

Equally compelling results were achieved for analyses evaluating the effect of data MNAR through multiple (30x) imputation of placebo response and worse-than-placebo response (Section 10.5.2.1). The analyses for TKV and renal function slope were significant, favoring tolvaptan and consistent with the prespecified primary analyses, at up to 210% and 150% of placebo risk, respectively. For the key secondary composite endpoint, significance was maintained at up to 110% of placebo risk, which includes up to 120% and 190% of placebo risk for the components of renal pain and worsening renal function, respectively.

Taken together with the other analyses described in Section 10.5, these analyses strongly suggest that missing data, no matter under the assumption of MAR or in reasonable sensitivity scenarios under MNAR, do not affect the validity of the trial outcomes based on the original, prespecified endpoint analyses.

5.12 Dose-Response Relationship

While the titration scheme employed in Trial 156-04-251 precluded direct dose comparison, a nominal trend for slower TKV growth in the high dose group (60/30 mg) compared to the low dose group (45/15 mg) was observed over the ~3-year fixed-dose treatment period of supportive open-label Trial 156-04-250.

Population PK/PD analyses were performed to explore both modal dose-response and exposure-response analyses on four clinical endpoints and one PD endpoint assessed during the double-blinded treatment period in the pivotal 156-04-251 trial; only subjects with estimated PK parameters and/or values for each endpoint being analyzed were included in the respective analyses.

The clinical endpoints were:

- Change in total kidney volume (TKV);
- Time to multiple ADPKD clinical progression events defined as either severe renal pain or worsening of renal function (25% reduction in reciprocal serum creatinine value);
- The rate of $eGFR_{CKD\text{-}EPI}$ change with time, also referred to as "eGFR slope";
- The rate of log-transformed percentage TKV change with time, also referred to as "TKV slope."

The PD endpoint was:

- change in urine osmolality at trough.

5.12.1 Clinical Endpoints

Tolvaptan treatment, but not tolvaptan dose, demonstrated a significant effect for all clinical endpoints:

- The mean ratio of TKV at Month 36 to the baseline was 1.18 for placebo, and 1.09, 1.07 and 1.09 for 45/15 mg, 60/30 mg, 90/30 mg split-dose regimens, respectively.
- The mean value of TKV slope, representing the rate of log-transformed percentage TKV change with time, in subjects treated with tolvaptan was 0.011 $year^{-1}$ versus a mean value of 0.023 $year^{-1}$ in placebo subject.
- The rate of decline in renal function, expressed using $eGFR_{CKD\text{-}EPI}$, in ADPKD subjects treated with tolvaptan was reduced to a mean value of −2.68 $mL{\cdot}min^{-1}{\cdot}year^{-1}/1.73\ m^2$ from a mean value of −3.57 $mL{\cdot}min^{-1}{\cdot}year^{-1}/1.73\ m^2$ in placebo subjects. Significant tolvaptan effect, a greater than 44% reduction in the

rate of eGFR decline, was observed for subjects with $eGFR_{CKD-EPI}$ less than 76.6 mL/min/1.73 m^2 at baseline.

- The percent of subjects with at least one ADPKD clinical progression event dropped from 25.1 in the placebo group to 10.5, 7.5, and 16.5 following 45/15 mg, 60/30 mg, and 90/30 mg treatment, respectively.

In order to perform exposure response analysis, the population PK model was used to derive individual estimates of tolvaptan exposure (AUC_{ss} [AUC_{0-24h} at steady state], C_{max}, minimum concentration from 0−24h [$C_{min,ss}$]) based on the modal dose reported for each subject. Each of the parameters was highly correlated with the others so only correlations with AUC_{ss} are presented below.

Figure 5.12.1-1 is a box plot of the calculated AUC_{ss} values for each dose regimen; the width of the gray bars represents the relative number of subjects on each dose. This plot confirmed that subjects grouped by model dose had significant overlap in exposures.

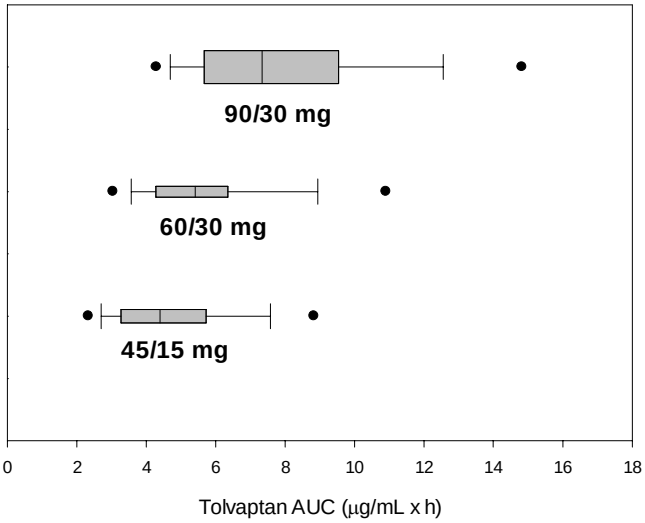


Figure 5.12.1-1 Box plots of AUCss Values Estimated Using Population Pharmacokinetic Model for Subjects in Trial 156-04-251

Gray boxes represent 25th to 75th percentile, error bars represent 10th and 90th percentiles, black dots represent 5th and 95th percentiles. Vertical line in gray box is median value. The width of the gray bars represents the relative number of subjects on each dose

There was no clear exposure response for the clinical endpoints. Subjects in the highest tolvaptan exposure quartile often had the least response in the endpoint. As observed in the renal impairment trial and confirmed in the population PK analysis, lower GFR results in slower clearance of tolvaptan and produces higher plasma concentrations, thus

confounding exposure-efficacy response analysis. Upon review, it was confirmed that subjects with highest tolvaptan exposure had higher TKV and lower eGFR values than subjects with lowest tolvaptan exposure.

5.12.2 Trough Urine Osmolality

In Trial 156-04-251, tolvaptan treatment significantly reduced mean trough urine osmolality when compared with placebo, by about 250 mOsm/kg at Week 3/EOT and by about 190 mOsm/kg at Month 36. The decrease in urine osmolality in tolvaptan subjects at Month 36 indicates that no significant tolerance to tolvaptan inhibition develops even after 3 years of treatment. Significantly more tolvaptan subjects, 76% to 85%, had urine osmolality decreased to below 300 mOsm/kg during the trial, compared with 22% to 24% of placebo subjects.

There was a significant relationship between tolvaptan exposure and the pharmacodynamic endpoint of change in urine osmolality. A direct response model, Hill equation, best described the relationship. The maximum effect was estimated to be 70% reduction from baseline urine osmolality (-432 mOsm/kg). The AUC_{ss} value associated with a 50% reduction in urine osmolality was 4.50 µg/mL·h, a value between the geometric mean AUC_{ss} values for 45/15mg, 3.7 µg/mL·h, and 60/30mg, 5.5 µg/mL·h. The AUC_{ss} geometric mean value at the 90/30mg split-dose regimen was 7.5 µg/mL·h, corresponding to 88% of the maximum effect.

5.12.3 Suppression of Urine Osmolality and Change in Clinical Outcomes

For placebo and tolvaptan subjects combined, a positive significant (p-value <0.001) correlation between TKV slope and change in urine osmolality was observed, with a regression coefficient of 0.0000139 $year^{-1}$·$mOsm^{-1}$·kg, suggesting that reduction in urine osmolality translates into slower growth in TKV. In an analysis of only placebo subjects, lower urine osmolality was associated with a slower rate of kidney growth. In an analysis of tolvaptan-treated subjects, subjects with the greatest mean changes from baseline in urine osmolality (−252 to −300 mOsm/kg) were more likely to achieve a complete response, meaning no change in TKV or renal function. Similar analyses using urine specific gravity, another indirect measure of urine concentrating ability, yielded similar results.

Time to multiple ADPKD clinical progression events (composite component endpoints of renal pain and worsening renal function) was investigated as a function of change in urine osmolality. The percentage of subjects with at least one event is presented in Table

5.12.3-1, by quartiles of urine osmolality change at the corresponding time of the event. Figure 5.12.3-1 presents a Kaplan-Meier plot of time to multiple ADPKD clinical progression events by quartiles of change in urine osmolality at the corresponding time of the event.

Table 5.12.3-1 Percentage of Subjects in Trial 156-04-251 with at Least One ADPKD Clinical Progression Event by Quartiles of Change from Baseline in Urine Osmolality

Quartile of change from baseline in urine osmolality (mOsm/kg)	Subjects with at least one ADPKD clinical progression event (%)
[-1119, -300]	12.1
(-300, -105]	19.5
(-105, 0]	19.2
(0, 548]	23.3

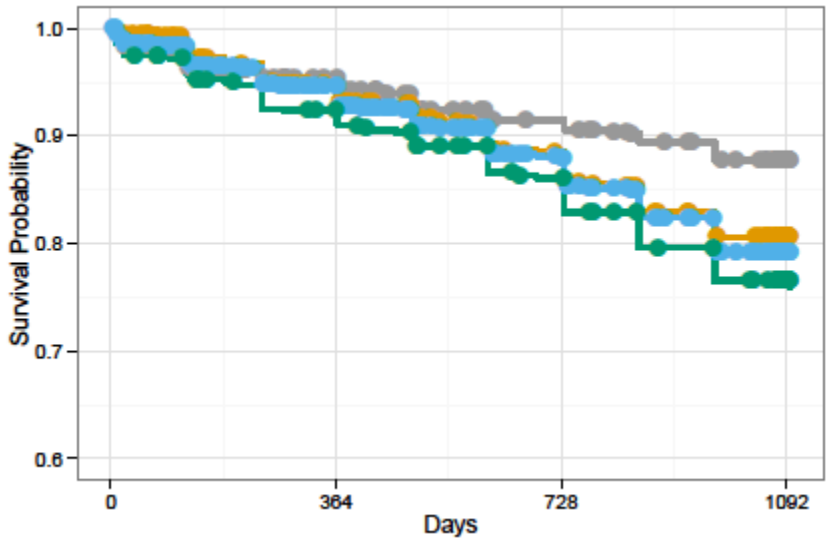


Figure 5.12.3-1 Kaplan-Meier Plot of Time to Multiple ADPKD Clinical Progression Events in Trial 156-04-251 by Quartiles of Change in Urine Osmolality at the Corresponding Time of the Event

In descending order at 1092 days, grey, orange, blue and green dots and lines represent increasing quartiles of change in urine osmolality: [-1190;-300], (-300;-105], (-105;0], (0;548] mOsm/kg.

These data suggest greater efficacy is achieved when urine osmolality is reduced by 250 to 300 mOsm/kg, regardless of baseline. On the basis of the Hill equation, only half of the subjects receiving the 45/15 mg split-dose regimen were receiving an optimal dose, as

defined by suppression of urine osmolality. In contrast, the majority of subjects receiving the 90/30 mg split-dose regimen were receiving an optimal dose. It is considered likely that monitoring urine osmolality (or urine specific gravity, which is highly correlated with urine osmolality and a measure easily performed in a clinician's office or patient's home) could provide guidance to physicians and their patients during tolvaptan titration and maintenance. Lesser degrees of suppression may also be beneficial, but less optimal.

5.12.4 Dosing Recommendations

The initial dosage of tolvaptan in the pivotal trial was 60 mg per day as a split-dose regimen of 45/15 mg (45 mg taken on waking and 15 mg taken 8 hours later). The initial dose should be titrated upward to a split-dose regimen of 90 mg (60/30 mg) then to a target split-dose regimen of 120 mg (90/30 mg) if tolerated with at least weekly intervals between titrations. Patients may down titrate to lower doses based on tolerability. Patients should be maintained on the highest tolerated dose. Tolvaptan may be taken with or without meals.

The aim of dose escalation is to block the activity of AVP at the renal V_2 receptor as completely and constantly as possible while maintaining adequate fluid balance. Urine osmolality measurement can be used to monitor the adequacy of AVP inhibition at a given dose. While the minimal dose required to produce an effective response can be determined by a reduction in urine osmolality below a set threshold, it is not clear at this time to what degree further reductions in urine osmolality will translate into additional clinical benefits.

Dose reduction of tolvaptan is recommended for patients prescribed strong CYP 3A inhibitors. The split-dose regimen of 90/30 mg should be adjusted to 30 mg once daily upon waking, and the split-dose regimen of 45/15 mg should be adjusted to 15 mg once daily upon waking.

There is no clinically significant effect of age, gender or race on tolvaptan exposure. The effect of heart failure or severe hepatic impairment on tolvaptan exposure in ADPKD patients has not been studied but would be expected to increase tolvaptan concentrations.

If a patient misses a dose of tolvaptan, the patient should take their next dose at its scheduled time and prescribed dose level.

5.13 Effect of Duration of Dosing

Physiological changes due to inhibition of AVP at the V_2 receptor (ie, increased urine volume, decreased urine osmolality) can be detected within 2 hours following a single oral administration of tolvaptan. Increases in serum creatinine, reflective of a decrease in

GFR, are measurable by 6 hours postdose. The continued suppression of trough urine osmolality at Month 36 in Trial 156-04-251 indicates that tolvaptan is still efficacious in inhibiting AVP at the V_2 receptor after 3 years of treatment. Also, after 3 years of treatment the inhibition of V_2 receptors is reversible, as demonstrated by the return of trough urine osmolality to baseline levels and a mean decrease of 0.05 mg/dL in serum creatinine concentrations within 14 days of treatment withdrawal (Follow-up Visit 2).

A reduction in mean TKV was observed as early as 8 and 21 days after start of tolvaptan treatment (Section 4.2.2.2). In the open-label treatment Trial 156-04-250, when using an MMRM analysis, the mean change (SD) from baseline in TKV after 2 months of dosing was −0.96% (5.17%) for the tolvaptan 45/15 mg group and −1.26% (5.31%) for the tolvaptan 60/30 mg group, and the reduction persisted for the first year of treatment in the 45/15 mg group (Table 5.13-1). From 12 months to 36 months of treatment, TKV increased, with the higher dose group (60/30 mg) showing smaller percent increases from baseline compared to the lower dose group (45/15 mg).

Table 5.13-1 MMRM Analysis of Percent Change from Baseline in Total Kidney Volume in Trial 156-04-250 - All Subjects - Intent to Treat

Visit	Tolvaptan Treatment Group	Kidney Volume[a] (mL)		Percent Change from Baseline		Treat-ment Effect[b]	95% CI	P-value
		N	Mean (SD)	N	Mean (SD)			
Baseline	45+15 mg	22	1566 (730)	-	-	-	-	-
	60+30 mg	24	1596 (1012)	-	-	-	-	-
Month 2	45+15 mg	23	1558 (713)	23	-0.96 (5.17)	-0.31	[-4.67, 4.05]	0.8891
	60+30 mg	24	1587 (1030)	24	-1.26 (5.31)			
Month 12	45+15 mg	19	1511 (765)	19	-0.12 (6.04)	2.41	[-2.19, 7.00]	0.3015
	60+30 mg	22	1604 (1036)	22	2.45 (6.62)			
Month 24	45+15 mg	18	1617 (859)	18	4.62 (8.43)	-2.79	[-7.44, 1.85]	0.2361
	60+30 mg	22	1618 (1078)	22	1.79 (8.86)			
Month 36	45+15 mg	18	1705 (947)	18	9.86 (11.81)	-4.57	[-9.26, 0.11]	0.0553
	60+30 mg	21	1654 (1132)	21	5.06 (9.77)			

CI = confidence interval; SD = standard deviation.

[a] MRI data obtained from Early Term were mapped to visits of Month 12, Month 24 and Month 36 based on 6-month visit windows.

[b] Derived from MMRM with factors of treatment, visit, treatment visit interaction, and covariate baseline. Inference statistics were derived from contrasts from each visit.

The pattern of increase in TKV shown in the table above was also observed in tolvaptan subjects treated for 3 years in Trial 156-04-251 (Figure 5.5.2-1).

From acute and chronic TKV data, it can be hypothesized that the initial effect of tolvaptan is on secretion of fluid into cysts, which results in the reduction of TKV in the early treatment period (up to 1 year). Tolvaptan's effects on the proliferation of cyst epithelial cells can account for the sustained decrease in the rate of TKV growth over the 3-year treatment period.

Treatment was stopped after 36 months in Trial 156-04-250 until a new protocol extending the treatment duration for another year could be approved (Figure 5.13-1). During the approximately 4-month off-drug period, the rate of increase in TKV was greater than the rates of increase observed while subjects were on-drug, both before and during the 12 Month extension. These data indicate that if tolvaptan treatment is stopped, TKV growth will become faster, but that TKV growth will be slowed following reinititation of tolvaptan treatment. Consequently, delayed treatment and treatment interruptions reduce the opportunity for maximizing reductions in TKV growth over a patient's lifetime.

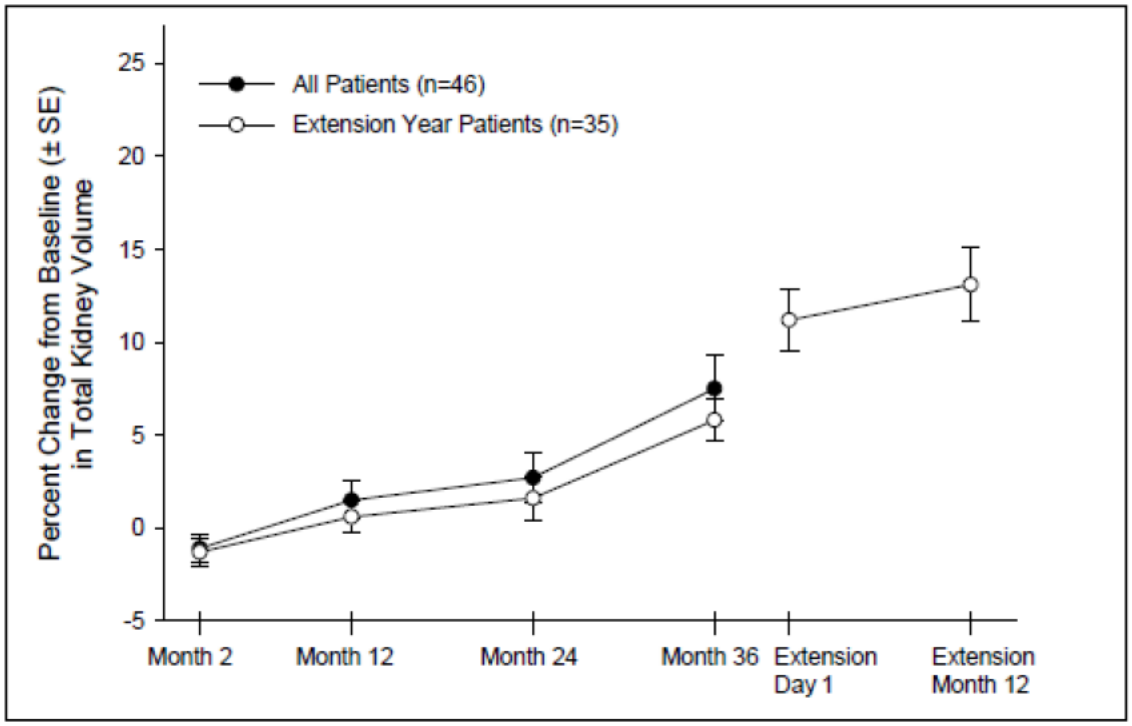


Figure 5.13-1 **Percent Change From Predose Baseline in Total Kidney Volume Through Month 36 (All Subjects and Extension Cohort) and Through the Extension (Extension Cohort) in Trial 156-04-250 (Using Perceptive Imaging Assessments)**

SE = standard error.

Over the course of 3 years, the pivotal Trial 156-04-251 has shown that tolvaptan not only measurably slows TKV growth but also decreases the rate of renal function decline and improves related clinical symptoms that are markers of ADPKD disease progression. Tolvaptan's effects on secretion and cystogenesis appeared to translate into an almost immediate benefit for reduced rate of renal pain (36%). Within 16 months of starting treatment, a reduced rate of worsening renal function events (61%) was also observed. Benefit was also observed in reduced rates of UTI and hematuria for subjects on tolvaptan treatment.

While the results from Trial 156-04-251 cannot be definitively extrapolated beyond 3 years, the observed effect of tolvaptan on urine osmolality and kidney volume even at 3 years makes it reasonable to expect continued reductions in TKV slope and eGFR slope with continued treatment.

5.14 Efficacy in Subgroups

Data on the first 3 endpoints of pivotal Trial 156-04-251 were analyzed by subgroups based on demographic characteristics, disease stage, comorbidities, or concomitant therapy to evaluate the effect of tolvaptan across the trial population. Characteristics like TKV, eGFR, hypertension, gender and albuminuria were selected because of their prognostic value for progression of ADPKD renal disease.[59]

It should be noted that tolvaptan was studied primarily in subjects with ADPKD whose renal function was preserved (ie, CKD Stages 1 to 3). The subject population was enriched on the basis of TKV ≥ 750 mL, a larger cyst burden being a predictor for more rapid progression.

As shown in the figures that follow, consistent results of subgroup analyses across the first 3 trial endpoints, TKV rate of change (Figure 5.14-1), key secondary composite (Figure 5.14-2), and renal function rate of change (Figure 5.14-3), support broad applicability of the efficacy results to patients with ADPKD. Tolvaptan efficacy was nominally consistent, with either a statistically significant difference or a favorable trend in all subgroups evaluated.

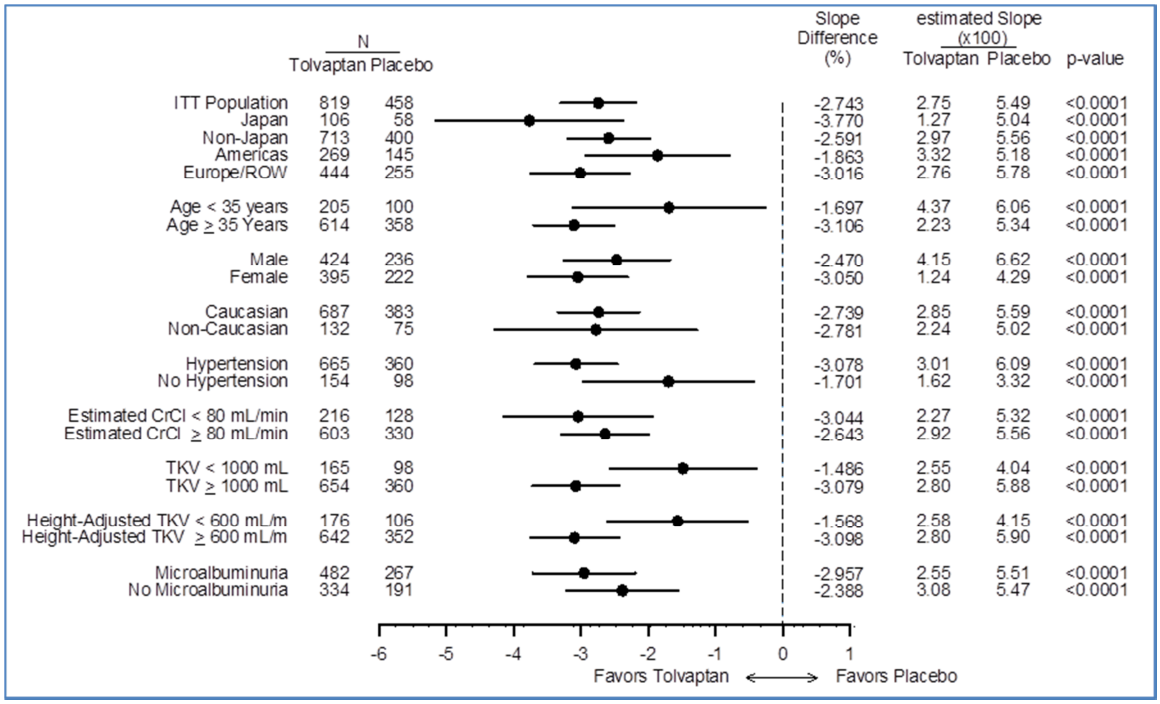


Figure 5.14-1 Subgroup Analyses of TKV Annualized Rate of Growth (%/year) and 95% Confidence Intervals in Trial 156-04-251

CrCl = creatinine clearance; ITT = intent-to-treat; ROW = rest of world; TKV = total kidney volume.
Note: Estimated slope is represented as a percentage of change over 1 year.

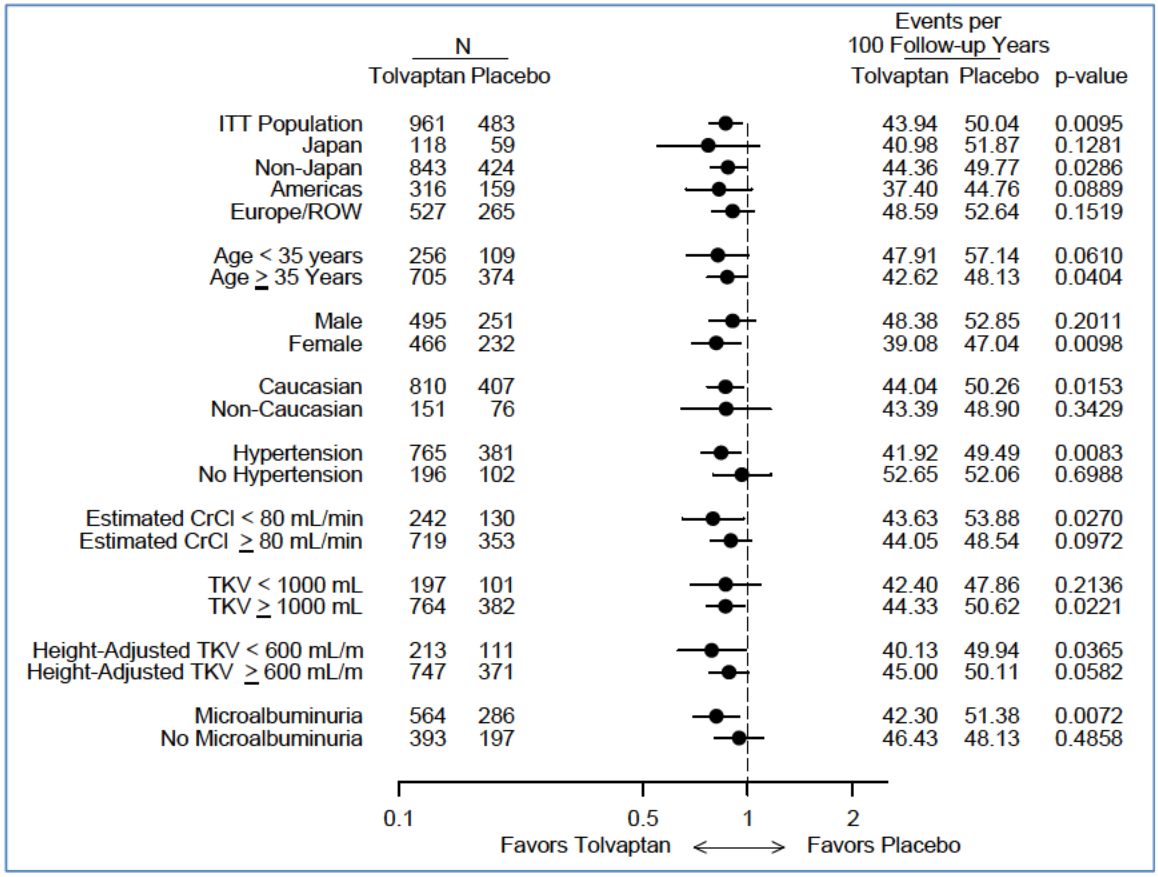


Figure 5.14-2 Subgroup Analyses of Time to Multiple Events of the Key Secondary Composite Endpoint and 95% CIs in Trial 156-04-251

CrCL = creatinine clearance; ITT = intent-to-treat; ROW = rest of world; TKV = total kidney volume.

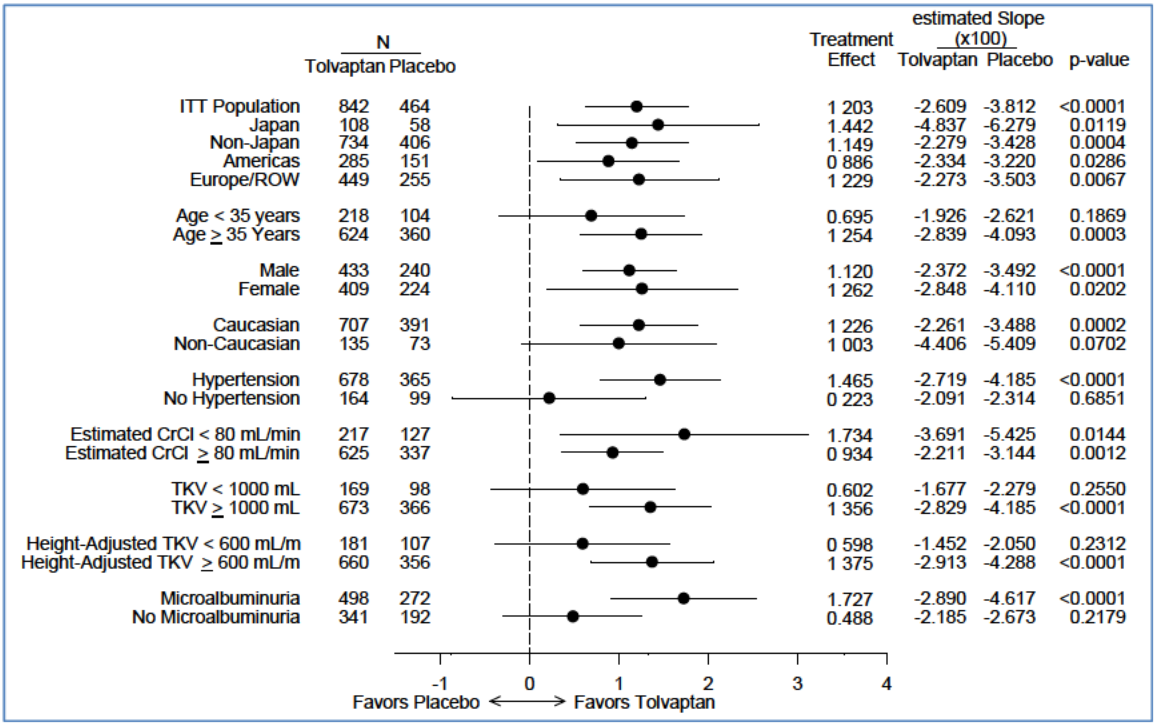


Figure 5.14-3 Subgroup Analyses of Annualized Change in Renal Function (1/Serum Creatinine [mg/mL]$^{-1}$ year^{-1}) and 95% CIs in Trial 156-04-251

CrCL = creatinine clearance; ITT = intent-to-treat; ROW = rest of world; TKV = total kidney volume.

Longitudinal placebo group data in Trial 156-04-251 confirm various baseline characteristics' importance in the progression of renal disease. Evaluation of the placebo group's rate of disease progression suggests that renal function deteriorated more rapidly in those who had larger TKV; or were female, hypertensive, had lower eGFR, or had albuminuria. Renal pain was more prevalent in those who had larger TKV; or were female, those who were had hypertension or albuminuria. TKV growth was more rapid in those who had larger TKV, were hypertensive or male. For each measure of renal disease, larger TKV was a predictor of more rapid progression. The predictors of rapid disease progression are also illustrated in Figure 5.14-4, in a plot of rate of renal function decline by rate of TKV growth.

In Figure 5.14-4, different symbols represent the mean annual rate of eGFR decline and TKV growth for each of the baseline characteristics for placebo group subjects. Subgroups with characteristics which are lower and to the right have faster worsening of TKV and eGFR, while those which are higher and to the left (nearer the intersection of zero change) represent slower worsening. For every baseline subgroup, equivalent subgroups of tolvaptan subjects (represented by the pointed arrows connected to the

placebo means) had annualized progression rates which were slower (upward and to the left). This indicates that tolvaptan benefits each subgroup, regardless of their rate of progression in a direction which is favorable for both TKV and eGFR, and that these benefits are directionally aligned.

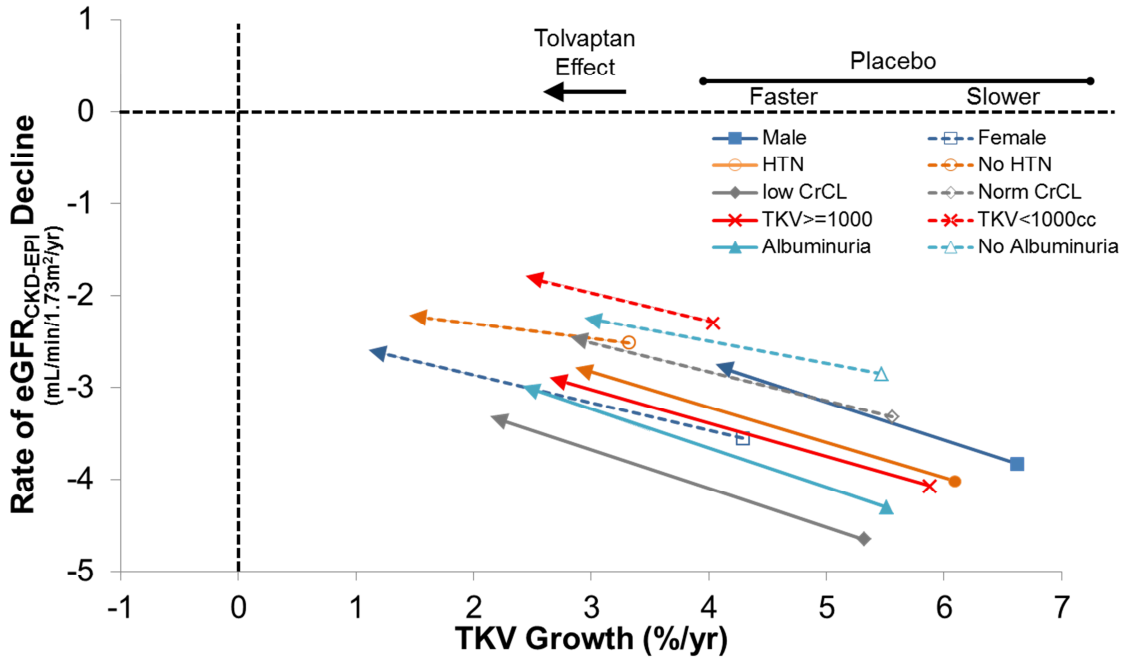


Figure 5.14-4 Characteristics Predictive of More Rapid Disease Progression

CrCL = creatinine clearance; eGFRCKD-EPI = estimated glomerular filtration rate using the formula for Chronic Kidney Disease Epidemiology Collaboration; HTN = hypertension; TKV = total kidney volume.

5.15 Summary of Efficacy

Efficacy endpoints selected in this pivotal trial were chosen based on the hypothesis that the binding of AVP to kidney V_2 receptors leads to increased cystogenesis, which leads to adverse renal outcomes. The primary efficacy outcome – rate of change in TKV – is a measure of cystogenesis. Cystogenesis disrupts normal kidney architecture and directly impacts nephron number and function; therefore both TKV and cystogenesis appear early on the path toward ESRD. By combining TKV with later outcomes on the path to ESRD, the sponsor hoped to establish a precedent for validated efficacy endpoints for interventional trials of earlier stage ADPKD patients such as those studied in Trial 156-04-251.

The key secondary endpoint was requested by the US FDA and included time to multiple ADPKD clinically relevant progression events. These events include clinically relevant

progression toward renal pain, worsening kidney function, hypertension and albuminuria. Each of these represents changes in a patient's symptoms, signs, function and/or is itself an accepted surrogate for later clinical outcomes. These endpoints are further supplemented by other trial endpoints and exploratory measures (eg, rate of change in renal function, PKD Outcomes) representing additional approaches to the evaluation of ADPKD progression. The results were statistically and/or directionally consistent in favoring the tolvaptan group, and confirmed the therapeutic benefit on kidney-related effects of tolvaptan treatment in ADPKD.

These endpoints were also clinically relevant. Events relating to kidney pain led to significantly more hospitalizations in the placebo group and a higher average maximum change in the renal pain score. This was driven not by a reduction in pain due to pain suppression, rather by tolvaptan's reduction in the types of events which typically lead to kidney pain in ADPKD (eg, urinary tract infection, nephrolithiasis, hematuria). Worsening renal function, as measured by eGFR, was also reduced. This was shown by fewer subjects reaching a 33.3% increase in serum creatinine, a threshold predictive of future ESRD risk.

The trend for renal function was also shown by lessening the slope of eGFR deterioration. This was seen across CKD thresholds and supports extrapolation. These analyses used an on-treatment comparison since tolvaptan has a known acute, reversible effect on eGFR. This effect has also been associated with renal-protective drugs which inhibit the renin-angiotensin system.

For example, Figure 5.15-2 depicts a trial involving 40 subjects who were treated with either enalapril or atenolol for 4 years. For analysis, change in GFR after the first 12 weeks of therapy was used to group subjects as those having an acute GFR fall (Group A, represented as black circles) versus those with minimal or positive change (Group B, represented as white circles). Group A subjects' GFR remained lower but had a flatter on-treatment slope than Group B, whose GFR declined more rapidly. The acute effect seen for Group A was reversible, as shown by the acute rise in values when treatment was stopped after 4 years.

Figure 5.15-1 depicts eGFR results from Trial 156-04-251 in a similar fashion. The figures demonstrate an acute hemodynamic effect resulting in a flatter slope, followed by a reversible effect on treatment withdrawal.

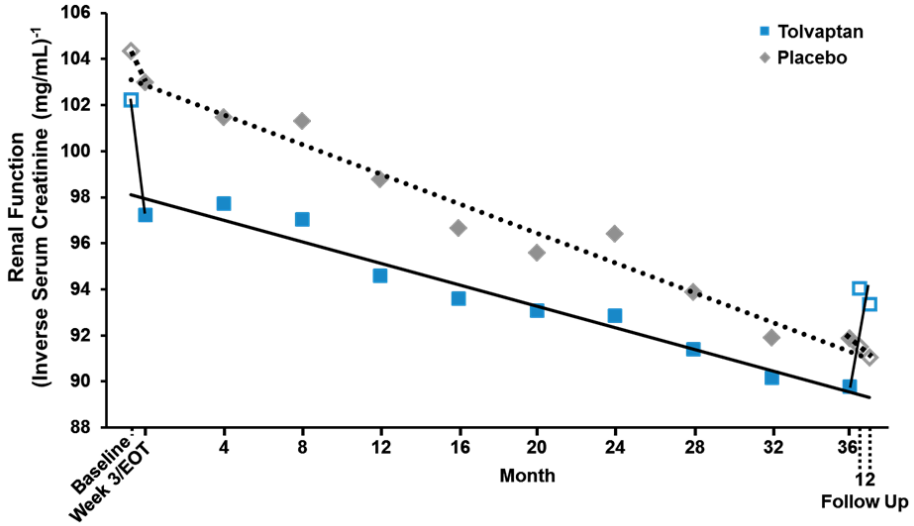


Figure 5.15-1 Time Course of GFR Before, During and After Withdrawal of Tolvaptan or Placebo Treatment; Trial 156-04-251

Filled symbols = on treatment, Empty symbols = pre- or post-treatment.

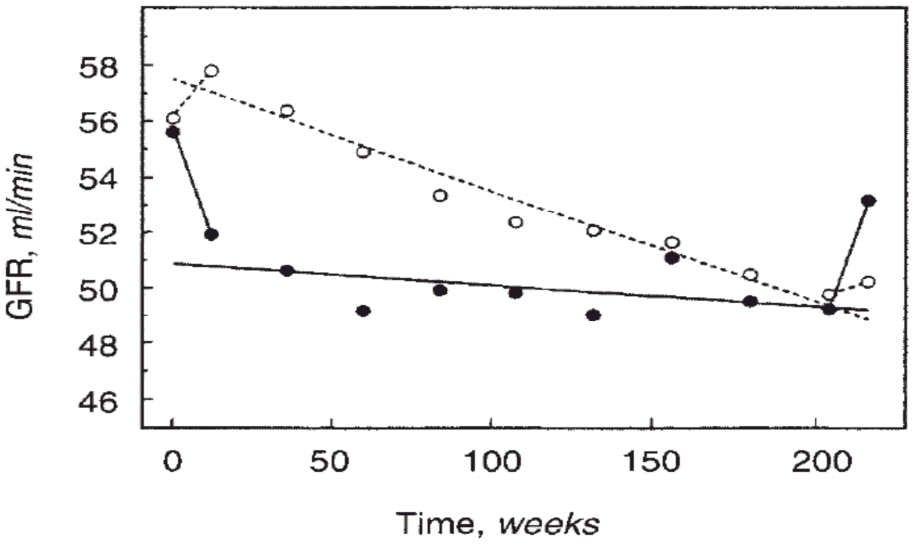


Figure 5.15-2 Time Course of GFR Before, During and After Withdrawal of Antihypertensive Treatment (Published Data)

Group A (black dot) are patients who initially showed an acute decrease in GFR and group B (white dot) are patients in whom GFR did not fall after start of treatment. The change in GFR after start and withdrawal of treatment is indicated as well as the slope of GFR during treatment.

From Apperloo AJ, de Zeeuw D, De Jong PE. A short-term antihyertensive treatment-induced fall in glomerular filtration rate predicts long-term stability of renal function. Kidney International 1997; 51: 793-797. Reprinted with permission.

A recently-studied example was presented by Holtkamp et al[17] using data from the RENAAL trial, a larger prospectively randomized, placebo-controlled trial of losartan in diabetic nephropathy. Losartan-treated individuals had an acute (3-month) decrease in eGFR compared with placebo (−2.3 [95% CI −2.7 to −1.8] versus −1.6 [−2.0 to −1.1] mL/min per 1.73m^2, p = 0.031), but a flatter slope over 3 years of treatment (−4.2 [95% CI −3.9 to −4.6] versus −5.0 [−4.7 to −5.4] mL/min per 1.73m^2 per year, p < 0.001). Additionally, losartan subjects had a lower rate of progression to ESRD. The acute and reversible effects of tolvaptan on serum creatinine do not impact our interpretation of its long-term benefits in preserving eGFR and, are consistent with data from inhibitors of the renin-angiotensin system, that have been shown to stabilize renal function and delay progression to ESRD in diabetic nephropathy.

The totality of evidence from the tolvaptan ADPKD program indicates that tolvaptan slows the progression of the kidney-related effects of ADPKD, including cyst growth and renal function decline, and improves related clinical symptoms that are markers of ADPKD disease progression, ie, renal pain, urinary tract infection (UTI), and hematuria. The results of the first 3 endpoints of pivotal Trial 156-04-251 indicate both clinically and statistically significant improvement favoring tolvaptan in comparison with placebo. ADPKD subjects on tolvaptan experienced an approximately 50% reduction in TKV growth (averaging approximately 30% over the last 2 years) and an approximately 30% reduction in renal function decline, as well as an approximately 14% decrease in rate of the composite clinical event progression markers of ADPKD (36% and 61% for renal pain and renal function components, respectively).

6 Clinical Safety of Tolvaptan

Because of differences in trial designs, dosing regimens and durations, and/or subject populations across trials in the ADPKD program, safety data were analyzed by individual trial. This approach permitted comparison of results from the individual supportive trials in relationship to important safety findings from the pivotal Trial 156-04-251. The one exception is exposure, which was pooled across the ADPKD program of trials and across the trials of subjects having ADPKD. (The ongoing, blinded Trial 156-09-290 was not included in the pooled exposure numbers.) In addition, findings from the ADPKD population were compared where relevant with the safety database of other tolvaptan indications as well as postmarketing experience.

6.1 Exposure

As of a 01 Feb 2013 data cutoff date for ongoing trials, the safety database for the ADPKD submission includes1682 subjects (1533 subjects with ADPKD) exposed to at least 1 dose of immediate-release (IR) tolvaptan in completed or ongoing clinical trials conducted in North America, South America, Europe, Asia, and Australia (refer to Section 10.6 for breakdown by individual trial). Of the ADPKD program subjects, 1398 subjects have been exposed for up to 6 months, 1208 for up to 12 months, 801 for up to 36 months, and 196 for up to 60 months (Table 6.1-1). In the combined exposure estimates, subjects were counted only once for exposures to IR tolvaptan tablets across multiple trials.

As of 01 Feb 2013, approximately 7551 adult patients worldwide have been exposed to oral tolvaptan in clinical trials in ADPKD and other indications, among these a pooled safety database of 3294 hyponatremia and heart failure subjects from multiple-dose, placebo-controlled trials analyzed in the prior tolvaptan NDA.

Cumulative exposure in Trial 156-04-251 is presented by modal dose in Section 5.3 and by time interval in Table 6.1-1.

Table 6.1-1 Cumulative Exposure to Tolvaptan by Dose Received			
Cumulative Exposure	**All Trials in the ADPKD Clinical Program Tolvaptan, n (%)**		
	15 to 45 mg (N = 83)	**60 to 120 mg (N = 1632)**	**Total (N = 1682)**
Any exposure	83 (100.0)	1632 (100.0)	1682 (100.0)
At least 2 weeks	17 (20.5)	1476 (90.4)	1493 (88.8)
At least 6 months	17 (20.5)	1381 (84.6)	1398 (83.1)
At least 12 months	15 (18.1)	1193 (73.1)	1208 (71.8)
At least 24 months	14 (16.9)	919 (56.3)	933 (55.5)
At least 36 months	13 (15.7)	788 (48.3)	801 (47.6)
At least 48 months	13 (15.7)	524 (32.1)	537 (31.9)
At least 60 months	12 (14.5)	184 (11.3)	196 (11.7)
Cumulative Exposure	**All Trials in ADPKD Subjects Tolvaptan, n (%)**		
	15 to 45 mg (N = 53)	**60 to 120 mg (N = 1513)**	**Total (N = 1533)**
Any exposure	53 (100)	1513 (100)	1533 (100)
At least 2 weeks	17 (32.1)	1476 (97.6)	1493 (97.4)
At least 6 months	17 (32.1)	1381 (91.3)	1398 (91.2)
At least 12 months	15 (28.3)	1193 (78.8)	1208 (78.8)
At least 24 months	14 (26.4)	919 (60.7)	933 (60.9)
At least 36 months	13 (24.5)	788 (52.1)	801 (52.3)
At least 48 months	13 (24.5)	524 (34.6)	537 (35.0)
At least 60 months	12 (22.6)	184 (12.2)	196 (12.8)
Cumulative Exposure	**Trial 156-04-251 Tolvaptan, n (%)**		
	15 to 45 mg (N = 0)	**60 to 120 mg (N = 961)**	**Total (N = 961)**
Any exposure	-	961 (100.0)	961 (100.0)
At least 2 weeks	-	943 (98.1)	943 (98.1)
At least 3 weeks	-	929 (96.7)	929 (96.7)
At least 4 months	-	915 (95.2)	915 (95.2)
At least 8 months	-	864 (89.9)	864 (89.9)
At least 12 months	-	836 (87.0)	836 (87.0)
At least 24 months	-	774 (80.5)	774 (80.5)
At least 36 months	-	742 (77.2)	742 (77.2)

ADKD subject trials: Trials 156-04-251, 156-08-271, 156-10-003, 156-04-250, 156-05-002, 156-09-003, 156-04-248, 156-04-249, 156-04-001, 156-09-285, 156-06-260, and 156-09-284. Additional ADPKD program trials: 156-07-262, 156-09-282, 156-11-295 and 156-KOA0801. Excludes ongoing blinded Trial 156-09-290.

Data cutoff for exposure was 01 Feb 2013 for ongoing Trials 156-10-003, 156-09-003, and Trial 156-08-271.

Note: Subjects summarized by dose received are not mutually exclusive. Subjects who participated in multiple arms in a trial (eg, crossover trials, sequential treatment period trials with trial medication and/or ascending doses) may be counted in both dose categories. Such subjects are counted only once toward the total exposed. However, 4 subjects (538S00362366, S20292029, S20362036, and S20042004) were double counted due to non-matching subject identifier in 156-08-271 with their parent trials.

6.2 Treatment-emergent Adverse Events

In pivotal Trial 156-04-251, the incidence of TEAE reports was comparable between tolvaptan (941/961; 97.9%) and placebo (469/484; 97.1%) subjects. Commonly reported TEAEs associated with tolvaptan were generally anticipated events due to underlying disease, tolvaptan's mechanism of action, or long-term participation in a clinical trial. Tolvaptan is a highly potent and specific human AVP V_2 receptor antagonist that produces aquaresis, an ideal effect for treatment of other conditions, such as hyponatremia and fluid overload. The more intensive treatment (ie, targeting 24/7 receptor blockade) in subjects with ADPKD, however, was associated with TEAEs of thirst, dry mouth, pollakiuria (frequency of urination), and polyuria, which were expected with tolvaptan use due to its aquaretic action.

Table 6.2-1 provides a summary of TEAEs experienced in at least 5% of subjects in either treatment group of Trial 156-04-251. The most frequently reported TEAEs in tolvaptan subjects (ie, reported at an incidence > 10% and at least twice that of placebo subjects) were Thirst (55.3% vs 20.5%), Polyuria (38.3% vs 17.2%), Nocturia (29.1% vs 13.0%), Pollakiuria (23.2% vs 5.4%), and Polydipsia (10.4% vs 3.5%). Treatment-emergent AEs reported more frequently (≥ 5% difference) in the placebo group versus the tolvaptan group included Renal Pain (27.1% tolvaptan vs 35.4% placebo) and Haematuria (7.8% tolvaptan vs 14.1% placebo).

Table 6.2-1 Incidence of Treatment-emergent Adverse Events in at Least 5% of Subjects in Any Group by MedDRA System Organ Class and Preferred Term in Trial 156-04-251

SOC PT	Tolvaptan (N = 961) n (%)	Placebo (N = 483) n (%)	Total (N = 1444) n (%)
Total[a]	941 (97.9)	469 (97.1)	1410 (97.6)
Blood and lymphatic system disorders			
Anaemia	27 (2.8)	24 (5.0)	51 (3.5)
Gastrointestinal disorders			
Abdominal Pain	62 (6.5)	32 (6.6)	94 (6.5)
Abdominal Pain Upper	63 (6.6)	42 (8.7)	105 (7.3)
Constipation	**81 (8.4)**	**12 (2.5)**	**93 (6.4)**
Diarrhoea	128 (13.3)	53 (11.0)	181 (12.5)
Dry Mouth	154 (16.0)	60 (12.4)	214 (14.8)
Dyspepsia	**76 (7.9)**	**16 (3.3)**	**92 (6.4)**
Nausea	98 (10.2)	57 (11.8)	155 (10.7)
Vomiting	79 (8.2)	40 (8.3)	119 (8.2)

Table 6.2-1 Incidence of Treatment-emergent Adverse Events in at Least 5% of Subjects in Any Group by MedDRA System Organ Class and Preferred Term in Trial 156-04-251

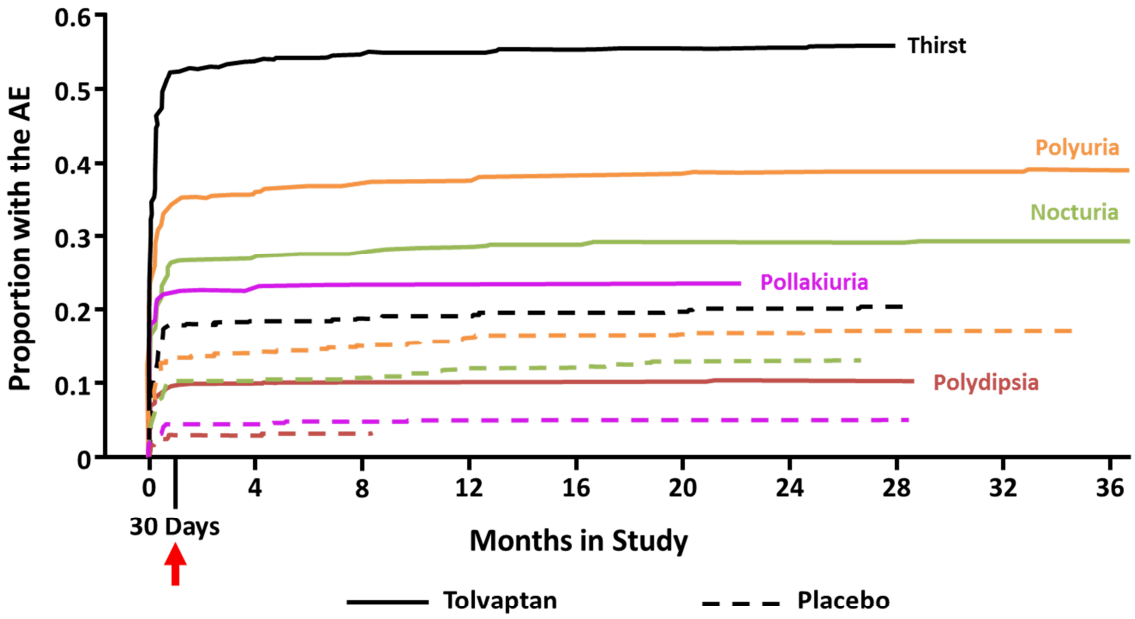
SOC PT	Tolvaptan (N = 961) n (%)	Placebo (N = 483) n (%)	Total (N = 1444) n (%)
General disorders and administration site conditions			
Asthenia	57 (5.9)	27 (5.6)	84 (5.8)
Fatigue	131 (13.6)	47 (9.7)	178 (12.3)
Oedema Peripheral	81 (8.4)	46 (9.5)	127 (8.8)
Pyrexia	45 (4.7)	42 (8.7)	87 (6.0)
Thirst	**531 (55.3)**	**99 (20.5)**	**630 (43.6)**
Infections and infestations			
Bronchitis	58 (6.0)	33 (6.8)	91 (6.3)
Gastroenteritis	54 (5.6)	21 (4.3)	75 (5.2)
Influenza	75 (7.8)	38 (7.9)	113 (7.8)
Nasopharyngitis	211 (22.0)	111 (23.0)	322 (22.3)
Sinusitis	53 (5.5)	23 (4.8)	76 (5.3)
Upper Respiratory Tract Infection	82 (8.5)	42 (8.7)	124 (8.6)
Urinary Tract Infection	81 (8.4)	61 (12.6)	142 (9.8)
Investigations			
Blood Creatinine Increased	135 (14.0)	71 (14.7)	206 (14.3)
Metabolism and nutrition disorders			
Decreased Appetite	**69 (7.2)**	**5 (1.0)**	**74 (5.1)**
Polydipsia	**100 (10.4)**	**17 (3.5)**	**117 (8.1)**
Musculoskeletal and connective tissue disorders			
Arthralgia	69 (7.2)	28 (5.8)	97 (6.7)
Back Pain	133 (13.8)	88 (18.2)	221 (15.3)
Myalgia	50 (5.2)	16 (3.3)	66 (4.6)
Pain In Extremity	42 (4.4)	27 (5.6)	69 (4.8)
Nervous system disorders			
Dizziness	109 (11.3)	42 (8.7)	151 (10.5)
Headache	241 (25.1)	121 (25.1)	362 (25.1)
Psychiatric disorders			
Insomnia	55 (5.7)	21 (4.3)	76 (5.3)
Renal and urinary disorders			
Haematuria	75 (7.8)	68 (14.1)	143 (9.9)
Nocturia	**280 (29.1)**	**63 (13.0)**	**343 (23.8)**
Pollakiuria	**223 (23.2)**	**26 (5.4)**	**249 (17.2)**
Polyuria	**368 (38.3)**	**83 (17.2)**	**451 (31.2)**
Renal pain	260 (27.1)	171 (35.4)	431 (29.8)
Respiratory, thoracic and mediastinal disorders			
Cough	77 (8.0)	38 (7.9)	115 (8.0)
Vascular disorders			
Hypertension	310 (32.3)	174 (36.0)	484 (33.5)

Note: A TEAE event is defined as an AE that occurred after start of trial medication, or if the event was continuous from baseline and was serious; related to the trial medication, or resulted in death, discontinuation, interruption or reduction of trial medication. Subjects were counted once, per term, for the most severe of multiple occurrences of a specific MedDRA preferred term. Adverse events are censored 7 days after trial medication end date.

Note: Bolded rows indicate individual TEAEs that were reported in the tolvaptan group at a percent incidence at least twice that of the placebo group.

[a]Subjects with TEAEs in multiple SOCs were counted only once toward the total.

The results of temporal analysis showed that the majority of new onset TEAEs associated with the aquaretic effects of tolvaptan occurred early in the trial (ie, in the first month of treatment) in both treatment groups (Figure 6.2-1).



† Time to first report.

Figure 6.2-1 **Kaplan-Meier Curves of Time to First Aquaretic-related Treatment-emergent Adverse Events in Trial 156-04-251**

The frequently reported TEAEs during the titration period of Trial 156-04-251 (ie, initial 3 weeks) were primarily related to the aquaretic effects of tolvaptan and were consistent with those observed overall. Events reported in at least 10% of subjects in either treatment group (listed from highest to lowest incidence in the tolvaptan group) were Thirst (51.4% on tolvaptan vs 17.8% on placebo), Polyuria (33.8% vs 13.0%), Nocturia (25.7% vs 9.9%), Pollakiuria (22.1% vs 4.6%), Dry Mouth (14.8% vs 10.6%), and Headache (11.4% vs 11.2%). These results were consistent with the reporting of TEAEs during titration of tolvaptan in supportive Trials 156-04-250 and 156-09-284, which utilized titration schemes similar to Trial 156-04-251.

In extension trials (156-08-271, 156-09-003, and 156-10-003) common TEAEs were similar to common TEAEs observed in pivotal Trial 156-04-251, with the exception of Hepatic Function Abnormal and Influenza, which were reported in >10% of subjects in

Trial 156-10-003. In Trial 156-08-271, the incidences of some TEAEs (eg, Constipation, Dry Mouth, Fatigue, Thirst, Polydipsia, Nocturia, and Polyuria) were lower in early-treated tolvaptan subjects (ie, on tolvaptan in Trial 156-04-251) compared with delayed-treated tolvaptan subjects (ie, on placebo in Trial 156-04-251). These differences are presumed to be due to improved tolerance of such symptoms from their prior tolvaptan exposure in the earlier trial.

Following single-dose administration of tolvaptan to healthy subjects (doses ranging from 15 to 90 mg), the most frequently reported TEAEs were those expected due to tolvaptan's mechanism of action. Frequently reported events included Polyuria, Thirst, and Constipation, which were predominantly mild in severity.

6.3 Serious Adverse Events

A total of 18.8% of subjects (18.4% tolvaptan vs 19.7% placebo) experienced a serious TEAE during pivotal Trial 156-04-251. Individual serious TEAEs that occurred more frequently (≥ 0.5% difference) in the tolvaptan group compared with placebo group included Alanine Aminotransferase (ALT) Increased, Aspartate Aminotransferase (AST) Increased, and Headache. Serious TEAEs that were reported more frequently (≥ 0.5% difference) in the placebo group were Appendicitis, Pyelonephritis, Urinary Tract Infection, Renal Cyst Haemorrhage, Renal Pain, and Hypertension. A tabular summary of SAEs reported during the pivotal trial is provided in Table 6.3-1.

Serious TEAEs reported in long-term, supportive trials were consistent with those in the pivotal Trial 156-04-251, and were predominantly related to underlying ADPKD disease. Across supporting, short-term trials, 2 subjects experienced serious TEAEs (Polyuria, Angina Pectoris) while receiving tolvaptan, both in Trial 156-09-284. No serious TEAEs have been reported in healthy subject trials.

Table 6.3-1 Incidence of Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term in Trial 156-04-251

SOC PT	Tolvaptan (N = 961) n (%)	Placebo (N = 483) n (%)	Total (N = 1444) n (%)
Total[a]	177 (18.4)	95 (19.7)	272 (18.8)
Blood and lymphatic system disorders			
Iron Deficiency Anaemia	0	1 (0.2)	1 (0.1)
Cardiac disorders			
Acute Myocardial Infarction	0	2 (0.4)	2 (0.1)
Angina Pectoris	2 (0.2)	0	2 (0.1)
Atrial Fibrillation	3 (0.3)	1 (0.2)	4 (0.3)

Table 6.3-1 Incidence of Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term in Trial 156-04-251

SOC PT	Tolvaptan (N = 961) n (%)	Placebo (N = 483) n (%)	Total (N = 1444) n (%)
Bradycardia	0	1 (0.2)	1 (0.1)
Coronary Artery Disease	1 (0.1)	0	1 (0.1)
Mitral Valve Incompetence	0	1 (0.2)	1 (0.1)
Mitral Valve Prolapse	1 (0.1)	0	1 (0.1)
Myocardial Infarction	1 (0.1)	0	1 (0.1)
Myocardial Ischaemia	1 (0.1)	0	1 (0.1)
Palpitations	2 (0.2)	0	2 (0.1)
Pericardial Effusion	1 (0.1)	0	1 (0.1)
Pericarditis	1 (0.1)	0	1 (0.1)
Sick Sinus Syndrome	1 (0.1)	0	1 (0.1)
Ventricular Extrasystoles	1 (0.1)	0	1 (0.1)
Congenital, familial, and genetic disorders			
Multiple Endocrine Adenomatosis	0	1 (0.2)	1 (0.1)
Ear and labyrinth disorders			
Deafness	1 (0.1)	0	1 (0.1)
Vertigo	2 (0.2)	0	2 (0.1)
Eye disorders			
Glaucoma	1 (0.1)	0	1 (0.1)
Retinal Detachment	2 (0.2)	0	2 (0.1)
Uveitis	0	1 (0.2)	1 (0.1)
Gastrointestinal disorders			
Abdominal Adhesions	0	1 (0.2)	1 (0.1)
Abdominal Distension	1 (0.1)	0	1 (0.1)
Abdominal Hernia Obstructive	0	1 (0.2)	1 (0.1)
Abdominal Pain	3 (0.3)	2 (0.4)	5 (0.3)
Abdominal Pain Upper	1 (0.1)	1 (0.2)	2 (0.1)
Anal Fissure	1 (0.1)	0	1 (0.1)
Anal Fistula	1 (0.1)	0	1 (0.1)
Colonic Polyp	1 (0.1)	0	1 (0.1)
Diverticulum Intestinal	1 (0.1)	0	1 (0.1)
Dysphagia	0	1 (0.2)	1 (0.1)
Gastritis	1 (0.1)	1 (0.2)	2 (0.1)
Gastrooesophageal Reflux Disease	1 (0.1)	0	1 (0.1)
Hiatus Hernia	1 (0.1)	0	1 (0.1)
Ileus	1 (0.1)	0	1 (0.1)
Inguinal Hernia	2 (0.2)	1 (0.2)	3 (0.2)
Intestinal Haemorrhage	0	1 (0.2)	1 (0.1)
Nausea	1 (0.1)	1 (0.2)	2 (0.1)
Pancreatitis Acute	0	1 (0.2)	1 (0.1)
Pancreatitis Relapsing	0	1 (0.2)	1 (0.1)
Periodontitis	1 (0.1)	0	1 (0.1)
Peritoneal Haemorrhage	0	1 (0.2)	1 (0.1)
Rectal Haemorrhage	1 (0.1)	0	1 (0.1)
Sigmoiditis	0	1 (0.2)	1 (0.1)
Umbilical Hernia	2 (0.2)	1 (0.2)	3 (0.2)
Umbilical Hernia Obstructive	0	1 (0.2)	1 (0.1)
Vomiting	1 (0.1)	1 (0.2)	2 (0.1)

Table 6.3-1 Incidence of Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term in Trial 156-04-251

SOC PT	Tolvaptan (N = 961) n (%)	Placebo (N = 483) n (%)	Total (N = 1444) n (%)
General disorders and administration site conditions			
Chest Pain	8 (0.8)	2 (0.4)	10 (0.7)
Exercise Tolerance Decreased	1 (0.1)	0	1 (0.1)
Fatigue	3 (0.3)	0	3 (0.2)
Pyrexia	0	2 (0.4)	2 (0.1)
Thirst	1 (0.1)	0	1 (0.1)
Hepatobiliary disorders			
Cholangitis	1 (0.1)	0	1 (0.1)
Hepatic Cyst	1 (0.1)	2 (0.4)	3 (0.2)
Hepatic Function Abnormal	3 (0.3)	0	3 (0.2)
Hepatic Pain	2 (0.2)	0	2 (0.1)
Hepatitis	1 (0.1)	0	1 (0.1)
Hepatomegaly	0	2 (0.4)	2 (0.1)
Liver Disorder	1 (0.1)	0	1 (0.1)
Immune system disorders			
Anaphylactic Shock	1 (0.1)	0	1 (0.1)
Infections and infestations			
Abscess Limb	1 (0.1)	0	1 (0.1)
Acute Tonsillitis	0	1 (0.2)	1 (0.1)
Appendicitis	1 (0.1)	4 (0.8)	5 (0.3)
Arthritis Bacterial	1 (0.1)	1 (0.2)	2 (0.1)
Bartholin's Abscess	1 (0.1)	0	1 (0.1)
Cellulitis	1 (0.1)	0	1 (0.1)
Diverticulitis	2 (0.2)	0	2 (0.1)
Febrile Infection	0	1 (0.2)	1 (0.1)
Gastroenteritis	1 (0.1)	0	1 (0.1)
Hepatic Cyst Infection	0	2 (0.4)	2 (0.1)
Hepatitis B	1 (0.1)	0	1 (0.1)
Kidney Infection	2 (0.2)	0	2 (0.1)
Liver Abscess	1 (0.1)	0	1 (0.1)
Malaria	1 (0.1)	0	1 (0.1)
Meningitis Viral	0	1 (0.2)	1 (0.1)
Mycoplasma Infection	1 (0.1)	0	1 (0.1)
Perineal Abscess	1 (0.1)	0	1 (0.1)
Pneumonia	3 (0.3)	0	3 (0.2)
Pyelonephritis	5 (0.5)	5 (1.0)	10 (0.7)
Renal Cyst Infection	6 (0.6)	4 (0.8)	10 (0.7)
Respiratory Tract Infection Viral	1 (0.1)	0	1 (0.1)
Sepsis	0	2 (0.4)	2 (0.1)
Syphilis	1 (0.1)	0	1 (0.1)
Urinary Tract Infection	1 (0.1)	3 (0.6)	4 (0.3)
Urogenital Infection Bacterial	1 (0.1)	0	1 (0.1)
Varicella	0	1 (0.2)	1 (0.1)
Viral Infection	1 (0.1)	1 (0.2)	2 (0.1)
Injury, poisoning, and procedural complications			
Ankle Fracture	1 (0.1)	1 (0.2)	2 (0.1)
Cartilage Injury	2 (0.2)	0	2 (0.1)

Table 6.3-1 Incidence of Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term in Trial 156-04-251

SOC PT	Tolvaptan (N = 961) n (%)	Placebo (N = 483) n (%)	Total (N = 1444) n (%)
Clavicle Fracture	1 (0.1)	0	1 (0.1)
Fall	1 (0.1)	0	1 (0.1)
Fracture	0	1 (0.2)	1 (0.1)
Hand Fracture	1 (0.1)	0	1 (0.1)
Head Injury	0	1 (0.2)	1 (0.1)
Induced Abortion Haemorrhage	1 (0.1)	0	1 (0.1)
Joint Dislocation	0	1 (0.2)	1 (0.1)
Joint Injury	0	1 (0.2)	1 (0.1)
Limb Injury	0	1 (0.2)	1 (0.1)
Lumbar Vertebral Fracture	1 (0.1)	0	1 (0.1)
Meniscus Lesion	0	1 (0.2)	1 (0.1)
Multiple Fractures	1 (0.1)	0	1 (0.1)
Post Procedural Haemorrhage	1 (0.1)	0	1 (0.1)
Spinal Compression Fracture	1 (0.1)	0	1 (0.1)
Spinal Fracture	1 (0.1)	0	1 (0.1)
Tibia Fracture	0	1 (0.2)	1 (0.1)
Ulna Fracture	1 (0.1)	0	1 (0.1)
Wrist Fracture	1 (0.1)	0	1 (0.1)
Investigations			
Alanine Aminotransferase Increased	9 (0.9)	2 (0.4)	11 (0.8)
Aspartate Aminotransferase Increased	9 (0.9)	2 (0.4)	11 (0.8)
Blood Bilirubin Increased	1 (0.1)	0	1 (0.1)
Gamma-glutamyltransferase Increased	1 (0.1)	1 (0.2)	2 (0.1)
Lipase Increased	0	1 (0.2)	1 (0.1)
Liver Function Test Abnormal	2 (0.2)	1 (0.2)	3 (0.2)
Transaminases Increased	4 (0.4)	0	4 (0.3)
Metabolism and nutrition disorders			
Dehydration	3 (0.3)	2 (0.4)	5 (0.3)
Hyperamylasaemia	0	1 (0.2)	1 (0.1)
Hypercreatininaemia	0	1 (0.2)	1 (0.1)
Hyperglycaemia	1 (0.1)	0	1 (0.1)
Hyponatraemia	1 (0.1)	1 (0.2)	2 (0.1)
Hypovolaemia	1 (0.1)	0	1 (0.1)
Musculoskeletal and connective tissue disorders			
Arthralgia	0	1 (0.2)	1 (0.1)
Back pain	1 (0.1)	2 (0.4)	3 (0.2)
Bursitis	0	1 (0.2)	1 (0.1)
Cervical Spinal Stenosis	1 (0.1)	0	1 (0.1)
Chondromalacia	0	1 (0.2)	1 (0.1)
Fistula	1 (0.1)	0	1 (0.1)
Foot Deformity	1 (0.1)	0	1 (0.1)
Intervertebral Disc Protrusion	2 (0.2)	1 (0.2)	3 (0.2)
Ligament Pain	1 (0.1)	0	1 (0.1)
Musculoskeletal Pain	1 (0.1)	0	1 (0.1)
Osteoarthritis	1 (0.1)	2 (0.4)	3 (0.2)
Osteoarthropathy	1 (0.1)	0	1 (0.1)
Rotator Cuff Syndrome	1 (0.1)	0	1 (0.1)

Table 6.3-1 Incidence of Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term in Trial 156-04-251

SOC PT	Tolvaptan (N = 961) n (%)	Placebo (N = 483) n (%)	Total (N = 1444) n (%)
Spondylolisthesis	0	1 (0.2)	1 (0.1)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)			
Breast Cancer	3 (0.3)	1 (0.2)	4 (0.3)
Cervix Carcinoma Stage 0	1 (0.1)	0	1 (0.1)
Cholesteatoma	0	1 (0.2)	1 (0.1)
Chronic Myeloid Leukaemia	1 (0.1)	0	1 (0.1)
Lipoma	0	1 (0.2)	1 (0.1)
Malignant Melanoma	2 (0.2)	0	2 (0.1)
Malignant Melanoma In Situ	1 (0.1)	0	1 (0.1)
Pituitary Tumour Benign	1 (0.1)	0	1 (0.1)
Uterine Leiomyoma	2 (0.2)	2 (0.4)	4 (0.3)
Nervous system disorders			
Cerebral Haemorrhage	1 (0.1)	0	1 (0.1)
Dizziness	1 (0.1)	0	1 (0.1)
Headache	5 (0.5)	0	5 (0.3)
Intracranial Aneurysm	3 (0.3)	1 (0.2)	4 (0.3)
Ischaemic Stroke	0	1 (0.2)	1 (0.1)
Loss Of Consciousness	2 (0.2)	0	2 (0.1)
Migraine With Aura	1 (0.1)	0	1 (0.1)
Nerve Root Compression	1 (0.1)	0	1 (0.1)
Paraesthesia	2 (0.2)	0	2 (0.1)
Parkinsonism	1 (0.1)	0	1 (0.1)
Presyncope	1 (0.1)	0	1 (0.1)
Sciatica	1 (0.1)	0	1 (0.1)
Subarachnoid Haemorrhage	1 (0.1)	2 (0.4)	3 (0.2)
Syncope	1 (0.1)	0	1 (0.1)
Transient Ischaemic Attack	0	2 (0.4)	2 (0.1)
Vertebral Artery Dissection	1 (0.1)	0	1 (0.1)
VIIth Nerve Paralysis	1 (0.1)	0	1 (0.1)
Psychiatric disorders			
Depression	1 (0.1)	1 (0.2)	2 (0.1)
Major Depression	1 (0.1)	0	1 (0.1)
Schizoaffective Disorder	0	1 (0.2)	1 (0.1)
Suicide Attempt	1 (0.1)	1 (0.2)	2 (0.1)
Renal and urinary disorders			
Bladder Prolapse	1 (0.1)	0	1 (0.1)
Calculus Urinary	0	1 (0.2)	1 (0.1)
Haematuria	4 (0.4)	1 (0.2)	5 (0.3)
Nephrolithiasis	2 (0.2)	3 (0.6)	5 (0.3)
Pollakiuria	2 (0.2)	0	2 (0.1)
Polyuria	1 (0.1)	0	1 (0.1)
Renal Colic	0	2 (0.4)	2 (0.1)
Renal Cyst	1 (0.1)	0	1 (0.1)
Renal Cyst Haemorrhage	3 (0.3)	4 (0.8)	7 (0.5)
Renal Cyst Ruptured	1 (0.1)	1 (0.2)	2 (0.1)
Renal Failure Acute	0	1 (0.2)	1 (0.1)
Renal Failure Chronic	1 (0.1)	0	1 (0.1)

Table 6.3-1 Incidence of Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term in Trial 156-04-251

SOC PT	Tolvaptan (N = 961) n (%)	Placebo (N = 483) n (%)	Total (N = 1444) n (%)
Renal Impairment	1 (0.1)	0	1 (0.1)
Renal Pain	1 (0.1)	4 (0.8)	5 (0.3)
Stress Urinary Incontinence	0	1 (0.2)	1 (0.1)
Urge Incontinence	0	1 (0.2)	1 (0.1)
Urinary Incontinence	1 (0.1)	0	1 (0.1)
Urinary Retention	0	2 (0.4)	2 (0.1)
Reproductive system and breast disorders			
Asthenospermia	0	1 (0.2)	1 (0.1)
Cervical Dysplasia	1 (0.1)	0	1 (0.1)
Hysterocele	0	1 (0.2)	1 (0.1)
Menorrhagia	3 (0.3)	0	3 (0.2)
Metrorrhagia	0	1 (0.2)	1 (0.1)
Ovarian Cyst	2 (0.2)	0	2 (0.1)
Ovarian Torsion	1 (0.1)	0	1 (0.1)
Pelvic Prolapse	1 (0.1)	0	1 (0.1)
Uterine Polyp	0	1 (0.2)	1 (0.1)
Uterine Prolapse	3 (0.3)	0	3 (0.2)
Uterovaginal Prolapse	1 (0.1)	0	1 (0.1)
Varicocele	0	1 (0.2)	1 (0.1)
Respiratory, thoracic, and mediastinal disorders			
Dyspnoea	2 (0.2)	0	2 (0.1)
Laryngeal Oedema	1 (0.1)	0	1 (0.1)
Nasal Septum Deviation	1 (0.1)	0	1 (0.1)
Pharyngeal Oedema	0	1 (0.2)	1 (0.1)
Productive Cough	1 (0.1)	0	1 (0.1)
Pulmonary Embolism	1 (0.1)	0	1 (0.1)
Respiratory Failure	1 (0.1)	0	1 (0.1)
Skin and subcutaneous tissue disorders			
Angioedema	1 (0.1)	0	1 (0.1)
Hidradenitis	1 (0.1)	0	1 (0.1)
Urticaria	1 (0.1)	0	1 (0.1)
Vascular disorders			
Deep vein thrombosis	0	1 (0.2)	1 (0.1)
Haematoma	1 (0.1)	0	1 (0.1)
Hypertension	1 (0.1)	3 (0.6)	4 (0.3)
Hypotension	3 (0.3)	1 (0.2)	4 (0.3)
Orthostatic Hypotension	1 (0.1)	0	1 (0.1)
Thrombophlebitis Superficial	1 (0.1)	0	1 (0.1)
Varicose Vein	1 (0.1)	0	1 (0.1)

[a]Subjects with TEAEs in multiple SOCs were counted only once toward the total.

6.4 Deaths

As of 01 Feb 2013, 2 subjects died during tolvaptan trial participation across the ADPKD program. Both occurred in supportive long-term trials: Gun Shot Wound that was assessed by the investigator to be not likely related to tolvaptan and Subarachnoid Hemorrhage that was assessed as unrelated. Brief narratives for these subjects are provided below:

- Subject 08271-107-0711, a 49-year-old Caucasian male with ADPKD, was enrolled in Trial 156-08-271 after completing Trial 156-04-251. He was found dead in his home due to a self-inflicted Gun Shot Wound to the head on Day 180. His wife and two children were also found dead. The subject had a history of anxiety since 1977, but did not have a history of suicidal tendencies. The subject was taking tolvaptan 45/15 mg/day at the time of the event. The subject also took lamotrigine (200 mg PO QD) within 14 days prior to the event. The event was assessed as not likely related to tolvaptan by the investigator.
- Subject 05002-006-0002, a 39-year-old Asian female with ADPKD, was enrolled in Trial 156-05-002. On Day 74, the subject was found unconscious and was subsequently diagnosed with a Subarachnoid Haemorrhage. The subject died on Day 91 due to the event. An autopsy was not performed; the cause of death was reported as a ruptured cerebral aneurysm. The date of the last dose of tolvaptan (45/15 mg) could not be confirmed. The event was assessed as unrelated to tolvaptan by the investigator. Because ADPKD is often associated with cerebrovascular disease and tolvaptan is not likely to cause acute development of aneurysm, the investigator suspected that the subject may have had a cerebral aneurysm prior to the initiation of trial treatment.

For Trial 156-04-251, no deaths occurred during the trial and none have been reported in the ongoing post-study vital status collection. As of 15 May 2013, 96% of all subjects enrolled in the pivotal trial (1387/1445) have been confirmed alive on or after their Month 36 trial visit. Subject follow-up is still in progress for 23 (1.6%) subjects (18/961, 1.9% tolvaptan subjects: 5/484, 1.0% placebo subjects). Thirty-five subjects (29/961, 3.0% tolvaptan subjects: 6/484, 1.2% placebo subjects) have an unknown vital status, ie, vital status could not be verified and the subject was considered lost to follow-up.

6.5 Adverse Events Leading to Treatment Discontinuation

In the pivotal Trial 156-04-251, TEAEs that led to discontinuation of trial medication were reported for 11.4% of subjects overall, which included a higher proportion of subjects in the tolvaptan group (15.0%) than in the placebo group (4.3%). Treatment-emergent AEs resulting in treatment discontinuation in ≥ 0.3% of subjects in the tolvaptan group were Nausea, Asthenia, Polyuria, Pollakiuria, Nocturia, Thirst, Abnormal

Hepatic Function, Alanine Aminotransferase Increased, Aspartate Aminotransferase Increased, Blood Creatinine Increased, Depression, Insomnia, Fatigue, and Hypertension. Each of these events was reported in a higher proportion of subjects on tolvaptan than on placebo (Table 6.5-1). In contrast, a smaller proportion of tolvaptan subjects discontinued trial medication due to TEAEs of Renal Pain compared with placebo subjects. Notably, while commonly reported, the aquaretic-related TEAEs did not result in discontinuation of trial medication in any great proportion of subjects. Approximately 4% and 2% of subjects on tolvaptan discontinued trial medication because of Polyuria and Pollakiuria, respectively.

Table 6.5-1 Incidence of Treatment-emergent Adverse Events Resulting in Discontinuation of Investigational Medicinal Product in at Least 0.3% of Subjects in Any Group by MedDRA System Organ Class and Preferred Term in Trial 156-04-251

SOC PT	Tolvaptan (N=961)	Placebo (N-483)	Total (N=1444)
Total[a]	144 (15.0)	21 (4.3)	165 (11.4)
Gastrointestinal disorders			
Nausea	3 (0.3)	0	3 (0.2)
General disorders and administrative site conditions			
Asthenia	3 (0.3)	0	3 (0.2)
Fatigue	5 (0.5)	0	5 (0.3)
Thirst	6 (0.6)	1 (0.2)	7 (0.5)
Hepatobiliary disorders			
Hepatic function abnormal	6 (0.6)	0	6 (0.4)
Investigations			
Alanine aminotransferase increased	4 (0.4)	0 (0)	4 (0.3)
Aspartate aminotransferase increased	4 (0.4)	0 (0)	4 (0.3)
Blood creatinine increased	3 (0.3)	0	3 (0.2)
Nervous system disorders			
Headache	2 (0.2)	2 (0.4)	4 (0.3)
Psychiatric disorders			
Depression	3 (0.3)	0	3 (0.2)
Insomnia	3 (0.3)	0	3 (0.2)
Renal and urinary disorders			
Nocturia	9 (0.9)	1 (0.2)	10 (0.7)
Pollakiuria	15 (1.6)	0	15 (1.0)
Polyuria	38 (4.0)	0	38 (2.6)
Renal pain	2 (0.2)	3 (0.6)	5 (0.3)
Vascular disorders			
Hypertension	3 (0.3)	1 (0.2)	4 (0.3)

Note: A TEAE event is defined as an AE that occurred after start of trial medication, or if the event was continuous from baseline and was serious; related to the trial medication, or resulted in death, discontinuation, interruption or reduction of trial medication. Subjects were counted once, per term, for the most severe of multiple occurrences of a specific MedDRA preferred term. Adverse events are censored 7 days after trial medication end date.

[a]. Subjects with AEs in multiple SOCs were counted only once toward the total.

An additional 5.5% of subjects discontinued trial medication in Trial 156-04-251 due to consent withdrawal by the subject, including similar proportions of subjects on tolvaptan and placebo. On independent physician review of these cases, 4 subjects were identified in whom it appeared AEs were implicated in the reason for consent being withdrawn (described in Section 5.1).

The overall rate of discontinuation of trial medication during the titration period of Trial 156-04-251 (up to Day 23) was 67/961 (7.0%) in the tolvaptan group and 3/483 (0.6%) in the placebo group. CRF completion guidelines required that only one TEAE be listed as a cause for each subject who withdrew. TEAEs reasonably attributable to acute aquaretic side effects accounted for 56/67 (84%) of these acute withdrawals in the tolvaptan group vs. placebo group: Thirst 5 vs. 0; Blood Creatinine Increased 1 vs. 0; Weight Decreased 1 vs. 0; Polydipsia 2 vs. 0; Insomnia 2 vs. 0; Nocturia 7 vs. 0; Pollakiuria 10 vs. 0; Polyuria 28 vs. 0. There were no withdrawals attributed to hepatic-related TEAEs during the titration period.

During the remaining 35 months of the trial's maintenance phase, the rates of discontinuation of trial medication due to TEAE were 77/915 (8.4%) in the tolvaptan group versus 18/475 (3.8%) in the placebo group, a difference higher for the tolvaptan group by approximately 4.6%. In the maintenance phase, 21/77 (27%) of tolvaptan group withdrawals due to AEs were accounted for by aquaretic-related TEAEs (Thirst 1 vs. 1; Blood Creatinine Increased 2 vs. 0; Insomnia 1 vs. 0; Nocturia 2 vs. 1; Pollakiuria 5 vs. 0; Polyuria 10 vs. 0). The placebo group had 2/18 (11%) withdrawals in these categories.

In contrast to the titration phase, where no hepatic TEAEs were seen, the maintenance phase tolvaptan group subjects reported hepatic-related TEAEs (Hepatic Function Abnormal 6 vs. 0; Hepatitis 1 vs. 0; Alanine Aminotransferase Increased 4 vs. 0; Aspartate Aminotransferase Increased 4 vs. 0; Blood Bilirubin Increased 1 vs. 0; Gamma-Glutamyltransferase Increased 1 vs. 0; Hepatic Enzyme Increased 1 vs. 0; Liver Function Test Abnormal 2 vs. 0; Transaminases Increased 1 vs. 0) at the same rate as aquaretic TEAEs 21/77 (27%). Combined, these TEAEs contributed to 42/77 (55%) of tolvaptan group TEAEs resulting in discontinuation of trial medication in the maintenance phase.

Combining both phases of the trial, aquaretic and hepatic TEAEs accounted for 56 + 42 or 98/144 (68%) of the total TEAE-related withdrawals which represents 98/961 (10.2%) of withdrawals overall. Thus, these two categories of TEAEs accounted for nearly the entirety of the 10.7% difference in AE withdrawal rates and the entirety of the 9.2% difference in overall withdrawal rates between tolvaptan and placebo. These adverse event categories are unrelated to the clinical endpoints for the trial (TKV, eGFR, renal

pain, albuminuria, hypertension). Therefore, it is unlikely the partial or complete loss of these subjects' data would contribute to a bias due to data "missing not-at-random."

Discontinuations in supportive trials followed a consistent pattern with the pivotal trial.

6.6 Clinical Laboratory Tests

In pivotal Trial 156-04-251, potentially clinically significant laboratory abnormalities reported more frequently in tolvaptan subjects compared with placebo subjects included increased sodium, increased uric acid, increased ALT, and increased AST (Table 6.6-1). The increased serum sodium was expected due to the aquaretic actions of tolvaptan and served as a clinical indicator of the need to further emphasize hydration efforts. The average increase in sodium was approximately 2 mmol/L and no AEs were reported as serious or leading to discontinuation of study medication. The increased uric acid was expected due to decreased uric acid clearance by the kidney following tolvaptan treatment. An overview of the hepatic effects of tolvaptan is provided in Section 6.8.2. Other differences were not considered to be clinically important. There were no clinically significant differences in hematology abnormalities between the 2 treatment groups reported during the pivotal trial. Laboratory results from the long-term extension Trial 156-08-271 were consistent with those from the pivotal Trial 156-04-251.

Table 6.6-1 Summary of Laboratory Parameters of Interest in Trial 156-04-251

Treatment Group/ Parameter	Mean (SD), Range						PCS Change n (%)
	Baseline	End of Titration	Month 12	Month 24	Month 36	Follow-up #2	
Serum Sodium (mEq/L)							
Tolvaptan	140.4 (2.1) 132-150	142.6 (2.6) 136-160	141.9(2.6) 131-162	141.7 (2.5) 131-153	141.6 (2.6) 128-156	140.9 (2.3) 128-148	Decreased: 1 (0.1) Increased: 38 (4.0)
Placebo	140.3 (2.0) 134-149	140.3 (2.2) 135-150	140.5(2.3) 133-150	140.3 (2.4) 131-151	140.3 (2.3) 131-148	140.3 (2.3) 134-151	Decreased: 1 (0.2) Increased: 7 (1.4)
Serum Creatinine (mg/dL)							
Tolvaptan	1.05 (0.3) 0.38-2.29	1.11 (0.3) 0.52-2.55	1.16 (0.4) 0.50-3.25	1.19 (0.4) 0.53-3.13	1.25 (0.5) 0.50-4.09	1.21 (0.5) 0.49-3.79	Increased: 159 (16.7)
Placebo	1.04 (0.3) 0.20-2.82	1.06 (0.3) 0.48-3.44	1.13 (0.4) 0.28-4.33	1.17 (0.5) 0.23-4.34	1.26 (0.6) 0.50-5.07	1.27 (0.6) 0.50-5.38	Increased: 101 (21.0)
Blood Urea Nitrogen (mg/dL)							
Tolvaptan	19.4 (5.4) 7-46	15.2 (5.7) 4-48	15.9 (6.0) 5-41	17.0 (6.6) 3-59	18.3 (7.6) 5-61	21.0 (7.4) 7-65	Increased: 150 (15.6)
Placebo	19.3 (5.4) 8-52	18.9 (5.7) 8-56	19.8 (5.7) 7-49	20.6 (6.6) 8-64	21.8 (7.9) 8-75	22.0 (7.6) 8-67	Increased: 142 (29.4)
Uric Acid (mg/dL)							
Tolvaptan	5.6 (1.7) 1.8-13.1	6.4 (1.8) 2.5-12.9	6.5 (1.8) 2.1-11.7	6.5 (1.8) 2.5-13.2	6.5 (1.7) 2.7-12.6	5.9 (1.7) 2.3-11.5	Increased: 59 (6.2)
Placebo	5.5 (1.5) 1.9-10.9	5.6 (1.6) 2.0-10.7	5.7 (1.6) 2.4-13.0	5.8 (1.6) 2.3-11.6	5.9 (1.6) 2.2-10.6	5.9 (1.6) 2.2-11.6	Increased: 8 (1.7)
ALT (IU/L)							
Tolvaptan	21.3 (12.7) 6-140	26.5(106.4) 4-3179	22.8(16.6) 5-213	21.6 (13.0) 5-122	20.8 (12.3) 6-138	21.4 (11.5) 6-100	Increased: 47 (4.9)
Placebo	21.0 (13.0) 5-188	20.4 (10.1) 6-76	20.7(11.7) 6-130	20.7 (12.7) 5-191	20.1 (9.0) 5-58	19.7 (10.0) 6-108	Increased: 6 (1.2)

Table 6.6-1 Summary of Laboratory Parameters of Interest in Trial 156-04-251

Treatment Group/ Parameter	Mean (SD), Range						PCS Change n (%)
	Baseline	End of Titration	Month 12	Month 24	Month 36	Follow-up #2	
AST (IU/L)							
Tolvaptan	20.9 (6.7) 9-78	25.8(120.6) 10-131	22.1 (9.4) 10-131	21.5 (7.4) 10-89	21.9 (15.6) 10-399	21.4 (6.6) 11-72	Increased: 31 (3.2)
Placebo	21.0 (9.6) 10-181	20.3 (5.6) 9-52	20.8 (6.7) 8-68	21.3 (8.0) 9-120	20.8 (5.8) 8-45	20.9 (6.6) 8-62	Increased: 4 (0.8)
Bilirubin, Total (mg/dL)							
Tolvaptan	0.54 (0.27) 0.2-2.5	0.50 (0.25) 0.2-2.4	0.52(0.24) 0.2-2.4	0.51 (0.25) 0.2-2.7	0.50 (0.25) 0.20-3.0	0.50 (0.24) 0.2-2.8	Increased: 9 (0.9)
Placebo	0.57 (0.32) 0.2-2.9	0.54 (0.32) 0.2-3.1	0.55(0.33) 0.3-3.7	0.53 (0.30) 0.2-2.6	0.51 (0.27) 0.2-2.8	0.51 (0.24) 0.2-2.0	Increased: 9 (1.9)
Urine Albumin/Creatinine Ratio (mg/mmol)							
Tolvaptan	7.2 (14.3) 0.5-207.9	7.4 (15.2) 0.3-235.8	7.0 (11.8) 0.3-127.1	7.2 (13.3) 0.0-128.9	8.3 (20.7) 0.3-290.6	7.5 (18.7) 0.0-219.3	Not Applicable
Placebo	8.6 (21.7) 0.4-220.8	7.1 (15.8) 0.0-189.6	8.9 (23.1) 0.5-232.5	9.2 (25.1) 0.0-296.4	9.4 (19.0) 0.5-209.6	9.1 (20.1) 0.0-219.3	Not Applicable

ALT = alanine aminotransferase; AST = aspartate aminotransferase; PCS = potentially clinically significant; SD = standard deviation; PCS = potentially clinically significant; SD = standard deviation.

6.7 Vital Signs and Electrocardiogram

No clinically meaningful changes in mean body weight, systolic or diastolic blood pressure, heart rate or ECG parameters were observed over time in Trial 156-04-251. Results of long-term supportive trials were consistent with those in the pivotal trial. Of note, tolvaptan has been investigated in a thorough QT trial at a maximum dose of 300 mg/day for 5 days without any evidence of effects on prolongation of QTc (individual correction method).[60]

6.8 Events of Special Interest

This section summarizes additional analyses relating to TEAEs of special interest that were identified during Trial 156-04-251, including TEAEs that were expected based on tolvaptan's mechanism of action, TEAEs consistent with the ADPKD subject population, and TEAEs identified through clinical trial experience that are of specific or general interest (including any rare, but potentially clinically important, events). Adverse events of special interest were reviewed in the context of potential drug-related risks identified through consultation with subject matter experts, literature review, consultant advice, and communication with regulatory agencies and regulatory guidance documents. The following safety topics were assessed in pivotal Trial 156-04-251, as well as supporting trials as applicable, and are discussed in this section:

- Renal Effects Plausibly Related to V_2 Inhibition (fluid balance, electrolytes, uric acid)
- Effects on Renal Function (CrCl, GFR)
- Extra-renal Effects Plausibly Related to V_2 Inhibition or AVP Increase
- ADPKD-related Conditions
- Cardiac Disorders
- Rare but Clinically Important Events
- Hepatic Transaminase Elevations - Potential Hepatotoxicity and "Hy's Law" Cases
- Neoplasms

As previously observed in other indications, increased incidences of TEAEs related to tolvaptan's aquaretic effects were observed in tolvaptan subjects compared with placebo subjects in Trial 156-04-251, as well as in other supportive long- and short-term tolvaptan trials. Progressive loss of kidney function is a consequence of ADPKD; thus, renal effects of tolvaptan (given that the kidney is its primary site of action) were evaluated, including renal function TEAEs, electrolytes, renal function parameters, etc. In prior trials in chronic heart failure and/or hyponatremia subject populations, small but

reversible increases in serum creatinine and uric acid, and decreased blood urea nitrogen (BUN) concentrations, were observed.

In pivotal Trial 156-04-251, tolvaptan increased serum creatinine by 0.05 mg/dL over placebo at Week 3/EOT in subjects with ADPKD. Recall that the long-term evaluation of kidney function as measured by serum creatinine was a component of the secondary composite endpoint, and showed a decreased rate of renal function decline in subjects who received tolvaptan compared with placebo.

Evaluation of renal function AEs included, for example, the incidence of reported TEAEs in the acute renal failure SMQ, which was nominally lower in tolvaptan subjects (16.0%) relative to placebo subjects (18.4%). The most frequently reported TEAE in this SMQ analysis was Blood Creatinine Increased, reported by 14.0% of tolvaptan subjects and 14.7% of placebo subjects. All reports of Blood Creatinine Increased were mild to moderate in severity. Serious TEAEs in this SMQ were infrequent. Few events led in this SMQ to trial medication discontinuation during the trial.

The increased reporting of events of Hyperuricemia/Gout was expected due to decreased uric acid clearance by the kidney caused by tolvaptan treatment.

Extra-renal effects were evaluated with regard to potential V_2 inhibition; V_2-receptor blockade results in a slight compensatory increase in circulating AVP, which in turn may promote increased activation of V_{1a} receptors in the vasculature. This could potentially have an impact on blood pressure, platelet aggregation, blood glucose, and intraocular pressure. Careful screening of clinical trial data involving analysis of individual event terms, and grouped term analysis by Standardized MedDRA Query, (SMQ), demonstrated no clear adverse effects of tolvaptan treatment on BP, thrombosis, or coagulation disorders. Though the rates of potentially clinically significant changes in glucose concentrations during the pivotal Trial 156-04-251 were similar between treatment groups, TEAEs of Diabetes Mellitus were reported exclusively in a small number of tolvaptan subjects (n = 7); thus, an association between tolvaptan and hyperglycemia/new-onset diabetes TEAEs could not be excluded.

For glaucoma, while there does not appear to be direct evidence for a causal association between tolvaptan and glaucoma, the possibility could not be excluded based on a higher incidence of glaucoma-related TEAEs in ADPKD subjects on tolvaptan versus placebo (ie, Glaucoma, Open Angle Glaucoma, Intraocular Pressure Increased, 0.7% [7/961] vs 0.4% [2/483]); a similar weak signal was observed in non-ADPKD populations during clinical development. (Note, after database lock of Trial 156-04-251, it was determined that an eighth subject randomized to tolvaptan was diagnosed with open angle glaucoma

[discovered while enrolled in Trial 156-04-271], an event not captured in the 156-04-251 clinical trial database. This increases the incidence on tolvaptan to 0.8%, [8/961].) The proposed product label includes guidance that appropriate eye examinations and management should be considered before and during treatment with tolvaptan.

ADPKD-related outcomes of worsening renal function, renal pain, worsening hypertension, and albuminuria were the components of the key secondary composite efficacy endpoint as described in Section 5.6.1. Additional analyses of safety and efficacy results, via customized MedDRA query or PKD Outcomes Survey, also demonstrate that tolvaptan reduced the incidence of renal pain, hematuria, and UTI in subjects with ADPKD. For events of nephrolithiasis and anaemia, incidences appeared to be nominally reduced in tolvaptan subjects in Trial 156-04-251, and the overall incidence of events was small; thus, the effect of tolvaptan on these components could not be fully assessed. Tolvaptan did not have a demonstrable, clinically meaningful effect on reducing events of albuminuria, colonic diverticulum, vascular abnormalities, abdominal and inguinal hernias, or hepatic or other cysts in subjects with ADPKD.

An evaluation of safety with regard to cardiovascular function included an analysis of cardiovascular TEAEs in Trial 156-04-251. No TEAEs in the bradyarrhythmia SMQ were reported in subjects on tolvaptan or placebo in the pivotal trial. There were no reports of clinically important cardiac arrhythmias, such as ventricular tachycardia, Torsades de Pointes, ventricular fibrillation, or cardiac arrest during the pivotal trial. In general, tachyarrhythmia-related TEAEs were infrequently reported and occurred at a similar incidence in tolvaptan and placebo subjects. The use of tolvaptan did not appear to increase cardiovascular risk, with regard to arrhythmias or incidence of myocardial infarction or ischemic heart disease, in subjects with ADPKD. In the placebo-controlled pivotal trial, there was no excess of myocardial infarction SAEs reported in the tolvaptan group. Of note, tolvaptan has been investigated in a thorough QT trial without any evidence of effects on prolongation of QTc (individual correction method).[60]

6.8.1 Rare but Clinically Significant Adverse Events

Safety analysis in Trial 156-04-251 included examination of rare, but clinically significant, TEAEs and other clinically important TEAEs that occurred during treatment with tolvaptan; these included potential immune-mediated reactions, neoplasms, and cytopenias and related concepts. Tolvaptan treatment was not associated with a clinically meaningful increase in potential immune-mediated reactions, pancytopenia, or agranulocytosis in subjects with ADPKD.

6.8.1.1 Neoplasms

A higher frequency of neoplasms was observed in ADPKD tolvaptan subjects compared with placebo subjects (from the malignant tumor SMQ and tumor of unspecified malignancy SMQ). In these queries new malignant tumor diagnoses occurred in 16 tolvaptan subjects (1.7%) vs 2 placebo subjects (0.4%) (Table 6.8.1.1-1).

This imbalance in neoplasm was driven principally by skin neoplasms, basal cell carcinoma in particular. Eight tolvaptan subjects (0.8%) were diagnosed with basal cell carcinoma. Seven of these 8 had a history of sun exposure sufficient to cause skin damage, ranging from multiple truncal nevi to multiple prior diagnosed skin cancers. All 7 of these subjects developed basal cell carcinoma on sun-exposed areas of skin, and 4 of these subjects had a history of prior basal cell carcinoma. The remaining tolvaptan subject had a basal cell carcinoma (Day 857) on a non-sun-exposed area of skin. Basal cell and squamous cell carcinomas were also reported in one placebo subject (0.2%) who entered the trial with a past medical history of multiple skin cancers. Two subjects on tolvaptan (0.2%) in the pivotal trial were diagnosed with melanoma, one of whom was also diagnosed with melanoma in situ, a premalignant condition. Both of these subjects had early stage disease, presumed cured by surgical excision. One of these subjects underwent removal of an atypical nevus 18 months following discontinuation of tolvaptan.

Table 6.8.1.1-1 Incidence of Treatment-emergent Adverse Events in the Neoplasm SMQs by MedDRA System Organ Class and Preferred Term; Trial 156-04-251

MedDRA Query PT	Tolvaptan (N=961) n(%)	Placebo (N=483) n(%)	Total (N=1444) n (%)
Malignant tumors SMQ, Total[a]	16 (1.7)	2 (0.4)	18 (1.2)
Skin neoplasms			
Basal Cell Carcinomas	8 (0.8)	1 (0.2)	9 (0.6)
Malignant Melanoma	2 (0.2)	0	2 (0.1)
Malignant Melanoma in Situ	1 (0.1)	0	1 (0.1)
Squamous Cell Carcinoma	0	1 (0.1)	1 (0.1)
Other neoplasms			
Breast Cancer	3 (0.3)	1 (0.2)	4 (0.3)
Cervix Carcinoma Stage 0	1 (0.1)	0	1 (0.1)
Chronic Myeloid Leukemia	1 (0.1)	0	1 (0.1)
Kaposi's Sarcoma	1 (0.1)	0	1 (0.1)
Tumor of Unspecified Malignancy SMQ, Total[a]	0	1 (0.2)	1 (0.1)
Thyroid Neoplasm	0	1 (0.2)	1 (0.1)

Note: Subject 04251-107-0701 reported separate TEAEs of Basal Cell Carcinomas and Squamous Cell Carcinoma. Subject 04251-115-4402 reported separate TEAEs of Malignant Melanoma In Situ and Malignant Melanoma.

[a]Subjects with TEAEs in multiple SOCs were counted only once toward the total.

Other diagnosed malignant tumors were histologically diverse. Three subjects on tolvaptan (0.3%) and 1 subject on placebo (0.2%) in the pivotal trial were diagnosed with early stage breast cancer. These breast cancers are all presumed cured by surgery and adjuvant therapy. The events of breast cancer were diagnosed in the tolvaptan group on Days 192, 328, and 1065. The breast cancer diagnosis in the placebo group was on Day 708. The tolvaptan subject whose diagnosis was on Day 192 had a self-identified breast mass that she noticed within 2 months after starting tolvaptan.

The subject on tolvaptan reported to have cervical cancer (0.1%) actually had carcinoma in situ, a premalignant condition. She was diagnosed on Day 140, following an evaluation that began with presentation of anemia due to hypermenorrhea on Day 5 of tolvaptan therapy in the pivotal trial.

The subject on tolvaptan with “endemic African Kaposi’s sarcoma” (0.1%) indicated that representative lesions of this disease had been present for years prior to initiation of tolvaptan in the pivotal trial.

One subject on tolvaptan was diagnosed on Day 1088 with Philadelphia chromosome-positive chronic myelogenous leukemia. The subject had no known significant prior radiation exposure.

In addition to the above, 1 subject on placebo (0.2%) was diagnosed with a thyroid neoplasm. It is not known at this time whether the thyroid neoplasm in the subject on placebo was benign or malignant.

Subjects in an ongoing, open-label, extension Trial 156-08-271 have contributed additional uncontrolled data to the safety analysis. Seven malignant tumor events have since been reported in Trial 156-08-271 including: Testicular Cancer (2 subjects), Breast Cancer (2 subjects), Malignant Melanoma (2 subjects), and Gastrointestinal Stromal Tumor (1 subject). In the cases of testicular cancer, one had a positive family history, and the second event was reported after 6 months of tolvaptan therapy. In the cases of breast cancer, one had a positive family history, and in the second case the diagnosis was made after 4.5 years of tolvaptan therapy in a 46-year-old female with no known risk factors. The 2 cases of malignant melanoma included one with a history of significant sun exposure and the second case was noticed 4 days after starting tolvaptan. Lastly, the gastrointestinal stromal tumor was diagnosed after 4.5 years of tolvaptan therapy. The ability to draw meaningful conclusions from non-placebo-controlled data is limited.

An imbalance of diagnosed malignant neoplasms has not been observed in prior placebo-controlled, non-ADPKD trials. Similarly, no neoplasm safety signal has been observed during post-marketing pharmacovigilance.

Tolvaptan was not carcinogenic in 2-year toxicity studies with rats or mice, and was not genotoxic in a series of in vitro and in vivo studies.[60] Nonetheless, an observed imbalance in skin neoplasms is apparent. Although a causal relationship cannot be established between tolvaptan and the higher incidence of neoplasms, proposed product labeling for tolvaptan therapy in ADPKD includes guidance that appropriate skin examinations and management should be considered before and during treatment with tolvaptan.

6.8.2 Hepatic Injury

An imbalance in the proportion of subjects with hepatic transaminase elevations (4.4% ALT [> 3x ULN] tolvaptan vs placebo 1.0%) was observed on unblinding of the pivotal trial (156-04-251) (Table 6.8.2-1). This imbalance in the proportion of subjects with elevated transaminases (tolvaptan > placebo) was unexpected given that no signal for drug-induced liver injury (DILI) had been observed during the clinical development programs for the hyponatremia and heart failure indications (data on file), nor had a signal been detected during the postmarketing experience to date for any approved indication. Therefore, in the design of the pivotal trial, liver enzyme evaluation was not done more frequently than the 4-month scheduled visits.

A case review with adjudication for possible causality with an expert, blinded panel was undertaken to evaluate the data. The review process is described in further detail in Section 6.8.2.1.

Table 6.8.2-1 Elevated Liver Function Tests as Assessed by Central and Local Laboratory Data Combined, All Randomized Subjects in Trial 156-04-251

Abnormality	Tolvaptan			Placebo		
	N[a]	n[b]	%	N[a]	n[b]	%
ALT						
> 3 × ULN	958	42	4.4	484	5	1.0
> 5 × ULN	958	22	2.3	484	2	0.4
> 10 × ULN	958	12	1.3	484	0	0
> 20 × ULN	958	6	0.6	484	0	0
AST						
> 3 × ULN	958	30	3.1	484	4	0.8
> 5 × ULN	958	18	1.9	484	2	0.4
> 10 × ULN	958	10	1.0	484	0	0
> 20 × ULN	958	3	0.3	484	0	0
ALT or AST > 3 × ULN	958	47	4.9	484	8	1.7
ALT or AST > 5 × ULN	958	24	2.5	484	3	0.6
BT > 2 × ULN	957	3	0.3	484	3	0.6
BT > 2 × ULN concurrent with:						
ALT > 3 × ULN[c]	957	2	0.2	484	0	0
ALT > 5 × ULN[c]	957	2	0.2	484	0	0
AST > 3 × ULN[c]	957	2	0.2	484	0	0
AST > 5 × ULN[c]	957	2	0.2	484	0	0
ALT or AST > 3 × ULN[c]	957	2	0.2	484	0	0
ALT or AST > 5 × ULN[c]	957	2	0.2	484	0	0

BT = bilirubin, total; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

Note, a third subject in the ADPKD safety database from ongoing ADPKD Trial 156-08-271 (delayed-treated [placebo] subject from Trial 156-04-251) met the criterion of ALT > 3x ULN concurrent with BT > 2x ULN.

[a]The total number of subjects with at least one postbaseline result for the test(s).

[b]The number of subjects meeting the criteria.

[c]The concurrent elevation in BT within 30 days after the elevation in ALT or AST.

6.8.2.1 Hepatic Adjudication Committee Methodology

The pivotal, placebo-controlled, phase 3 ADPKD trial (Trial 156-04-251) was monitored by an Independent Data Monitoring Committee, supported by the Statistical Data Analysis Center (SDAC) from the University of Wisconsin, and sponsor according to GCP and the FDA guidance on drug-induced liver injury (DILI) upon its release in July 2009.[61] A pattern of elevated transaminase levels emerged in this cohort of ADPKD subjects; however, data were blinded except to the IDMC. Based on the advice of hepatic experts, the sponsor formed an independent, blinded, expert Hepatic Adjudication

Committee for the post-hoc sequential evaluation and adjudication of these events in the 17 trials in the ADPKD program (data from completed trials and data from ongoing trials received through 31 Mar 2012). In addition, the Hepatic Adjudication Committee also evaluated selected subjects from previous studies in heart failure, hyponatremia, and cirrhosis as well as relevant patients from post-marketing reports. Since the NDA cutoff date of 31 Mar 2012, ongoing safety surveillance has continued.

The independent panel of gastroenterologists with expertise in assessing hepatotoxicity, and with the advice of the US FDA, defined safety criteria related to reported TEAEs and clinical laboratory data (central and local laboratory data) to identify more clearly the subjects potentially at risk of clinically significant liver injury. Data for subjects meeting one or more of the following criteria were reviewed by the Hepatic Adjudication Committee:

- A nonserious TEAE leading to discontinuation of trial medication or any serious TEAE matching a lower level MedDRA term in one of the following hepatic SMQs
  - Cholestasis and jaundice of hepatic origin
  - Hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions
  - Noninfectious hepatitis
  - Liver-related investigations, signs, and symptoms
  - Liver-related coagulation and bleeding disturbances
  - ALT > 3 × ULN and BT > 2 × ULN
  - AST > 3 × ULN and BT > 2 × ULN
  - ALT or AST > 5 × ULN
  - BT > 2 × ULN

All subjects among the 17 trials in the ADPKD program were screened to identify those meeting the specified criteria for hepatic events: 9 completed trials in ADPKD subjects, 4 ongoing ADPKD trials (3 open-label trials and 1 randomized double-blind trial), and 4 trials supportive to the ADPKD program (3 in healthy subjects and 1 special population trial). (Note, for the initial adjudication effort, the NDA data cutoff dates were applied: 01 Dec 2011 for Trials 156-10-003 and 156-09-003, and 31 Mar 2012 for Trials 156-08-271 and 156-09-290.) All available data through 31 Mar 2012 were included in the screening process for hepatic event adjudication, and in addition, one subject in the extension trial was identified using local laboratory data obtained after the 31 Mar 2012 cutoff date.) The process for screening and evaluation of the hepatic safety data from the ADPKD program is depicted in Figure 6.8.2.1-1.

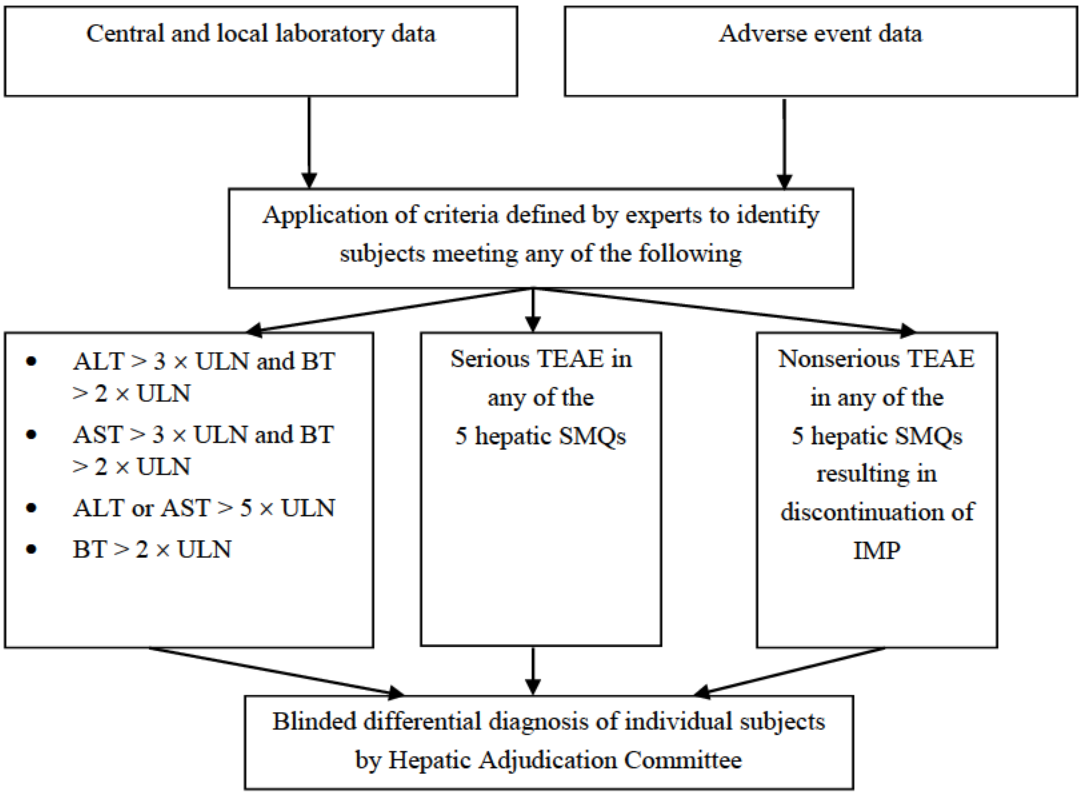
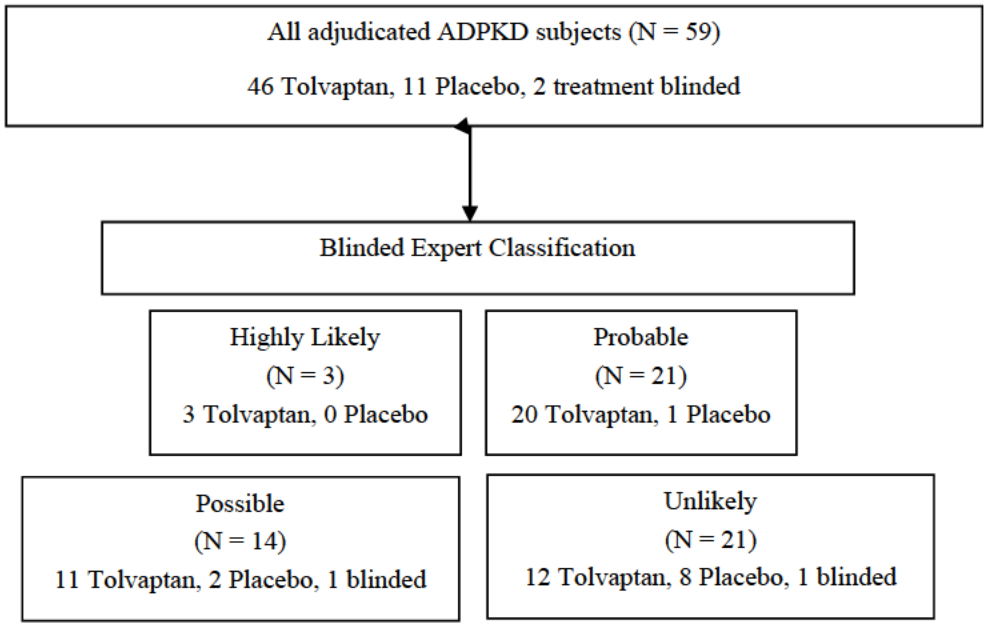


Figure 6.8.2.1-1 Process for Screening and Evaluation of Hepatic Safety Data From the ADPKD Program

6.8.2.2 Hepatic Adjudication Committee Outcomes

Based on the above process, 59 subjects from ADPKD clinical trials were identified as meeting the hepatic event criteria for further evaluation: 46/1444 treated subjects from the completed pivotal trial (Trial 156-04-251), 9/904 treated subjects from the ongoing open-label extension (Trial 156-08-271), 2/108 treated subjects from the ongoing open-label trial in Japan (Trial 156-10-003; note that a third subject met criteria for adjudication in both this trial and parent Trial 156-04-251, and is counted in the parent trial only), and 2/18 treated subjects from the ongoing double-blind trial in the US (Trial 156-09-290). In addition to the evaluation of laboratory data, medical differential diagnosis is essential when assessing potentially clinically important liver injury to exclude other plausible alternative explanations for the findings; therefore, all available clinical data for these 59 subjects were reviewed and evaluated by the independent blinded Hepatic Adjudication Committee. Results of the adjudication as of the NDA cutoff of 31 Mar 2012 are presented in Figure 6.8.2.2-4 and a report of the Hepatic Adjudication Committee's findings was prepared.[62]

For ongoing ADPKD trials, subjects with liver function test elevations or liver abnormalities that did not meet criteria for adjudication continue to be monitored and adjudication of events will proceed on an ongoing basis until trial completion as cases are identified per established criteria.



Note: Events for Subject 08271-468-4301 ("highly likely"), Subject 04251-302-4053 ("probable"), and Subject 04251-731-2738 ("probable") were confirmed to be "Hy's Law" cases by the Hepatic Adjudication Committee.

Figure 6.8.2.2-1 Adjudication Results for the ADPKD Program as of the NDA Cutoff of 31 Mar2012

The Hepatic Adjudication Committee observed a signature presentation of hepatocellular injury consisting of an onset between 3 and 14 months of treatment, based on time to first elevation of ALT > 3x ULN (Figure 6.8.2.2-2), with a continued rise in transaminases followed by gradual resolution over 1 to 4 months. While no subjects experienced hepatic failure, required liver transplantation or died, expert adjudication concluded that 3 tolvaptan subjects in the ADPKD program (2 in Trial 156-04-251 and 1 in Trial 156-08-271) met the requirements of "Hy's Law" (ie, ALT > 3 x ULN and bilirubin > 2 x ULN) for clinical evidence of hepatocellular injury.[62] Based on these 3 cases, the Hepatic Adjudication Committee estimated the risk of liver failure to be 1:3000. They further noted "...the risk estimate of liver failure is based on the clinical trial data and assumes the monitoring regimen used in the clinical trials would be followed. It is reasonable to assume that the risk of liver failure would be lower with more frequent monitoring to catch the liver injury earlier in its course." Each of the 3 Hy's Law cases has

subsequently been documented to have returned to normal (≤ 1 x ULN). The time course of the hepatic laboratory values for each of the Hy's Law cases are presented in Figure 6.8.2.2-4, Figure 6.8.2.2-3, and Figure 6.8.2.2-5 Narratives of these events are provided in Section 10.7.

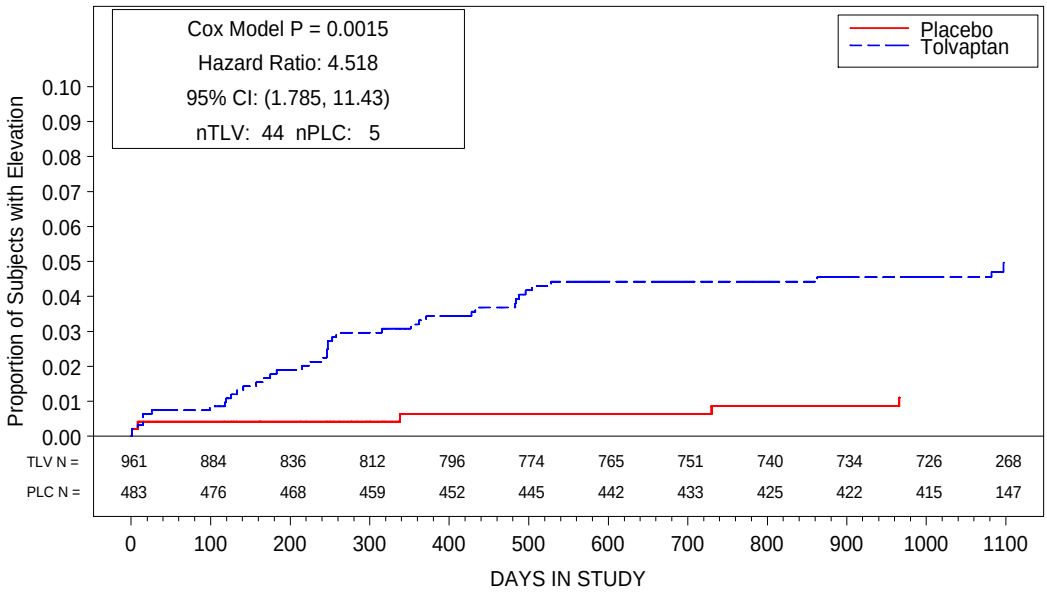


Figure 6.8.2.2-2 Kaplan-Meier Curves for Time to First Elevation in ALT of Greater Than 3 Times ULN, Safety Population

PLC = placebo; TLV = tolvaptan.
Note: Included central and local laboratory data.

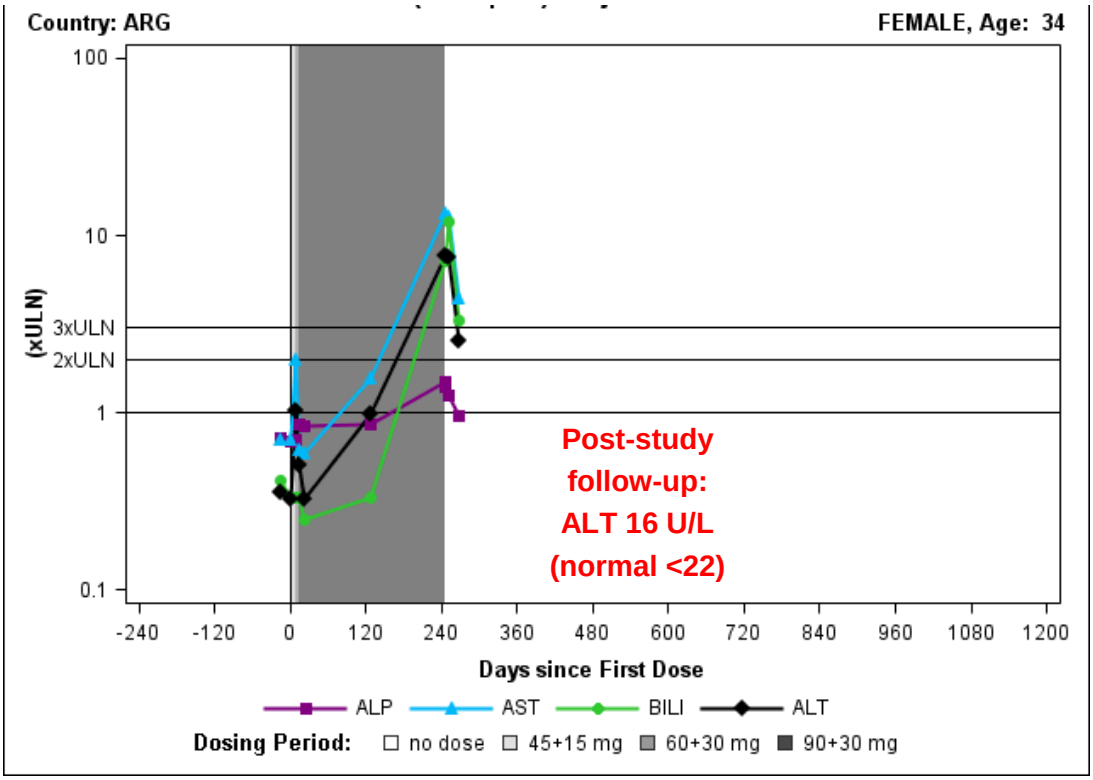


Figure 6.8.2.2-3 Subject 0451-302-4053 (Tolvaptan) – Adjudicated: Probable

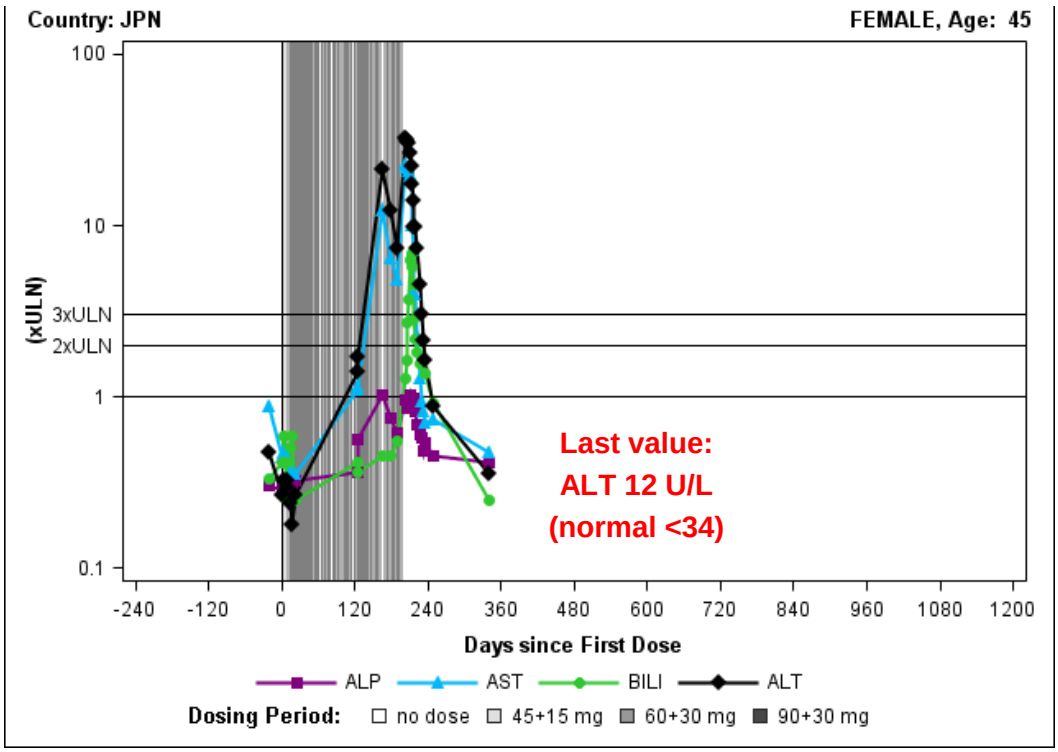


Figure 6.8.2.2-4 04251-731-2738 (Tolvaptan) – Adjudicated: Probable

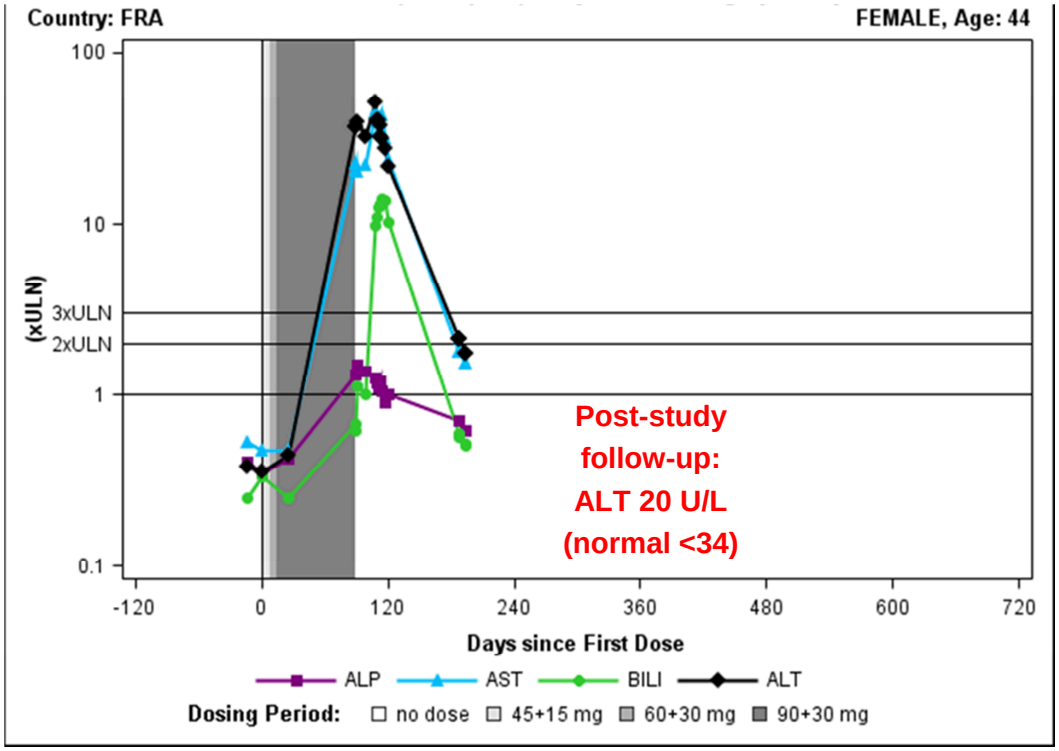


Figure 6.8.2.2-5 08271-468-4301 (Tolvaptan) – Adjudicated: Highly Likely

Evaluation of the baseline characteristics of adjudicated subjects does not appear to suggest a strong association with intrinsic (host) factors; subjects who were adjudicated for hepatic injury were older, more likely to be female, and more likely to be Asian than their non-adjudicated counterparts. Analyses of the association of hepatocellular injury with tolvaptan dose and extent of tolvaptan exposure in adjudicated subjects did not suggest a relationship. The mechanisms underlying tolvaptan-induced liver injury have not been determined. However, the prolonged latency to onset and the relatively prompt recurrence upon rechallenge support involvement of the adaptive immune system. No evidence of hepatotoxicity was observed in experimental animals treated with tolvaptan for up to 2 years.[60] There have been no new cases meeting Hy's laboratory criteria or Hy's Law in the 120-day safety update.

As of a cutoff date of 01 Feb 2013, the incidence of early-treated subjects in Trial 156-08-271 (on tolvaptan in Trial 156-04-251 and continuing on tolvaptan) experiencing an elevation in ALT (> 3x ULN, based on central plus local lab data; 4/555; 0.7%) is one-fifth that of the incidence in delayed-treated tolvaptan subjects (11/313; 3.5%). This outcome is not unexpected based on results from the pivotal Trial 156-04-251 that identified an 18-month window of susceptibility for hepatotoxicity from the time of treatment initiation. Notably, the rate of elevation in early-treated subjects (0.7%) does

not exceed the rate observed in the placebo arm of Trial 156-04-251 (5/484, 1.0%). The 5-fold increased risk of ALT elevation in delayed-treated versus early-treated subjects in Trial 156-08-271 is comparable to the 4.4-fold increased risk observed in tolvpatan versus placebo subjects in Trial 156-04-251. These data support that the rates of new ALT elevation beyond the 18-month period of susceptibility remain comparable to the placebo rate, even beyond 3 years of observation. Analysis of other open-label trials is still ongoing.

Without clear identification of a population at particular risk, or a better understanding of the mechanism of injury, the sponsor has addressed this risk with a boxed warning in the proposed label as well as a comprehensive risk mitigation strategy for all patients treated with tolvaptan. The mitigation strategy includes monthly monitoring, physician and patient training, and attestation of compliance with the program by both physicians and patients.

6.9 Worldwide Pharmacovigilance Data

Tolvaptan is marketed in the US, EU, Japan, and other regions. The most recent postmarketing data were reported in a periodic safety update report issued on 16 Jul 2012. Since the first marketing approval of tolvaptan (19 May 2009) through 31 Mar 2013, total postmarketing exposure to tolvaptan is estimated at approximately 9666.4 patient-years.

Since the last Periodic Safety Update Report was issued, covering the period 19 Nov 2011 through 18 May 2012, 1422 medically confirmed, unsolicited events and related solicited events were reported to the sponsor. These included 523 medically confirmed, serious, unlisted AEs from unsolicited cases and related solicited cases. The most common (≥ 10 cases) serious events were Cardiac Failure (19 cases), Pneumonia (11 cases), Altered State of Consciousness (11 cases), and Hyponatraemia (10 cases). Based on review of postmarketing cases, there appears to be no clear trend or pattern to suggest evidence of a new safety signal with tolvaptan relative to the TEAEs of special interest observed in the ADPKD program. No signal of tolvaptan-induced hepatotoxicity has been detected during the postmarketing experience to date for any currently approved indication.

6.10 Safety Conclusions

Extensive safety evaluation of tolvaptan and its therapeutic benefit support its use in ADPKD patients with appropriate patient guidance and monitoring to mitigate both common and uncommon observed and potential risks. Observed risks based on tolvaptan's mechanism of action include those arising from aquaresis (eg, polyuria,

pollakiuria, nocturia, thirst, dry mouth), dehydration, hypernatremia, and hyperuricemia/gout.

Blocking AVP in unaffected cells/nephrons leads to increased urine output and the most frequent aquaretic TEAEs of tolvaptan: Thirst, Polyuria, Nocturia, Pollakiuria, and Polydipsia. While aquaretic events did not contribute to significant patient morbidity over the 3 years of study in the pivotal placebo-controlled trial 156-04-251, they do represent adverse reactions (ADRs) most likely to limit a patient's ability to continue therapy long enough to provide substantial benefit. However, because these ADRs are related to the mechanism of action, they are well understood and controllable through careful maintenance of fluid balance through physician and patient education, and dose adjustment.

The most notable safety issue associated with chronic tolvaptan use, which was newly identified in the ADPKD pivotal Trial 156-04-251, is the potential for drug-induced liver injury (DILI). In the pivotal trial, there was an imbalance in the proportion of subjects with elevated transaminases (tolvaptan > placebo) that led to a blinded review of individual cases by an expert panel, which identified a total of 3 subjects in the ADPKD program who met "Hy's Law" criteria for potential increased risk of permanent and potentially life-threatening DILI (2 subjects from the pivotal trial and 1 subject from a supportive trial). Transaminase elevations in subjects treated with tolvaptan characteristically occurred within 3 to 14 months after trial medication initiation, were reversible (typically within 1 to 4 months), and did not lead to liver failure or permanent liver injury or dysfunction. The sponsor believes appropriate patient monitoring and management should be implemented to mitigate this potential risk in the ADPKD population.

In summary, the most prevalent adverse drug reactions (ADRs) associated with tolvaptan (aquaresis, dehydration, hypernatremia, and hyperuricemia/gout) were balanced by reductions in risks of ADPKD outcomes related to kidney complications (refer to Section 5.9), including renal pain, urinary tract infection, hematuria, anemia, and nephrolithiasis. Overall, tolvaptan treatment slowed the rate of TKV growth and renal function decline, and reduced the risk of medically significant renal pain and dysfunction (refer to Section 5.6.3) in subjects with ADPKD. The potential risk of permanent or life--threatening hepatocellular injury should be evaluated in the context of the significant unmet medical need in ADPKD and the consequences of no treatment. Appropriate monitoring for evidence of hepatic injury coupled with timely intervention is expected to mitigate the potential for adverse outcomes resulting from hepatic injury. Signals for

other potential risks could not be attributed to tolvaptan therapy. However, appropriate monitoring for skin neoplasms and glaucoma should be considered.

7 Risk Management and Net Benefit

7.1 Risk Evaluation

Continuous suppression of the AVP V_2 receptor is necessary to inhibit cystogenesis and its sequelae in ADPKD. In patients with ADPKD, tolvaptan's aquaretic effects are not associated with significant morbidity, but do produce clinically appreciable symptoms like thirst, polyuria, and pollakiuria. These constrain adherence to therapy. The risk of dehydration due to inability to drink (eg, during concurrent illness) can be managed in ADPKD by drug interruption. Hypernatremia was seen more frequently in tolvaptan subjects, but was easily managed without sequelae, while potentially clinically significant hyponatremia occurred rarely and with a frequency comparable to the placebo group. The potential risks of tolvaptan's aquaretic effects can be managed by appropriate monitoring and fluid intake and may be mitigated by appropriate labeling and instruction.

Increased uric acid and gout were also expected side-effects of tolvaptan, but did not appear to result in any significant sequelae other than the increased need for use of allopurinol in those who became symptomatic. A potential signal for increased reports of glaucoma in those receiving tolvaptan observed previously was again seen in the ADPKD program. Although a definitive causal association with tolvaptan cannot be made, monitoring should be considered.

Imbalance in neoplasms, particularly basal cell carcinoma, is a new finding which contrasts with nonclinical toxicology. Therefore, monitoring consisting of skin examinations should be considered.

Evidence for idiosyncratic DILI in ADPKD is a significant new finding. In the pivotal trial, transaminase or bilirubin elevations or TEAEs potentially associated with liver injury were seen in 46 subjects (35/961 tolvaptan and 11/483 placebo), characteristically appearing during the 3- to 14 month period after treatment initiation. In all subjects with ALT > 3 x ULN, laboratory abnormalities resolved to < 3 x ULN during continued therapy or after cessation of treatment. The dataset for this program has permitted characterization of the time to onset and offset of transaminase elevation. Hepatic events adjudicated in blinded review as having > 50% likelihood of attribution to treatment were seen in 17 subjects (16 tolvaptan and 1 placebo). Of these, 2/961 (0.21%) tolvaptan

subjects met “Hy’s Law” criteria for potential DILI. Exposure during other ADPKD trials added one additional “Hy’s Law” case from an open-label trial.

Based on the observed incidence of “Hy’s Law” cases, an estimate for the risk of progressive DILI leading to end-stage hepatic disease (ESHD) is 1:3000 subjects exposed throughout the 3 to 14 month period of susceptibility (3 cases/~1000 exposed × 10 = 1:3000).[62] While it is likely the risk of DILI and ESHD cannot be completely eliminated, the apparently reversible pattern with tolvaptan suggests that a proposed education and monthly monitoring program may substantially mitigate this risk.

Aquaretic symptoms led to withdrawal from further trial participation in approximately 8% of tolvaptan subjects, most of these occurring in the first 4 months. One percent of subjects withdrew due to hepatic AEs or elevations in liver transaminase levels. These 2 categories accounted for the vast majority of excess withdrawals due to TEAEs in the tolvaptan group. Adherence to effective therapy should be addressed through improved education and physician training.

7.1.1 Risk Evaluation and Mitigation Strategy

Otsuka proposes to address this risk through labeling and a Risk Evaluation and Mitigation Strategy (REMS), which is under active discussion with the FDA. The REMS will ensure that access to tolvaptan is limited to prescribers, pharmacies, and patients who are educated on the risk of hepatotoxicity of tolvaptan and who agree to adhere to a schedule of monthly monitoring of hepatic labs as a condition of safe use. Attestation by physicians of compliance with this program is a proposed element of the REMS.

Otsuka will develop communication tools such as Dear Healthcare Provider Letter, Medication Guide, Tolvaptan ADPKD REMS informational website and REMS brochure. All patients must be registered into the REMS in order to receive tolvaptan, which will be dependent on meeting hepatic laboratory monitoring requirements. In addition, all hepatic events that lead to tolvaptan discontinuation will be comprehensively followed up by Otsuka Clinical Safety & Pharmacovigilance, including with independent adjudication of suspect cases of DILI. The design of the REMS will allow reinforcement of the need for hepatic monitoring and ensure that patients will not receive tolvaptan if conditions of safe use are not met.

8 Risk-Benefit Analysis

Available natural history data suggests certain covariates, including family history/genotype, gender, age, TKV, albuminuria, and hypertension, may predict rate of

disease progression. This is supported by the differences in average rates of TKV growth and renal function decline seen in the placebo subgroups for the pivotal tolvaptan trial. Each patient should be informed of the potential benefits and risks of tolvaptan therapy in the context of the best available information and his/her own individual prognosis.

The totality of evidence from the tolvaptan ADPKD program indicates that tolvaptan slows the progression of the kidney-related complications of ADPKD, including cyst growth and renal function decline, and improves related clinical symptoms that are markers of ADPKD disease progression, eg, renal pain events requiring intervention.

Observed risks include those arising from aquaresis, dehydration, electrolyte abnormalities, and gout. Over 3 years of study, these risks did not rise to produce significant morbidity and no mortality was observed. More significant events related to liver toxicity, glaucoma, and skin cancers were also observed; however, for glaucoma and skin cancer the causal relationship to tolvaptan remains uncertain.

These adverse reactions were balanced by reductions in risks of ADPKD kidney complications, including renal pain, infection, hemorrhage, anemia, and nephrolithiasis. These reductions were associated with decreased rates of clinic visits, hospitalizations, procedures, and lost productivity.

The most significant potential for benefit is delay of renal failure, currently occurring in at least 50% of patients by the 6th decade of life.[19] The most significant potential for risk is drug-induced liver injury leading to liver failure, which, while not observed, may occur in 1 in 3000 patients based on historical risk estimates.

The sponsor believes that in ADPKD there is a significant unmet medical need for therapies effective in delaying serious complications of disease, such as ESRD; therefore, the risk of hepatocellular injury should be evaluated in this context. The sponsor believes that the clinical benefit conferred to a majority of patients including all subgroups tested (eg, reduced renal pain and slowing of renal function decline) outweighs the risk of idiosyncratic hepatocellular injury. In the ADPKD population, appropriate patient monitoring and management should be implemented to mitigate the potential risk of progression to irreversible liver injury.

The goal of therapy is to positively affect patients' long-term prognosis. If patients can be successfully managed through early treatment (the first 4 months during which most aquaretic withdrawals are observed) and through the 18-month period of susceptibility (during which tolvaptan appeared to increase cases of serious and attributable liver injury), then short-term benefits (renal pain and other ADPKD outcomes which lead to increased hospitalizations during the 3 years of the pivotal trial) and long-term benefits

(decreased rate of kidney cyst growth and loss of renal function) can accrue over the long term.

The potential for long-term benefits including a delay in ESRD outweigh these potential risks. Tolvaptan therapy was associated with a clinically manageable safety profile, supporting a net benefit for the chronic treatment of patients at risk for rapidly progressing ADPKD.

9 Reference List

1 U S Renal Data System, USRDS 2012 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2012.

2 The Japanese Society of Nephrology Project for Developing the Japanese Equation for Estimating GRF. Japanese Equations for Estimating GRF. Proceedings of the 51st Annual Meeting of the Japanese Society of Nephrology, 2008.

3 Chapman AB, Guay-Woodford LM, Grantham JJ, Torres VE, Bae KT, Baumgarten BA, et al. Renal structure in early autosomal-dominant polycystic kidney disease (ADPKD): The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) cohort. Kidney Int. 2003 Sep;64(3):1035-45.

4 Klahr S, Breyer JA, Beck GJ, Dennis VW, Hartman JA, Roth D, et al. Dietary protein restriction, blood pressure control, and the progression of polycystic kidney disease. Modification of Diet in Renal Disease Study Group. J Am Soc Nephrol. 1995 Jun;5(12):2037-47. Erratum in J Am Soc Nephrol. 1995 Oct;6(4):1318.

5 Otsuka Pharmaceutical Development & Commercialization, Inc. Analytic validation of MRI measurement of change in total kidney volume (dTKV) as a response marker for tolvaptan interventional trials. Document no. 1165142-000-00. Otsuka report, issued 26 October 2012.

6 Apperloo AJ, de Zeeuw D, De Jong PE. A short-term antihyertensive treatment-induced fall in glomerular filtration rate predicts long-term stability of renal function. Kidney International 1997; 51: 793-797.

7 Rubin, D. Multiple imputation for nonresponse in surveys. John Wiley & Sons, New York, 1987.

8 Lentine KL, Xiao H, Machnicki G, Gheorghian A, Schnitzler MA. Renal function and healthcare costs in patients with polycystic kidney disease. Clin J Am Soc Nephrol. 2010 Aug;5(8):1471-9.

9 Wallace DP. Cyclic AMP-mediated cyst expansion. Biochim Biophys Acta. 2011 Oct;1812(10):1291-300.

[10] Torres VE, Wang X, Qian Q, Somlo S, Harris PC, Gattone VH 2nd. Effective treatment of an orthologous model of autosomal dominant polycystic kidney disease. Nat Med. 2004 Apr;10(4):363-4.

[11] Belibi FA, Reif G, Wallace DP, Yamaguchi T, Olsen L, Li H, et al. Cyclic AMP promotes growth and secretion in human polycystic kidney epithelial cells. Kidney Int. 2004 Sep;66(3):964-73.

[12] Wang X, Wu Y, Ward CJ, Harris PC, Torres VE. Vasopressin directly regulates cyst growth in polycystic kidney disease. J Am Soc Nephrol. 2008 Jan;19(1):102-8.

[13] Levey AS, Gassman JJ, Hall PM, Walker WG. Assessing the progression of renal disease in clinical studies: effects of duration of follow-up and regression to the mean. Modification of Diet in Renal Disease (MDRD) Study Group. J Am Soc Nephrol. 1991 Mar;1(9):1087-94.

[14] Kasiske B, Cosio FG, Beto J, Bolton K, Chavers BM, Grimm R Jr, et al.; National Kidney Foundation. Clinical practice guidelines for managing dyslipidemias in kidney transplant patients: a report from the Managing Dyslipidemias in Chronic Kidney Disease Work Group of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative. Am J Transplant. 2004;4 Suppl 7:13-53.

[15] Weir MR. Acute fall in glomerular filtration rate with renin-angiotensin system inhibition: a biomeasure of therapeutic success? Kidney Int. 2011 Aug;80(3):235-7.

[16] Hansen HP, Rossing P, Tarnow L, Nielsen FS, Jensen BR, Parving HH. Increased glomerular filtration rate after withdrawal of long-term antihypertensive treatment in diabetic nephropathy. Kidney Int. 1995 Jun;47(6):1726-31.

[17] Holtkamp FA, de Zeeuw D, Thomas MC, Cooper ME, de Graeff PA, Hillege HJ, et al. An acute fall in estimated glomerular filtration rate during treatment with losartan predicts a slower decrease in long-term renal function. Kidney International 2011; 80 (3): 282-7.

[18] Grantham JJ, Chapman AB, Torres VE. Volume progression in autosomal dominant polycystic kidney disease: the major factor in determining clinical outcomes. Clin J Amer Soc Nephrol. 2006 Jan;1(1):148-57.

[19] Hateboer N, v Dijk MA, Bogdanova N, Coto E, Saggar-Malik AK, San Millan JL, Torra R, Breuning M, Ravine D. Comparison of phenotypes of polycystic kidney disease types 1 and 2. European PKD1-PKD2 Study Group. Lancet. 1999 Jan 9;353(9147):103-7.

[20] NIH Publication No. 08-4008. Polycystic Kidney Disease. National Kidney and Urologic Diseases Information Clearinghouse, Bethesda, MD. November 2007 (last updated 02 Sep 2010) http://kidney.niddk.nih.gov/kudiseases/pubs/polycystic/#dominant . Accessed 04 Apr 2013.

[21] Grantham JJ, Mulamalla S, Swenson-Fields KI. Why kidneys fail in autosomal dominant polycystic kidney disease. Nat Rev Nephrol. 2011 Aug 23;7(10):556-66.

[22] Grantham JJ, Mulamalla S, Grantham CJ, Wallace DP, Cook LT, Wetzel LH, et al. Detected renal cysts are tips of the iceberg in adults with ADPKD. Clin J Am Soc Nephrol. 2012 Jul;7(7):1087-93.

[23] Grantham JJ. Clinical practice. Autosomal dominant polycystic kidney disease. N Engl J Med. 2008;359:1477-85.

[24] Torres VE. Cyclic AMP, at the hub of the cystic cycle. Kidney Int. 2004 Sep;66(3):1283-5.

[25] Wang X, Gattone V 2nd, Harris PC, Torres VE. Effectiveness of vasopressin V2 receptor antagonists OPC-31260 and OPC-41061 on polycystic kidney disease development in the PCK rat. J Am Soc Nephrol. 2005 Apr;16(4):846-51.

[26] Yamaguchi T, Pelling JC, Ramaswamy NT, Eppler JW, Wallace DP, Nagao S, et al. cAMP stimulates the in vitro proliferation of renal cyst epithelial cells by activating the extracellular signal-regulated kinase pathway. Kidney Int. 2000 Apr;57(4):1460-71.

[27] Gabow PA. Definition and natural history of autosomal dominant polycystic kidney disease. In: Watson ML, Torres VE, editors. Polycystic kidney disease. New York: Oxford University Press; 1996.

[28] National Institute of Diabetes and Digestive and Kidney Diseases [homepage on the Internet]. Bethesda: National Institutes of Health; [updated 2004 Apr 13; cited 2012 May 30] Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP). Available from: http://www.niddk.nih.gov/patient/crisp/rp-crisp.htm.

[29] Iglesias CG, Torres VE, Offord KP, Holley KE, Beard CM, Kurland LT. Epidemiology of adult polycystic kidney disease, Olmsted County, Minnesota: 1935-1980. Am J Kidney Dis. 1983;2:630-9.

[30] Torres VE, Harris JC. Autosomal dominant polycystic kidney disease: the last 3 years. Kidney Intl. too9:76:149-68.

[31] Halvorson CR, Bremmer MS, Jacobs SC. Polycystic kidney disease: inheritance, pathophysiology, prognosis, and treatment. Int J Nephrol Renovasc Dis. 2010;3:69-83.

[32] Szklo M, Nieto FJ. Measuring disease occurrence. In: Epidemiology: Beyond the Basics. Gaithersburg, MD: Aspen Publishers; 2000. p 47-76.

[33] Perrone RD, Ruthazer R, Terrin NC. Survival after end-stage renal disease in autosomal dominant polycystic kidney disease: contribution of extrarenal complications to mortality. Am J Kidney Dis. 2001 Oct;38(4):777-84.

[34] Willey C. Autosomal dominant polycystic kidney disease. The epidemiologic evidence for orphan drug status in Europe. EpiSource Consultants, LLC. Epidemiology report, issued 12 October 2012.

[35] Higashihara E, Nutahara K, Kojima M, Tamakoshi A, Yoshiyuki O, Sakai H, et al. Prevalence and renal prognosis of diagnosed autosomal dominant polycystic kidney disease in Japan. Nephron 1998; 80: 421-7.

[36] Reed BY, McFann K, Bekheirnia MR, Nobkhthaghighi N, Masoumi A, Johnson AM, et al. Variation in age at ESRD in autosomal dominant polycystic kidney disease. Am J Kidney Dis 2008; 51(2): 173-83.

[37] Yamamura Y, Nakamura S, Itoh S, Hirano T, Onogawa T, Yamashita T, et al. OPC-41061, a highly potent human vasopressin V2-receptor antagonist: pharmacological profile and aquaretic effect by single and multiple oral dosing in rats. J Pharmacol Exp Ther. 1998 Dec;287(3):860-7.

[38] Gattone V. OPC41061 in the treatment of polycystic disease in pcy mice. Otsuka Report No. 018373, 2007.

[39] Torres V. OPC-41061 treatment of polycystic kidney disease Part I: effects of OPC-41061 in PCK rats. Otsuka Report No. 016916, 2005.

[40] Torres V. OPC-41061 treatment of polycystic kidney disease Part II: effects of OPC-41061 in Pkd2-/WS25 mice. Otsuka Report No. 017968, 2005.

[41] Wang S, Gattone VH, Somlo S, Harris PC, Torres, VE. Effectiveness of OPC-41061 on polycystic kidney disease development in Pkd2WS25/- [Abstract]. J Am Soc Nephrol. 2005; 16: 361A.

[42] Nagao S, Nishii K, Katsuyama M, Kurahashi H, Marunouchi T, TakahashiH, Wallace DP: Increased water intake decreases progression of polycystic kidney disease in the PCK rat. J Am Soc Nephrol. 2006; 17:2220–7.

[43] Reif GA, Yamaguchi T, Nivens E, Fujiki H, Pinto CS, Wallace DP. Tolvaptan inhibits ERK-dependent cell proliferation, Cl- secretion, and in vitro cyst growth of human ADPKD cells stimulated by vasopressin. Amer J Physiol Renal Physiol. 2011 Nov;301(5):F1005-13.

[44] Micheel CM, Ball JR, editors. Evaluation of biomarkers and surrogate endpoints in chronic disease. Washington, DC: National Academies Press; 2010.

[45] Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med 2012; 367 (25): 2407-18.

[46] Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.

[47] Levey AS, Cores J, Balk E, Kausz AT, Levin A, Steffes MW, et al. MD National Kidney Foundation Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. Annals of Internal Medicine. 2003;139(2):137-147.

[48] Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999;130(6):461-70.

[49] Kistler AD, Poster D, Krauer F, Weishaupt D, Raina S, Senn O, et al. Increases in kidney volume in autosomal dominant polycystic kidney disease can be detected within 6 months. Kidney Int. 2009;75:235-41.

[50] National Institute of Diabetes and Digestive and Kidney Diseases [homepage on the Internet]. Bethesda: National Institutes of Health; [updated 2006 Jan 11; cited 2012 May 30] HALT PKD: A Clinical Research Study to HALT Progression of Polycystic Kidney Disease. Available from: www.niddk.nih.gov/fund/divisions/kuh/kdcsi/halt-pkd.pdf.

[51] Lefante JJ. The power to detect differences in average rates of change in longitudinal studies. Stat Med. 1990 Apr;9(4):437-46.

[52] Therneau TM, Grambsch PM. Modeling Survival Data, Extending the Cox Model: Springer; 2000.

[53] Irazabal MV, Torres VE, Hogan MC, Glockner J, King BF, Ofstie TG, et al. Short-term effects of tolvaptan on renal function and volume in patients with autosomal dominant polycystic kidney disease. Kidney Int. 2011 Aug;80(3):295-301.

[54] Bankir L. Antidiuretic action of vasopressin: Quantitative aspects and interaction between V1a and V2 receptor-mediated effects. Cardiovasc. Res. 2001;51:372-390

[55] Bardoux P, Bichet DG, Martin H, Gallois Y, Marre M, Arthus MF, et al. Vasopressin increases urinary excretion in rats and humans: involvement of V2 receptors and the renin-angiotensin system. Nephrol Dial Transpant 2003;18:497-506.

[56] Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro III AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009 May 5;150(9):604-12. Erratum in: Ann Intern Med. 2011 Sep 20;155(6):408.

[57] Higashihara E, Torres VE, Chapman AB, Grantham JJ, Bae K, Watnick TJ, et al. Tolvaptan in autosomal dominant polycystic kidney disease: three years' experience. Clin J Am Soc Nephrol. 2011 Oct;6(10):2499-507.

[58] Chapman AB, Bost JE, Torres VE, Guay-Woodford L, Bae KT, Landsittel D, Li J, et al. Kidney volume and functional outcomes in autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol. 2012 Mar;7(3):479-86.

[59] Gabow PA, Johnson AM, Kaehny WD, Kimberling WJ, Lezotte DC, Duley IT, et al. Factors affecting the progression of renal disease in autosomal-dominant polycystic kidney disease. Kidney Int. 1992; 41: 1311-19.

[60] Otsuka Pharmaceutical Development & Commercialization. OPC-41061 Investigator's Drug Brochure, edition 18. Otsuka Report, issued 16 Jul 2012.

[61] U.S. Food and Drug Administration. Guidance for Industry. Drug-induced liver injury: premarketing clinical evaluation [report on the internet]. 2009 Jul [cited 2012 Oct 10];[about 23 p.]. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

[62] Watkins PB. A review of the liver safety database for tolvaptan in the treatment of autosomal dominant polycystic kidney disease. Adjudication Committee Report, issued 28 Oct 2012.

10 Appendices

10.1 Table of Studies for the Tolvaptan ADPKD Clinical Program

Pivotal and Supportive Tolvaptan Trials in ADPKD							
Protocol Number (Trial Location) Phase	**Trial Objective(s)**	**Trial Design and Type of Control**	**Treatment Groups**	**Number of Subjects Enrolled/ Treated**	**Main Subject Eligibility Criteria**	**Treatment Duration**	**Trial Status; Data Cutoff Date, if applicable**
Pivotal Trial							
156-04-251 (Multinational) Phase 3	Long-term efficacy and safety, as well as PK, PD, and exploratory measures	Randomized, double-blind, placebo-controlled, parallel-arm	45 AM/15 PM mg 60/30 mg 90/30 mg (titrated) Placebo split-dose (titrated)	961/961 484/483	ADPKD subjects 18 to 50 years inclusive (20 to 50 years in Japan) and eCrCLCG ≥ 60 mL/min and TKV ≥ 750 mL	Up to 36 months	Completed
Supportive Long-term Trials							
156-08-271 (Multinational) Phase 3b	Demonstrate if tolvaptan modifies ADPKD progression	Open-label extension	45 AM /15 PM mg 60/30 mg 90/30 mg (titrated)	904/904	ADPKD subjects who had completed a phase 1, 2, or 3 tolvaptan trial, including Trial 156-04-251, and had eGFRMDRD ≥ 30 mL/min/ 1.73 m^2	Minimum of 24 months	Ongoing; 1 Feb 2013

Pivotal and Supportive Tolvaptan Trials in ADPKD							
Protocol Number (Trial Location) Phase	**Trial Objective(s)**	**Trial Design and Type of Control**	**Treatment Groups**	**Number of Subjects Enrolled/ Treated**	**Main Subject Eligibility Criteria**	**Treatment Duration**	**Trial Status; Data Cutoff Date, if applicable**
156-10-003 (Japan) Phase 3	Long-term safety and efficacy	Open-label extension	45 AM /15 PM mg 60/30 mg 90/30 mg (titrated)	115/108	ADPKD subjects in Japan who completed Trial 156-04-251	Until manufacturing and marketing approval is granted in Japan	Ongoing; 1 Feb 2013
156-09-003 (Japan) Phase 3	Long-term safety and efficacy	Open-label extension	15 AM /15 PM mg	13/13	ADPKD subjects who completed Trial 156-05-002 or withdrew for reasons other than AEs	Until manufacturing and marketing approval is granted in Japan	Ongoing; 1 Feb 2013
156-04-250 (United States) Phase 2	Long-term safety, tolerability, and pilot efficacy of split-dose regimens ranging from 30 to 120 mg/day	Open-label extension, with optional 1-year extension after an off-treatment period	Titration: 15 AM /15 PM mg; 30/15 mg; 45/15 mg; 60/30 mg; 90/30 mg Fixed Dose and Optional Extension: 45/15 mg 60/30 mg	Titration: 46/46 Fixed Dose: 45/15 mg: 22/22 60/30 mg: 24/24 Optional Extension: 45/15 mg: 17/17 60/30 mg: 18/18	ADPKD subjects who previously participated in Trial 156-04-248 or Trial 156-04-249	Titration: 2 to 4 weeks (7 days per regimen), then subject's MTD to Month 2 Fixed Dose: up to Month 36 Optional Extension: 12 months	Completed

Pivotal and Supportive Tolvaptan Trials in ADPKD							
Protocol Number (Trial Location) Phase	**Trial Objective(s)**	**Trial Design and Type of Control**	**Treatment Groups**	**Number of Subjects Enrolled/ Treated**	**Main Subject Eligibility Criteria**	**Treatment Duration**	**Trial Status; Data Cutoff Date, if applicable**
156-05-002 (Japan) Phase 2	Long-term safety and efficacy	Open-label extension	15 AM /15 PM mg	17/17	ADPKD subjects who previously completed Trial 156-04-001	Up to 36 months	Completed
Supportive Short-term Trials							
156-04-248 (United States) Phase 2	Single-dose safety, tolerability, PK, and PD	Randomized, double-blind, placebo-controlled, ascending dose	15 mg 30 mg 60 mg 120 mg Placebo	8/8 3/3	ADPKD subjects 18 to 55 years (inclusive)	Single doses with 72-hour washout between doses	Completed
156-04-249 (United States) Phase 2	Safety, tolerability, PK and PD of multiple doses and regimens	Randomized, double-blind, parallel-arm	15 AM /15 PM mg 30 mg /placebo 30/15 mg 30/30 mg	9/9 9/9 9/9 10/10	ADPKD subjects 18 to 60 years (inclusive)	5 days	Completed
156-04-001 (Japan) Phase 2	Safety, PK, and PD	Randomized, open-label	Group I: Period 1: 15 mg Period 2: 30 mg Period 3: 15 AM /15 PM mg split-dose Group II: Period 1: 15 mg Period 2: 30 mg Period 3: 30 mg	9/9 9/9	ADPKD subjects 20 to 60 years (inclusive)	Periods 1 and 2: single dose; Period 3: 5 days; 1- to 3-week washout between treatments (depending on body weight)	Completed

Pivotal and Supportive Tolvaptan Trials in ADPKD							
Protocol Number (Trial Location) Phase	**Trial Objective(s)**	**Trial Design and Type of Control**	**Treatment Groups**	**Number of Subjects Enrolled/ Treated**	**Main Subject Eligibility Criteria**	**Treatment Duration**	**Trial Status; Data Cutoff Date, if applicable**
156-09-285 (United States) Phase 2	Compare PK, PD, and tolerability of multiple doses of tolvaptan administered as either IR tablets or MR capsules	Randomized, double-blind, placebo-masked, multiple dose, parallel-group, with 3-period crossover for each of 2 separate groups	Group 1: IR 90 AM /30 PM mg split-dose; MR 20 mg QD; MR 20 AM /20 PM mg split-dose; MR 60 mg QD; MR 120 mg QD Group 2: MR 20 mg QD; MR 20/20 mg split-dose; MR 60 mg QD	Total: 25/25 IR 90/30 mg split-dose: 12/12 MR 20 mg QD: 17/17 MR 20/20 mg split-dose: 17/17 MR 60 mg QD: 17/17 MR 120 mg QD: 12/12	Subjects with ADPKD 18 to 50 years (inclusive) with $eGFR_{MDRD}$ > 60 mL/min/ 1.73 m^2 and BMI 19 to 35 kg/m^2 (inclusive)	21 days (7 days for each regimen)	Completed
156-09-290 (United States) Phase 2	Compare efficacy, safety, and tolerability of IR and MR formulations	Randomized, double-blind, placebo-controlled, placebo-masked, parallel-group	IR 60 AM /30 PM mg split-dose MR 50 mg QD MR 80 mg QD Matched placebo	20/18 Total planned enrollment: 180	ADPKD subjects 18 to 50 years (inclusive) with $eGFR_{CKD-EPI}$ > 45 mL/ min/1.73 m^2, height-adjusted TKV, and BMI 19 to 35 kg/m^2 (inclusive)	8 weeks	Ongoing; 1 Feb 2013

Pivotal and Supportive Tolvaptan Trials in ADPKD							
Protocol Number (Trial Location) Phase	**Trial Objective(s)**	**Trial Design and Type of Control**	**Treatment Groups**	**Number of Subjects Enrolled/ Treated**	**Main Subject Eligibility Criteria**	**Treatment Duration**	**Trial Status; Data Cutoff Date, if applicable**
Supportive Short-term Trials in ADPKD and non-ADPKD Subjects With Varying Degrees of Renal Function							
156-06-260 (United States) Phase 1	Effect of multiple doses on renal function	Open-label, multiple dose	45 AM /15 PM mg Group A1: $eCrCL_{CG} \geq$ 60 mL/min & normal BP Group A2: $eCrCL_{CG} \geq$ 60 mL/min & high BP Group B: $eCrCL_{CG} \geq$ 45 to < 60 mL/min Group C: $eCrCL_{CG} \geq$ 30 to < 45 mL/min	 6/6 6/6 5/5 3/3	Subjects with ADPKD 18 to 60 years (inclusive) with varying degrees of renal function and BMI 19 to 32 kg/m^2	8 days (only am dose on Day 8)	Completed

Pivotal and Supportive Tolvaptan Trials in ADPKD							
Protocol Number (Trial Location) Phase	**Trial Objective(s)**	**Trial Design and Type of Control**	**Treatment Groups**	**Number of Subjects Enrolled/ Treated**	**Main Subject Eligibility Criteria**	**Treatment Duration**	**Trial Status; Data Cutoff Date, if applicable**
156-09-284 (Netherlands) Phase 2a	Effect of maximally tolerated doses at steady state on renal function; effects on urine volume, FWC, and TKV; and plasma concen-trations	Open-label, multiple dose	45 AM /15 PM mg 60/30 mg 90/30 mg (titrated) Group A: $eGFR_{MDRD}$ > 60 mL/min/1.73 m2 Group B: $eGFR_{MDRD}$ 60 to 30 mL/min/1.73 m2 Group C: $eGFR_{MDRD}$ < 30 mL/min/1.73 m2	 10/10 10/10 9/9	Subjects with ADPKD 18 to 70 years (inclusive) with varying degrees of renal function and BMI ≤ 35 kg/m^2	21 days (stepwise titration for 7 days at each split-dose as tolerated)	Completed
156-09-282 (United States) Phase 1	Effects of renal impairment on PK and PD of tolvaptan (60 mg), and safety	Open-label, parallel-group	60 mg CrCL < 30 mL/min CrCL 30 to 60 mL/min CrCL > 60 mL/min	 12/12 12/12 13/13	Non-ADPKD subjects ≥ 18 years with varying degrees of renal function (otherwise healthy) and BMI ≤ 35 kg/m^2	Single dose	Completed

Pivotal and Supportive Tolvaptan Trials in ADPKD							
Protocol Number (Trial Location) Phase	**Trial Objective(s)**	**Trial Design and Type of Control**	**Treatment Groups**	**Number of Subjects Enrolled/ Treated**	**Main Subject Eligibility Criteria**	**Treatment Duration**	**Trial Status; Data Cutoff Date, if applicable**
Supportive Healthy Subject Trials							
156-07-262 (United States) Phase 1	Relative BA of 3 MR capsule formulations of tolvaptan compared with the IR tablet formulation, and effect on urine osmolality	Open-label, 4-period, randomized, incomplete crossover	60 mg MR-1 capsule 60 mg MR-2 capsule 60 mg MR-3 capsule IR 45 AM /15 PM mg split-dose	18/18	Healthy subjects 18 to 45 years (inclusive) and BMI 15 to 32 kg/m^2 (inclusive)	4 single doses; 96-hour washout between doses	Completed
156-11-295 (United States) Phase 1	Determine dose-strength equivalence of 3 x 30 mg tablets to 90 mg tablet and food effect of 90 mg tablet	Open-label, randomized crossover: Part 1: 3 x 30 mg vs 90 mg tablets Part 2: 90 mg with and without high-fat meal	3 x 30 mg or 90 mg 90 mg fed or fasted	44/44 14/14	Healthy subjects 18 to 45 years (inclusive) and BMI 19 to 32 kg/m^2 (inclusive)	Parts 1 and 2: single doses separated by 96-hour washout	Completed
156-KOA-0801 (Korea) Phase 1	Single-dose safety, tolerability, PK, and PD	Dose block-randomized, double-blind, placebo-controlled, single dose, dose-escalation	15 mg 30 mg 60 mg Placebo	7/6 26/24 6/6 10/10	Healthy male Korean subjects 20 to 45 years (inclusive), weight ≥ 50 kg and BMI 20 to 26 kg/m^2	Single dose	Completed

ADPKD = autosomal dominant polycystic kidney disease; AE = adverse event; BA = bioavailability; BMI = body mass index; CrCL = creatinine clearance; $eCrCL_{CG}$ = eCrCL using Cockcroft-Gault formula; eGFR = estimated glomerular filtration rate; $eGFR_{MDRD}$ = eGFR calculated using Modification of Diet in Renal Disease formula; FWC = free water clearance; IR = immediate release; MR = modified release; PD = pharmacodynamic; PK = pharmacokinetic; QD = once daily; TKV = total kidney volume; vs = versus.

10.2 Stages of Chronic Kidney Disease

Table 10.2-1 Stages of Chronic Kidney Disease

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with mild decreased GFR	60-89
3	Moderately decreased GFR	30-59
4	Severely decreased GFR	15-29
5	Kidney failure	<15 (or dialysis)

CVD = cardiovascular disease; GFR = glomerular filtration rate.

Chronic kidney disease is defined as either kidney damage or GFR < 60 mL/min/1.73 m^2 for ≥ 3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

Source: National Kidney Foundation. KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. Am J Kidney Dis 39:S1-S000, 2002 (suppl 1).

10.3 Summaries of Long-term Studies in ADPDK Subjects

10.3.1 Open-label Extension Trial 156-04-250

Design: Trial 156-04-250 was a multicenter, open-label trial to determine long-term safety, tolerability, and efficacy of split-dose oral regimens of tolvaptan in a range of 30 mg/day to 120 mg/day in subjects with ADPKD who had participated in the preceding clinical pharmacology trials 156-04-248 and 156-04-249. The primary objective of this trial was the evaluation of long-term safety. The secondary objectives of the trial were the evaluation of MTD regimens during a brief titration phase, and acquisition of long-term (3-year) pilot efficacy data after randomization to either 60 mg/day or 90 mg/day split-dose regimens followed by an extension of 1 year after an interruption in therapy.

Subjects were titrated in weekly intervals for the first 2 to 4 weeks among split doses of 30/15 mg (down-titration to 15/15 mg allowed for tolerability) to 90/30 mg, then maintained at their MTD through Month 2 (Titration Period). Following a determination of final long term dosing regimens based on objective criteria (trough spot urine osmolality, median tolerability) using data from the Titration Period, subjects were randomly allocated to a fixed high dose regimen (60/30 mg) and fixed low dose regimen (45/15 mg) for up to Month 36 (Fixed-dose Period). This was followed by an off-treatment period with the option to enter an Extension Period for an additional 12 months. This trial provided information used for dose selection in pivotal Trial 156-04-251.

This was the initial pilot trial, so efficacy data were preliminary, but because of the long-term nature of the trial it provides long-term data plus withdrawal effects resulting from on/off treatment periods.

Setting and Participants: A total of 47 subjects were screened. Of these, 46 entered the Titration Period and were treated with tolvaptan. All 46 of the subjects who entered the Titration Period were treated in the Fixed-dose Period and were included in the analysis of safety, including 22 subjects in the tolvaptan 45/15 mg group and 24 subjects in the tolvaptan 60/30 mg group. Of the 46 enrolled subjects, 39 subjects (84.8%) completed the trial through the Month 36 visit, with similar percentages of subjects in the 2 treatment groups completing the trial (18/22 or 81.8% tolvaptan 45/15 mg; 21/24 or 87.5% tolvaptan 60/30 mg). A total of 35 subjects entered the Extension Period, including 17 subjects in the tolvaptan 45/15 mg group and 18 subjects in the tolvaptan 60/30 mg group.

Demographic and baseline characteristics were generally similar between the 2 treatment groups in the All Subjects population. In both groups, most subjects were females (16/22, 72.7% in the tolvaptan 45/15 mg group and 18/24, 75.0% in the tolvaptan 60/30 mg group), and most were Caucasian (21/22, 95.5% and 24/24, 100.0%, respectively). The mean age was 39.3 years for the tolvaptan 45/15 mg group and 43.9 years for the tolvaptan 60/30 mg group. For the Extension Cohort, the demographic and baseline characteristics were similar to those for All Subjects.

Results: Trough urine osmolality prior to the first daily dose decreased from baseline throughout the course of the trial and was sustained through 36 months in both treatment groups. Mean urine osmolality for the total population was maintained at < 300 mOsm/kg throughout the 36 months of the trial. In the 38 subjects completing 36 months of therapy at either a 45/15 mg or 60/30 mg split dose, the mean (SD) change from baseline in TKV was 7.50% (11.0%), or approximately 2.2%/year. The annualized percent growth rate (mean [SD]) in TKV over the first 3 years was equivalent in the tolvaptan 45/15 mg group (2.220 [9.567] %/year) and the tolvaptan 60/30 mg group (2.209 [11.560] %/year).

After 4-6 months off treatment, 35 subjects completed a fourth year of treatment (ie, Extension Period). Despite a number of subjects in the higher randomly assigned dose group having decreased their dose to 45/15 mg, this trial showed a nominal advantage to higher dose regimen. TKV in those assigned to 45/15 mg grew by 15.7% (12.7%) while those assigned 60/30 mg grew 10.7% (10.4%).

On MMRM analysis, TKV decreased from baseline through Month 2 in the tolvaptan 60/30 mg group and through Month 12 in the tolvaptan 45/15 mg group. The mean (SD) negative renal volume growth of −0.96% (5.17%) in the tolvaptan 45/15 mg group and −1.26% (5.31%) in the tolvaptan 60/30 mg group after 2 months of dosing suggest an acute effect of tolvaptan. At Month 36, TKV increased from baseline in both groups, with a higher mean (SD) percent increase seen in the tolvaptan 45/15 mg group (9.86% [11.81%]) compared with the tolvaptan 60/30 mg group (5.06% [9.77%]; p = 0.0553). From the absolute TKV (SD) values of subjects entering the Extension Period, it is evident that TKV increased within the no-treatment period between Month 36 and the baseline of the Extension Period (Extension Day 1), which averaged 126.5 ± 19.0 days: 1612 (888) mL to 1720 (971) mL in the tolvaptan 45/15 mg group and 1638 (1162) mL to 1695 (1172) mL in the tolvaptan 60/30 mg group. At Extension Month 12, mean TKV (SD) increased from baseline in both groups: 1.42% (7.55%) in the tolvaptan 45/15 mg group and 2.22% (7.23%) in the tolvaptan 60/30 mg group. These results suggest the

benefits achieved during treatment largely persist after treatment withdrawal; however, rapid progression resumes. Treatment effects return upon reinitiation of tolvaptan.

Estimated GFR_{MDRD} (MMRM analysis) tended to decrease from baseline in both groups at each visit, with mean (SD) decreases seen at Month 36 in the tolvaptan 45/15 mg group (-4.43 [8.50] mL/min/1.73 m^2) and the tolvaptan 60/30 mg group (-2.90 [11.37] mL/min/1.73 m^2). Estimated renal function using $eCrCL_{CG}$ and reciprocal of serum creatinine showed similar results. Additional post-hoc analyses by $eGFR_{CKD\text{-}EPI}$ at Month 36 showed similar results: mean (SD) change of -7.59 (8.94) mL/min/1.73 m^2 in the tolvaptan 45/15 mg group and -5.61 (11.87) mL/min/1.73 m^2 in the tolvaptan 60/30 mg group.

From the absolute $eGFR_{MDRD}$ (SD) values of subjects entering the Extension Period, it is evident that $eGFR_{MDRD}$ did not substantially change within the no-treatment period between Month 36 and Extension Day 1: 60.19 (21.22) mL/min/1.73 m^2 to 59.31 (20.48) mL/min/1.73 m^2 in the tolvaptan 45/15 mg group and 53.25 (20.43) mL/min/1.73 m^2 to 54.75 (21.02) mL/min/1.73 m^2 in the tolvaptan 60/30 mg group. At Extension Month 12, mean $eGFR_{MDRD}$ (SD) increased from baseline in the tolvaptan 45/15 mg group (2.85 ± 10.26 mL/min/1.73 m^2) and decreased from baseline in the tolvaptan 60/30 mg group (-1.30 ± 7.71 mL/min/1.73 m^2), a non-significant difference between groups.

The mean (SD) annual rate of change from post-titration baseline in $eGFR_{MDRD}$ was −0.818 (13.218) mL/min/1.73 m^2/year in the tolvaptan 45/15 mg group and −0.987(3.401) mL/min/1.73 m^2/year in the tolvaptan 60/30 mg group.

The mean (SD) annual rate of change from post-titration baseline in $eCrCL_{CG}$ was −2.17 (14.45) mL/min/year in the tolvaptan 45/15 mg group and −0.450 (4.86) mL/min/year in the tolvaptan 60/30 mg group.

Few clinically relevant events were reported for the PKD Outcomes assessed.

Small increases from baseline were seen for mean serum creatinine concentrations at every postdose sampling time; this result was expected at the earliest visits as is expected for this population based on prior experience with tolvaptan. Mean sBP and dBP decreased slightly throughout the trial. However, assessments of BP were confounded by the fact that most subjects were taking agents acting on the renin-angiotensin system at baseline (37/46, 80.4%) and during the trial (40/46, 87.0%).

Conclusions: Over the course of 36 to 48 months of open-label tolvaptan treatment, the completion rate was high (39/46, 84.8% for the 36-month portion of the trial and 35/35, 100% for the 12-month Extension Period).

The efficacy results demonstrated the expected effects of AVP V_2 receptor suppression over the course of the trial. Trough urine osmolality and eGFR decreased from baseline in both treatment groups. A nominal treatment difference was seen for $eGFR_{MDRD}$ but no difference was observed for $eCrCL_{CG}$ or reciprocal serum creatinine, so no conclusions could be drawn. At Month 36, TKV increased from baseline in both groups,

with a higher mean (SD) percent increase seen in the tolvaptan 45/15 mg group (9.86% [11.81%]) compared with the tolvaptan 60/30 mg group 5.06% [9.77%]; nominal p = 0.0553). Data from the Extension Cohort showed that while there seems to have been an acceleration of renal volume growth during the period off treatment compared with the treatment periods (ie, 36-month portion of the trial and the Extension) there seemed to be little effect on renal function based on GFR. Therefore, the results on renal function suggested the need for controlled, long-term evaluation of tolvaptan in this population.

10.3.2 Open-label Extension Trial 156-05-002

Design: Trial 156-05-002 was a multicenter, 3-year, open-label trial to determine long-term safety and efficacy of repeated oral doses of tolvaptan as a split-dose regimen of 15/15 mg in subjects with ADPKD in Japan who had participated in the preceding clinical pharmacology Trial 156-04-001. The objectives of this trial were the evaluation of long-term safety and efficacy of tolvaptan. Trial 156-05-002 is similar to Trial 156-04-250, conducted in a population of Japanese subjects, but did not include a titration phase or optional 1 year treatment extension. A 30 mg/day dose was the highest dose that was acceptable to the Japanese Pharmaceuticals and Medical Devices Agency at the time the trial was initiated.

Setting and Participants: A total of 17 subjects were enrolled in the trial and received tolvaptan in Trial 156-05-002. There were 8 males and 9 females. Their mean (SD) age was 41.8 (8.6) years.

Results: Percent change results of TKV indicated mean negative cyst growth at Months 12 and 24, with positive cyst growth at Month 36. The mean percent change (SD) from baseline to the final visit in TKV and log-transformed TKV were -0.95% (8.91%) and -0.19% (1.24%), respectively. At Month 36, results were 0.37% (9.77%) for TKV and -0.01% (1.34%) for log-transformed TKV. Renal function was decreased from baseline at nearly all visits. There was a decrease from baseline to the final visit in mean (SD) eCrCLCG (−9.47% [13.82%]) and mean (SD) eGFR calculated using an equation developed by the Japanese Society for Nephrology[2] (−10.22% [13.31%]). At Month 36, results were −7.24% (14.17%) for $eCrCL_{CG}$ and −9.38% (13.21%) for eGFR. Conversely, cystatin C was increased from baseline in nearly all visits. This reflected a change (SD) of 8.50% (10.51%) at the final visit and 8.44% (10.45%) at Month 36.

Urine osmolality during the long-term administration of tolvaptan decreased at all visits compared with baseline (range of −111.0 to −160.3 mOsm/kg).

Conclusions:

- The renal function test values (eCrCLCG, eGFR, and cystatin C) worsened slightly in a few subjects but TKV showed no increase in most subjects.

10.3.3 Matched Historical Control Study 156-09-283

Design: This matched historical control study evaluated quantitative change in rate of renal growth and decline in renal function (ie, TKV % and eGFR decrease) in tolvaptan subjects from Trial 156-04-250 and Trial 156-05-002 versus standard-of-care subjects from the CRISP I[3] and MDRD[4] studies matched by gender, hypertension status, age, and baseline TKV or eGFR. Assessment visits for rate of change in TKV, eGFR, and presence of hypertension were Baseline, Year 1, Year 2, and Year 3.

Setting and Participants: Subjects selected from the CRISP I and MDRD cohorts were compared with the open-label ADPKD 156-04-250 and 156-05-002 trial group (N = 63 subjects) matched for gender and the following baseline variables: age ± 5 years; TKV by MRI ± 25%; serum creatinine ±15%; and hypertension status (present, not present). Subjects missing TKV could be considered for matching for evaluation of GFR and hypertension endpoints. In order to sufficiently analyze tolvaptan treatment effect over time, data for 63 subjects who were observed for a minimum of 1 year in the ADPKD 156-04-250 and 156-05-002 trials were matched with 63 to 126 subjects from the CRISP I and MDRD cohorts. Matching 2 standard-of-care subjects to each tolvaptan-treated subject, if possible, was expected to provide a more accurate estimate of the changes that occurred.

Results: The growth in TKV in completer tolvaptan subjects was 1.7% per year compared with 5.8% per year for control CRISP I subjects ($p < 0.0001$, ratio of geometric mean 0.96, 95% CI 0.95 to 0.97). This represents a 71% slower growth rate per year in tolvaptan subjects compared with control subjects. The effect of tolvaptan on kidney growth was confirmed by the MMRM sensitivity analysis. At each visit, average TKV trended upward. Over 3 years, mean TKV increased by 98 mL (5.3%, from 1635.2 to 1733.5 mL) in the completers tolvaptan group compared with 300 mL (19.0%, from 1422.4 to 1722.3 mL) in the matched-control group. These TKV changes were all significantly different between the groups (in favor of treatment with tolvaptan) at each yearly assessment ($p \leq 0.0197$).

The annualized slopes of $eGFR_{MDRD}$ were −0.71 mL/min/1.73 m^2/year in tolvaptan subjects (completers) and −2.1 mL/min/1.73 m^2/year in CRISP I (N = 66) and MDRD (N = 36) control subjects ($p = 0.0122$, linear mixed-model group difference 1.1, 95% CI 0.24 to 1.9) for a group difference of approximately 65%. MMRM analysis of $eGFR_{MDRD}$ showed a decline from a baseline mean of 61.6 to 55.9 mL/min/1.73 m^2 at Year 3 for completers tolvaptan subjects and from 61.9 to 55.4 mL/min/1.73 m^2 for matched controls. The difference between groups in the mean change at Year 3 in eGFR was 1.1 mL/min/1.73 m^2. The maximum difference was 2.9 mL/min/1.73 m^2 at Year 2, reflecting a high degree of variability of average eGFR over time and yielding nonsignificant differences between the groups at 1, 2, and 3 years. Results were similar at Month 36 for $eGFR_{CKD\text{-}EPI}$: treatment effect of 1.1 mL/min/1.73 m^2 (95% CI 4.4 to −2.2, $p = 0.5048$).

Mean decreases in sBP and dBP were observed in both tolvaptan subjects and control cohorts at Years 1, 2, and 3. The small number of tolvaptan subjects in the

nonhypertensive category at baseline precluded useful analyses of effects on hypertension progression.

Greater increases in TKV were correlated with greater declines in eGFR, with lesser changes for both occurring in the tolvaptan subjects ($r = -0.21$, $p < 0.01$).

Conclusions:

- The annual growth rate in TKV in tolvaptan subjects who completed 3 years of treatment was significantly lower compared with control subjects.
- The annual decreases in eGFR in tolvaptan subjects who completed 3 years of treatment was significantly lower compared with control subjects for a group difference of approximately 65%.
- The slopes for TKV and eGFR were significantly and negatively correlated. Greater increases in TKV were correlated with greater declines in eGFR, with lower changes for both occurring in the tolvaptan subjects than control subjects.

10.4 Sensitivity Analyses for the First Three Endpoints of Trial 156-04-251

10.4.1 Sensitivity Analyses of the Primary Endpoint - Total Kidney Volume Slope

10.4.1.1 MMRM Analysis for Non-linearity

In addition to the primary analysis provided in Section 5.5.2, a prospectively defined MMRM analysis was applied to the repeated measures of change from baseline in TKV (based on logarithm transformed data) as a sensitivity analysis. While the primary analysis relied on the linearity of the TKV slope, MMRM analysis accounts for potential nonlinearity in the percent change in TKV over time.

The least squares (LS) mean difference of the 2 treatment groups at Year 3 under the MMRM was used to estimate the treatment effect at Year 3. The MMRM included stratification factors (hypertensive status, kidney volume status, and creatinine clearance status at baseline and by geographic regions), visit, treatment, and treatment visit interaction as class variables and baseline kidney volume and baseline kidney volume-visit interaction as the covariates. The observed cases (OC) dataset within the double-blind treatment period (within 14 days of the subject's last dose) was used in this MMRM analysis.

Consistent with the primary analysis, the least squares mean TKV growth at Month 36 for tolvaptan (9.56%) was halved relative to placebo (18.75%), for a treatment group difference of −9.19% (95% CI −11.1 to −7.32, $p < 0.0001$; Figure 10.4.1.1-1). Statistically significant differences favoring tolvaptan were also observed at Month 12 and Month 24 (each, $p < 0.0001$).

The effect of tolvaptan in the pivotal trial was greatest in the first year, representing negative TKV growth on tolvaptan (−1.65%) compared with positive growth on placebo (4.62%), for a treatment effect of −6.27% ($p < 0.0001$). During the second and third years, kidney enlargement progressed in both groups; this progression was significantly slower in tolvaptan subjects compared with placebo subjects (2.93% vs 11.10% for a treatment effect of −8.17% by Month 24 and 9.56% vs 18.75% for a treatment effect of −9.19% by Month 36; each, $p < 0.0001$). The effects of tolvaptan persisted into the second and third year of therapy, with a year-to-year accrual of effect over time, leading to continued incremental separation from placebo over the entire 3-year duration of therapy. This incremental treatment effect for reduction in the increase in TKV during the second year was −1.92% ($p < 0.0001$) and during the third year was −1.78% ($p = 0.0005$).

An acute effect on TKV was not expected at the outset of the pivotal trial 156-04-251. In retrospect, the early data from a phase 2, open label trial 156-04-250, which started just prior to the pivotal trial, supported such an effect at its 2-month time point, but the overall change during the first year of treatment indicated little change (See Section 5.13). Once recognized, this acute effect was also discovered in other trials: during a post-hoc evaluation of TKV at 8 days (−1.9%) in Trial 156-06-260 and in a prospective 3 week time point (−3.7%) in Trial 156-09-284 (Section 4.2.2.2).

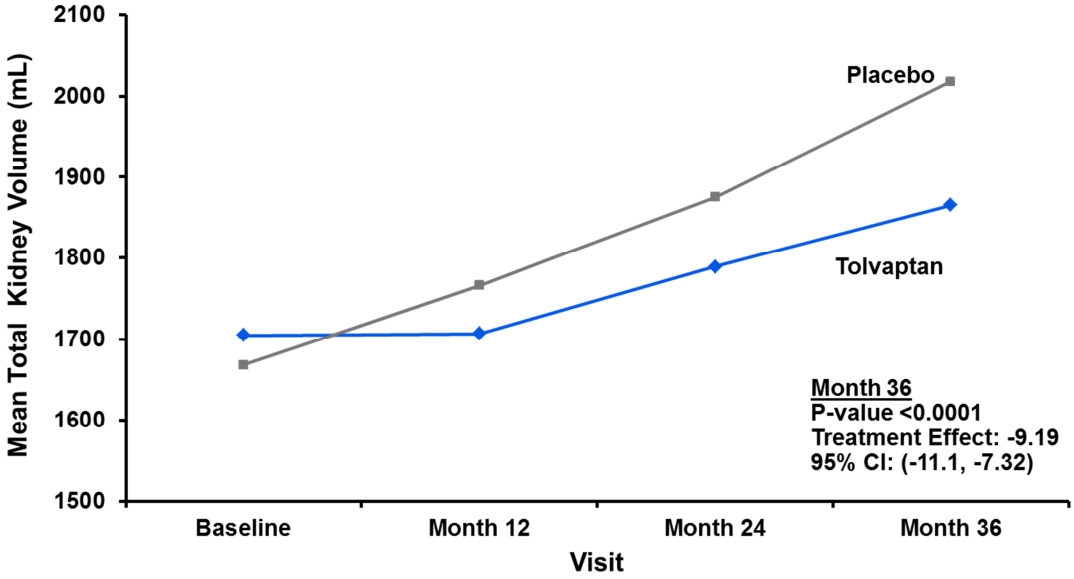


Figure 10.4.1.1-1 MMRM Analysis of Percent Change from Baseline in Total Kidney Volume in Trial 156-04-251; ITT - Within the Treatment Period

10.4.1.2 Sensitivity Analysis of Primary Endpoint Analysis Using All Available Data (Regardless of Treatment Period)

While the primary analysis used a restricted ITT dataset (relying on on-treatment observations), sensitivity analysis using a nonrestricted ITT approach with all available data, ie, regardless of treatment period, was performed for the linear mixed model analysis. This analysis therefore includes all available data from all randomized subjects with postbaseline data, whether receiving trial medication or not.

Results of this sensitivity linear mixed model analysis were consistent with the primary endpoint result for TKV growth: 2.9% per year for tolvaptan versus 5.6% per year for placebo, indicating a 47.2% reduction in growth rate in the tolvaptan group (ratio of geometric mean 0.975; CI 0.970 to 0.980, $p < 0.0001$; Figure 10.4.1.2-1).

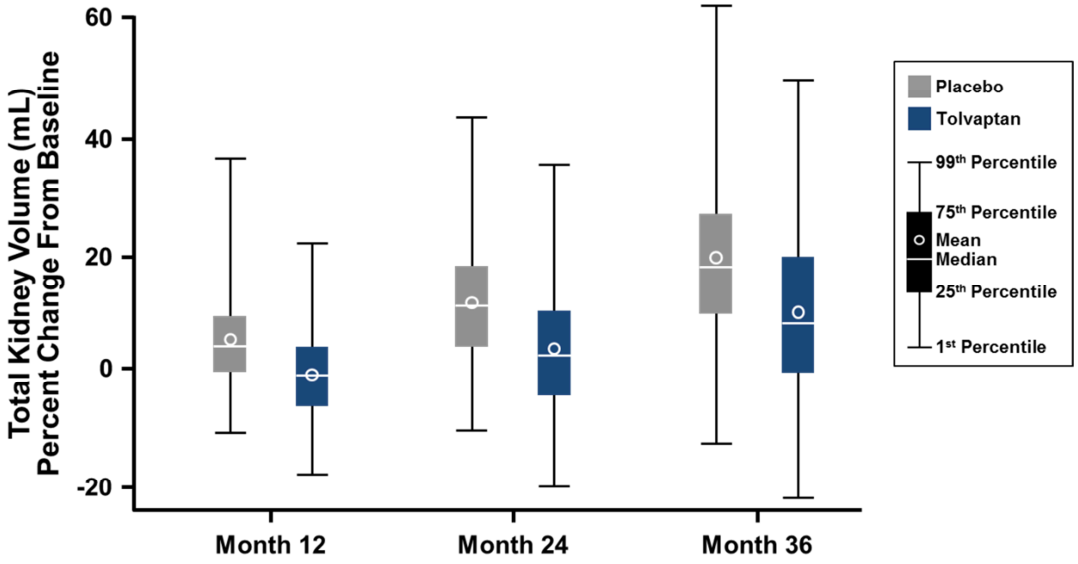


Figure 10.4.1.2-1 MMRM Analysis of Percent Change from Baseline in Total Kidney Volume in Trial 156-04-251; ITT - Regardless of Treatment Period

10.4.1.3 Non-Parametric Analyses Accounting for Non-normal Distribution

A variety of non-parametric tests were applied to TKV slope and TKV percent change data. These include the Wilcoxon Test, Median Test, Van der-Waerden Test, Savage Test, Kolmogorov-Smirnov Test, and Kuiper Test.

The results of each of these analyses were nominally statistically significant ($p < 0.0001$) for each test.

10.4.1.4 Tests Evaluating the Impact of Outlier Data and Error of TKV Measurement

The primary endpoint relies on quantitation of MRI-derived kidney volumes. The TKV Validation Report[5] provides an assessment of the accuracy and reproducibility of these MRI measurements. Analyses evaluating the potential impact of measurement error on the results of TKV analyses are presented.

- Sensitivity analyses excluding subjects identified as outliers and therefore potential MRI reading errors based on blinded pre-database-lock visual inspection within treatment period ($p = 0.0002$) and regardless of treatment period ($p < 0.0001$) were statistically significant. Sensitivity analyses excluding subjects identified as outliers and therefore potential MRI reading errors based on more than 1.5 times the inter-quartile range (IQR) below the first quartile or 1.5 times the IQR above the third

quartile within the treatment period ($p = 0.0011$) and regardless of treatment period ($p < 0.0001$) were statistically significant.

- A sensitivity analysis excluding all TKV data with comments related to their MRI quality (and therefore potentially flawed data) was performed to assess their impact and was also highly significant ($p < 0.0001$).
- The intra-reader and inter-reader variations in TKV were low. An analysis of intra-reader variability had a relative error of 0.62%, while inter-reader variability had a relative error of 1.23%.

In conclusion, the observed variability in TKV measurements in Trial 156-04-251 was not considered to have a meaningful impact on primary endpoint results.

10.4.1.5 Analysis by Modal Dose

Because Trial 156-04-251 used a titration design, it was not possible to assess the effects of individual doses directly. A modal dose analysis, which excluded the placebo dose, was performed to evaluate whether any strong modal dose related-effects were present. Modal dose was determined as the total daily dose (60, 90 or 120 mg) most frequently taken in the time period prior to the assessment visit (Month 12, 24 or 36). The modal dose analysis demonstrated an apparent dose response effect of tolvaptan ($p < 0.05$ for each year's percent change in TKV).

10.4.1.6 Analysis by Center or Country

A by-center analysis of the rate of percent growth in TKV demonstrated that the treatment effects favored tolvaptan for the majority of the trial centers (Figure 10.4.1.6-1).

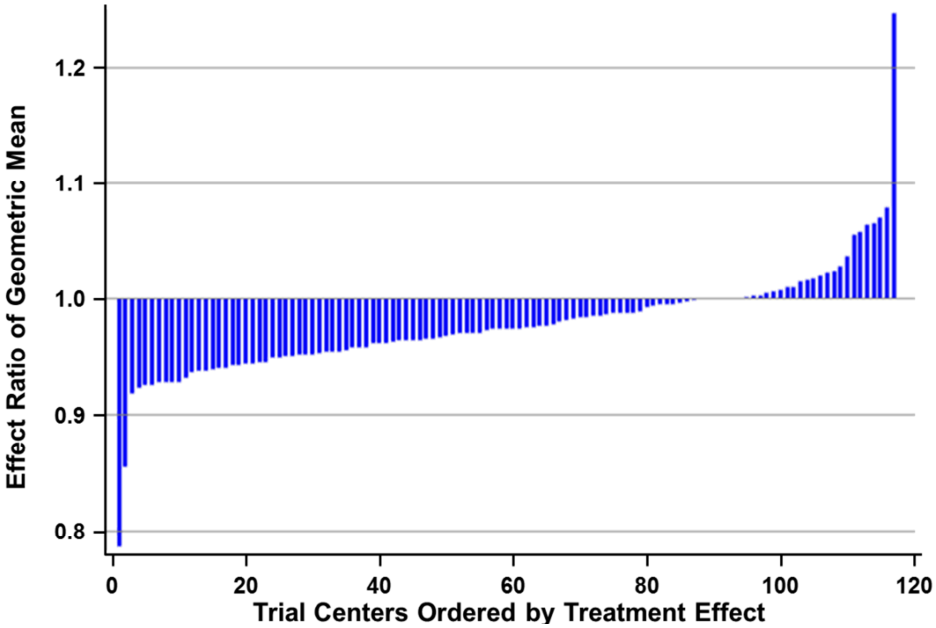


Figure 10.4.1.6-1 By-Center Analysis of Rate of Growth in TKV in Trial 156-04-251; ITT, Within Treatment Period

Results reflect estimates of the ratio of geometric mean of annualized growth rate of tolvaptan and placebo, ranked by center. A geometric mean ratio < 1 favors tolvaptan.

A similar by-country analysis of the rate of TKV change showed that all 15 countries demonstrated a treatment effect in favor of tolvaptan. The percent improvement in the US was 40.4% (geometric mean ratio 0.980, 95% CI 0.968 to 0.993, p = 0.0026).

10.4.2 Sensitivity Analyses of the Key Secondary Composite Endpoint

10.4.2.1 Independent Adjudication by a Clinical Endpoints Committee Using Time to Multiple Event Sensitivity Analysis

The adjudication of ADPKD clinical progression events involved review of available CRF data to determine if events were consistent with a clinically meaningful definition of disease progression. For example, the CEC reviewed and required 10 mmHg or 5 mmHg changes in sBP or dBP, and not simply a few mmHg between categories, in order to call an event meaningful. Analysis of urine albumin/creatinine ratio similarly required a doubling of the baseline value in conjunction with a change across thresholds to be clinically meaningful. Medications used to treat renal pain were assessed based on their pharmacologic actions and placed in the appropriate intensity category. Serum creatinine values were assessed only after each subject completed all visits, so that the

entire subject's profile of change in renal function would be examined in the context of identifying events.

The analysis of the adjudicated data provided independent verification of events as a sensitivity analysis. The finding of the key secondary composite endpoint analysis was confirmed when using outcomes that had been independently adjudicated (p = 0.0044) (Table 10.4.2.1-1).

Table 10.4.2.1-1 Key Secondary Composite Endpoint: Time to Multiple Composite ADPKD Events in Trial 156-04-251; ITT, Within Treatment Period

Parameter	Nonadjudicated Composite Events		Adjudicated Composite Events	
	Tolvaptan (N = 961)	Placebo (N = 483)	Tolvaptan (N = 961)	Placebo (N = 483)
Number of events	1049	665	1067	688
Total follow-up years	2387	1329	2387	1329
Events/100 follow-up years	43.94	50.04	44.69	51.77
Mean follow-up years	2.48	2.75	2.48	2.75
HR[a]	0.865		0.852	
95% CI[a]	0.775, 0.965		0.764, 0.951	
p-value[a]	0.0095		0.0044	

ADPKD = autosomal dominant polycystic kidney disease; CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat.

[a]Derived from rate and mean model of time to recurrent event analysis with factor treatment.

10.4.2.2 Evaluation of Individual Contributions to the Key Secondary Composite Using Time to First Event Sensitivity Analysis

Analysis using time to first event examined whether the primary endpoint result was driven by the treatment effects on most of the subjects, rather than a few subjects having multiple events.

Analyses of time to the first composite ADPKD event demonstrated fewer ADPKD progression events in the tolvaptan group (HR 0.826; 95% CI 0.722 to 0.944, p = 0.0051).

Analyses of time to the first CEC-adjudicated composite ADPKD event demonstrated fewer ADPKD progression events in the tolvaptan group (HR 0.835, 95% CI 0.729 to 0.955, p = 0.0087).

These findings support the conclusion that the primary endpoint results were driven by initial events in a broad range of subjects and not just recurrent events in a small subgroup of subjects.

10.4.2.3 Sensitivity Analyses Specifically Requested by the FDA

Two sensitivity analyses of the key secondary composite endpoint were added at the request of the FDA.

On 12 May 2010, after receiving an approved SAP (version 1, 10 Jan 2010), FDA expressed a "concern that knowledge of study findings could have influenced the design of your analytic plan" for the analysis of the key secondary composite endpoint with respect to ADPKD clinical progression events occurring before and after the SAP approval. It is important to note that the SAP adhered to the detailed statistical analysis prospectively planned for this endpoint as described in the original protocol submitted to FDA for their review prior to initiation of study conduct. Prior to 10 Jan 2010, 1122 events had been reported whereas 636 events were reported after SAP finalization.

Before SAP finalization, available data produced a HR of 0.925 (95% CI 0.811 to 1.057, p = 0.2522). Data available after SAP finalization produced a HR of 0.790, (95% CI 0.669 to 0.934, p = 0.0057). While tolvaptan had a numerically favorable effect in both time periods, it reached nominal statistical significance for the second time period. This is likely due to the increasing impact of renal function events which occurred late in the trial (refer to Figure 5.6.4-1).

The SAP had specified that subjects would be censored at the point in which the last no-event visit occurred while assessments of any of the components were conducted. FDA was interested in an analysis which would limit subjects' contributions to the analysis to those having assessments for each of the 4 event types. Therefore, they requested an analysis where subjects were censored at the last visit in which they were evaluable for all components. This analysis also favored tolvaptan treatment (HR 0.878, 95% CI 0.787 to 0.979, p = 0.0194).

10.4.2.4 Sensitivity Analyses Restricting Data and Events During the First 3 Weeks of Treatment, During the Treatment Period

Analyses were performed to exclude the noise associated with trial initiation and in particular the initiation of trial medication (eg, subjects adjusting antihypertensives after discontinuing diuretics). These analyses relied on more restrictive ITT analyses excluding data prior to Week 3/EOT (and using this time point as a post-titration baseline) for event derivation. These analyses were restricted to data obtained during the treatment period. Both analyses of time to multiple events (HR 0.877, 95% CI 0.785 to 0.980, p = 0.0203) and the time to the first event (HR 0.884, 95% CI 0.770 to 1.014, p = 0.0777) favored tolvaptan.

10.4.2.5 Sensitivity Analyses Using or Restricting Data and Events During the First 3 Weeks of Treatment, Regardless of Treatment Period

The primary analysis and the analysis conducted immediately above were performed during the treatment period. Less restrictive ITT analyses were used to include all available data whether on or off treatment up to Month 36. In the analysis matching the primary analysis, baseline was pretreatment Day 1 for hypertension, albuminuria, and renal pain; and Week 3/EOT for renal function. The result of this time to multiple event analysis was consistent with the primary analysis (HR 0.874, 95% CI 0.784 to 0.974, p = 0.0147).

In the time to multiple event analysis using Week 3/EOT as baseline, the result of this analysis was also consistent with the primary analysis (HR 0.889, 95% CI 0.797 to 0.992, p = 0.0354).

10.4.2.6 Sensitivity Analysis by Center or Country

The by-center analysis of the key secondary composite endpoint demonstrated that treatment effect came from most of the centers, instead of from a few large centers (Figure 10.4.2.6-1).

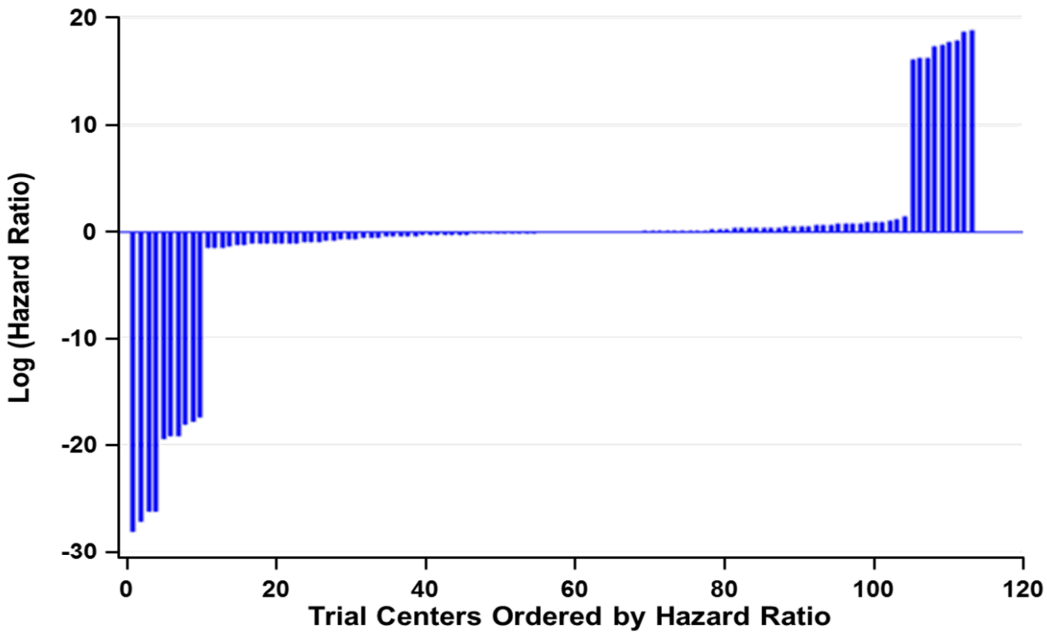


Figure 10.4.2.6-1 By-Center Analysis of Time to Multiple Events of the Key Secondary Composite Endpoint in Trial 156-04-251; ITT, Within Treatment Period

Represents log-transformed hazard ratio. A value < 0 corresponds to a hazard ratio less than 1, favoring tolvaptan.

The by-country analysis of the key secondary composite endpoint showed 9 out of 15 countries demonstrated a treatment effect in favor of tolvaptan for the endpoint. For the US, the result was nominally favorable and consistent with the overall result (HR = 0.847, 95% CI 0.663 to 1.083; p = 0.1866; Figure 10.4.2.6-2).

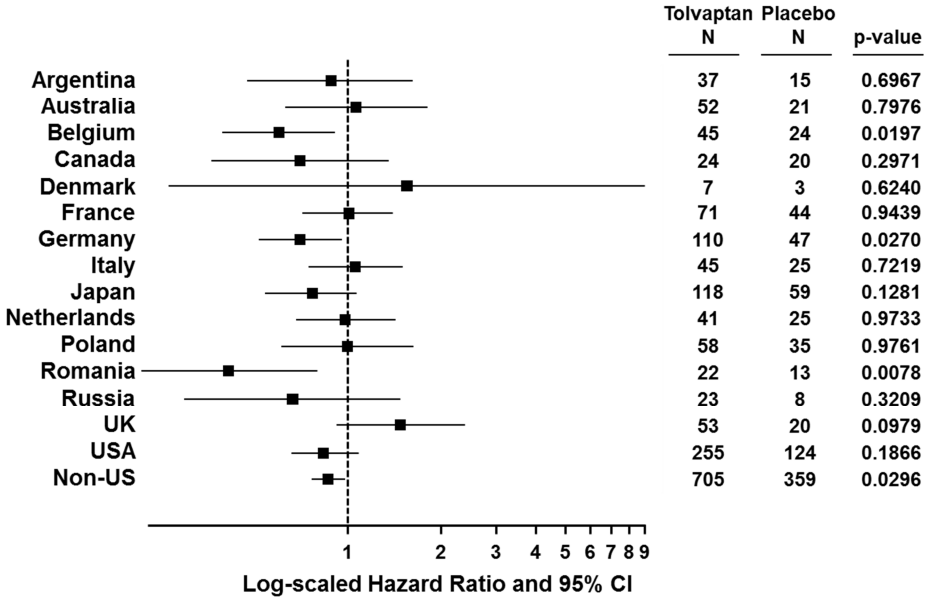


Figure 10.4.2.6-2 By-Country Analysis of Time to Multiple Events of the Key Secondary Composite Endpoint in Trial 156-04-251; ITT, Within Treatment Period

Represents hazard ratio presented in log-scale. A value < 1 favors tolvaptan.

10.4.3 Sensitivity Analyses of Components of the Key Secondary Composite Endpoint

10.4.3.1 Independent Adjudication by a Clinical Endpoints Committee Using Time to Multiple Event Sensitivity Analysis for Composite Components

The analysis of the adjudicated data provided independent verification of events for the sensitivity analysis. Adjudication confirmed that tolvaptan was more effective in reducing events of worsening renal function and renal pain than placebo

- worsening renal function events: time to multiple event HR 0.401, 95% CI 0.247 to 0.588, p < 0.0001; time to first event HR 0.385, 95% CI 0.260 to 0.570, p < 0.0001
- renal pain events: time to multiple event HR 0.600, 95% CI 0.439 to 0.818, p = 0.0013; time to first event HR 0.624, 95% CI 0.466 to 0.835, p = 0.0015).

Adjudication had no clinically meaningful effect on the point estimate and significance of hypertension events (improved) and albuminuria events (worsened).

10.4.3.2 Evaluation of Individual Contributions to Composite Components of Worsening Renal Function and Renal Pain Events Using Time to First Event Sensitivity Analysis

Analysis using time to first event examined whether the result was driven by the treatment effects on most of the subjects, rather than a few subjects having multiple events. Analysis of time to first renal pain event (HR 0.653, 95% CI 0.484 to 0.881, p = 0.0052) and analysis of time to first worsening renal function event (HR 0.368, 95% CI 0.249 to 0.546, p < 0.0001) demonstrated significantly fewer events on tolvaptan, indicating that the treatment effect on these 2 components did not originate from multiple events reported by only a few subjects.

10.4.3.3 Sensitivity Analyses Restricting Data and Events During the First 3 Weeks of Treatment, During the Treatment Period

More restrictive ITT analyses were performed for renal pain, hypertension and albuminuria events using Week 3/EOT as baseline to exclude noise due to trial initiation and the initiation of trial medication to examine the time to multiple events and the time to the first event.

Statistically significantly fewer renal pain events were observed with Week 3/EOT as baseline on a time to multiple event basis (HR 0.636, 95% CI 0.454 to 0.891, p = 0.0086) and time to first event basis (HR 0.648, 95% CI 0.475 to 0.885, p = 0.0063). There was no meaningful impact of this sensitivity assessment on hypertension or albuminuria event analyses.

10.4.3.4 Sensitivity Analyses of the Number of Subjects Meeting a 33.3% Increase in Serum Creatinine at Follow-up Visits from Day 1 Baseline

The analyses above were not required for renal function due to its prespecified use of the Week 3/EOT baseline. This baseline was prespecified for this endpoint because an acute and reversible effect on GFR and serum creatinine is known to occur with tolvaptan treatment. Therefore, an alternate analysis using pre-treatment and post-treatment serum creatinine measurements was performed to verify the findings of the renal function event component were not affected by use of change from Week 3/EOT visit. The results indicate that significantly fewer tolvaptan than placebo subjects had increased their serum creatinine by at least 1/3 in both Follow up Visit 1 and 2 (56/679 [8.25%] versus 59/383 [15.4%], respectively, p = 0.0003).

10.4.3.5 Sensitivity Analyses Using or Restricting Data and Events During the First 3 Weeks of Treatment, Regardless of Treatment Period

Less restrictive ITT analyses were performed of the time to multiple events using a nonrestricted ITT approach (regardless of treatment period) using predose baseline and Week 3/EOT as baseline. Statistically significantly fewer renal pain events were observed regardless of treatment period using predose baseline (HR 0.641, 95% CI 0.465 to 0.882, p = 0.0064) and Week 3/EOT as baseline (HR 0.634, 95% CI 0.453 to 0.886, p = 0.0077). In addition, fewer worsening renal function events occurred on tolvaptan regardless of treatment period and using Week 3/EOT as baseline (HR 0.383, 95% CI 0.263 to 0.559, p < 0.0001). There was no meaningful impact of this sensitivity assessment on hypertension or albuminuria event analyses.

10.4.3.6 Sensitivity Analysis of Renal Pain Event Component Including Covariates for Renal Pain Disease History

An exploratory analysis of the component of renal pain, after correction of pain-related baseline covariates from subjects' ADPKD disease history (eg, renal pain, kidney stones, upper UTI), maintained the statistical significance of the pain component at a level of p < 0.01 for time to multiple event and time to first event.

10.4.3.7 Sensitivity Analysis Describing Categories Contributing to Renal Pain Event Component

The renal pain event component of the key secondary composite endpoint categorizes events into three levels. Surgical/radiological interventions are the most "intense" category, narcotic and prescription antinociceptive (eg, tricyclic antidepressant) medications being next and the lowest-intensity category being a group of non-narcotic analgesics combined with medical leave or activity restriction. The distribution of events across these categories is presented in Table 10.4.3.7-1.

This table also breaks out renal pain events attributed to the use of the non-narcotic analgesic paracetamol as requested by FDA.

Table 10.4.3.7-1 Categories of Renal Pain Interventions in Trial 156-04-251

Period Included in Analysis	Treatment Group	Total Subjects	Total Events		Renal Pain Intervention Categories[a] (Decreasing Severity from Left to Right)									
					Surgical /Radiologic		"Narcotic/ Tricyclic" Medication		Med. Leave or Activity Restriction		Non-Paracetamol Medication		Paracetamol Medication	
			n	%	n	%	n	%	n	%	n	%	n	%
Within Treatment Period	Tolvaptan	961	114	11.86	5	0.52	49	5.10	14	1.46	24	2.50	22	2.29
	Placebo	483	98	20.29	5	1.04	39	8.07	14	2.90	25	5.18	15	3.11
Regardless of Treatment	Tolvaptan	961	116	12.07	5	0.52	51	5.31	14	1.46	24	2.50	22	2.29
	Placebo	484	101	20.87	6	1.24	40	8.26	15	3.10	25	5.17	15	3.10

[a]Represents number of events divided by the total number of subjects.

10.4.3.8 Sensitivity Analysis of Time to Multiple Renal Pain Events Excluding Those Attributed to Paracetamol Use

Replication of the time to multiple event analysis for renal pain events using an additional category excluding those attributed to paracetamol use was also requested by FDA. This required reprogramming and reanalysis both including and excluding this new category. The results of these analyses (Table 10.4.3.8-1 and Table 10.4.3.8-2, respectively) are not significantly different than the original pre-specified analysis.

Table 10.4.3.8-1 provides a revised sensitivity analysis of the key secondary composite's renal pain component analysis after reprogramming. The resulting hazard ratio is identical to the original pre-specified analysis (both HR = 0.642); however, the p-value is slightly improved (new p = 0.0066 compared with original p = 0.0071). This means that reprogramming did not introduce any bias to the original renal pain component. The slight improvement in p-value is probably the result of reprogramming having added one event in each treatment group.

Table 10.4.3.8-2 provides a sensitivity analysis of the key secondary composite renal pain component where events arising from paracetamol use are excluded when using the reprogrammed method. Removal of paracetamol events from the pain component sensitivity analysis yields an improved hazard ratio compared to the original (new HR = 0.611 compared with original HR = 0.642) and with a slightly larger p-value (0.0086 vs 0.0066, respectively). The improvement in hazard ratio probably reflects that, among the subjects who had renal pain events, the percentage of subjects who had paracetamol events was higher in tolvaptan group (19.3%, = 22/114) than the placebo group (15.3%, = 15/98). The increased p-value likely reflects the overall reduction in events used for this analysis.

These sensitivity analyses support the conclusion that, even after post-hoc removal of these events, essentially the same signal for clinical benefit of tolvaptan remains. Removal does not introduce bias towards tolvaptan or change the conclusions of these analyses.

Table 10.4.3.8-1	Sensitivity Analysis of Key Secondary Composite Endpoint Re-programmed Renal Pain Component - Time to Multiple Events - ITT, Within Treatment Period								
Treatment Group	Subjects	# Events	Total Follow-up years	Events Per 100 Follow-up years	Mean Follow-up years	HR	95% CI Limits		P-value
							Lower	Upper	
Tolvaptan	961	114	2387	4.77	2.48	0.642	0.466	0.884	0.0066
Placebo	483	98	1329	7.37	2.75				

CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat.

Table 10.4.3.8-2	Sensitivity Analysis of Key Secondary Composite Endpoint Re-programmed Renal Pain Component with Paracetamol Events Removed - Time to Multiple Events - ITT, Within Treatment Period								
Treatment Group	Subjects	# Events	Total Follow-up years	Events Per 100 Follow-up years	Mean Follow-up years	HR	95% CI Limits		P-value
							Lower	Upper	
Tolvaptan	961	92	2387	3.85	2.48	0.611	0.423	0.882	0.0086
Placebo	483	83	1329	6.25	2.75				

CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat.

10.4.3.9 Sensitivity Analysis by Country

By-country analyses of time to multiple renal pain events (Figure 10.4.3.9-1) and time to multiple worsening renal function events (Figure 10.4.3.9-2) were similar, each revealing that 12 countries favored tolvaptan numerically, one country had no event in either treatment group, and 2 countries favored placebo numerically. In the US, renal pain events trended toward significance (HR = 0.597, 95% CI 0.324 to 1.099, p = 0.0975), as did worsening renal function events (HR = 0.464, 95% CI 0.191 to 1.128, p = 0.0902).

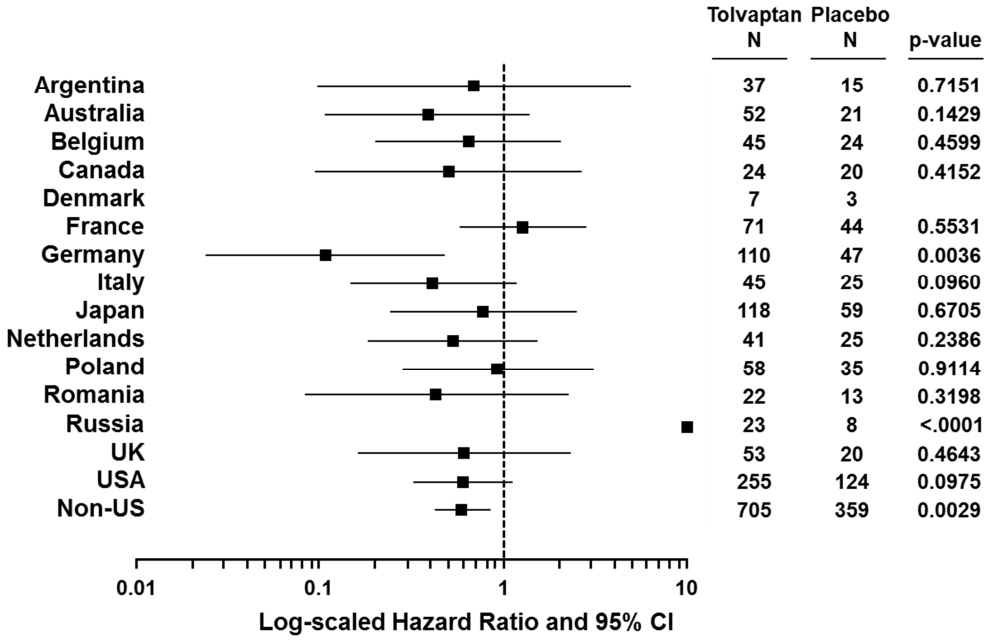


Figure 10.4.3.9-1 By-Country Analysis of Time to Multiple Events of the Renal Pain Component of the Key Secondary Composite in Trial 156-04-251; ITT, Within Treatment Period

Represents hazard ratio presented in log-scale. A value < 1 favors tolvaptan.

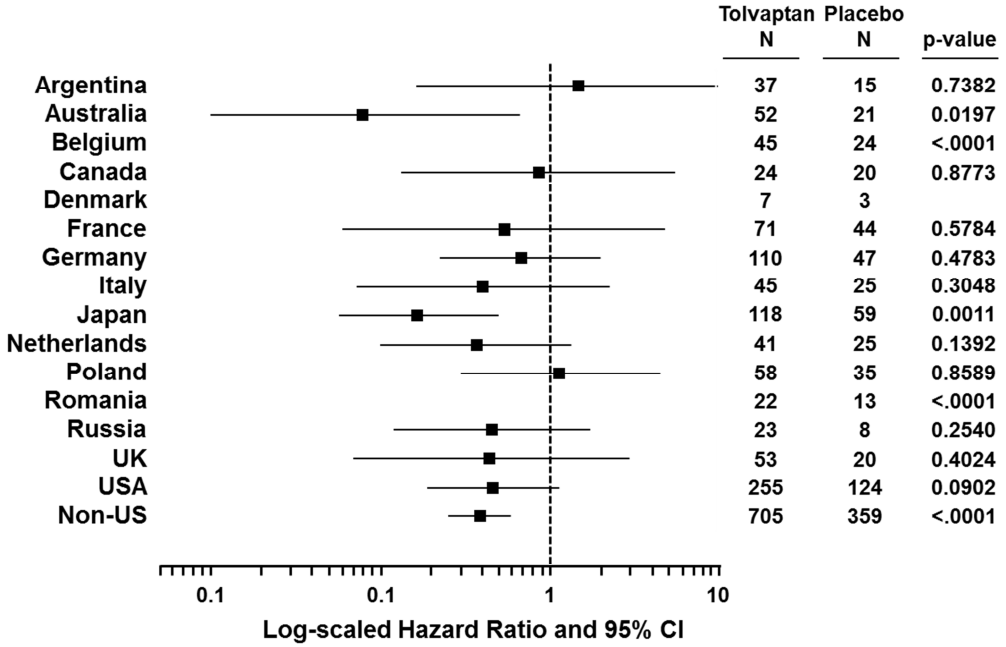


Figure 10.4.3.9-2 By-Country Analysis of Time to Multiple Events of the Renal Function Component of the Key Secondary Composite in Trial 156-04-251; ITT, Within Treatment Period

Represents hazard ratio presented in log-scale. A value < 1 favors tolvaptan.

10.4.4 Sensitivity Analyses of the Slope of Renal Function

Sensitivity analyses were performed to evaluate the robustness of slope of renal function and to further examine the effects of using various alternative formulae for estimating renal function, various tests for non-linearity, non-normality, and to test the effects of including additional data (eg, serum creatinine measures deemed unreliable by the investigator) or data points (pre- and post-treatment values).

10.4.4.1 Sensitivity Analysis Using Alternate Formulae for Estimating Renal Function Using Serum Creatinine

The primary analysis of renal function slope data uses units ($[mg/mL]^{-1}$) which produce values in the same range as traditional estimates of renal function (eCrCL or eGFR). For comparison, renal function was estimated using the CKD-EPI formula ($eGFR_{CKD-EPI}$), the MDRD formula ($eGFR_{MDRD}$) or the Cockcroft-Gault formula ($eCrCL_{CG}$).

The results for each formula were similar:

- 1/serum creatinine $(mg/mL)^{-1}$ $year^{-1}$:
  - treatment effect +1.194 (95% CI 0.610 to 1.777, p = 0.0001)
- $eGFR_{CKD-EPI}$ mL/min/1.73 m^2 $year^{-1}$:
  - treatment effect +0.989 (95% CI 0.607 to 1.371, p < 0.0001)
- $eGFR_{MDRD}$ mL/min/1.73 m^2 $year^{-1}$:
  - treatment effect +0.931 (95% CI 0.464 to 1.398, p < 0.0001)
- $eCrCL_{CG}$ mL/min $year^{-1}$:
  - treatment effect +1.334 (95% CI 0.727 to 1.942, p < 0.0001)

10.4.4.2 Sensitivity Analysis of Slope from Pre-treatment to Post-treatment Renal Function

This treatment effect was confirmed by comparing data from pretreatment value to the last two post-treatment visits (Follow-up Visit 1 and Follow-up Visit 2). These results are consistent with the primary analysis result. The results using each method of renal function estimation were similar to those using the slope derived from only data collected while on treatment (in Section 10.4.4.1):

The results for each formula were similar:

- 1/serum creatinine $(mg/mL)^{-1}$ $year^{-1}$:
  - treatment effect +1.611 (95% CI 0.789 to 2.433, p < 0.0001)

- $eGFR_{CKD-EPI}$ mL/min/1.73 m^2 $year^{-1}$:
  - treatment effect +1.029 (95% CI 0.598 to 1.461, p < 0.0001)
- $eGFR_{MDRD}$ mL/min/1.73 m^2 $year^{-1}$:
  - treatment effect +1.308 (95% CI 0.521 to 2.095, p = 0.0011)
- $eCrCL_{CG}$ mL/min $year^{-1}$:
  - treatment effect +1.519 (95% CI 0.731 to 2.308, p = 0.0002)

10.4.4.3 Sensitivity Analysis of Renal Function Effects by Pre-treatment CKD Stage

The enrolled population represented subjects in various stages of ADPKD, with reference to both total kidney volume and renal function (Figure 5.2-1). To determine whether the effects on renal function might vary across CKD stage (using $eGFR_{CKD-EPI}$), the a renal function slope analysis was conducted for subjects in CKD 1, 2 or 3 (Table 10.4.4.3-1).

Table 10.4.4.3-1 Rate of Change in Renal Function by CKD Stage Using CKD-EPI Formula in Trial 156-04-251; ITT, Including Observations at Pretitration Baseline and Follow-up Visit 1 and 2

CKD Stage	Treatment Group	Rate of Change (mL/min/1.73m^2 per year)				Slope	Treatment Effect (95% CI)	Relative Treatment Effect	p-value
		N	Mean	Median	SD				
CKD Stage 1	Tolvaptan	330	-6.28	-1.70	29.63	-1.93	0.94 (0.34, 1.53)	33%	0.0022
	Placebo	173	-3.91	-2.50	8.25	-2.86			
CKD Stage 2	Tolvaptan	465	-2.74	-2.52	21.25	-2.64	1.21 (0.74, 1.68)	31%	<0.0001
	Placebo	224	-2.92	-3.64	10.08	-3.85			
CKD Stage 3	Tolvaptan	163	-4.06	-3.59	6.95	-3.58	1.73 (0.97 2.50)	33%	<0.0001
	Placebo	84	-5.32	-5.77	4.17	-5.32			

CI = confidence interval; CKD = chronic kidney disease; ITT = intent-to-treat; SD = standard deviation.

While the absolute difference in renal function between tolvaptan and placebo subjects was smallest in CKD stage 1 and successively greater in CKD stages 2 and 3, so was the rate of overall decline in the placebo group. In contrast, the relative effect size in each stage of CKD was between 31-33%, indicating that the activity and potential benefits of tolvaptan did not dissipate as renal function declined. This is consistent with short-term trials showing tolvaptan's continued pharmacodynamic effects even as GFR approached CKD stage 5 (15 mL/min/1.73 m^2).

10.4.4.4 Sensitivity MMRM Analysis of Change from Pretreatment to Post-treatment Renal Function

Additional MMRM sensitivity analyses using a non-restricted ITT approach with all available data, regardless of treatment period, and assessing change from pretreatment to Follow-up Visit 2 were performed to examine changes in renal function during the trial.

These analyses also account for the expected initial nonlinearity in the response to tolvaptan. Results of these MMRM sensitivity analyses assess change from the pretreatment visit to each subsequent visit, culminating in the changes to the post-treatment Follow up 2 Visit. This analysis (Figure 10.4.4.4-1) shows the expected acute decline in eGFR for the tolvaptan group. Over the next 3 years, eGFR for both treatment groups converge, crossing at the Month 32 visit, thereafter showing a nominal benefit for tolvaptan. Around this point (Month 36), treatment was withdrawn for all subjects, reversing the acute effect and demonstrating a nominally significant benefit for tolvaptan at Follow-up Visits 1 and 2, which appears to continue for at least 3 months post-treatment (pretreatment baseline data from ongoing open-label extension Trial 156-08-271).

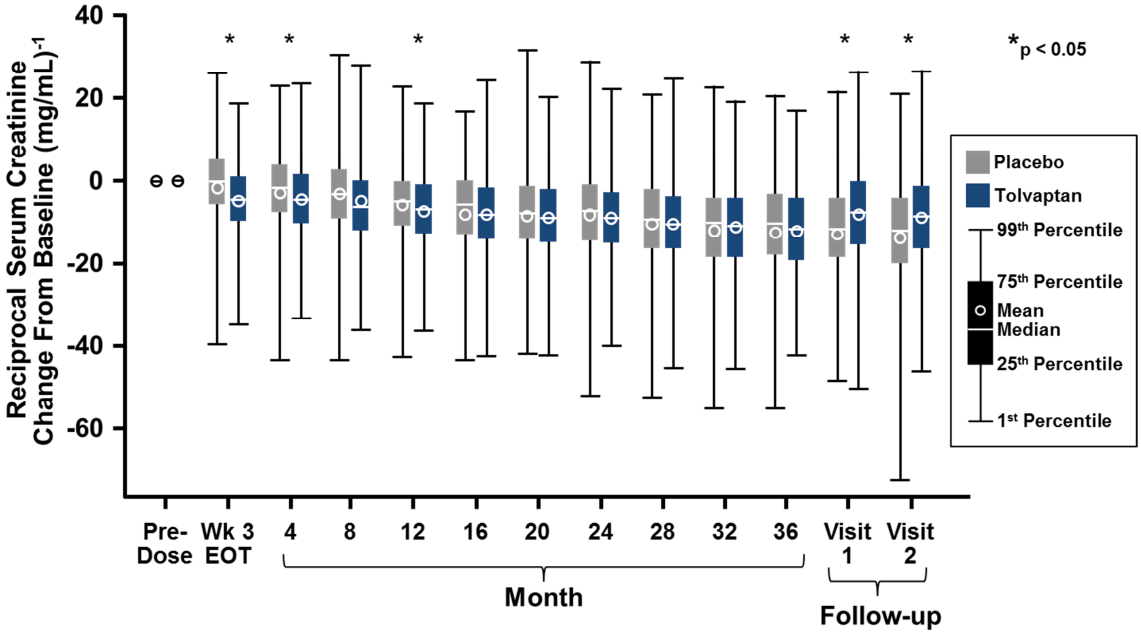


Figure 10.4.4.4-1 MMRM Analysis of Change from Pretitration Baseline in Renal function, Estimated by Reciprocal of Serum Creatinine in Trial 156-04-251 - ITT Regardless of the Treatment Period

The results of treatment difference at Follow up Visit 2 were similar regardless of formula used and comparable to the non-MMRM ANCOVA analysis in Section 10.4.4.5:

- 1/serum creatinine $(mg/mL)^{-1}$:
  - treatment effect +4.93 (95% CI 2.96 to 6.89, $p < 0.0001$)
- $eGFR_{CKD-EPI}$ mL/min/1.73 m^2:

  - treatment effect +3.61 (95% CI 2.28 to 4.93, p < 0.0001)
- $eGFR_{MDRD}$ mL/min/1.73 m^2:
  - treatment effect +3.56 (95% CI 1.94 to 5.18, p < 0.0001)
- $eCrCL_{CG}$ mL/min:
  - treatment effect +5.17 (95% CI 3.03 to 7.32, p < 0.0001)

10.4.4.5 Sensitivity Analysis of Change from Pretreatment to Post-treatment Renal Function

This treatment effect was confirmed by comparing renal function data from pretreatment value to the last post-treatment visit (Follow-up Visit 2). This analysis showed a mean decrease for tolvaptan from 102.27 to 93.35 $(mg/mL)^{-1}$ or −8.70 $(mg/mL)^{-1}$ and for placebo from 104.30 to 91.11 $(mg/mL)^{-1}$ or −13.7 $(mg/mL)^{-1}$, for a relative renal function preservation treatment difference of 4.1 $(mg/mL)^{-1}$ (95% CI 2.1 to 6.2, p = 0.0001). This relative 3-year difference is greater than the 4-year post-treatment difference seen by Apperloo et al (Figure 5.15-2).[6]

10.4.4.6 Sensitivity Analysis Including Serum Creatinine Data Regardless of Treatment Period

The primary analysis for this endpoint relies on data collected during an “within treatment period.” Sensitivity analyses were conducted using a non-restricted ITT approach with all available data, ie, regardless of treatment period in a linear mixed model.

The results using each method of renal` function estimation were similar to those using data “within treatment period” (see Section 10.4.4.1):

- 1/serum creatinine $(mg/mL)^{-1}$ $year^{-1}$:
  - treatment effect +1.199 (95% CI 0.619 to 1.778, p < 0.0001)
- $eGFR_{CKD\text{-}EPI}$ mL/min/1.73 m^2 $year^{-1}$:
  - treatment effect +1.008 (95% CI 0.628 to 1.387, p < 0.0001)
- $eGFR_{MDRD}$ mL/min/1.73 m^2 $year^{-1}$:
  - treatment effect +0.928 (95% CI 0.464 to 1.391, p < 0.0001)
- $eCrCL_{CG}$ mL/min $year^{-1}$:
  - treatment effect +1.363 (95% CI 0.756 to 1.969, p < 0.0001)

10.4.4.7 Non-Parametric Analyses Accounting for Non-normal Distribution

A variety of non-parametric tests were applied to renal function slope and percent change data. These include the Wilcoxon Test, Median Test, Van der-Waerden Test, Savage Test, Kolmogorov-Smirnov Test, and Kuiper Test.

The results of each of these analyses were nominally statistically significant for each test (each, $p < 0.005$).

10.4.4.8 Analysis by Center or Country

A by-center analysis of the rate of decline for $eGFR_{CKD\text{-}EPI}$ demonstrated that the treatment effects of the rate of renal function change favored tolvaptan for the majority of the trial centers (Figure 10.4.4.8-1).

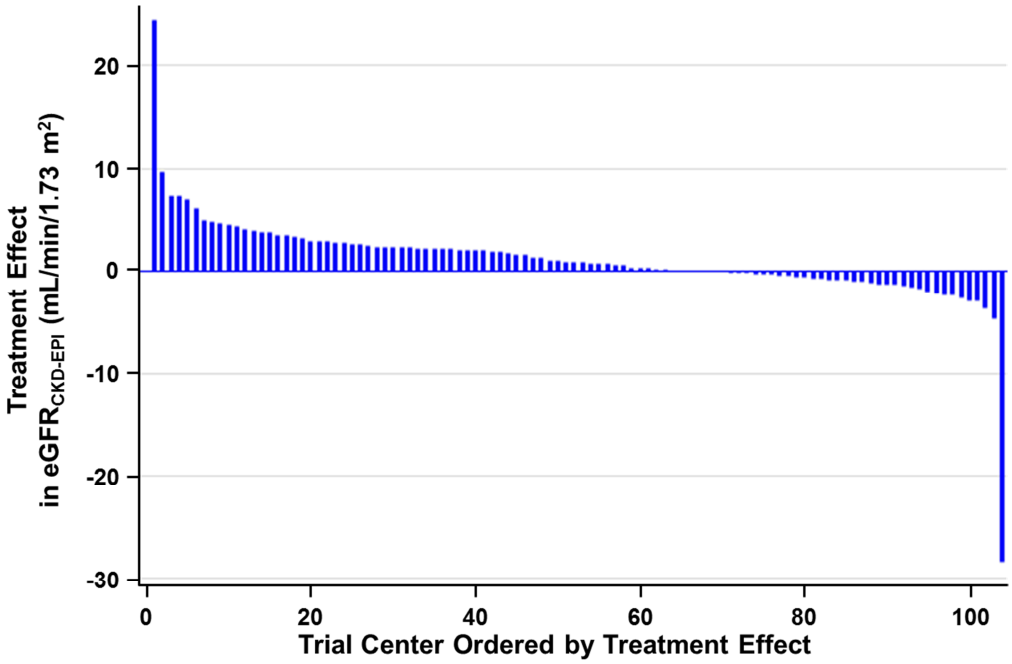


Figure 10.4.4.8-1 By-Center Analysis of Rate of Change in GFR Estimated by CKD-EPI Formula in Trial 156-04-251; ITT Subjects With at Least 4-month Follow-up, Excluding Observations Deemed Unreliable by Investigators, Within Treatment Period

Treatment effect > 0 favors tolvaptan.

A similar by-country analysis of the rate of $eGFR_{CKD\text{-}EPI}$ change showed that in 12 out of 14 countries tolvaptan demonstrated a favorable treatment effect (not evaluable in 1 country, Denmark) (Figure 10.4.4.8-2).

The relative improvement in the US was 22% (estimated treatment effect 0.701 mL/min/1.73 m^2, 95% CI −0.067 to 1.469, p = 0.0737).

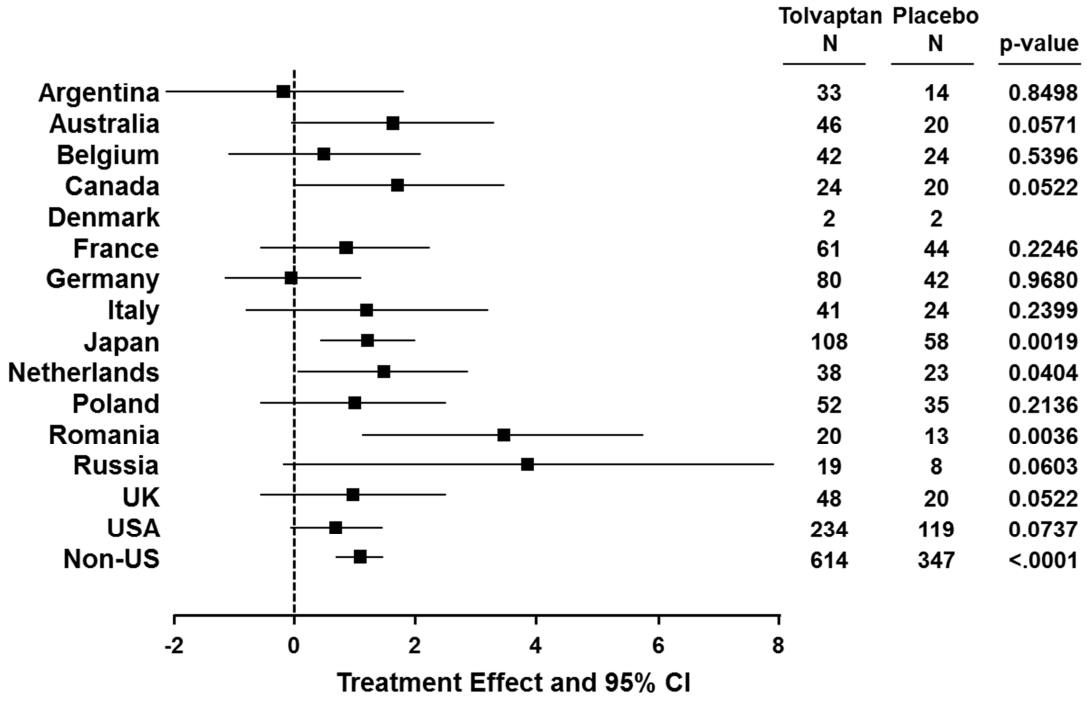


Figure 10.4.4.8-2 By-Country Analysis of Rate of Change in GFR Estimated by CKD-EPI Formula in Trial 156-04-251; ITT Subjects With at Least 4-month Follow-up, Excluding Observations Deemed Unreliable by Investigators, Within Treatment Period

A treatment effect > 0 favors tolvaptan.

10.5 Analyses on Missing Data

10.5.1 Responder Analyses

Post hoc responder analysis was undertaken to understand the effect of data MNAR using 3 responder definitions:

3) subjects in whom both TKV growth and eGFR decline slopes were less than 20% of the placebo slopes.

4) subjects who met the criteria in item 1) and also had no event in the 2 positive components of the key secondary composite endpoint, worsening renal function and renal pain; and
5) subjects who met the criteria in item 1) and also had no event in any of the 4 components of the key secondary composite endpoint.

The responder analyses were conducted using 1) all subjects, with withdrawn subjects in both treatment groups considered as non-responders; and 2) all subjects, with withdrawn subjects considered as non-responders in the tolvaptan group only. Chi-square test was used in the responder analysis. As shown in Table 10.5.1-1, the proportion of responders was statistically significantly greater in the tolvaptan group versus placebo group in all analyses, irrespective of the influence of missing data.

Table 10.5.1-1 Sensitivity Analysis: Responder Analysis - ITT, Within Treatment Period

Response Type	Group	N		%	Odds Ratio	95% CI	P-value[a]
		Subjects	Responders				
All Subjects with Withdrawn Subjects (both treatment groups) Considered as Non-responders							
Responder Definition #1[b]	Tolvaptan	961	302	31.43	2.006	1.537 - 2.619	<0.0001
	Placebo	484	90	18.60			
Responder Definition #2[c]	Tolvaptan	961	272	28.30	2.119	1.598 - 2.810	<0.0001
	Placebo	484	76	15.70			
Responder Definition #3[d]	Tolvaptan	961	127	13.22	2.081	1.395 - 3.104	0.0003
	Placebo	484	33	6.82			
All Subjects with Withdrawn Subjects Considered as Non-responders in Tolvaptan Group Only							
Responder Definition #1[b]	Tolvaptan	961	302	31.43	1.852	1.426 - 2.406	<0.0001
	Placebo	484	96	19.83			
Responder Definition #2[c]	Tolvaptan	961	272	28.30	2.055	1.553 - 2.719	<0.0001
	Placebo	484	78	16.12			
Responder Definition #3[d]	Tolvaptan	961	127	13.22	1.954	1.321 - 2.889	0.0007
	Placebo	484	35	7.23			

[a] P-value derived from chi square test.

[b] Responder is defined as a subject in whom both TKV growth and eGFR decline slopes were less than 20% of the placebo slopes.

[c] Responder is defined as a subject who met the criteria given in footnote b with no event in the 2 positive components of the key secondary composite endpoint, renal function and renal pain.

[d] Responder is defined as a subject who met the criteria given in footnote b, with no event in any of the 4 components of the key secondary composite endpoint.

10.5.2 Imputation and Multiple Imputation Analyses

10.5.2.1 Multiple Imputation Analyses

A reasonable method of imputation of available placebo response data into analyses for subjects missing data models the expected point estimates and variability associated with multiple simulations of actual placebo subject data. To search for the "tipping point" in these multiple imputation analyses, a factor, k, was multiplied to the "expectation" of placebo data used in the imputation in order to make tolvaptan subjects worse than placebo once they discontinued the trial.

Multiple imputation procedure was used to explore the robustness of the statistical tests results against MNAR, for the endpoints of TKV, key secondary composite as well as its renal function renal pain components, and renal function as continuous variable. For placebo dropouts, missing data were imputed based on placebo data (distribution at a visit, or intensity in a visit interval) using random number generators of normal distribution or Poisson distribution, respectively. For tolvaptan dropouts, missing data were similarly imputed using k times the placebo risk (placebo distribution at a visit with its mean multiplied by k, or placebo intensity in a visit interval multiplied by k), where k = 1, 1.1, 1.2, etc. After the imputation, the imputed data were combined with the observed data for an analysis, using methods of time to multiple events or MMRM, respectively, according to the variables. Thirty imputations were run for each k and their results were combined based on Rubin' rule[7] to make a conclusion for the multiple imputation analysis with the factor k.

Results of analyses using increasing increments of placebo risk (up until loss of statistical significance) are provided in Table 10.5.2.1-1 (TKV growth, renal function decline) and Table 10.5.2.1-2 (key secondary composite and its components).

These analyses indicate robust results for all endpoints shown under the assumption of data MNAR that are concordant with the original prespecified endpoint analyses. The analyses for TKV and renal function are significant up to 210% and 150% of placebo risk, respectively. For the key secondary composite endpoint, significance is maintained at up to 110% of placebo risk, notable considering that the majority of the events came from components that exhibited a neutral treatment effect (ie, HTN and albuminuria). The results of the individual components for renal pain, renal function, and (data not shown) combined renal pain/function are robust at up to 120% (renal pain) of placebo risk and beyond, consistent with the original component analyses.

Table 10.5.2.1-1 Multiple Imputation on MMRM Analysis of Change from Baseline in TKV Growth (%) and Renal Function Decline (Reciprocal of Serum Creatinine) at Month 36; ITT, Regardless of Treatment Period

% of Plc Group Response Imputed for Missing Tolvaptan Subjects	TKV Growth (%)				Renal Function Decline (Reciprocal of Serum Creatinine)			
	Difference[a]	95% CI Lower Limit[a]	95% CI Upper Limit[a]	P-value[a]	Difference[a]	95% CI Lower Limit[a]	95% CI Upper Limit[a]	P-value[a]
100%	0.938	0.923	0.954	<.0001	3.054	1.565	4.542	<0.0001
110%	0.942	0.927	0.957	<.0001	2.882	1.312	4.451	0.0003
120%	0.944	0.929	0.960	<.0001	2.540	1.022	4.057	0.0010
130%	0.948	0.932	0.964	<.0001	2.338	0.815	3.861	0.0026

Imputation was based on the observed change from baseline of placebo group at each visit. Random number generator of normal distribution was used to generate missing response, with placebo subjects using placebo's response distribution and tolvaptan subjects using a factor (starting from 1 and up) to multiply the mean of placebo response distribution in the simulation. The simulated data were combined with the observed data in the analysis.

[a]Statistics were derived based on 30 imputations.

Table 10.5.2.1-2 Multiple Imputation on Analysis of Time to Multiple Event (Key Secondary Composite and Renal Pain and Renal Function Components); ITT, Regardless of Treatment Period

% of Plc Group Response Imputed for Missing Tolvaptan Subjects	Key Secondary Composite Endpoint				Renal Pain Component				Renal Function Component			
	HR[a]	95% CI Lower Limit[a]	95% CI Upper Limit[a]	P-value[a]	HR[a]	95% CI Lower Limit[a]	95% CI Upper Limit[a]	P-value[a]	HR[a]	95% CI Lower Limit[a]	95% CI Upper Limit[a]	P-value[a]
100%	0.891	0.802	0.990	0.0325	0.701	0.518	0.951	0.0223	0.511	0.360	0.727	0.0002
110%	0.900	0.809	1.000	0.0498	0.699	0.514	0.950	0.0223	0.512	0.360	0.727	0.0002
120%	0.917	0.826	1.018	0.1055	0.716	0.527	0.973	0.0328	0.540	0.384	0.759	0.0004
130%	0.928	0.836	1.030	0.1596	0.742	0.547	1.007	0.0551	0.559	0.400	0.781	0.0007

Imputation is based on placebo's hazard in each interval between two adjacent protocol specified visits, inclusive to the latter visit. Random number generator of Poisson process is used in each visit interval based on the hazard and the duration of a discontinued subject in the interval. Events in general are assigned to the end of their visit intervals. In case more than one event is simulated in a visit interval, say two events, one is assigned to the end and the other is assigned to the middle of the visit interval. The simulated data of all discontinued subjects are combined with their data regardless of treatment period for analysis of time to multiple events.

[a]Statistics were derived based on 30 imputations.

10.5.2.2 Imputation Analyses

An MMRM change from baseline analysis of TKV was performed, in which subjects who did not have a postbaseline observation in TKV had their results conservatively imputed using the estimated placebo slope. This analysis addresses data MNAR including lack of postbaseline data. Mean TKV growth at Month 36 for tolvaptan (185 mL) was approximately half that of placebo (348 mL), a statistically significant difference (ratio of geometric mean 0.947; 95% CI 0.932 to 0.962, $p < 0.0001$). Results at Month 12 and Month 24 were also consistent with the primary analysis.

MMRM change from post-titration baseline analyses in renal function were performed using imputation methodology, for the reciprocal of serum creatinine, $eCrCL_{CG}$, $eGFR_{MDRD}$, and $eGFR_{CKD\text{-}EPI}$. In these analyses, data for subjects who did not have a postbaseline observation in renal function measurements were conservatively imputed using the estimated placebo slopes for the respective renal function measurements. This addresses data MNAR including lack of postbaseline data. All analyses were consistent with the primary analysis, with statistically significant differences between groups in renal function, favoring tolvaptan, at Month 36 (each, $p < 0.0001$).

10.5.3 Sensitivity Analyses of the Key Secondary Composite and Its Components, Including AE Withdrawals as Events

To further explore the effect of data MNAR, post-hoc sensitivity analyses of the key secondary composite endpoint and its components were performed, as shown in Table 10.5.3-1, to treat SAEs as well as non-serious, severe AEs resulting in withdrawal of trial medication as additional contributing events in tolvaptan or placebo subjects. Results were robust for all analyses performed, significantly favoring the tolvaptan group, suggesting that missing data did not influence the original analysis outcomes.

Table 10.5.3-1 Time to Event Sensitivity Analyses for the Key Secondary Composite Endpoint and Combined Renal Function/Pain Components Accounting for Missing Data (Withdrawals Due to SAEs or Non-Serious Severe Adverse Events Counted as Events in the Analysis)

Analysis, Group	Recurrent Events					HR	95% CI	P-value[a]
	# of Patients	# of Total Events	Total F/U Years	Events per 100 F/U Years	Mean F/U Years			
Time to multiple event +AE withdrawal, key secondary composite								
Tolvaptan	961	1097	2393	45.83	2.49	0.885	0.795, 0.986	0.0269
Placebo	483	679	1331	51	2.76			
Time to first event +AE withdrawal, key secondary composite								
Tolvaptan	961	608	1331	45.70	1.38	0.866	0.759, 0.988	0.0322
Placebo	483	346	648.8	53.33	1.34			
Time to multiple event +AE withdrawal, combined renal pain/function								
Tolvaptan	961	205	2393	8.57	2.49	0.652	0.516, 0.823	0.0003
Placebo	483	174	1331	13.07	2.76			
Time to first event +AE withdrawal, combined renal pain/function								
Tolvaptan	961	174	2213	7.86	2.30	0.695	0.554, 0.872	0.0017
Placebo	483	131	1164	11.25	2.41			

Note: Withdrawals due to adverse events (serious and non-serious, severe) are considered as an event in the analysis.

[a]Derived from Cox regression model with factor treatment.

10.5.4 Analyses of PKD Outcomes

When subjects withdrew from trial medication, they could still elect to provide PKD Outcomes data via telephone contact. Follow up was collected in 40.3% to 46.2% of subjects who withdrew from trial medication early.

For each of the 13 components of PKD Outcomes collected which are measures of ADPKD progression, the proportion of subjects in the tolvaptan group that experienced each outcome was either less than or similar to the proportion of subjects in the placebo group that experienced that outcome, consistent with the primary and secondary endpoints. Similar analyses were conducted on all subjects and subjects followed after trial medication discontinuation for each of the PKD Outcomes. In general, PKD Outcomes event rates in those who received tolvaptan and then discontinued therapy early were no worse than those who received placebo but discontinued therapy. These data are likely representative of those who terminated the trial early but did not willingly provide follow-up data based on their having a similar demographic profile. Therefore, available data from those who withdrew make it unlikely that missing data changed the

key secondary composite endpoint findings and therefore support the clinical benefit of tolvaptan.

In sensitivity analyses for missing data, subjects' self-report of renal pain collected as part of PKD Outcomes were used to impute renal pain events after a subject's discontinuation from trial medication. Analyses of the time to multiple renal pain events and time to first renal pain events significantly favored tolvaptan, with HRs of 0.701 ($p = 0.0197$) and 0.709 ($p = 0.0173$).

Taken together, these analyses render it unlikely that missing data affected the original trial conclusions.

10.5.5 Analyses Adjusting for Demographic and Baseline Characteristics as Covariates in the Model

In order to account for the effect of missing data influenced by demographic and baseline characteristic factors on the treatment comparison under the assumption of data MAR, a likelihood-based slope analysis for TKV was performed with these factors added to the model of the protocol-specified analysis. The analysis was still highly statistically significant (estimated slope for tolvaptan 3.0 vs placebo 5.6% per year, translating to a 46.8% relative improvement; ratio of geometric mean 0.975; 95% CI 0.970 to 0.980; $p < 0.0001$), and confirms that missing data do not alter the conclusion of this endpoint, under the assumption of MAR.

Similarly, a likelihood-based slope analysis for renal function decline was performed with these factors added to the model of the protocol-specified analysis. The analysis was still highly statistically significant (estimated slope for tolvaptan −2.553 vs placebo −3.765 $[mg/mL]^{-1}$ $year^{-1}$; treatment effect 1.213; 95% CI 0.634 to 1.792; $p < 0.0001$; and confirms that missing data do not change the conclusion of this endpoint, under the assumption of MAR.

In addition, results of the renal pain component analysis adjusted by covariates of demographic and baseline characteristic factors were consistent with the result of the protocol-specified analysis (4.78 events/100 patient-years on tolvaptan vs 7.39 /100 patient-years on placebo; HR 0.635; 95% CI 0.460 to 0.879; $p = 0.0061$).

Moreover, results of the renal function component analysis adjusted by covariates of demographic and baseline characteristic factors were consistent with the results of protocol-specified analysis (2.62 events/100 patient-years on tolvaptan vs 2.80 events/100 patient-years on placebo; HR 0.382; 95% CI 0.265 to 0.551; $p < 0.0001$).

10.5.6 Influence of Demographic and Baseline Characteristics in Completer Subjects

The demographics characteristics of the completer versus withdrawn subjects from Trial 156-04-251 were examined for potential imbalances that may predict a MNAR effect on trial results (Table 10.5.6-1). In general, in both treatment groups, withdrawn subjects were younger and had higher TKV and eGFR. More subjects withdrew on placebo who were Caucasian, male, and had hypertension and history of renal pain. More subjects withdrew on tolvaptan who were female and had a history of proteinuria. Overall, however, those factors which would predict a worse renal outcome (baseline GFR, hypertension, proteinuria, age) were fairly well balanced between groups, and do not support a MNAR effect on the trial outcomes.

Table 10.5.6-1 Demographics, Baseline Characteristics, and ADPKD Medical History in Completer and Early Withdrawn Subjects in Trial 156-04-251

Characteristic	Tolvaptan			Placebo		
	Completed	Withdrew	Total	Completed	Withdrew	Total
Subjects, N (%)	740 (77.0)	221 (23.0)	961 (100.0)	417 (86.2)	67 (13.8)	484 (100.0)
Age, mean (SD), years	39.0 (6.9)	37.3 (7.6)	38.6 (7.1)	39.2 (7.1)	36.7 (7.1)	38.8 (7.1)
Race, %						
Caucasian	625 (84.5)	185 (83.7)	810 (84.3)	347 (83.2)	61 (91.0)	408 (84.3)
Non-Caucasian	115 (15.5)	36 (16.3)	151 (15.7)	70 (16.8)	6 (9.0)	76 (15.7)
Gender						
Male	390 (52.7)	105 (47.5)	495 (51.5)	215 (51.6)	36 (53.7)	251 (51.9)
Female	350 (47.3)	116 (52.5)	466 (48.5)	202 (48.4)	31 (46.3)	233 (48.1)
TKV, mean (SD),[a] mL	1696.1 (877.10)	1734.0 (1057.5)	1704.8 (921.27)	1653.6 (845.87)	1755.8 (1031.8)	1667.5 (873.11)
$eGFR_{CKD-EPI}$, mean (SD),[b] mL/min/1.73m^2	80.79 (20.67)	83.21 (22.09)	81.35 (21.02)	81.74 (22.83)	84.59 (22.05)	82.14 (22.73)
Proteinuria history,[c] %	161 (21.8)	72 (32.6)	233 (24.2)	97 (23.3)	19 (28.4)	116 (24.0)
Hypertension, %	605 (81.8)	160 (72.4)	765 (79.6)	327 (78.4)	55 (82.1)	382 (78.9)
Renal pain history,[d] %	373 (50.4)	123 (55.7)	496 (51.6)	194 (46.5)	45 (67.2)	239 (49.4)

SD = standard deviation.

[a] N=66 in placebo withdrawn group.

[b] N=737 tolvaptan completed group; N=415 placebo completed group.

[c] N=739 tolvaptan completed group.

[d] N=720 tolvaptan completed group; N = 217 tolvaptan withdrawn group; N=408 placebo completed group.

To further evaluate the possibility that missing data may have influenced the analysis, the sponsor looked at important baseline characteristics to see if they were imbalanced in

subjects completing the trial, focusing on those characteristics that appear to be important predictors of endpoint progression. If a baseline characteristic has no effect on discontinuation, the characteristics of completers should be a mirror reflection of the characteristics in those who withdrew. Although these characteristics were very similar in each treatment group, the small differences were examined for any potential impact on the conclusions drawn from the primary analysis. The data evaluated in this analysis are presented in Table 10.5.6-2.

Table 10.5.6-2 includes in its left-most columns various subject characteristics' apparent impact on key endpoint progression using placebo response data. In the table's right-most columns, the similarities or differences for these baseline characteristics among completer subjects are shown by treatment group. The bottom two rows describe results of an analysis specifically assessing the impact of a positive ADPKD history of renal pain, nephrolithiasis or upper UTI on the development of a renal pain event during the trial with the adjusted hazard ratio for time to multiple or first event to the left and the prevalence of the most important factor, renal pain, on the right.

These data allow one to infer the likely directional quality (but not quantity) of impact of missing data on the outcomes of interest by providing the characteristics of those who fully contributed their data to the endpoint and allowing for inference to those whose data were partially missing. In general, those characteristics associated with faster disease progression were represented in nearly the same proportion of tolvaptan completers as compared with placebo completers. This would allow one to infer that any imbalances would have little influence on the ability to detect a slowing of disease progression or reduction of ADPKD related events by tolvaptan. As a result, the data support the conclusion that missing data under the assumption of MAR did not have a tendency to affect the trial outcomes. These data are further supported by the baseline-adjusted results discussed in Section 10.5.5.

Table 10.5.6-2 Analyses of Demography, Medical Status and Medical History on Primary and Secondary Endpoints of Interest in Trial 156-04-251

Characteristic and Its Apparent Influence on Endpoint (PLC Response Shown)					Baseline Status for Completer Subjects	
Characteristic	**TKV Growth (%/Yr)**	**Pain Events (#/100 FU Yrs)**	**Worsening Renal Function Events (#/100 FU Yrs)**	**Reciprocal of SC Decline $(mg/mL)^{-1}Yr^{-1}$**	**Characteristic and Treatment Group**	**Mean Age or Proportion Completing Trial**
Age (years)						
< 35	6.06	10.29	4.31	−2.621	Mean Age TLV (years)	39.0 years
≥ 35	5.34	6.49	4.98	−4.093	Mean Age PLC (years)	39.2 years
Race						
Caucasian	5.59	8.11	4.43	−3.488	% Caucasian TLV	84.5%
Non-Caucasian	5.02	3.20	6.95	−5.409	% Caucasian PLC	83.2%
Gender						
Female	4.29	9.47	4.99	−4.110	% Male TLV	52.7%
Male	6.62	5.26	4.69	−3.492	% Male PLC	51.6%
HTN Status						
HTN	6.09	7.83	5.29	−4.185	% HTN TLV	81.8%
No HTN	3.32	5.31	3.19	−2.314	% HTN PLC	78.4%
Renal Function (eCrCL [mL/min])						
< 80	5.32	7.24	8.38	−5.425	% < 80 TLV	26.4%
≥ 80	5.56	7.32	3.46	−3.144	% < 80 PLC	28.8%
Albuminuria (micro- or greater)						
Yes	5.51	8.07	6.69	−4.617	% Yes TLV	21.8%
No	5.47	6.20	2.20	−2.673	% Yes PLC	23.3%
TKV (mL)						
<1000	4.04	6.43	1.08	−2.279	% <1000 TLV	20.7%
≥ 1000	5.88	7.53	5.83	−4.185	% <1000 PLC	21.1%
Renal Pain Events (Time to Event, Factoring Renal Pain, Nephrolithiasis, UTI History)						
Multiple Event	HR = 0.645, 95% CI 0.470 to 0.885, p = 0.0067				% History of renal pain TLV	50.4%
First Event	HR = 0.658, 95% CI 0.488 to 0.889, p = 0.0063				% History of renal pain PLC	46.5%

ACEi = angiotensin-converting enzyme inhibitor; ADPKD = autosomal dominant polycystic kidney disease; ARB = angiotensin receptor blocker; CI = confidence interval; eCrCL = estimated creatinine clearance; FU = follow up; HR = hazard ratio; HTN = hypertension; PKD = polycystic kidney disease; PLC = placebo; SC = serum creatinine; TLV = tolvaptan; TKV = total kidney volume; UTI = urinary tract infection.

Note: The differences in each endpoints' apparent outcomes are presented in the first 5 columns of the table. The relative proportion of subjects (or average if a continuous variable) who fell into the completer, or discontinuation (with or without additional FU) groups having that baseline characteristic thought to be potentially prognostic of outcome in ADPKD.

10.6 Numbers of Subjects Exposed to Immediate-release Tolvaptan Tablets in Completed or Ongoing Trials in the ADPKD Program

Table 10.6-1 Numbers of Subjects Exposed to Immediate-release Tolvaptan Tablets in Completed or Ongoing Trials in the ADPKD Program

Clinical Trials[a]	**Subjects Exposed, N, to Oral Tolvaptan IR**
Phase 3 Pivotal (Multinational) 156-04-251	961
Phase 2 and 3 Supportive (Multinational, US, Japan)	
Phase 2 or 3 open-label extension:	
-156-04-250	46 (43)
-156-05-002	17 (17)
-[156-08-271]	1021 (686)[b]
-[156-09-003]	13 (13)
-[156-10-003]	135 (85)
Phase 1 and 2 Clinical Pharmacology Trials in ADPKD or Renally Impaired Subjects (US, Japan)	
Single-dose trials:	
-156-04-248	8
-156-09-282	37[c]
Single- and multiple-dose or multiple-dose trials:	
-156-04-001	18
-156-04-249	37
-156-06-260	20
-156-09-284	29
-156-09-285	12[d]
Phase 1 Clinical Pharmacology Trials in Healthy Subjects (US, Japan, Korea)	
Single-dose trials:	
-156-07-262	18[d]
-156-KOA-0801	36
-156-11-295	58
TOTAL, All Trials - ADPKD subjects - Healthy subjects	1682 1533 112

ADPKD = autosomal dominant polycystic kidney disease; IR = immediate-release (formulation); MR = modified-release (formulation); US = United States.

[ ] Indicates ongoing trial.

( ) Indicates subjects who were exposed to tolvaptan IR tablets in more than one trial.

Note: Only exposure to IR tolvaptan tablets is counted. Subjects are counted only once in totals where exposed to tolvaptan IR tablets in more than one trial. However, 4 subjects (538S00362366, S20292029, S20362036, and S20042004) were double counted due to non-matching subject identifier in 156-08-271 with their parent trials. Exposure from ongoing, double-blind Trial 156-09-290 is excluded.

[a] Data cut-off date for ongoing trials: 01 Feb 2013.

[b] Considered as unique exposures to tolvaptan IR are subjects from Trial 156-09-285 exposed previously to tolvaptan MR capsules, placebo subjects rolling over from Trial 156-04-251, and rollover subjects from ongoing, double-blind Trial 156-09-290 (treatment assignment yet unknown).

[c] Included healthy and renally impaired subjects. Though ADPKD subjects were allowed, none enrolled.

[d] Only includes exposures to IR oral tolvaptan tablets (MR oral tolvaptan capsules were also studied).

10.7 Narratives for Subjects Meeting Hy's Law

10.7.1 Subject 04251-302-4053

Subject 04251-302-4053, a 34-year-old Caucasian female diagnosed with ADPKD at the age of 27, was started on oral tolvaptan 45/15 mg daily on Day 1 ( ). The Subject was titrated to 60/30 mg at Week 1 visit ( ) after affirming she could tolerate taking the 45/15 mg dose for the rest of her life, 90/30 mg at Week 2 visit (and remained at 90/30 mg at Week 3 visit ( ) (end of titration). Tolvaptan was interrupted on Day 246 ( ) and the Subject discontinued from the study on the same day due to a serious adverse event (SAE) of hepatitis. The overall compliance with tolvaptan intake was 100%. The Subject's medical history included nephrolithiasis, upper urinary tract infection, and hypertension.

On Day 246 (the Subject experienced an SAE of hepatitis (HEPATITIS). The Subject was taking tolvaptan 90/30 mg the day prior to the event onset. The Subject received approximately 35 weeks of tolvaptan before the onset of the SAE. The Subject had pronounced jaundice at the Month 8 Visit (Day 246 [Laboratory tests from the same day confirmed that hepatic enzymes and bilirubin were increased. An abdominal ultrasound showed polycystic kidneys, liver without discernible parenchymatous lesions, and rest of the abdominal ultrasound scan within normal limits. The Subject declared that she took (around the end of Dec 2008) 8 gm of amoxicillin/clavulanate in one day (due to toothache). The Investigator commented that cholestatic jaundice is a well-known side effect of amoxicilin/clavulanate and it can resolve slowly. No laboratory tests were performed between Dec 2008 and Day 246 (Viral serology was negative on Day 252 (The Investigator confirmed that autoantibodies were not tested to rule out autoimmune hepatitis and a liver biopsy was not performed. The Subject did not have strenuous activity prior to the event. The Investigator reported that the Subject had not taken any over the counter or herbal medications prior to the event onset. The Subject had no past history of alcohol consumption, use of recreational drugs, special diet, or exposure to chemicals or solvents. Also, there was no family history of liver disease. The Subject's occupation was not reported. The Subject was followed-up at the clinic until Day 266 (when laboratory tests showed decreases in hepatic enzymes and bilirubin. The Investigator reported that eight attempts were made to contact the Subject. The Subject started feeling better without taking tolvaptan; therefore, never returned to the site. After the last telephone contact with the Subject on Day 429 (the Investigator decided to discontinue the Subject from the study. Early termination visit

and procedures were not done. No clinically significant abnormalities of vital signs or electrocardiograms were reported. Clinically significant laboratory test results are presented below.

Laboratory Test Results					
	ALT	AST	ALP	GGT	Bilirubin, Total
Reference Range (unit)	6-34 (IU/L)	9-34 (IU/L)	31-106 (IU/L)	4-49 (IU/L)	0.2-1.2 (mg/dL)
Baseline	12	24	76	51*	0.5
Day 128 ((b) (6)	33	53*	90	42	0.4
Day 246	316*	499*	358*	84*	9.8*
Day 252	307*	470*	325*	59*	15.99*
Day 266 (	103*	165*	247*	68*	4.5*

ALT=alanine aminotransferase; ALP=alkaline phosphatase; AST=aspartate aminotransferase; GGT=gamma-glutamyltransferase; NA= not available.

*=outside normal range

Corrective treatments were not provided. Tolvaptan was discontinued due to the event and the last dose was taken on Day 245 (The event resolved on Day 438 (The Investigator assessed the event to be mild in intensity and probably related to tolvaptan. The Sponsor assessed the event as related to tolvaptan.

The following nonserious adverse events occurred in parallel with the SAE described above: vomiting (VOMITING) and nausea (NAUSEA).

Concomitant medications taken within 14 days prior to onset date of the event included amlodipine (10 mg PO QD starting on Day 128 [enalapril (20 mg PO BID starting on Day 22 [and progesterone (0.05 mg PO QD started in 1995 and stopped on Day 245 [(b) (6)

10.7.2 Subject 04251-731-2738

Subject 04251-731-2738, a 45-year-old Asian female diagnosed with ADPKD at the age of 35, was started on oral tolvaptan 45/15 mg daily on Day 1 The Subject was titrated to 60/30 mg at Week 1 visit (after affirming she could tolerate taking the 45/15 dose for the rest of her life, 90/30 mg at Week 2 visit (and remained at 90/30 mg at Week 3 visit ((end of titration). Tolvaptan was interrupted from Day 202 (to Day 340 (due to a serious adverse event (SAE) of hepatic function abnormal. The Subject discontinued from the study on Day 340 (due to the AE. The overall compliance with tolvaptan intake was 87.5%. The Subject's medical history included hepatic cysts, hematuria, anemia, hypertension, and kidney pain.

On Day 202 (the Subject experienced an SAE of hepatic function abnormal (HEPATIC FUNCTION ABNORMAL) and was hospitalized. The Subject was taking tolvaptan 90/30 mg the day prior to the event onset. The Subject had received approximately 29 weeks of tolvaptan therapy before the SAE of hepatic function abnormal. The Subject did not have past medical history of liver disorder, hepatitis nor alcohol and drug abuse. The Subject did not undergo strenuous physical activities. The Subject did not eat or drink enough between Day 162 (and Day 182) due to busy lifestyle. The Subject complained of nausea and stomach discomfort on Day 166 (The symptom persisted despite continual improvement of AST and ALT results on Day 177 ((b) (6) and Day 190 ((b) (6) . The Subject experienced worsening of nausea on Day 202). The Subject was not exposed to any drugs, alcohol, herbs, chemicals, organic or solvents that could have caused the enzyme elevation. The Subject only drank small amounts of

alcohol occasionally. The Subject did not have family history of liver disease. Abdominal computed tomography (CT) scan on Day 204 (revealed multiple cystic lesions in the liver and both kidneys. Content fluid of the cystic lesions was considered to be hemorrhagic. Abdominal ultrasound on Day 206 (showed that hepatic parenchyma was composed of almost normal appearance despite many cysts. The abdominal ultrasound also revealed there were no significant intrahepatic bile duct (IHBD) dilatation and no significant SOL. On Day 213 (no improvement was observed on hepatic function data despite the treatment with fluid replacement and bed rest. In addition, total bilirubin value and coagulation test results worsened (relevant test results were not provided). The Subject was treated with prednisolone infusion and fresh frozen plasma (FFP) transfusion. On Day 220 (laboratory data improved and the prednisolone infusion was changed to oral administration. Nausea had resolved on the same day. On Day 237 (the Subject was discharged from the hospital and the event was ongoing at the time of discharge. No clinically significant abnormalities of vital signs or electrocardiograms were reported. Clinically significant abnormalities of laboratory test results are presented below.

Laboratory Test Results					
	ALT	AST	ALP	GGT	Bilirubin, Total
Reference Range (unit)	6-34 (IU/L)[a] 6-27[b]	9-34 (IU/L)[a] 13-33[b]	117-350 (U/L)	4-49 (IU/L)[a] 9-109[b]	0.2-1.2 (mg/dL)[a]
Baseline (b) (6) [a]	16	30	NA	14	0.4
Day 123	46*	38*	196	31[a]	0.5
Day 166	570*	403*	358*	274*	0.5
Day 176 [b]	570*	403*	NA	274*	0.5
Day 177 [b]	332*	213*	262	246*	0.5
Day 190	197*	159*	215	199*	0.6
Day 202 [b]	882*	757*	338	323*	1.4*
Day 204	840*	720*	300	265*	1.8*
Day 206	857*	722*	300	256*	3.0*
Day 207	809*	681*	316	244*	4.1*
Day 211	716*	641*	361*	243*	6.9*
Day 213 [b]	598*	627*	325	206*	7.6*
Day 214 [b]	467*	333*	323	177*	6.4*
Day 215	379*	235*	344	179*	5.0*
Day 217	267*	134*	332	203*	3.1*
Day 219	265*	130*	289	236*	2.4*
Day 222	200*	75*	240	189*	2.0*
Day 226	121*	42*	209	163*	1.7*
Day 229	82*	31*	200	147*	1.7*
Day 232	57*	27*	170	124*	1.8*
Day 234 [b]	44*	23	188	126*	1.5*
Day 249 [a]	30	25	NA	62*	1.1

ALT=alanine aminotransferase; ALP=alkaline phosphatase; AST=aspartate aminotransferase; GGT=gamma-glutamyltransferase; NA= not available.

*=outside normal range

a. Reference range, baseline values, and GGT on Day 123, and Day 249 come from patient profile. All other values are from Medical Summary.

b. Reference ranges from Medical Summary.

Corrective treatments included bed rest, life style improvements, vitamin K, famotidine, dextrose in lactated ringer's, metoclopramide, glucose, ascorbic acid, flebobag ring lact, pyridoxal phosphate, riboflavin sodium phosphate, thiamine hydrochloride, sodium chloride, prednisolone sodium succinate, plasma, menatetrenone, omeprazole, and prednisolone. Tolvaptan was discontinued due to the event and the last dose was taken on Day 201 ((b) (6) The event resolved on Day 305 ((b) (6) The Investigator assessed the event to be severe in intensity and definitely related to tolvaptan. The Sponsor assessed the event as related to tolvaptan.

Adverse events ongoing in parallel to the event of hepatic function abnormal included appetite loss increased (ANOREXIA), nausea (NAUSEA), stomach upset (STOMACH DISCOMFORT), pollakiuria (POLLAKIURIA), thirst (THIRST), hemorrhoid (HAEMORRHOIDS), constipation (CONSTIPATION), palpitation (PALPITATIONS), headache (HEADACHE), itching skin (PRURITIS), vomiting (VOMITING), choloplania (BILE OUTPUT), abdominal pain (ABDOMINAL PAIN), abdominal distension (ABDOMINAL DISTENSION), pharyngodynia (PHARYNGOLARYNGEAL PAIN), proctoptosia (RECTAL PROLAPSE) and worsening hypertension (HYPERTENSION).

Concomitant medications taken within 14 days prior to onset date of the event included atenolol (25 mg PO QD started in 1998), imidapril hydrochloride (5 mg PO QD started in 1998), olmesartan medoxomil (20 mg PO QD started on Day -42 [(b) (6) and rabeprazole sodium (10 mg PO QD started on Day 177 [(b) (6) and stopped on Day 190 [(b) (6)

10.7.3 Subject 08271-468-4301

Subject 08271-468-4301, a 44-year-old Caucasian female diagnosed with ADPKD at the age of 35, completed tolvaptan study 156-04-251, randomized to placebo on 28 Sep 2011. The Subject was started on oral tolvaptan 45/15 mg daily on Day 1 ((b) (6)) in study 156-08-271. The Subject was titrated to 60/30 mg starting on Day 9 ((b) (6) and 90/30 mg starting on Day 15 ((b) (6) (end of titration). The tolvaptan was discontinued on Day 90 ((b) (6) due to an adverse event (AE) (elevated liver function test [LFT]) on Day 89 ((b) (6) followed by serious adverse events (SAEs) of acute cytolytic hepatitis and cholestatic hepatitis on Day 108 ((b) (6) The Subject's medical history included proteinuria, hypertension, kidney pain, hepatic cysts, hematuria (blood in urine), upper urinary tract infection (kidney/bladder), chronic renal failure, right knee patella femoral chondropathy with a

small knee excentration, appendectomy, rhinoplasty, amoxicillin allergy, magnesium deficiency, ectopic pregnancy, and history of smoking.

On Day 89 (the Subject experienced a non-serious AE of elevated LFT (LIVER FUNCTION TEST ABNORMAL). The Subject was taking tolvaptan 90/30 mg at the event onset; tolvaptan was discontinued on Day 90 (The Subject received approximately 13 weeks of tolvaptan therapy before the onset of the non-serious AE of liver function test abnormal. On Day 89 (the Subject reported to the site for her Month 3 visit and laboratory test results revealed elevated alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyltransferase [GGT], alkaline phosphatase, and lactate dehydrogenase [LDH] (see table below for select abnormal laboratory results). On Day 98 (the Subject reported hot flushes, an increase in right hypochondrium pain, and the appearance of dark urine and pale stools preceding the onset of mucocutaneous jaundice. Liver function tests remained elevated.

On Day 108 (the Subject experienced SAEs of acute cytolytic hepatitis (CYTOLYTIC HEPATITIS) and cholestatic hepatitis (HEPATITIS CHOLESTATIC) and was hospitalized. The Subject also experienced emergence of jaundice with a significantly elevated total bilirubin on this date. The Subject was not taking tolvaptan at the onset of these events. Liver function tests were also performed on Day 108 and remained elevated. The Subject was subsequently diagnosed with acute cytolytic and cholestatic hepatitis (factor V limit at 71% [50-150%]) with jaundice but without encephalopathy. On Day 109 (an abdominal ultrasound showed no blood vessel, hepatic vein, or portal vein abnormality. On Day 111 (serology for Hepatitis A, Epstein Barr virus (EBV), and varicella were positive; serology for hepatitis E, cytomegalovirus, and herpes simplex virus were negative. Hepatitis A, EBV, and varicella tests showed that the Subject had old immunity. On Day 119 (a magnetic resonance imaging (MRI) scan showed multiple cysts disseminated in the parenchyma, an enlargement of the main bile duct at 10 mm without visible obstacle or dilatation of the associated intrahepatic bile duct. The gall bladder was collapsed, probably due to the enlargement of the bile duct secondary to collapse, without argument for a compression. A liver biopsy was performed on Day 120 and showed cytolytic and cholestatic hepatitis with moderate centrilobular necrosis, ductal neogenesis, and centrilobular inflammation consistent with drug-induced hepatitis. The same day, LFTs were improving with a decrease in cytolysis and cholestasis (see laboratory values table). In the Investigator's opinion, there was no argument for the event being viral acute hepatitis, due to extensive testing and also no argument for an autoimmune hepatitis, or Wilson disease. The

Investigator reported that the Subject had no prior history of abnormal liver function tests, no jaundice, and no obstructive medical history. The Subject did not drink alcohol. In addition, the Subject was not exposed to any herbs, chemicals, nor organic solvents that could have caused the enzyme elevation and no other new drug had been introduced aside from the treatment for magnesium deficiency in Feb 2012. Selected relevant abnormal laboratory values are reported below.

Laboratory Values									
	Reference Range 1 (unit)	**Base-line** (b) (6)	**Day 89[a]** (b) (6)	**Day 98** (b) (6)	**Refer-ence Range 2 (unit)**	**Day 108[b]** (b) (6)	**Day 120[c]** (b) (6)	**Day 194** (b) (6)	**Day 232** (b) (6)
Alanine aminotrans-ferase	6-34 (U/L)	12	1243H	1098H	5-34 (U/L)	1742H	746H	59H	59H[d]
Aspartate aminotrans-ferase	9-34 (U/L)	16	703H	751H	5-31 (U/L)	1412H	734H	52H	53Hd
Gamma-glutamyl-transferase	4-49 (U/L)	16	122H	190H	5-38[d] (U/L)	208H[d]	164H[d]	63H[d]	54H[d]
Lactate dehydrogen-ase	53-234 (U/L)	125	314H	282H	NR	NR	NR	NR	NR
Total bilirubin (total)	0.2-1.2 (mg/dL)	0.4	0.8	1.2	1-17[d] (µmol/L)	165H[d]	173H[d]	0.6[e]	NR

NR = not reported; H = high, ie, value is above the upper limit of the normal range; L = low, ie, value is below the lower limit of the normal range.

Note: Reference Range 1 applies to baseline-Day 98; Reference Range 2 applies from Days 108-232 unless otherwise specified

[a] Month 3 visit, day of start of adverse event leading to discontinuation of tolvaptan; last dose was taken on Day 90 ((b) (6)

[b] Day of onset of SAEs and first day of hospitalization

[c] Day of liver biopsy

[d] Lab values obtained from medical summary

[e] Reference range bilirubin Day 194= 0.2-1.2 mg/dL

The Subject did not receive any corrective treatment for this event. On Day 121 (b) (6)), the Subject was discharged from the hospital with continuing jaundice and elevated liver enzymes. The Subject was prescribed liver function test monitoring 2 days a week for the first week and once a week for the following month. Tolvaptan was discontinued due to the events and the last dose was taken on Day 90 ((b) (6) The Subject had completed the early termination visit on Day 187 ((b) (6) and the 7-day follow-up visit on Day 194 ((b) (6) The events were resolving at the time

of reporting. The Investigator assessed the events as moderate in intensity and related to tolvaptan. The Sponsor assessed the events as possibly related to tolvaptan.

When the Subject was seen for a consultation on [redacted] her liver function was almost back to normal. Anti-tissue antibody tests performed in April were negative.

The Subject was seen for a consultation on [redacted] about 9 months after discontinuation from the study. The patient indicated weakness which had lasted for about a week, without an obvious explanatory factor: no change to treatment, no significant additional physical activity, no symptoms. The liver function panel showed no significant change. Transaminases were still slightly increased but stable, with a slight decrease compared to June.

The Subject was seen for a nephrology consultation on [redacted] to follow up her chronic renal failure. She was enrolled in an observational monitoring protocol without further treatment (Protocol 291). On perindopril 8 mg in the morning, blood pressure was 135/80 while seated. The intermittent weakness she described may be due to a combination of her chronic renal failure, although not very progressive with recent creatinine at 131 µmol/L, which corresponds to a glomerular filtration rate of 42 mL/min/1.73m^2 using the MDRD formula, possible decreases in blood pressure and liver function which remained sub-normal.

The Subject was seen for a further consultation on [redacted] Her infrequent episodes of fatigue had resolved. Her liver function was almost normal with transaminases, both AST and ALT, at 1.5 times the normal value (no lab results provided). GGT and alkaline phosphatase were normal. The physician did not schedule another visit for the patient again, but regular liver function panels were recommended. The Subject complained of symptoms of difficulty digesting and frequent burping for which there was no obvious explanation.

The Subject recovered with sequelae from the elevated liver function test and the drug induced hepatitis on [redacted] The sequelae consisted of a continued slight elevation of AST and ALT. No clinically relevant AEs occurred in parallel to the events. As of this writing, this event is pending formal adjudication.

The Subject had taken the following concomitant medication within 14 days prior to the onset of the event: perindopril (4 mg PO QD started Day -155 [redacted]