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*APPLICATION NUMBER:*

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**CLINICAL REVIEW(S)**

Clinical Review  
 Nhi Beasley, Pharm. D., and Melanie Blank, M.D.  
 NDA 204441  
 Tolvaptan (JYNARQUE®)

### CLINICAL REVIEW

<b>Application Type</b>	NDA
<b>Application Number(s)</b>	204441
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<b>Submit Date(s)</b>	24 October 2017
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<b>Division/Office</b>	Division of Cardiovascular and Renal Products
<b>Reviewer Name(s)</b>	Nhi Beasley, Pharm.D. and Melanie Blank, MD
<b>Review Completion Date</b>	19 April 2018
<b>Established/Proper Name</b>	Tolvaptan
<b>(Proposed) Trade Name</b>	JYNARQUE
<b>Applicant</b>	Otsuka Pharmaceutical Co., Ltd.
<b>Dosage Form(s)</b>	Tablet
<b>Applicant Proposed Dosing Regimen(s)</b>	Recommended starting dose: 60 mg to be administered as a split-dose regimen of 45 mg/15 mg (45 mg taken on waking and 15 mg taken 8 hours later). Titrate to 90 mg per day (60 mg/30 mg split dose regimen) then to a target of 120 mg per day (90 mg/30 mg split-dose regimen) as tolerated
<b>Applicant Proposed Indication(s)/Population(s)</b>	To slow kidney function decline <span style="background-color: #cccccc; padding: 0 20px;">(b) (4)</span> in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD)
<b>Recommendation on Regulatory Action</b>	Approval
<b>Recommended Indication(s)/Population(s) (if applicable)</b>	To slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD), CKD stage 1-4

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## Glossary

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AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CC	Collaborative Cross
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
DPMH	Division of Pediatric and Maternal Health
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
f.u.	follow-up
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IMP	investigational medicinal product
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities

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mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OND	Office of New Drugs
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

## 1. Executive Summary

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### 1.1. Product Introduction

Tolvaptan (proposed proprietary name: JYNARQUE) is a selective, competitive vasopressin V2 antagonist that is currently marketed for the treatment of clinically significant hypervolemic and euvolemic hyponatremia [serum sodium < 125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction], including patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone under the trade name of SAMSCA®. In the current application, the applicant is proposing to market tolvaptan for the following indication: to slow kidney function decline (b) (4) in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD). For this indication, the sponsor proposes to market tolvaptan as immediate release tablets for oral administration in 15 mg, 30 mg, 45 mg, 60 mg and 90 mg strengths. The recommended starting dose for this indication is 60 mg to be administered as a split-dose regimen of 45 mg/ 15 mg (45 mg taken on waking and 15 mg taken 8 hours later). This dose should be titrated to 90 mg per day (60mg/30mg split dose regimen) then to a target of 120 mg per day (90 mg/30 mg split-dose regimen) as tolerated.

### 1.2. Conclusions on the Substantial Evidence of Effectiveness

Based on evidence from two adequate and well-controlled clinical trials, TEMPO and REPRISE, it can fairly and responsibly be concluded that tolvaptan will have one of the effects it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling, namely to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD). (b) (4)

(b) (4)

### 1.3. Benefit-Risk Assessment

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### Benefit-Risk Integrated Assessment

Autosomal dominant polycystic kidney disease (ADPKD) is a slowly progressive genetic kidney disease with multiple systemic effects that cause considerable morbidity and decreased quality of life. The life time risk of end stage renal disease (ESRD) resulting in dialysis or renal transplantation is between 50-75%. Increased total kidney volume (TKV) due to a high cyst burden is associated with risk for ESRD.

There are no approved products for slowing progression of kidney disease in patients with ADPKD. Hence, there is unmet need for a drug that would have ADPKD disease-modifying properties.

Evidence from 2 randomized, placebo-controlled, double-blind trials [one conducted in chronic kidney disease (CKD) Stage 1 and 2 disease (TEMPO), and one conducted in later stage disease, CKD Stages 2-4 (REPRISE)] provide support for the claim that tolvaptan slows kidney function decline in patients with rapidly progressive ADPKD. The first completed trial (TEMPO) enrolled 1454 subjects with early rapidly progressing ADPKD (as determined by TKV criteria) who had relatively preserved estimated glomerular filtration rate (eGFR) by the Cockcroft Gault equation  $> 60$  mL/min] and followed them over a 3-year period. In this trial, study subjects' doses were titrated to a maximum tolerated daily split dose of tolvaptan of up to 120 mg (90 mg in a.m. and 30 mg in the p.m.) or matching placebo. The TEMPO trial showed that reduction in eGFR in the tolvaptan treatment group was 25% less than the reduction in eGFR in the placebo group, but the absolute treatment difference was small (0.9 mL/min/  $1.73\text{m}^2$  per year). This trial also showed an early effect on total kidney volume (TKV). The second pivotal trial (REPRISE) enrolled 1370 subjects with later stage rapidly progressing ADPKD and reduced eGFR [defined by the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) between 65 and 25 mL/min/ $1.73\text{m}^2$ ]. REPRISE had several study periods: a prerandomization single-blind, open-label placebo run-in period; a single blind tolvaptan titration and run-in period designed to minimize drop out during the 12-month randomized-withdrawal period. After the double-blind period, all subjects were taken off randomized treatment and followed for up to 40 days. Treatment doses were the same as for the TEMPO trial. For the primary endpoint analysis, eGFR by CKD-EPI was measured before tolvaptan was started and end of treatment eGFR values were measured at least one week after last dose. REPRISE showed that reduction in eGFR in the tolvaptan treatment group was 36% less than the reduction in eGFR in the placebo group, but the absolute treatment difference was still small (1.3 mL/min/  $1.73\text{m}^2$  per year). Tolvaptan was shown in both trials to have a persistent effect on the slowing of kidney function decline in patients with rapidly progressing ADPKD CKD stages I to early stage IV (eGFR between normal values and 25 mL/min/ $1.73\text{m}^2$ ). It is reasonable to conclude that if taken chronically, tolvaptan should allow rapidly progressing ADPKD patients to delay or avoid dialysis or transplantation by slowing kidney disease progression. The effect of tolvaptan on TKV appears to occur early following tolvaptan initiation and evidence from the TEMPO extension

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study suggests that there may be no effect on subsequent growth of kidney size over time.

The safety database from the two pivotal trials in ADPKD includes 1,642 subjects who had any tolvaptan exposure and 1,418 subjects exposed for at least one year (836 from TEMPO and 582 from REPRISE). The average daily dose was a split dose between 95 mg (for TEMPO) and 108 mg (REPRISE). There is also post-marketing data from other countries where tolvaptan is approved for ADPKD to inform our understanding of its safety in the ADPKD population. The most common AEs in ADPKD patients who took tolvaptan in the pivotal clinical trials are related to its mechanism of action, i.e., aquaresis, causing polyuria and thirst. The common AEs observed in the pivotal trials in ADPKD were mostly mild to moderate in severity.

The most pressing safety concern for tolvaptan is the risk of drug induced liver injury, seen to date only in the ADPKD population and first discovered after the unblinding of TEMPO and its open label extension study. In these trials, there were 3 Hy's law cases (see footnote 7), all of which recovered after drug discontinuation. The more intensive liver monitoring in REPRISE appeared to reduce the impact and severity of liver injury. There were no Hy's Law cases identified in REPRISE, and many subjects who had medication stopped because of liver enzyme and/or bilirubin elevation, did not develop clinical symptoms.

Although we have evidence from REPRISE that an intensive hepatic monitoring strategy reduces the risk of irreversible liver injury, we also have evidence that it does not eliminate it. During review of the application, the Agency received a report of a Japanese post-marketing case of a woman who despite having her liver enzymes monitored per a monitoring program like that used in REPRISE, developed liver failure requiring liver transplantation.

It is the reviewers' opinion that the uncommon risk of liver failure resulting in transplantation or death despite an intensive liver monitoring program is outweighed by the reduction in risk for ESRD, dialysis and transplantation in patients with rapidly progressing ADPKD who take tolvaptan on a chronic basis. It is unquestionable that reducing the risk of liver failure is paramount for safe use of tolvaptan in this population. Therefore, we recommend regulatory approval of tolvaptan with a REMS that will include Elements of Safe Use, a label that will include a boxed warning alerting physicians and patients to the risk of serious liver injury and need for intensive monitoring, and a PMR to establish a patient registry to describe the incidence and cases of irreversible or fatal liver injury in the post-marketing period and to evaluate the adequacy of the liver safety monitoring program.

**Benefit-Risk Dimensions**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><a href="#">Analysis of Condition</a></p>	<ul style="list-style-type: none"> <li>ADPKD is a systemic disease with multiple renal and extra-renal manifestations.</li> <li>ADPKD affects 1 in every 400 to 1,000 live births in the US, with 5,000–6,000 new cases diagnosed each year and approximately 600,000 Americans affected by the disease (prevalence ~ 1/588).</li> <li>Patients with ADPKD may develop end-stage renal disease (ESRD) at some point in their lives.</li> <li>ADPKD is considered the fourth most common renal disease requiring RRT. There are two PKD genetic variants. The mean age of onset of ESRD for the more common <i>PKD1</i> variant (71-85%) is 54.3 years, whereas that for the <i>PKD2</i> variant is 74 years.<sup>1</sup> ESRD occurs in 50-75% of patients with ADPKD.<sup>2</sup></li> <li>The hallmark of the renal manifestation of ADPKD is the progressive and continuous enlargement and proliferation of fluid-filled cysts, leading to enlargement of the kidney up to five times the normal volume in the years prior to the development of end stage kidney failure.</li> <li>Other renal manifestations include hypertension, urinary tract infection, an inability to concentrate urine, hematuria, renal stones, and acute or chronic flank and abdominal pain. Enlarged kidneys may obstruct the iliac vein or inferior vena cava, with possible thrombus formation and pulmonary embolism.</li> </ul>	<p>ADPKD is a slowly progressive kidney disease with multiple systemic effects that cause considerable morbidity and decreased quality of life. The life time risk of dialysis, transplantation or death is between 50-75%. Enlarged kidneys or increased total kidney volume (TKV) due to a high cyst burden is associated with risk for ESRD.</p>

<sup>1</sup> Hogan MC, Torres V. Polycystic kidney disease. *BMJ Best Practice*. 2015. Available from: <http://bestpractice.bmj.com/best-practice/monograph/481.html>. Accessed March 20, 2016.

<sup>2</sup> <https://www.uptodate.com/contents/polycystic-kidney-disease-beyond-the-basics>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> <li>The most common extra-renal manifestation is polycystic liver disease.</li> <li>Other extra-renal manifestations include cerebral and coronary artery aneurysms, cardiac valve disease, colonic diverticula, abdominal wall and inguinal hernias, and bronchiectasis.</li> <li>ADPKD has a considerable negative impact on quality of life.<sup>3,4,5,6</sup></li> </ul>	
<a href="#">Current Treatment Options</a>	<ul style="list-style-type: none"> <li>There are no approved products for slowing progression of kidney disease in patients with ADPKD. Existing therapies are used to treat complications of disease including pain, infections and hypertension.</li> </ul>	<p>There are no approved products for slowing progression of kidney disease in patients with ADPKD. Hence, a drug that had ADPKD disease-modifying properties would fulfill an unmet medical need.</p>

<sup>3</sup> de Barros BP, et al. Anxiety, depression, and quality of life in patients with familial glomerulonephritis or autosomal dominant polycystic kidney disease. *J Bras Nefrol.* 2011;120–128.

<sup>4</sup> Tong A, et al. A painful inheritance- patient perspectives on living with polycystic kidney disease: thematic synthesis of qualitative research. *Nephrol Dial Transplant.* 2015;30:790–800.

<sup>5</sup> Simms RJ, et al, Increased psychosocial risk, depression and reduced quality of life living with autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant.* 2016;31:1130–1140.

<sup>6</sup> Miskulin DC, et al, Health-related quality of life in patients with autosomal dominant polycystic kidney disease and CKD stages 1–4: a cross-sectional study. *Am J Kidney Dis.* 2014;63:214–226.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><a href="#">Benefit</a></p>	<ul style="list-style-type: none"> <li>• Tolvaptan was initially shown in a randomized, placebo-controlled double-blind trial (TEMPO) that enrolled 1454 subjects to slow the progression of kidney disease in patients with early rapidly progressing ADPKD, when renal function is preserved, over a 3-year period. The magnitude of the treatment effect was a reduction in eGFR decline of 25%, but the absolute treatment difference was small (0.9 mL/min/ 1.73m<sup>2</sup> per year) by the CKD-EPI equation (-2.7 mL/min/1.73 m<sup>2</sup> per year decline for the tolvaptan treatment group and -3.6 mL/min/1.73m<sup>2</sup> per year decline for the placebo treatment group); This trial also showed an early effect on total kidney volume (TKV). TEMPO also showed a reduction in renal pain events.</li> <li>• Tolvaptan was subsequently shown in a second randomized, placebo-controlled, double-blind trial (REPRISE) that enrolled 1370 subjects to slow the progression of kidney disease in patients with later stage rapidly progressing ADPKD and reduced eGFR over a 12-month treatment period. The magnitude of the treatment effect was a reduction in eGFR decline of 36%, but the absolute treatment difference was still small (1.3 mL/min/ 1.73m<sup>2</sup> per year) by the CKD-EPI equation (-2.3 mL/min/1.73 m<sup>2</sup> per year decline for the tolvaptan treatment group and -3.6 mL/min/1.73m<sup>2</sup> per year decline for the placebo treatment group).</li> <li>• The results of the TEMPO extension trial suggest that there is no effect on subsequent growth of the kidney over time.</li> </ul>	<p>Evidence from 2 randomized, placebo-controlled, double-blind trials [one conducted in CKD Stage 1-2 disease (TEMPO), and one conducted in later stage disease, CKD Stages 2-4 (REPRISE)] and the TEMPO extension study provide support for the claim that tolvaptan has disease modifying properties in rapidly progressive ADPKD. More specifically, tolvaptan has a persistent effect on the slowing of kidney function decline and if taken chronically will allow patients to delay or avoid dialysis or transplantation. The effect of tolvaptan on TKV appears to occur at the early stages of treatment and evidence from the TEMPO extension trial suggests that there is no effect on subsequent growth of the kidney over time.</p>
<p><a href="#">Risk and Risk Management</a></p>	<ul style="list-style-type: none"> <li>• A total of 3,114 subjects were exposed to tolvaptan in the ADPKD program. The median exposure was ≥ 18 months and included 744 subjects who were exposed to tolvaptan for ≥ 60 months. The safety database from the two placebo-controlled trials in ADPKD includes 1,418 subjects exposed to tolvaptan for at least one year (836 from TEMPO and</li> </ul>	<p>The safety profile of tolvaptan in ADPKD of common AEs (i.e., aquaresis and thirst) has been corroborated in two placebo-</p>

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>582 from REPRISE).</p> <ul style="list-style-type: none"> <li>• Tolvaptan’s safety profile is also informed by over 4,000 subjects exposed to tolvaptan in a clinical development program for the treatment of hyponatremia and heart failure and post-marketing data. However, most of these data are limited to a lower dose and frequency of 30 mg daily and duration of treatment of less than 6 months.</li> <li>• The most consequential safety concern with tolvaptan in ADPKD is the risk of Drug Induced Liver Injury (DILI). This was an unexpected safety finding discovered after unblinding of the first trial, TEMPO. There was a higher rate of liver enzyme elevations in tolvaptan treated subjects compared to placebo treated subjects, which is a sensitive signal of the potential to cause DILI, but it is not a specific signal for hepatotoxic drugs. [4.4% versus 1.0% for ALT, respectively]. However, there were 3 Hy’s Law subjects (thus indicating altered liver function) out of 860 subjects treated for ~ 14 months.<sup>7</sup> All three subjects were women taking the highest dose of tolvaptan, 90 mg followed by 30 mg 9 hours later. At the time of the TEMPO review, there were no known cases of liver injury resulting in liver transplantation or death in any development program or post-marketing report.</li> <li>• In the second trial, REPRISE, the applicant tested a strategy to mitigate the risk of</li> </ul>	<p>controlled trials, although the difference in study design between the two trials accounts for some of the differences in rates of AEs. Tolvaptan’s mechanism of action, a vasopressin antagonist, accounted for the most common adverse events (aquaresis and thirst), and intolerability was one of the top reasons for medication discontinuation. The common AEs do not preclude the approval of tolvaptan as most were mild to moderate in severity.</p> <p>The most consequential safety concern is the risk of drug induced</p>

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<sup>7</sup> Dr. Hyman Zimmerman noted that drugs causing hepatocellular injury and clinical jaundice lead to acute liver failure with a case fatality rate of ~ 10% (ranging from ~5 - 50%). Hy’s Law according to the FDA Drug-induced liver injury guidance is defined as a subject with ALT>3x ULN, total bilirubin >2xULN and 1)hepatocellular injury without initial findings of cholestasis (i.e., serum alkaline phosphatase < 2xULN or the R value (ratio of serum ALT xULN/alkaline phosphatase xULN) > 5.0, 2) there should not be a more likely explanation for the liver injury, and 3) there should be a higher incidence of ALT elevations > 3xULN in drug treated subjects relative to control.

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	<p>serious DILI. A lower threshold (liver tests &gt; 2xULN) than would generally warrant clinical investigation was a criterion for exclusion, medication interruption, and medical investigation into the cause of enzyme elevation. In addition, liver tests were measured more frequently in REPRISÉ – at baseline, Day 14, 28, 35, and monthly for 12 months relative to the first dose of tolvaptan. These measures appeared to mitigate the risk since no new Hy’s Law subjects were identified in REPRISÉ, and there were no cases of DILI resulting in liver transplant or death. However, there was again greater elevations in transaminase on tolvaptan compared to placebo [5.6% vs. 1.2%, in ALT respectively].</p> <ul style="list-style-type: none"> <li>• During this review period of the resubmission, we became aware of a post-marketing report of the first case of irreversible tolvaptan induced liver injury after ~six months of tolvaptan treatment resulting in liver transplant.</li> <li>• The pattern of liver enzyme elevation can be described as 1) hepatocellular injury with an R value of &gt; 5.0, 2) onset between 1 and 18 months on treatment, and 3) progressive rise in serum ALT/AST for several weeks after stopping treatment with tolvaptan followed by a return to baseline over one to several months.</li> <li>• There are 3 Hy’s Law cases and one case of severe liver injury requiring transplant among the clinical trials and post-marketing. The Hepatic Adjudication Committee estimated a risk of acute liver failure based on 3 Hy’s Law/1940 subjects exposed for 18 months in the clinical trials, or 1 out of 620. A 10% fatality rate would be 1 out of 6200.<sup>8</sup></li> <li>• In REPRISÉ during the titration period, the most common serious adverse event was</li> </ul>	<p>liver injury. The more intensive liver monitoring in REPRISÉ appeared to mitigate the risk as no Hy’s Law subjects were identified in REPRISÉ. Many patients who had medication stopped because of liver injury did not yet have clinical symptoms, just laboratory signs. Elevations in hepatic labs was the most common AE during the randomized period. The intensive monitoring strategy used in REPRISÉ appeared to mitigate the risk of serious liver injury. However, we know that we cannot eliminate the risk as evidenced by the post-marketing case that resulted in liver transplant.</p> <p>Because the consequences of drug induced liver injury are serious and can quickly progress to liver</p>

<sup>8</sup> Note that I calculate 1 out of 6500. The applicant’s calculation is more conservative.

Dimension	Evidence and Uncertainties	Conclusions and Reasons																																													
	<p>aquaretic effects [9 (0.6%)] followed by increase in liver test [8 (0.5%)]. The most common treatment emergent adverse events (TEAE) were aquaresis (44%) and thirst (38%).</p> <ul style="list-style-type: none"> <li>In REPRISE during the double-blind randomized period, the most common SAE was liver test elevations [30(4.4% versus 4 (0.6%), tolvaptan versus placebo, respectively]. The most common TEAE with a risk difference of at least 1.5% are shown below.</li> </ul> <table border="1" data-bbox="325 613 1486 1073"> <thead> <tr> <th></th> <th colspan="2">Tolvaptan (N=681)</th> <th colspan="2">Placebo (N=685)</th> </tr> <tr> <th>Preferred Term</th> <th>Number of subjects</th> <th>Proportion (%)</th> <th>Number of subjects</th> <th>Proportion (%)</th> </tr> </thead> <tbody> <tr> <td>Aquaretic CMQ</td> <td>76</td> <td>11.2</td> <td>25</td> <td>3.7</td> </tr> <tr> <td>Liver enzyme increase CMQ</td> <td>68</td> <td>10.0</td> <td>32</td> <td>4.7</td> </tr> <tr> <td>Diarrhea</td> <td>47</td> <td>6.9</td> <td>23</td> <td>3.4</td> </tr> <tr> <td>Thirst or polydipsia CMQ</td> <td>39</td> <td>5.7</td> <td>16</td> <td>2.3</td> </tr> <tr> <td>Fatigue</td> <td>46</td> <td>6.8</td> <td>24</td> <td>3.5</td> </tr> <tr> <td>Decreased appetite</td> <td>17</td> <td>2.5</td> <td>5</td> <td>0.7</td> </tr> <tr> <td>Abdominal pain</td> <td>25</td> <td>3.7</td> <td>15</td> <td>2.2</td> </tr> </tbody> </table> <ul style="list-style-type: none"> <li>In REPRISE, adverse events were the most common reason for medication discontinuation. During the titration period medication intolerance was the most common reason cited (5.2%). During the randomized period, hepatic lab abnormality was the most common AE [37(5.4% vs. 4 (0.6%), respectively], followed by medication intolerance [33(4.8% vs. 7 (1.0%), respectively]</li> <li>Tolvaptan can raise serum sodium, uric acid, and glucose.</li> <li>Tolvaptan is metabolized by CYP3A4, and is a substrate and inhibitor of p-glycoprotein.</li> </ul>		Tolvaptan (N=681)		Placebo (N=685)		Preferred Term	Number of subjects	Proportion (%)	Number of subjects	Proportion (%)	Aquaretic CMQ	76	11.2	25	3.7	Liver enzyme increase CMQ	68	10.0	32	4.7	Diarrhea	47	6.9	23	3.4	Thirst or polydipsia CMQ	39	5.7	16	2.3	Fatigue	46	6.8	24	3.5	Decreased appetite	17	2.5	5	0.7	Abdominal pain	25	3.7	15	2.2	<p>transplant or death, we recommend several other strategies to mitigate the risk: a box warning about the risk of serious liver injury and need for monitoring, a REMS with Elements of Safe Use, and a PMR to establish a patient registry to describe the incidence and cases of irreversible or fatal liver injury and to evaluate the adequacy of the liver safety monitoring.</p>
	Tolvaptan (N=681)		Placebo (N=685)																																												
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	<ul style="list-style-type: none"><li>• The applicant has proposed a REMS to mitigate the risk of serious and fatal liver injury. Elements of the REMS include prescriber and pharmacy certification, liver monitoring, patient enrollment and education about risk and monitoring, and a patient registry. As part of the communication plan, the applicant will also send a Healthcare Provider REMS letter to providers likely to prescribe tolvaptan.</li><li>• Because of the risk of serious liver injury and the uncertainty of the actual risk once approved, the Division along with the Office of Surveillance and Epidemiology recommend a Post-Marketing Requirement (PMR) to establish the incidence of serious liver injury and describe the cases of serious liver injury via data gathered in the registry. Using these data, the incidence of severe liver injury in the post-marketing setting will be compared to that observed in the development program. The clinical information collected as part of the registry will also allow an assessment of the adequacy of monitoring in patients who experience a severe liver injury.</li></ul>	

#### 1.4. Patient Experience Data

The only patient experience data relevant to this application is the patient reported outcome (PRO) measure that was used to assess the renal pain endpoint, part of the composite secondary endpoint from TEMPO. This experience is discussed in detail in the July 7, 2013 primary clinical review of Tolvaptan.

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of this or the previous application include:	Section where discussed, if applicable
	<input type="checkbox"/> Clinical outcome assessment (COA) data, such as	
X	Patient reported outcome (PRO)- for the renal pain endpoint.	See Aliza Thompson and Nhi Beasley's July 7, 2013 primary review of Tolvaptan
	<input type="checkbox"/> Observer reported outcome (ObsRO)	
	<input type="checkbox"/> Clinician reported outcome (ClinRO)	
	<input type="checkbox"/> Performance outcome (PerFO)	
	<input type="checkbox"/> Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	<input type="checkbox"/> Patient-focused drug development or other stakeholder meeting summary reports	
	<input type="checkbox"/> Observational survey studies designed to capture patient experience data	
	<input type="checkbox"/> Natural history studies	
	<input type="checkbox"/> Patient preference studies (e.g., submitted studies or scientific publications)	
	<input type="checkbox"/> Other: (Please specify)	
	<input type="checkbox"/> Patient experience data that were not submitted in the application, but were considered in this review:	
	<input type="checkbox"/> Input informed from participation in meetings with patient stakeholders	
	<input type="checkbox"/> Patient-focused drug development or other stakeholder meeting summary reports	
	<input type="checkbox"/> Observational survey studies designed to capture patient experience data	
	<input type="checkbox"/> Other: (Please specify)	
	<input type="checkbox"/> Patient experience data was not submitted as part of this application.	

## 2. Therapeutic Context

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### Analysis of Condition

There are two types of polycystic kidney disease (PKD): autosomal dominant PKD (ADPKD) and autosomal recessive PKD (ARPKD). ARPKD is most commonly encountered in infants and children and is far less common than ADPKD. ADPKD is the most common inherited cause of kidney disease, affects all races and has no gender or age predilection. Published statistics suggest that ADPKD affects 1 in every 400 to 1,000 live births in the US, with 5,000–6,000 new cases diagnosed each year and approximately 600,000 Americans affected by the disease (prevalence ~ 1/588). More than 2,000 ADPKD patients start renal replacement therapy annually. ADPKD is less prevalent in other countries, such as France (~1 per 1,111), Wales (~1 per 2,459), and Japan (~1 per 4,033).<sup>9,10,11</sup> ADPKD is a systemic disease with multiple renal and extra-renal manifestations. Patients with ADPKD may develop end-stage renal disease (ESRD) at some point in their lives, and ADPKD is considered the fourth most common renal disease requiring renal replacement therapy (RRT). There are two PKD genetic variants. The mean age of onset of ESRD for the *PKD1* variant is 54.3 years, whereas that for the *PKD2* variant is 74 years.<sup>12</sup> The hallmark of the renal manifestation of ADPKD is the progressive and continuous enlargement and proliferation of fluid-filled cysts, leading to enlargement of the kidney up to five times the normal volume in the years prior to the development of end stage kidney failure. Patients progress at different rates and while total kidney volume is the most important predictor for the development of renal insufficiency and progression of ADPKD, two interventional studies have failed to show a correlation between changes in kidney volume and changes in kidney function.<sup>13, 19, 20</sup>

Other renal manifestations include hypertension, urinary tract infection, an inability to concentrate urine, hematuria, renal stones, and acute or chronic flank and abdominal pain, either due to kidney enlargement or kidney stones. Kidneys may grow so large that they obstruct the iliac vein or inferior vena cava, with possible thrombus formation and pulmonary

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<sup>9</sup> Barnawi RA, et al, Is the light at the end of the tunnel nigh? A review of ADPKD focusing on the burden of disease and tolvaptan as a new treatment, *International Journal of Nephrology and Renovascular Disease*, 2018;11:53-67.

<sup>10</sup> Srivastava A, Patel N. Autosomal dominant polycystic kidney disease. *Am Fam Phys*. 2014;90:303–307.

<sup>11</sup> Baur BP, Meaney CJ. Review of tolvaptan for autosomal dominant polycystic kidney disease. *Pharmacotherapy*. 2014;34(6):605–616.

<sup>12</sup> Hogan MC, Torres V. Polycystic kidney disease. *BMJ Best Practice*. 2015. Available from: <http://bestpractice.bmj.com/best-practice/monograph/481.html>. Accessed March 20, 2016.

<sup>13</sup> Chapman AB, et al, Renal manifestations of autosomal dominant polycystic kidney disease. Available from: <http://www.uptodate.com/contents/renal-manifestations-of-autosomal-dominant-polycystic-kidney-disease#H9123853>. Accessed March 14, 2016.

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embolism. The most common extra-renal manifestation is polycystic liver disease. Usually asymptomatic, hepatic cysts occasionally produce abdominal pain or discomfort, dyspnea, early satiety, gastroesophageal reflux, mechanical lower back pain, hepatic venous outflow obstruction, or bile duct compression presenting as obstructive jaundice. Other serious complications include cyst hemorrhage, infection, and torsion or rupture. Cysts can also grow in the pancreas, seminal vesicle, arachnoid membrane, and spinal meninges. Other extra-renal manifestations include cerebral and coronary artery aneurysms, cardiac valve disease, colonic diverticula, abdominal wall and inguinal hernias, and bronchiectasis. Several studies indicate that ADPKD has a considerably negative impact on quality of life.<sup>14,15,16,17</sup>

There are no approved products for slowing progression of kidney disease in patients with ADPKD. Existing therapies are used to treat complications of disease including pain, infections and hypertension.

### 3. Regulatory Background

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#### 3.1. U.S. Regulatory Actions and Marketing History

Tolvaptan was approved by the US FDA on May 19, 2009 under the trade name of SAMSCA® for the indication of hyponatremia associated with congestive heart failure, cirrhosis and syndrome of inappropriate antidiuretic hormone. The dose regimen for the hyponatremia indication (15 mg by oral administration QD which may be titrated up to a maximum dose of 60 mg p.o. QD) is considerably less than for the ADPKD indication. It should not be used for longer than 30 days to minimize the risk of liver toxicity.

#### 3.2. Summary of Presubmission/Submission Regulatory Activity

Considering the lack of approved therapies and unmet need for treatments for ADPKD, a potentially life-threatening condition, the tolvaptan development program was granted access

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<sup>14</sup> de Barros BP, et al. Anxiety, depression, and quality of life in patients with familial glomerulonephritis or autosomal dominant polycystic kidney disease. *J Bras Nefrol.* 2011;120–128.

<sup>15</sup> Tong A, et al. A painful inheritance- patient perspectives on living with polycystic kidney disease: thematic synthesis of qualitative research. *Nephrol Dial Transplant.* 2015;30:790–800.

<sup>16</sup> Simms RJ, et al, Increased psychosocial risk, depression and reduced quality of life living with autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant.* 2016;31:1130–1140.

<sup>17</sup> Miskulin DC, et al, Health-related quality of life in patients with autosomal dominant polycystic kidney disease and CKD stages 1–4: a cross-sectional study. *Am J Kidney Dis.* 2014;63:214–226.

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to available programs (i.e., fast track status, rolling review and priority review during the first review cycle. After the initial complete response (CR), active discussions with FDA recommenced and an SPA was submitted and agreed upon. Important regulatory history that pertains to this Class 2 resubmission is presented in the table below.

**Table 1: Pertinent Regulatory History**

Important Dates and Events	Description of Main Event and/or Main Changes	Comments
20 January 2006	Fast Track Designation granted	
6 April 2012	Orphan Drug Designation granted by Office of Orphan Products Development	
15 August 2013	Advisory committee meeting	The FDA Advisory Committee voted 9 to 6 against approval of tolvaptan for ADPKD echoing concerns of FDA reviewers; mainly the concerns centered around judging efficacy from the single trial with a large amount of missing data. The hepatotoxicity signal was also a concern discussed at the AC.
28 August 2013	Complete Response to first NDA	
SPA submission and Statistical Analysis Plan submission 02-April 2014 for protocol 156-13-210, "REPRISE" (Named Amendment 1 because of Presubmission modifications)		
SPA Agreement Letter 13-May 2014		
21 May 2014- First patient first visit		10 months before 2 <sup>nd</sup> amendment
25 June 2014 – Administrative change and revised SAP	<ol style="list-style-type: none"> <li>1. Change the primary analysis to weighted analysis.</li> <li>2. Change the sensitivity</li> </ol>	On 8/5/14 the Division informed the sponsor that the revised protocol and SAP were acceptable.

	<p>analysis of the primary endpoint for subjects who discontinue treatment.</p> <p>3. Clarify that the “acute hemodynamic effect” in the model is a covariate in the model</p> <p>4. Provide an algorithm to derive the weight for each subject used in the primary analysis.</p>	
26 March 2015- Amendment 2 (final protocol); Submitted on 01-May 2015	Clarification of the inclusion criterion for older subjects (exclude elderly ADPKD patients who are progressing more slowly than 2 mL/min/1.73 m <sup>2</sup> ).	
November 26, 2014 –Country Specific Amendment	Added additional exclusion criteria for France: Hypersensitivity to tolvaptan or one of the excipients, are hypovolemic (volume depletion), cannot perceive thirst. Additionally, subjects with baseline screening abnormalities of serum sodium concentrations (hyponatremia or hypernatremia) may not be enrolled in the trial until these abnormalities resolve and then must be monitored accordingly. <sup>18</sup>	
18 Apr 2017- Last patient last visit of REPRISE		

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<sup>18</sup> Source of information: email correspondence to Anna Park 12/26/17

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### 3.3. Foreign Regulatory Actions and Marketing History

On 24 March 2014, 26 February 2015, and 27 February 2015, tolvaptan was approved for ADPKD by the Pharmaceuticals and Medical Devices Agency (PMDA), Health Canada and the European Medicines Agency (EMA), respectively.

## 4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

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### 4.1. Office of Scientific Investigations (OSI)

No clinical site inspections were done for following reasons:

- The previous inspections in the first review cycle were unremarkable
- No clinical sites in REPRISE drove study results
- No significant financial disclosure concerns

### 4.2. Product Quality

The drug product used in the clinical drug development program is the same as the “to be marketed” product. There are no product quality deficiencies or review issues.

### 4.3. Clinical Microbiology

Not applicable.

### 4.4. Nonclinical Pharmacology/Toxicology

There are no approvability issues for tolvaptan based on nonclinical toxicity testing program. In this cycle the sponsor explored a strain of mouse that is genetically sensitive to tolvaptan-induced ALT elevation. Results from this study were not conclusive but suggested that tolvaptan may cause bile acid transporter inhibition and mitochondrial toxicity. The study results also raised the possibility that genetic factors might play a role in tolvaptan-induced hepatotoxicity in ADPKD patients.

### 4.5. Clinical Pharmacology

Tolvaptan is a selective vasopressin V2-receptor antagonist. Renal cysts in ADPKD are thought to originate from the renal collecting duct where V2-receptors are found. Stimulation of the V2-receptor on cystic epithelial cells increases the intracellular level of adenosine 3', 5'-cyclic monophosphate (cAMP) which is thought to lead to cellular proliferation and cyst growth.

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Tolvaptan is thought to reduce cyst growth and/or formation by inhibiting vasopressin-stimulated cAMP production.

Tolvaptan also causes an increase in urine water excretion and decrease in urine osmolality by preventing vasopressin-mediated activation of aquaporin 2 water channels in the collecting ducts. Activation of these water channels increases the water permeability of the collecting ducts and thus the reabsorption of water into the systemic circulation.

Tolvaptan's blockade of the V<sub>2</sub>-receptor results in an increase in urine output and decrease in urine osmolality. Dose selection was guided by the premise that more constant and complete inhibition of the V<sub>2</sub> receptor would result in greater efficacy. At maximum recommended dosing (90mg/30 mg split-dosing) urine osmolality is maximally suppressed reflecting maximum inhibition of vasopressin-binding to the V<sub>2</sub>-receptor in the kidney.

Tolvaptan is metabolized by CYP3A4, and is a substrate and inhibitor of p-glycoprotein. The half-life of tolvaptan increases (3 hours to 12 hours) with increasing doses because of prolonged absorption. Its major metabolite is DM-4103 has a half-life of 183 hours (about 7.5 days). Both tolvaptan and its metabolite are highly protein bound. In the SAMSCA label, tolvaptan is contraindicated with strong CYP3A inhibitors, should be avoided with moderate CYP3A inhibitors, might need dose reduction with p-gp inhibitors, and might need dose increase with CYP3A inducers. No dose adjustments are recommended with p-gp substrates, such as digoxin.

Please see Dr. Martina Sahre's Clinical Pharmacology review in DARRTs dated 4/17/2018.

### **4.6. Devices and Companion Diagnostic Issues**

N/A.

### **4.7. Consumer Study Reviews**

N/A.

## **5. Sources of Clinical Data and Review Strategy**

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### **5.1. Table of Clinical Studies**

The studies that provide support for this application are listed in tabular form below.

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**Table 2: Studies that provide support for this application**

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
<b>Controlled Studies to Support Efficacy and Safety</b>								
156-04-251* (TEMPO)	NCT00428948	Phase 3, multi-center, double-blind, placebo-controlled, parallel-arm trial to determine long-term safety and efficacy of oral tolvaptan tablets in adult subjects with rapidly progressing ADPKD (defined by a TKV of $\geq$ 750 cc by MRI) and preserved renal function [eGFR $\geq$ 60 mL/min (CKD stage 1-2)]	Participants received the highest tolerated split-dose regimen (upon awakening and 9 hours later) of tolvaptan 45/15 mg, 60/30 mg, or 90/30 mg orally for 36 months.	Percentage change per year in total kidney volume from baseline to Month 36 [Time Frame: Baseline to Month 36] Key Secondary Endpoint: Number of ADPKD clinical progression events per 100 follow-up years from baseline to month 36. The 4 events were: (1) Onset or progression of hypertension; (2) severe renal pain; (3) worsening albuminuria; and (4) worsening renal function, defined as a 25% decrease in 1/serum creatinine from baseline.	3 years	1445	Patients with rapidly progressing ADPKD (defined by a TKV of $\geq$ 750 cc by MRI) and preserved renal function [eGFR $\geq$ 60 mL/min (CKD stage 1-2)]	133 centers and, 15 countries
156-08-271 (REPRISE)	NCT02160145	Phase 3, multi-center, randomized-withdrawal, placebo-controlled, double-blind, parallel-group trial to compare the	Starting daily tolvaptan dose of 45mg/15mg titrated to 60mg/30mg, then 90mg/30mg based on tolerability. All	Primary Endpoint: Treatment difference in the change of eGFR from pre-treatment baseline to post-treatment follow-up, normalized (divided) by	5 week tolvaptan titration and run-in period, 12- month randomized	1370 in the randomized period	Patients with rapidly progressing CKD between late stage 2 to early Stage	231 centers, 22 countries

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		efficacy and safety of tolvaptan (45 to 120 mg/day, split-dose) to placebo in subjects with rapidly progressing CKD between late stage 2 to early Stage 4 due to ADPKD. For this trial, rapidly progressing was defined as historical data showing an eGFR decline of > 2.0 mL/min/1.73 m <sup>2</sup> per year	subjects titrated, then randomized withdrawal phase to previously tolerated dose or matching placebo.	each subject's treatment duration [ Time Frame: prior to and post 13 1/2 months of treatment] Key Secondary Endpoint: Treatment difference in annualized slope of eGFR calculated for individual subjects using an appropriate baseline and available, post-randomization, on-treatment assessments.	double-blind period, and 3-week to 40-day follow-up period.		4 (eGFR = 25-65 mL/min/1.73m <sup>2</sup> ) due to ADPKD (defined as historical data showing an eGFR decline of > 2.0 mL/min/1.73 m <sup>2</sup> per year.	
<b>Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)</b>								
156-08-271 (Extension Study for 156-04-251)	NCT01214421	OL, Extension Study of 156-04-251 where all patients were treated with tolvaptan.	Starting daily tolvaptan dose of 45mg/15mg titrated to 60mg/30mg, then 90mg/30mg based on tolerability.	For subjects continuing from protocol 156-04-251; Primary outcome measure: Percent Change in TKV early treatment group (previously treated with tolvaptan) to delayed -treatment group (those previously treated with placebo). Key secondary outcome Measure: Change in eGFR.	2 years	1083 (only 871 were from Study 156-08-271). All Japanese sites from 156-08-271 were enrolled in another extension study.	Completed Study 156-04-251 and were not previously enrolled in Japanese sites.	99 Centers, 13 countries

\*Reviewed in depth in Dr. Aliza Thompson's and Nhi Beasley's primary clinical review of July 7, 2013

## 5.2. Review Strategy

The safety analyses focused on the REPRISE trial data. The applicant's REPRISE CSR, Safety update report, Hepatic Adjudication Committee reports and adjudication reviews were also reviewed. Dr. Beasley confirmed the Applicant's REPRISE safety analyses. Generally, the applicant's safety analyses as presented in the CSR was acceptable and based on the data in the datasets which are reflective of the CRF data. However, Dr. Beasley closely examined the reasons for medication discontinuation, and thus her review provides a more descriptive analysis of the reasons for medication discontinuation. In addition, similar common adverse events were grouped together to provide a less granular/dilution of the common AE data.

The primary application used for analyses was SAS version 9.4, but the following applications were also used: Empirica Study, Empirica Signal, Jump, Jump Clinical 6, and Excel. MedDRA Adverse Event Detection (MAED), an internal FDA tool, was used to analyze most adverse events. The safety data were reported in MedDRA version 20.0. All figures and tables are for the REPRISE trial and were created by the reviewer unless otherwise noted.

The efficacy analyses also focused on REPRISE, and considered data and conclusions from the first cycle of reviews (specifically regarding the TEMPO trial) because the results of this trial are an important part of the totality of evidence supporting approval. The Extension Study of TEMPO (156-08-271) was reviewed to assess the sponsor's claim that tolvaptan could reduce the rate of kidney volume growth. JMP and EXCEL were used.

## 6. Review of Relevant Individual Trials Used to Support Efficacy

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### 6.1. Study 156-13-210: REPRISE

#### 6.1.1. Study Design

##### **Overview and Objective:**

The objective of REPRISE was to compare rates of eGFR decline in subjects treated with tolvaptan to subjects treated with placebo in preselected patients who could tolerate tolvaptan in a tolvaptan titration and run-in phase (to minimize drug discontinuation and drop-out).

##### **Study Design:**

Study 156-13-210 was a 15-month 3-phase study. The first phase was an 8-week prandomization period that included a screening period, 3 single-blinded (blinded to subject only) run-in/ titration periods (a placebo run-in period, a tolvaptan titration period and a

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tolvaptan run-in period). The second phase was a randomized withdrawal, double-blind, placebo-controlled period. The third phase was an intended 3-week final follow-up period that could last up to 40 days if needed to capture end-of treatment data. The tolvaptan titration and run-in periods were included in the trial to mitigate subject noncompliance, drug discontinuation, or drop-out because of inability to tolerate the aquaretic effects of the therapeutic dose during the following 12-month double-blind period.

### **Enrollment Criteria:**

To be eligible for enrollment, the diagnosis of ADPKD needed to be confirmed using historical imaging data and recorded total kidney volume (TKV), if available. In addition, eligibility had to be confirmed via subjects' calculated mean eGFRs (using the CKD-EPI formula<sup>19</sup>). Creatinine assays were calibrated to be traceable to an isotope dilution mass spectrometry (IDMS) reference standard. The eGFR enrollment criteria were age dependent. If potential subjects were between the ages of 18 and 55 years of age their mean eGFRs needed to be between 25 and 65 mL/min/1.73m<sup>2</sup>, inclusive, whereas if subjects were between the ages of age 56 and 65 years of age their mean eGFRs needed to be between 25 and 44 mL/min/1.73m<sup>2</sup>, inclusive, and there needed to be evidence of ADPKD progression, i.e., historical data demonstrating an eGFR decline of > 2.0 mL/min/1.73 m<sup>2</sup> per year. The lower range of eGFR and evidence of rapid progression required for enrollment per the protocol of older subjects reflects the sponsor's goal to enroll patients whose renal dysfunction was due to ADPKD and not to other potentially confounding conditions such as hypertension or diabetes or age-related declines. Enrolling only rapid progressors in the older subjects was also an enrichment strategy, employed to increase the sponsor's chances of showing a difference in ADPKD progression between the tolvaptan and placebo arms. These eGFR criteria also helped to ensure that adult subjects with more advanced ADPKD-renal dysfunction compared to those enrolled in the first pivotal trial (TEMPO) would be enrolled. To enroll, subjects were required to have a diagnosis of ADPKD by modified Pei-Ravine criteria:

- With family history: several cysts per kidney (3 if by sonography, 5 if by computerized tomography or magnetic resonance imaging).
- Without family history: 10 cysts per kidney (by any radiologic method, above) and exclusion of other cystic kidney diseases. Conditions to be excluded included: multiple simple renal cysts, renal tubular acidosis, cystic dysplasia of the kidney, multicystic kidney, multilocular cysts of the kidney, medullary cystic kidney and acquired cystic disease of the kidney.

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<sup>19</sup> Levey AS, Stevens LA, Schmid CH et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150:604-12.

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- Distribution and number of cysts consistent with the observed level of renal function deficit.

Renal function was confirmed during screening by the mean eGFR calculated from the subjects' first 2 pretreatment, central-lab serum creatinine assessments.

Reasons for exclusion included need for chronic diuretic use, hepatic impairment other than that expected for ADPKD with typical cystic liver disease, evidence of significant renal disease aside from ADPKD and advanced diabetes. Because tolvaptan is a cytochrome P450 (CYP) 3A4 substrate, patients on potent CYP3A4 inhibitors apart from amiodarone were excluded. Subjects were supposed to be tolvaptan-naïve.

**Reviewer's Comment:** *The enrollment criteria were selected to ensure that patients with more advanced renal disease than the TEMPO trial would be enrolled in the REPRISE trial.*

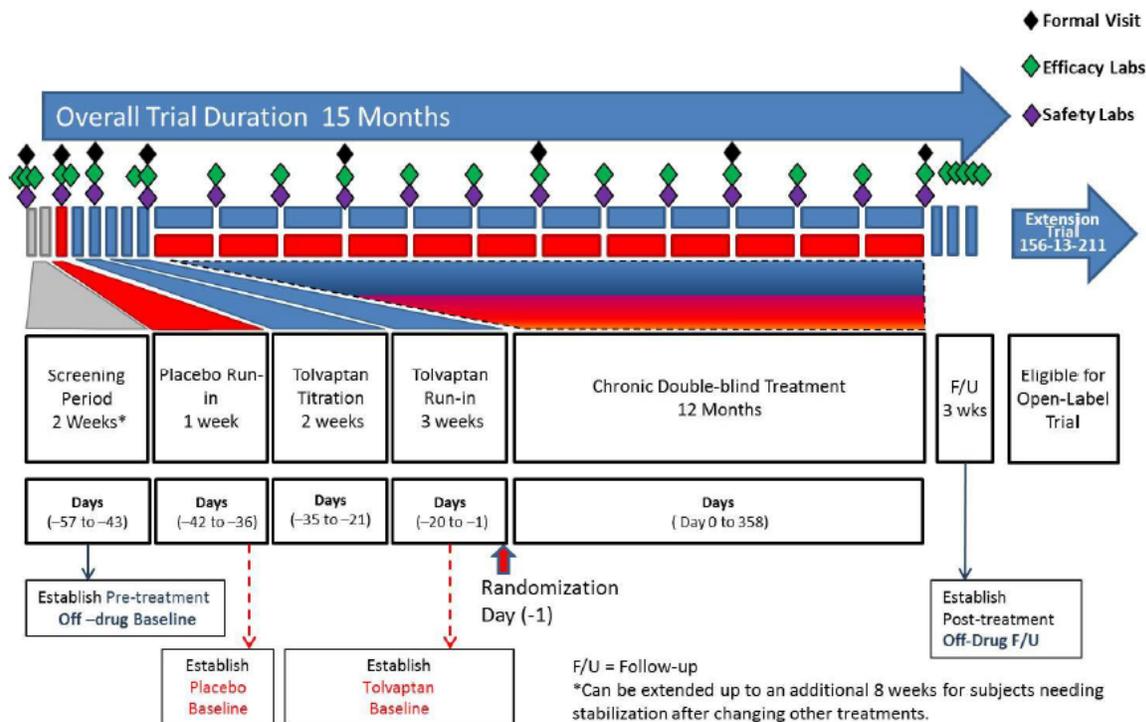
### **Study Schema:**

See Figure 1 for a pictorial representation. During the single-blinded (blinded to subject only) placebo run-in period, eligible subjects received a daily split dose of 0 mg (abbreviated 0/0 mg), in a form identical to tolvaptan tablets at the 15/15-mg dose. Subjects unable to tolerate the single-blinded placebo dose regimen were considered run-in failures. Assessments taken during the screening and placebo run-in periods were used as the pretreatment baseline for the primary efficacy endpoint.

The placebo run-in period was followed by a single-blind (blinded to subject only), 2-week tolvaptan titration period during which all subjects received 2 strengths of tolvaptan: 15-mg and 30-mg. Subjects were instructed to take tolvaptan at a split dose of 30/15 mg (as two 15-mg tablets upon waking and one 15-mg tablet ~ 8 to 9 hours later) and to titrate up every 3 to 4 days (as tolerated); first to 45/15, then 60/30, then up to the maximum dose of 90/30 mg. Those subjects unable to tolerate at least a 60/30 mg tolvaptan dose regimen were considered run-in failures.

Subjects who tolerated at least 60/30 mg tolvaptan entered the single-blind (blinded to subject only), 3-week, tolvaptan run-in period and continued the tolvaptan dose that had been achieved in the prior tolvaptan titration period (60/30 mg or 90/30 mg) to confirm tolerability over a longer period and to establish a tolvaptan prerandomization baseline. At the end of the tolvaptan run-in period, subjects who did not tolerate at least 60/30 mg tolvaptan were considered run-in failures and were withdrawn from the trial.

Figure 1: Study Schema



**Reviewer's Comments:** The placebo run-in, tolvaptan titration and tolvaptan run-in periods prior to randomization were instituted to minimize subject withdrawal during the randomized treatment phase due to aquaretic adverse events (AEs).

Dropout in the first pivotal study 156-04-25 (TEMPO), submitted during the first cycle, was high and was more frequent in the tolvaptan treatment group because of aquaretic-related tolerability issues. Otsuka and FDA met to discuss how to mitigate this problem in REPRISE. Inclusion of a tolvaptan titration and run-in period makes the interpretation of safety more difficult for two reasons:

1. Subjects who can't tolerate tolvaptan may drop out prior to randomization and not be counted in the safety analysis of the randomized part of the trial
2. Subjects who are randomized to placebo could have an AE early on after randomization that might be due to the previous period on tolvaptan but not counted as such.

Both potential consequences of a run-in period will have the effect of reducing the detection of safety signals. However, the concern of reduced safety information was outweighed by the need to have an interpretable trial vis a vis efficacy. The strategy of employing a run-in period helped to ensure the elimination of large patient withdrawal, drop-outs and missing data during the randomized phase of the trial. FDA conveyed to

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*the sponsor that eliminating as much missing data as possible was paramount for conducting a trial that would be interpretable.*

**Randomization:** Subjects who could tolerate 60/30- or 90/30-mg dose of tolvaptan were randomized to tolvaptan or placebo.

Randomization (1:1) was stratified as follows:

- By baseline eGFR ( $\leq 45$  or  $> 45$  mL/min/1.73 m<sup>2</sup>)
- By age ( $\leq 55$  or  $> 55$  years)
- By TKV ( $\leq 2000$  mL,  $> 2000$  mL, or unknown)

**Reviewer's Comments:** *The sponsor's selection of factors by which to stratify randomization was reasonable and was agreed upon in the SPA agreement letter of 5/13/14.*

### **Randomized Period:**

Subjects randomized to tolvaptan continued to take the same tolvaptan dose that they had received during the tolvaptan run-in period. Subjects randomized to placebo received placebo tablets matching their tolerated tolvaptan dose during the tolvaptan run-in period. Subjects' treatment duration was 12 months from their date of randomization. Subjects were to be followed (and laboratory tests continued) for the entire 12 months regardless of their ability to continue investigational medical product (IMP) unless consent was withdrawn; subjects who withdrew consent were asked to complete end of treatment (EoT) visit assessments.

Tolvaptan, or matching placebo, was administered at 60/30 or 90/30 mg, as split doses, but could be down-titrated to 45/15 and 30/15 mg as needed for tolerability.

**Reviewer's Comments:** *Down titration as needed was intended to reduce study drug discontinuation and/or subject drop-out due to tolerability issues.*

**Follow-up period ( $\leq 3$  weeks):** Subjects were to be followed for 21 days, starting immediately after the last dose of IMP, to assess any ongoing AEs; in addition, for the efficacy follow-up, 3 serum creatinine samples were collected (for efficacy, a  $\leq 40$ -day follow-up period was allowed). Subjects not continuing in the trial completed EoT assessments and were followed for 21 days to assess any ongoing AEs (for efficacy,  $\leq 40$  days).

No follow-up assessments were done during the first week of the follow-up period. During the last 2 weeks (Days 8-21), 3 follow-up visits were scheduled, which were to occur  $> 24$  hours apart. Blood samples were collected at each follow-up visit for serum creatinine measurements. The blood sample collected at the last follow-up visit included measurements for post-treatment efficacy and safety (including hepatic transaminases). To decrease intrasubject variability, up to 3 serum creatinine measurements were taken both pre- and post-treatment

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for each subject, to calculate average eGFR; variability was further reduced by having the subjects maintain consistent dietary protein, exercise, and sample timing and by batched analysis of samples.

**Reviewer's Comments:** *Tolvaptan is known to have an acute and reversible hemodynamic effect that reduces eGFR, confounding pretreatment to on-treatment comparisons. In the TEMPO trial, the baseline creatinine and eGFR levels were calculated when the subjects were already on treatment. This was one of many review issues in the first trial. As stated earlier, large differential patient dropout was the largest review issue affecting interpretability of the results. Using a post-randomization eGFR (taken at ~3 weeks after randomization) as the baseline in the TEMPO trial was also an additional source of bias. Comparing a post-randomization value to end of study value (designed this way to correct for hemodynamic effects of tolvaptan) violates statistical assumptions of having a randomized sample. For these reasons, the sponsor was encouraged in the January 9, 2014 FDA advice letter to calculate the primary endpoint in REPRISE using off-drug baseline eGFR levels and post-drug discontinuation eGFR levels. Conducting the efficacy analysis using endpoint serum creatinine measurements taken at a minimum of 1-week after discontinuing study drug was necessary to assess efficacy because of the long terminal half-life of drug/metabolite and prolonged hemodynamic effects. (This concept is discussed further in the section below).*

**Protocol-Specific instructions to minimize study withdrawal:**

The protocol indicated that unless the subject provided written withdrawal of consent or the investigator confirmed the subject's verbal intent to completely withdraw from the trial, subjects should be followed for all protocol-specified evaluations and assessments. Complete withdrawal of consent required a subject's refusal of all the following methods of follow up (these methods of follow up were to be noted in the trial ICF):

- Participation in all follow-up procedures specified in the protocol (whether in-clinic, by telephone, or by an in-home visit).
- Participation in a subset of protocol specified follow-up procedures (by a frequency schedule and method as agreed by subject and staff).
- Participation in all regularly scheduled, study-related follow-up visits and end-of-treatment visits.
- Contact of the subject by trial personnel, even if only by telephone, to assess current medical condition and obtain necessary medical or laboratory reports relevant to the trial's objectives.
- Contact of alternative person(s) who have been designated in source records as being available to discuss the subject's medical condition, even if only by telephone, mail or e-mail (e.g., family, spouse, partner, legal representative, friend, neighbor, physician).

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- Access to medical information from alternative sources (e.g., hospital/clinic medical records, referring doctor's notes, public records, dialysis, transplantation or vital registries, social media sources).

The protocol also stated that if a subject in the double-blind, randomized treatment period wished to withdraw from the trial, multiple steps would be taken to ensure low discontinuation and study withdrawal rates including in-home or weekend visits, down-titration of study drug, and/or temporary interruption of study drug:

**Reviewer's comment:** *In the SPA agreement letter of 5/13/14, the Division responded "Yes" to the following question: "Does the Agency concur with the approach outlined in the study protocol to avoid patient withdrawals and patient loss to follow-up, thereby minimizing the occurrence of missing data?"*

### **Dietary Restrictions:**

Of note, there were the following dietary restrictions and recommendations, agreed upon by FDA in the correspondence of 5/13/14 in response to Otsuka's Special Protocol Assessment:

1. In the absence of alternate regional practices, the following restrictions should be given: dietary salt < 5g/day, dietary cooked meat protein < 1 g/kg/day, and caffeinated foods/drinks ≤ 2 coffee equivalents/day.
2. Subjects should be advised to avoid the ingestion of pomelo, grapefruit, or Seville orange products because they would be expected to increase tolvaptan concentrations.
3. All subjects should be instructed to ingest fluids in anticipation of, or at the first sign of thirst to avoid excessive thirst or dehydration. Upon consent, all subjects should receive the recommendation to ingestion of at least 2-3 liters of fluid (including in solid, semi-solid, and liquid foods) per day, unless otherwise directed by study subject's doctor. This recommendation should start during screening and continue through the end of the trial. Additionally, subjects should ingest 1 to 2 cups of water before bedtime regardless of perceived thirst and replenish fluids overnight with each episode of nocturia. Acute changes of > 3% of body weight (increase or decrease) over any 7-day period should be noted.
4. Subjects should be instructed to report acute changes in body weight to the trial physician for further evaluation and recommendations.

**Reviewer's Comments:** *The SPA referenced preliminary recommendations from a meeting of ADPKD experts in January 2014 organized by KDIGO to develop guidelines for the management of ADPKD. According to the submission, the panel's preliminary assessment was as follows: "There is experimental data that increasing water intake*

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*may be beneficial. However, formal human data are lacking. Still we advise to increase water intake to have a 24-hour urinary volume of at least 2.5 liter in adults.”*

## Study Endpoints

### **Efficacy:**

**Primary efficacy endpoint:** Treatment difference in the change of eGFR (by CKD-EPI) from pretreatment baseline to post-treatment follow-up, annualized (divided) by each subject’s trial duration.

The primary endpoint efficacy population included all subjects in the randomized population who took at least 1 dose of IMP (investigational medicinal product) after randomization, and had a baseline and at least 1 valid post-treatment evaluation of eGFR (after at least 1 week off treatment).” Missing data were not to be imputed in deriving the pre-treatment and post-treatment eGFR observations used for the primary analysis. Data missing at random (MAR) was assumed for the primary analysis. The primary endpoint was analyzed by analysis of covariance (ANCOVA) with effects of treatment and randomization stratification factors and covariate baselines applied to the analysis. As agreed upon in the SPA, a two-sided alpha of 0.05 was applied to the primary analysis of the primary endpoint.

Normalization of the data to time on treatment was necessary; otherwise the treatment group having more dropouts or more earlier dropouts may have had an unfair advantage (less time to have their eGFR decline). To reduce the impact of the outliers created by the annualized eGFR change in early dropout subjects, all annualized changes of dropout subjects that were greater (or less) than the maximum (or minimum) of the annualized eGFR change of all on-treatment completers assumed the maximum (or minimum) value as their annualized eGFR changes used in the primary analysis. This was because of the possibility that annualization of very variable short-term data (1 or 2 months) by requiring a multiplication factor of 12 or 6 could have resulted in an exaggerated estimate of annualized eGFR change. To reduce the variation in this primary endpoint, the last 3 observations of eGFR up to placebo run-in were observed at baseline (screening and placebo run-in periods) and another first 3 observations were observed after 1 week of post-treatment follow-up during a 2-week interval (within a total of 3-week post-treatment follow-up). This was later expanded to 7-40 days after the last dose of IMP to reduce exclusion of subjects from the primary analysis due to failure to have follow-up data within this 2-week period. For tolvaptan subjects, this window definition was conservative, since a few days of no treatment was added to the duration of tolvaptan treatment for the annualization. The dates of baseline and post-treatment observations were also set to the median of the dates of the (up to) 3 baseline and the (up to) 3 post-treatment follow-up observations respectively, and the duration was equal to the date of post-treatment follow-up minus the date of baseline plus 1. This duration was used in the calculation of the annualized

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change. Data collected after day 40 after IMP completion was excluded to reduce the possibility of inclusion of subjects who had moved to an alternate treatment regimen.

There were two sensitivity analyses for the primary efficacy analysis:

One was a weighted ANCOVA of annualized change in eGFR (by CKD-EPI) from pre-treatment baseline with unadjusted annualized eGFR changes of the outliers (mL/min/1.73 m<sup>2</sup>/year) in the primary endpoint efficacy population as defined above. Effects of treatment and randomization stratification factors and covariate baselines were applied to the analysis. In contrast to the primary analysis where only the first 3 and last 3 eGFR observations were included, *all* postrandomization on-treatment eGFR observations in the protocol-specified visits for placebo subjects were also included. The linear mixed effect model with effects of treatment, time (as a continuous variable), treatment time interaction, randomization stratification factors, and baseline as covariate was used to fit the eGFR data, in which the intercept and time were both a fixed effect and a random effect. An unstructured variance-covariance matrix was assumed for the random intercept and time. The time variable used in the model began at the first eGFR observation and the first eGFR counted as the eGFR baseline. Missing data were ignored (not imputed) in this analysis under MAR assumption. The estimated annualized eGFR change was from the average of  $\leq 3$  pretreatment baseline observations to the average of  $\leq 3$  post-treatment follow-up observations.

Another sensitivity analysis deviated from the MAR assumption to include the post-discontinuation follow-up data in the analysis. It was a weighted ANCOVA of annualized change in eGFR (by CKD-EPI) from pre-treatment baseline (mL/min/1.73 m<sup>2</sup>/year) with month 12 data used for off-treatment completers, also using the primary endpoint efficacy population. Effects of treatment and randomization stratification factors and covariate baselines were applied to the analysis. The estimated annualized eGFR change was from the average of 3 pretreatment baseline observations to the average of 3 post-treatment follow-up observations. For subjects with early IMP discontinuation, eGFR observations at Month 12 replaced the average of the 3 post-treatment follow-up observations in the analysis.

### **Reviewer's comment:**

*The sponsor chose this primary endpoint to align with the advice provided in the FDA advice letter of January 9, 2014. This is discussed further in the Reviewer's Comment under the secondary endpoint discussion below.*

*In the 5/13/14 SPA agreement letter we stated that "we concur with this primary endpoint and your approach for annualizing data in subjects (including those) who discontinue therapy prematurely. Because of the steps being taken to ensure that there will be very few subjects who do not complete the 12- month treatment period on study drug, we expect that for nearly all subjects, the value that is used in this analysis will be*

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*the same as the actual change over one year. We also note that subjects who discontinue therapy prematurely will continue to be followed for the 12-month treatment period. Hence, we will be able to compare the results of the analysis using the annualized change at the time of stopping treatment with the results obtained using the actual one-year change.” This comparison is in alignment with the sponsor’s proposed sensitivity analysis described above.*

*Also, in the SPA agreement letter, in response to the following question from the sponsor, “If the value of  $p < 0.05$  is met for the primary endpoint, the proposed Protocol 156-13-210, in combination with the prior trial (Trial 156-04-251), would provide sufficient data to support approval of tolvaptan for the proposed indication, i.e., to slow kidney disease in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD)?”, the Division responded, “Yes, assuming the trial is well-conducted. The phrasing of the indication statement will be a review issue.” This echoed what was stated in the CR letter of 8/26/13, where we stated, “you need to conduct an additional efficacy trial that tests the hypothesis that tolvaptan slows the loss of renal function and is successful at a  $p$ -value  $< 0.05$ .”*

### **Secondary efficacy endpoint:**

There was only one secondary efficacy endpoint called “the key secondary efficacy endpoint” and there were multiple sensitivity analyses. The secondary endpoint was, “treatment difference in annualized slope of eGFR using the CKD-EPI formula calculated for individual subjects using all eGFR data observed in the placebo run-in, tolvaptan run-in (not including tolvaptan titration), double-blind treatment, and post-treatment follow-up (not including data collected in the first week after the last IMP dose) periods.” The tolvaptan run-in and tolvaptan data in the double-blind treatment periods were flagged (yes = 1 and no = 0) because of the tolvaptan acute hemodynamic effect. The secondary endpoint efficacy population included all subjects in the randomized population who took at least 1 dose of IMP after randomization, and had a baseline and at least 1 post-randomization evaluation of eGFR. A linear mixed effect model with effects of time (as a continuous variable), treatment, time-treatment interaction, “acute hemodynamic effect” (flag 0 or 1), pre-treatment baseline (of the primary endpoint), and randomization stratification factors was used to fit the GFR estimates, in which the intercept and time were both a fixed effect and a random effect. The time variable used in the model began at the first observation of eGFR obtained from the placebo run-in period. The starting point of the eGFR slope analysis was the eGFR observation during the placebo-run-in period. Missing data were ignored (not imputed) in this analysis under MAR assumption. The data collected during the follow-up period were not included in the key secondary endpoint analysis.

***Reviewer’s Comment:*** *In the December 16, 2013 meeting, Otsuka explained that this slope-based endpoint (which they originally wanted to make their primary endpoint)*

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*provided less variability and greater power and felt that the proposed approach (using on-treatment values for the primary analysis and sensitivity analysis with imputation for missing data) represented a conservative approach to analyzing the data. The Division noted that Dr. Lawrence had done preliminary analyses comparing the efficiency of a slope-based endpoint against one using the change from baseline to end of treatment as the endpoint; his analyses suggested that the number of subjects would need to be increased by ~30% if the endpoint were defined as the change from pre- to post-treatment creatinine values.*

*The Division emphasized that it would be difficult to interpret the results of the trial if a difference was detected using the slope-based endpoint but no difference was observed when comparing pre- to post-treatment creatinine measurements. The Division stated that an endpoint defined as the change from the pre-treatment baseline measurement to the post-treatment measurement would be more readily interpretable. In a follow-up correspondence on January 9, 2014, the Division stated, "We believe that an endpoint defined as the change from a pre- to post-treatment creatinine value would be more readily interpretable, and we recommend that you use this as the [primary] endpoint in your new trial. To decrease variability and improve trial efficiency, we strongly encourage you to obtain multiple creatinine measurements in the pre- and post-treatment periods and use the average of these measurements in the analysis."*

There were several sensitivity analyses of the key secondary endpoint. They are described below:

1. One compared the linear trend of eGFR between tolvaptan and placebo groups. This sensitivity analysis did not depend on the assumption made in the key secondary analysis of linearity and equal tolvaptan hemodynamic onset and offset effects. The change from the pretreatment baseline during the on-treatment visits in the double-blind treatment period was included in the analysis. Since the hemodynamic effects of tolvaptan were believed to begin to reverse within 1 to 2 days, on-treatment was defined as within 24 hours of the last IMP dose.

Analysis of mixed model repeated measures (MMRM) was applied to the data of change from baseline in eGFR in Month 1, Month 2, and up to Month 12. The model had fixed effect of treatment, visit, treatment visit interaction, randomization stratification factors, and covariate baseline and baseline visit interaction. An unstructured variance-covariance matrix was assumed for the repeated measurements. A linear contrast of the treatment differences in these 12 months was used as the sensitivity analysis of the key secondary endpoint.

The following sensitivity analyses imputed missing data using various assumptions.

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2. This sensitivity analysis deviated from the MAR assumption to include the post-discontinuation follow-up data in the analysis of the key secondary endpoint. Subjects who discontinued treatment after randomization without withdrawing consent were followed for additional eGFR (not including the eGFR observed in the 3-week period immediately post the last dose of IMP) up to Month 12.
3. In this sensitivity analysis, for all randomized subjects who withdrew early, imputation of missing data was applied to projected visits up to their planned end of the trial visit (12 months postrandomization). The subjects' reasons for discontinuation were captured and categorized to help determine the missing data pattern. Imputation was based on the data used in the MMRM model. To perform the analysis of random coefficient regression model specified for the key secondary endpoint, simulated value of a missing data point was assigned a value for the time variable used in regression which was equal to the time of its previous visit plus 30.5 days. For placebo subjects, and in the absence of evidence suggesting biased missing data pattern, the imputation followed the placebo trend.
4. Delta Adjustment Imputation Method was another sensitivity analysis. This MNAR sensitivity analysis was planned to investigate the departure from MAR assumption by progressively decreasing the treatment differences over the missing visits in those treated subjects who fell into an assumed MNAR pattern. This progressive decrease of treatment slope difference was carried out by subtracting  $k$  times the expected treatment difference (in the absent of the hemodynamic effect) from the imputed missing data after dropout using tolvaptan slope in those treated subjects who fell into an assumed MNAR pattern, with  $k$  starts from 0%, 10%, 20%, etc., and up to 100% or higher, until conclusion from the analysis of the key secondary endpoint was overturned (it was called tipping-point analysis), or it became clinically meaningless to go even higher. The expected treatment difference between tolvaptan and placebo at a visit could have been derived from the treatment difference in slope, multiplied by the visit month number and divided by 12. Note that when 0% was used, the multiple imputation procedure would produce an analysis which was essentially MAR. When 100% was used, the multiple imputation procedure would produce an analysis which was essentially something called "copy placebo".

***Reviewer's Comment:*** *These sensitivity analyses represent reasonable ways of assessing how sensitive the results of the primary analyses are to the MAR assumption.*

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### **Exploratory Efficacy Outcomes:**

Exploratory analyses were applied to the primary and the key secondary endpoints with tolvaptan subjects coded by their modal doses in the trial, using the same analytic approaches specified for these endpoints.

Assessment of ADPKD outcomes was specified as exploratory endpoints in this protocol. Exploratory analysis was applied to a few frequent and clinical meaningful outcomes (kidney pain, urinary tract infection, and hematuria) as well as a composite of those outcomes which were more closely related to kidney enlargement as potential events. The composite included kidney pain, hematuria, nephrolithiasis, urinary tract infection, anemia, and significant drop in kidney function. Events in this analysis were defined if at least 1 of the PKD outcomes was checked in the CRF at a visit. Summary data were also provided to ADPKD outcomes and medical resource utilization collected in the PKD outcome CRF page.

Analysis of time to multiple events, which was the analysis of the intensity model (Andersen-Gill model) using the sandwich covariance matrix estimate to derive standard errors for the Wald test was applied. The analysis dataset of this analysis was set up where the data had a counting process style of input; the timing of an event was set to the visit when the eCRF was recorded; and a subject had only 1 event at a visit in the analysis even if the subject had more than one PKD outcome at the visit. This analysis covered the double-blind treatment period from randomization to Month 12.

### **Statistical Analysis Plan**

Agreed upon statistical testing methods are discussed in the previous section. Also, see Dr. John Lawrence's statistical review.

### **Other Statistical Considerations:**

*Sample size:* Based on a mixed model repeated measures (MMRM) analysis of the non-Japanese Stage 3 subjects from Trial 156-04-251, the treatment difference in renal function at Month 12 was projected to be 1.07 mL/min/1.73 m<sup>2</sup> in the sample size calculation. This degree of change represented an ~ 25% reduction for a subject with 4.5 mL/min/1.73 m<sup>2</sup> annual decline in GFR.

To reduce intrasubject variation, 3 eGFR observations at pretreatment baseline and 3 eGFR observations at post-treatment follow-up were to be taken. It was estimated that the resulting variance would be 32.8. Thus, with an assumption of a 10% dropout rate, 1336 randomized subjects would provide 90% power to detect a treatment difference of 1.07 for a 0.05 two-sided alpha.

*Key Datasets for analysis:* The following datasets were defined for this trial:

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- Randomized population: All subjects who were randomized in this trial.
- Randomized safety population: All subjects who were randomized in this trial and took at least 1 dose of IMP after randomization. This was the primary safety population.
- Treated safety population: All subjects who took at least 1 dose of IMP during the tolvaptan titration/run-in periods. This was a secondary safety population.
- Efficacy populations:
  - Primary endpoint efficacy population: All subjects who were in the randomized population, took at least 1 dose of IMP after randomization, and had a baseline and at least 1 valid post-treatment evaluation in eGFR (i.e., after at least 1 week off treatment). The primary endpoint's baseline was defined as the average of up to 3 eGFR values observed during the screening and placebo run-in periods.
  - Key secondary endpoint efficacy population: The secondary endpoint efficacy population included all subjects in the randomized population who took at least 1 dose of IMP after randomization, and had a baseline and at least 1 post-randomization evaluation of eGFR. The starting point of the eGFR slope analysis was the eGFR observation during the placebo-run-in period and included all values in the pre- and post-randomization period. (but not the follow-up period).

### Protocol Amendments

There were no protocol amendments that limit the interpretability of the study findings. See Table 1 for a description of the protocol amendments.

### 6.1.2. Study Results

#### Compliance with Good Clinical Practices

The applicant has provided attestation that the study was conducted in accordance with the CFR governing the protection of human subjects (21 CFR part 50 Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with good clinical practice (GCP).<sup>24</sup>

#### Financial Disclosure

The applicant has adequately disclosed financial interests/ arrangements with clinical investigators. None of the disclosed interests/ arrangements raise questions about the integrity of the data.

#### Patient Disposition

##### Disposition:

Of the 2292 screened subjects, only 59.8% of the screened population made it to the randomization period where they were randomized (1:1) to treatment (683 subjects to

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tolvaptan; 687 subjects to placebo); 2 subjects per group were randomized, but not treated with IMP. See Table 3 for a tabular listing of subject disposition during the screening periods and during the randomized period. While approximately equal numbers of subjects completed the double-blind treatment and follow-up period in both treatment groups, there were approximately three times as many subjects in the tolvaptan group who completed “off-treatment” than in the placebo groups (76 subjects in the tolvaptan group and 22 subjects in the placebo groups completed off treatment).

**Table 3: Subject disposition before Randomized Period and During Randomized Period**

Period	Subject number at start of period	Subject number at end of period	% of total Screened that remained at end of period	% lost during this period (1-subject number at end of period/subject number at start of period*100)
Screening	2292	1519	66.3	33.7
Placebo-run-in	1519	1496	65.3	1.5
Tolvaptan-titration and run-in period	1496	1370	59.8	8.4
Completion of Month 12 Visit and post-treatment period	1370	1313	57.3	4.2
Period	Subject number at start of randomized period	Subject number completed Month 12 visit and 7-40-day post-treatment period	% of total Randomized subjects that remained at end of 12-month period and 7-40-day post-treatment period	% lost during this period (1-subject number at end of period/subject number at start of period*100)
Tolvaptan – Completion of Month 12 Visit and 7-40-day post-treatment period	683	654	95.8	4.2
Tolvaptan –	683	578	84.6	15.4

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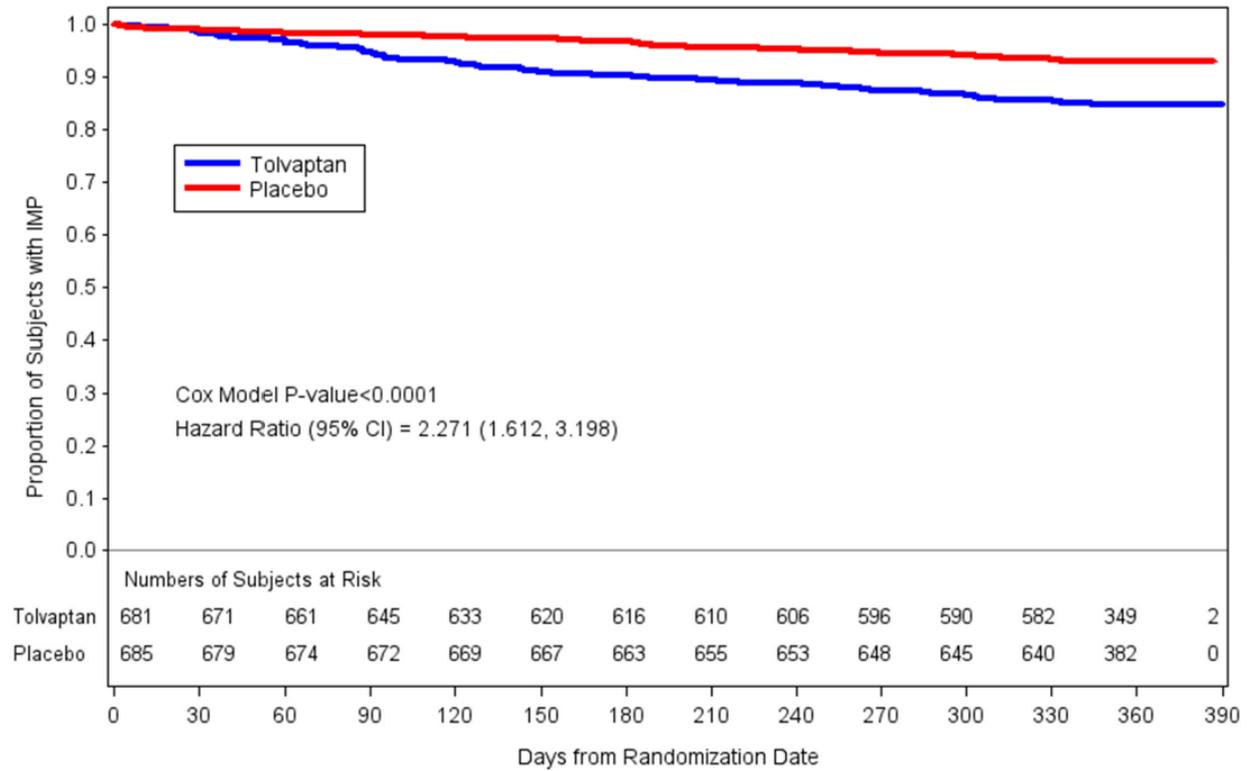
Completion of Month 12 Visit on Drug and 7-40-day post-treatment period				
Placebo – Completion of Month 12 Visit and 7-40-day post-treatment period	687	659	95.9	4.1
Placebo – Completion of Month 12 Visit on drug and 7-40-day post-treatment period	687	637	92.7	7.3

Source: Study 156-13-210, p. 98-100.

As shown by Kaplan-Meier plot, the difference between groups in time to discontinuation from the IMP in the randomized phase of the trial was statistically significant ( $p < 0.0001$ ), Figure 2. But the time to discontinuation from the study was similar between groups.

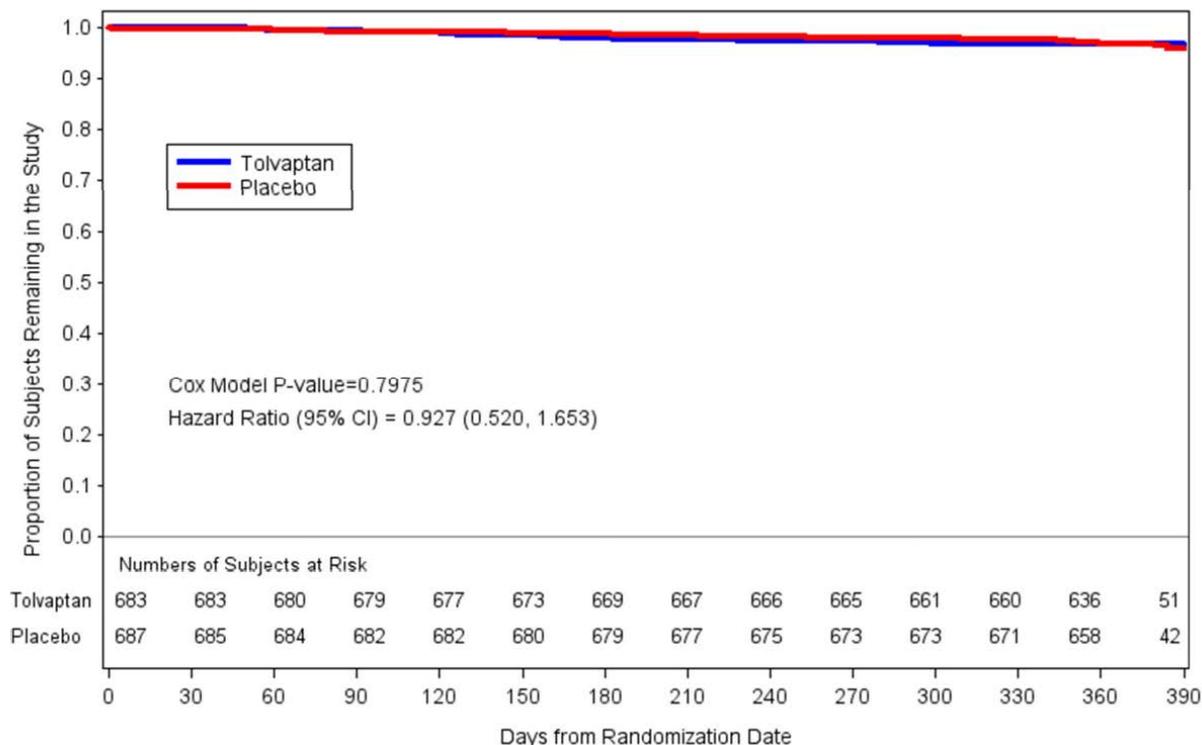
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**Figure 2: K-M plot of time to discontinuation from IMP- Primary Safety Population**



Source: Clinical Study Report for Study 156-13-210; p. 101

**Figure 3: K-M Curves to Time of Discontinuation from the Trial- All Randomized Subjects**



Source: Clinical Study Report for Study 156-13-210; p. 102

**Reviewer’s Comment:** *There was excellent retention of subjects in the double-blind treatment phase of REPRISE. 9.9% were lost during the run-in periods as would be expected because of tolerability issues mostly and 4.2% were lost during the double-blind aspect of the trial, equal in both treatment groups. Also, as shown in Table 4 in the next section, only 1 subject in the randomized group was completely lost to follow-up. (i.e., no vital status confirmed). The high study retention provides confidence in the overall study conduct and findings.*

**Reasons for Discontinuation:**

Among 1519 participants who entered the run-in phase, 23 did not complete the placebo run-in, and an additional 126 did not complete the tolvaptan run-in phase. Of the subjects who did not complete the placebo run-in phase, 10/23 discontinued for a non-serious AE and 1 discontinued for an SAE. The others discontinued because of not meeting eligibility criteria (5), personal reasons (3), progression of disease (3), or lost to follow-up (1). Of the subjects who did not complete the tolvaptan titration/ run-in phase, 1/126 died (never having received tolvaptan), 10/126 had hepatic enzyme elevation and 4/126 discontinued for an SAE. The others discontinued because of not meeting eligibility criteria (12), progression of disease (1),

personal reasons, such as finding the trial too burdensome (13). Of those who discontinued from the tolvaptan titration and run-in phase, 90 had side effects most often related to aquaresis. Four subjects were lost to follow-up during this period.

Among the 1370 subjects who entered the randomized period, there were 155 subjects who continued to be followed for the length of the 12-month double-blind post-randomization period who discontinued treatment prior to the 12-month end. Considerably more subjects in the tolvaptan group discontinued treatment (105/ 683, 15.4%) than in the placebo group (50/687, 7.3%). The most frequently reported events associated with IMP discontinuation were hepatic laboratory abnormalities /hepatic AEs [5.4% in the tolvaptan group (0.9% SAE) and 0.6% in the placebo group (0% SAE)] and intolerable aquaretic effects (4.8% in the tolvaptan group; 1.0% in the placebo group). Trial too burdensome, progression of disease, non-hepatic SAEs were less common factors associated with IMP discontinuation and occurred in approximately the same percent of treated subjects in both treatment groups.

Refer to the safety section of the review for a more detailed discussion on reasons for discontinuation, including AEs that resulted in discontinuation.

**Reviewer’s Comment:** *Despite only 4.2% of randomized subjects dropping out of the double-blind randomized phase of the study, 15.4% of the group randomized to tolvaptan and 7.3% of the group randomized to placebo stopped study treatment during that phase. The main reasons for the difference in IMP discontinuation were a considerably higher incidence of hepatic enzyme elevation/ hepatic AEs in the tolvaptan group than the placebo group (5.4% vs. 0.6%, respectively) and a considerably higher incidence of aquaretic side effects in the tolvaptan group than the placebo group (4.8% vs. 1%, respectively).*

**Reasons for Study Non-completion**

There were 57 non-completers (subjects who failed to complete 12 months in the study). As shown in Table 4, the reasons for noncompletion were well matched regardless of treatment and there were equal numbers of non-completers in each treatment arm. Most non-completers did not complete because the trial was too burdensome or a preceding non-hepatic AE.

**Table 4: Reasons for/ Events associated with non-completion during the randomized period**

	Tolvaptan N=683 n (%)	Placebo N=687 n (%)
Total Non-completers	29 (4.2)	28 (4.1)
Withdrawal Reason		

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AE	15 (2.2)	7 (1.0)
SAE	0 (0.0)	1(1.0) *
Hepatic AE/ Hepatic lab abnormality	5 (0.7)	2 (0.3)
Medication Intolerable	10 (1.5)	2 (0.3)
Other AE	0 (0.0)	2 (0.3)
Progression of disease	3 (0.4)	2 (0.3)
Taking marketed tolvaptan	0 (0.0)	1 (0.1)
Lost to follow up	1 (0.1)	4 (0.6)
Trial too burdensome	1 (0.1)	2 (0.3))
Other	9 (1.3)	12 (1.7)

\*subject had a stroke (from ADAE dataset)

Source: Dr. Beasley; Reviewer's analysis:ds\ds\noncompleters reason. Datasets: adsl, adae

### **Lost-to-follow-up**

At database lock in May 2017, 4 subjects were considered lost to follow-up. Vital status was subsequently confirmed for two of the subjects at Month 12 and a third subject at Month 10. Efforts to locate the remaining subject were ongoing at the time of this CSR.

### **Protocol Violations/Deviations**

During the trial, major protocol deviations were recorded and classified as: entry criteria, procedural, dosing, and concomitant medication. Among randomized subjects, major protocol deviations were reported for 129 subjects (72 in the tolvaptan and 57 in the placebo group). The entry criteria and procedural major protocol deviations were well matched between groups (8 and 7 for entry criteria major protocol deviations for tolvaptan and placebo, respectively; 5 and 6 for procedural major protocol deviations<sup>20</sup> for tolvaptan and placebo, respectively). There were no major protocol deviations related to concomitant medications.<sup>21</sup> The

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<sup>20</sup> Any of the following:

IMP administered following a positive urine pregnancy test

Study procedures were performed prior to signing the ICF

Subject missed >=7 consecutive days of IMP, did not restart treatment and did not have all 3 follow-up serum creatinines performed

Subject missed an entire monthly visit (post randomization) including end of treatment visit

Randomized subject missed serum creatinine laboratory testing at any scheduled visit (post randomization)

Randomized subject missed serum creatinine laboratory testing at any pre-randomization timepoint

Randomized subject missed any scheduled LFT laboratory testing

Randomized subject missed any scheduled sodium laboratory testing

Randomized subject missed any scheduled biomarker plasma sample and/or PK laboratory testing

Randomized subject missed any scheduled PD/biomarker urine sample

<sup>21</sup> Any of the following :

Diuretics taken within 7 days of pharmacodynamic and biomarker urine sample collections

Excluded medications (potent CYP3A4 inhibitors with the exception of amiodarone) were taken during the study

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classification of dosing major protocol deviations is the only category where there was a discrepancy between treatment groups (59 subjects in the tolvaptan dosing group and 44 subjects in the placebo group). Most subjects who met the criteria for this classification either missed  $\geq 30$  or more consecutive days or  $> 30\%$  of total doses intended. Because the prespecified efficacy analyses followed the ITT principle, subjects were included in the efficacy analyses regardless of their protocol deviation status.

During the trial, 1 subject was unblinded by an investigator (Subject (b) (6), on 07 Sep 2015). This subject had a serious TEAE that the investigator suspected may have been related to the IMP. No other subjects were unblinded by investigators. When reporting to health authorities, subjects were unblinded as required (33 cases for 29 subjects) for safety; only safety personnel were made aware of these subjects' treatment assignment.

**Reviewer's comment:** *The unblinding of one subject does not impact the integrity of the study or compromise the interpretation of study results.*

### Table of Demographic Characteristics

Baseline characteristics are presented in tabular form in Table 5. Almost half (49.6%) of the subjects were male and the great majority were white (91.8%) and non-Hispanic (93.4%). The mean age of the subjects was 47.3 years and the mean BMI was 27.8 kg/m<sup>2</sup>.

Most subjects had eGFR between 30-44 mL/min/1.73 m<sup>2</sup> (CKD Stage 3b) (~45%) The next most common eGFR range was 45-59 mL/min/1.73m<sup>2</sup> (Stage 3a) (30.0%). Approximately 20% of subjects were in Stage 4 (15-30 mL/min/1.73m<sup>2</sup>), and ~5 % had Stage 2 (eGFR between 60-89 mL/min/1.73m<sup>2</sup>). Most subjects (~65%) had eGFR (CKD-EPI)  $\leq 45$  mL/min/1.73 m<sup>2</sup>. Mean eGFR at baseline was well balanced between groups (~41 mL/min/1.73 m<sup>2</sup>). For most subjects (~80%), baseline total kidney volume (TKV) was not known; however, for subjects with a known TKV, baseline TKV was well balanced between groups (1982.5 mL, tolvaptan arm; 2070.2 mL placebo arm). The average BMI was in the overweight range (~29 kg/m<sup>2</sup>, tolvaptan arm; ~28 kg/m<sup>2</sup>, placebo arm). Most subjects had a history of hypertension, most were on ACEI's and ARBs and mean baseline BP was ~131/82 for both treatment groups. The average age of diagnosis was ~30 (SD 11). Most subjects were diagnosed with ADPKD because of hypertension, kidney pain, hematuria, and urinary tract infection in that order. This and other medical history parameters at baseline were equally distributed between treatment groups.

**Table 5: Baseline Demographics and CKD Characteristics – Randomized Population**

<b>Variable</b>		<b>Tolvaptan</b>	<b>Placebo</b>
		N=683	N=687
Age in years	Mean (SD)	47.3 (8.2)	47.2 (8.2)
	Range	23, 65	21, 65
Male gender	n (%)	347 (50.8%)	333 (48.5%)
Height (cm)	Mean (SD)	173.7 (10.4)	172.8 (10.2)
	Range	134.0, 206.0	145.0, 205.0
Weight [kg]	Mean (SD)	84.6 (19.9)	83.2 (19.3)
	Range	46.0, 227.0	41.9, 193.6
BMI (kg/m <sup>2</sup> )	Mean (SD)	28.0 (5.8)	27.7 (5.6)
	Range	17.1, 78.5	16.5, 52.0
<b>Race</b>			
Caucasian	n (%)	626 (91.7)	632 (92.0)
African American or Black	n (%)	25 (3.7)	23 (3.3)
American Indian or Alaska native	n (%)	3 (0.4)	1 (0.1)
Asian	n (%)	22 (3.2)	19 (2.8)
Native Hawaiian or Pacific Islander	n (%)	0 (0.0)	0 (0.0)
Other	n (%)	7 (1.0)	12 (1.7)
<b>Ethnicity</b>			
Hispanic	n (%)	44 (6.4)	35 (5.1)
<b>CKD Stage</b>			
CKD 2 (60 -89 mL/min/1.73 m <sup>2</sup> )	n (%)	32 (4.7)	39 (5.7)
CKD 3a (45-59 mL/min/1.73 m <sup>2</sup> )	n (%)	209 (30.6)	202 (29.4)
CKD 3b (30-44 mL/min/1.73 m <sup>2</sup> )	n (%)	303 (44.4)	315 (45.9)
CKD 4 (15-39 mL/min/1.73 m <sup>2</sup> )	n (%)	139 (20.4)	128 (18.6)
Unknown	n (%)	0(0.0)	3 (0.4)
<b>Age</b>			
≤ 55 years old	n (%)	585 (85.7)	588 (85.6)

<b>eGFR (CKD-EPI)</b>			
≤ 45 ml/min/1.73m <sup>2</sup>	n (%)	442 (64.7)	438 (63.8)
<b>Total Kidney Volume</b>			
≤ 2000 mL	n (%)	76 (11.1)	73 (10.6)
> 2000 mL	n (%)	60 (8.8)	60 (8.7)
Unknown	n (%)	547 (80.1)	554 (80.6)
<b>History of Hypertension</b>	n (%)	634 (92.8)	640 (93.2)
<b>Baseline SBP</b>	Mean (SD)	131.3 (13.7)	131.5 (14.3)
	Range	(97, 202)	(93, 189)
<b>Baseline DBP</b>	Mean (SD)	82.1 (9.7)	82.6 (9.7)
	Range	(52, 112)	(51, 119)
<b>On ARB or ACE post- randomization*</b>			
yes	n (%)	604 (88.4)	593 (86.3)
no	n (%)	79 (11.6)	94 (13.7)

Source: Clinical Study Report for Study 156-13-210; p. 104, \*ADCM (concomitant medications ADAM data set) and \*ADVS (vital sign ADAM data set)

**Reviewer's Comment:** Based on data on racial and ethnic make-up of patients with ADPKD who are on dialysis, fewer Blacks were randomized than might have been expected. This finding can partly be explained by where the study was conducted. In the U.S., 51/588 (8.7%) randomized subjects were Black, closer to what would be expected. For the "rest of the world" only 9/782 (1.2%) of randomized subjects were Black. The large majority of the "rest of the world" in this study were subjects from Western Europe. Because ADPKD is a genetic disease, it is likely that the results of this study are generalizable. It may be difficult to detect any subgroup differences in efficacy and safety because of the lack of power to do so. It is also notable that most subjects were in CKD Stage 3 at baseline. The results in this subgroup are expected to drive the results of the trial. The absence of TKV data was by design to reduce trial burden that could lead to subject drop-out and because the presence or absence of change in TKV would not be a determining factor for an approval decision. There was also no concern that this baseline TKV would independently influence outcomes. The sponsor did not analyze ARB yes/no as a subgroup for efficacy. Dr. Lawrence did an exploratory efficacy analysis, the results of which will be discussed later.

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**Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

**Geographic Distribution of Subjects:**

Of the 1370 randomized subjects, 782 subjects were in non-US centers and 588 subjects were in US centers. See Table 6 for more details.

**Table 6: Countries where study was conducted**

Country/ Region	Number of Subjects
US	588
Non-US	782
Western Europe	519
Eastern Europe and Russian Federation	101
Israel	38
Australia	34
Canada	47
Argentina	20
South Africa	23

Source: ADSL dataset

**Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

92.9% of the tolvaptan-treated subjects and 97.7% of the placebo-treated subjects were compliant with treatment (defined as taking >90% of medications).

**Reviewer's Comment:** *The high compliance is indicative of a well-conducted trial.*

**Efficacy Results – Primary Endpoint**

The primary analysis included 1313 participants. The study was successful on its primary endpoint and the p value was low (< 0.0001). As previously stated, the primary endpoint was a weighted ANCOVA of annualized change in eGFR measured as mL/min/1.73 m<sup>2</sup>/year (CKD-EPI) from pretreatment baseline to post-treatment follow up in the primary endpoint efficacy population (all subjects who were in the randomized population, took at least 1 dose of IMP after randomization, and had a baseline and at least 1 valid post-treatment evaluation in eGFR (i.e., after at least 1 week off treatment). The annualized treatment effect was 1.27 mL/year difference in eGFR decline which represents a 35% annual decrease in decline of eGFR. The results are shown in tabular form in Table 7 and in graphic form in Figure 4.

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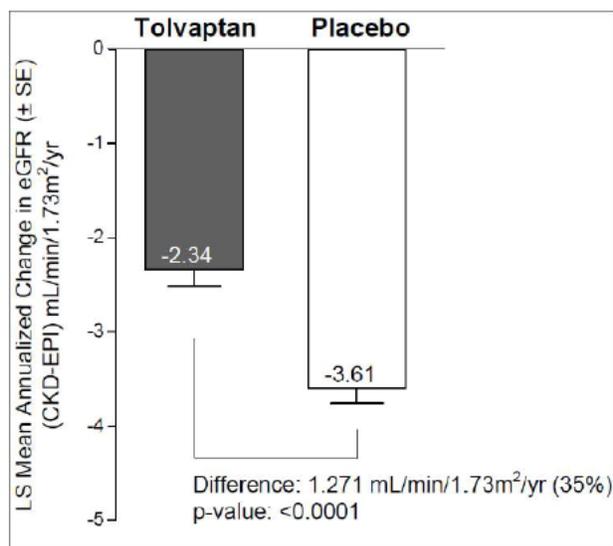
**Table 7: Primary Endpoint: weighted ANCOVA of annualized change in eGFR (CKD-EPI) from pretreatment baseline to post-treatment follow up (mL/min/1.73 m<sup>2</sup>/year) in the primary endpoint efficacy population**

	Tolvaptan	Placebo
N	668	663
Mean rate of change per year	-2.96	-4.25
LS mean	-2.34	-3.61
Treatment effect	1.27	
95% CI	(0.86, 1.68)	
p-value	< 0.0001	

Source: Clinical Study Report for Study 156-13-210; p. 107

CI = confidence interval; LS = least squares. Note: The estimated annualized eGFR change was from the average of  $\leq 3$  pretreatment baseline observations to the average of  $\leq 3$  post-treatment follow-up observations. The LS mean and 95% CI was derived from weighted ANCOVA with effects of treatment and randomization stratification factors and covariate baseline. The assessment of serum creatinine was the enzymatic method.

**Figure 4: Annualized change in eGFR (CKD-EPI) from pretreatment baseline to post-treatment follow-up (primary endpoint efficacy population)**



Source: p. 108, Clinical Study Report for Study 156-13-210

**Reviewer's comment:** *The low p-value provides confidence in the reliability of the results. The modest treatment effect over the course of one year is likely to be an*

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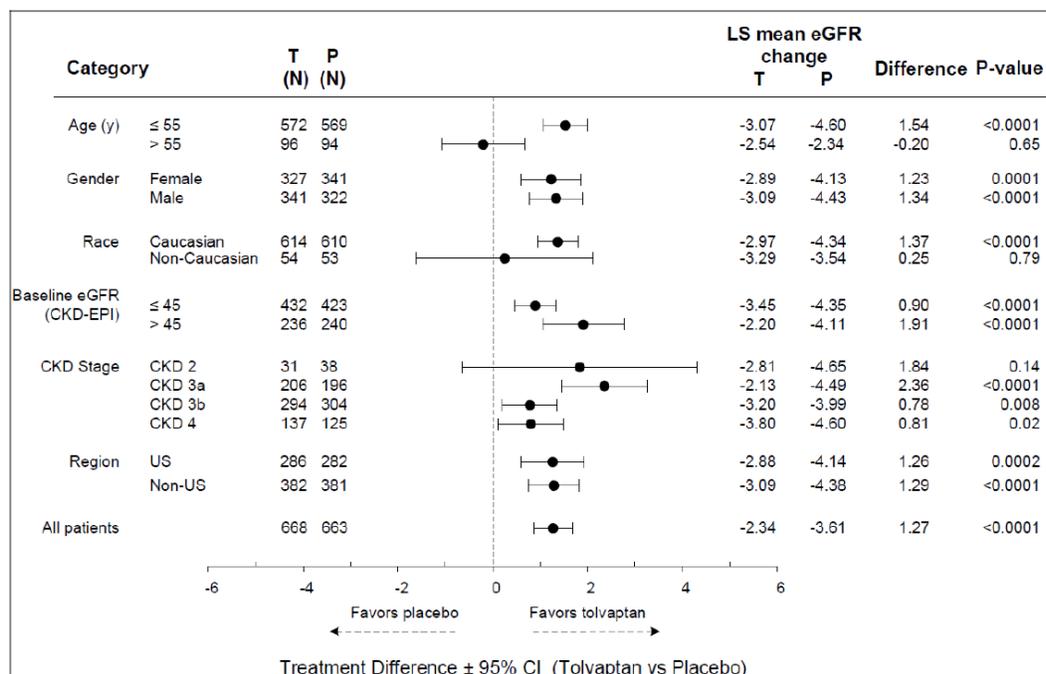
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*underestimate of the impact that the treatment will have on the life of a patient with ADPKD. Because ADPKD is a life-long disease, the benefits of treatment (if patients continue to take it) should accrue and compound over time as evidenced by the durable effects shown in TEMPO (Study 156-04-251), at earlier phases of disease and in REPRISE at later phases of disease. The conclusion that there is a persistent effect on decline in renal function is also supported by the results of the TEMPO extension study (to be discussed later in the review).*

As shown in Figure 5, subgroup analyses for the primary endpoint revealed nominally statistically significant differences between tolvaptan and placebo for most subgroups. While one would not expect to see favorable trends in all subgroups, for completeness of this review I note that effects appeared to be neutral in the following relatively small subgroups where power to show a difference was low: older than 55 years (14.3% of subjects), and non-Caucasian race (8.0% of subjects). Subgroup analysis by CKD stage provided evidence of treatment effects for all CKD stages. The effect size was nominally larger in the subjects in the earlier stages (Stages 2 and 3a) but a treatment effect was maintained through Stages 3b and 4. The results of the study were driven by subjects in Stage 3.

**Figure 5: Subgroup analysis of the primary endpoint**



Source: p. 114 of Clinical Study Report for Study 156-13-210

**Reviewer's comment:** *There are no data on patients older than age 55 in the previous trial, TEMPO, because this study excluded patients over age 50. However, there was no*

*decrease in effect with age over the age range studied in TEMPO (Study 156-04-251). For this reason, I think it is unlikely that the effect of tolvaptan diminishes by age, even in the elderly. However, it is possible that other factors such as concomitant medical conditions (such as hypertension and diabetes) and medications could reduce effectiveness of tolvaptan and these conditions would be more common in the elderly; but I think this finding is no more than hypothesis generating. There are no other baseline demographics that would seem to have a plausible effect on the response to treatment.*

*Dr. John Lawrence, statistician, did an exploratory post-hoc analysis at my request of subgroup findings in subjects were/ were not on ACEIs/ARBs to explore for any potential differences. Both subgroups trended in the right direction, with tolvaptan showing an advantage over placebo. See Table 8.*

**Table 8: Subgroup Findings by ACEIs/ARBs (Yes/No)**

Category	Tolvaptan (N=668) n (%)	Placebo (N=663) n (%)	Mean Age	Mean eGFR in mL/min per 1.73 m <sup>2</sup>	Mean treatment effect in mL/min per 1.73 m <sup>2</sup> (95% CI)
Did NOT use ARBs/ACEIs during REPRISE	76 (11.4)	89 (13.4)	48	43	2.21 (0.91, 3.52) *
Did use ARBs/ACEIs during REPRISE	592 (88.6)	574 (86.6)	47	41	1.17 (0.73, 1.61) **

\*mean decline in eGFR in the tolvaptan arm was -2.36 mL/min per 1.73 m<sup>2</sup> per year and mean decline in eGFR in the placebo group was -4.58 mL/min per 1.73 m<sup>2</sup> per year.

\*\* mean decline in eGFR in the tolvaptan arm was -3.07 mL/min per 1.73 m<sup>2</sup> per year and mean decline in eGFR in the placebo arm was -4.24 mL/min per 1.73 m<sup>2</sup> per year.

The key secondary endpoint was the linear mixed effect model of annualized eGFR change slope. This showed a statistically significant difference of 1.01 mL/min/1.73 m<sup>2</sup>/year (p < 0.0001) in favor of tolvaptan. See Table 9 and Figure 6 for tabular and graphic displays of data on rate of change, slope, and 95% CI.

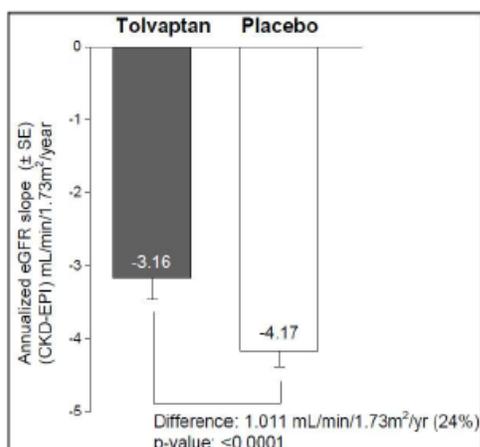
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**Table 9: Key Secondary Endpoint: Linear Mixed Effect Model of Annualized eGFR (CKD-EPI) Change slope (mL/min/1.73m<sup>2</sup>/year)- Key Secondary Endpoint Efficacy Population**

Summary Statistics	Tolvaptan	Placebo
N	680	682
Mean rate of change per year	-2.55	-3.2
Slope	-3.16	-4.17
Treatment Effect	1.01	
95% CI	(0.62,1.4)	
P-Value	<0.0001	

Source: p. 115, CSR

**Figure 6: Linear Mixed Effect Model of Annualized eGFR (CKD-EPI) Change Slope-Key Secondary Endpoint Efficacy Population**



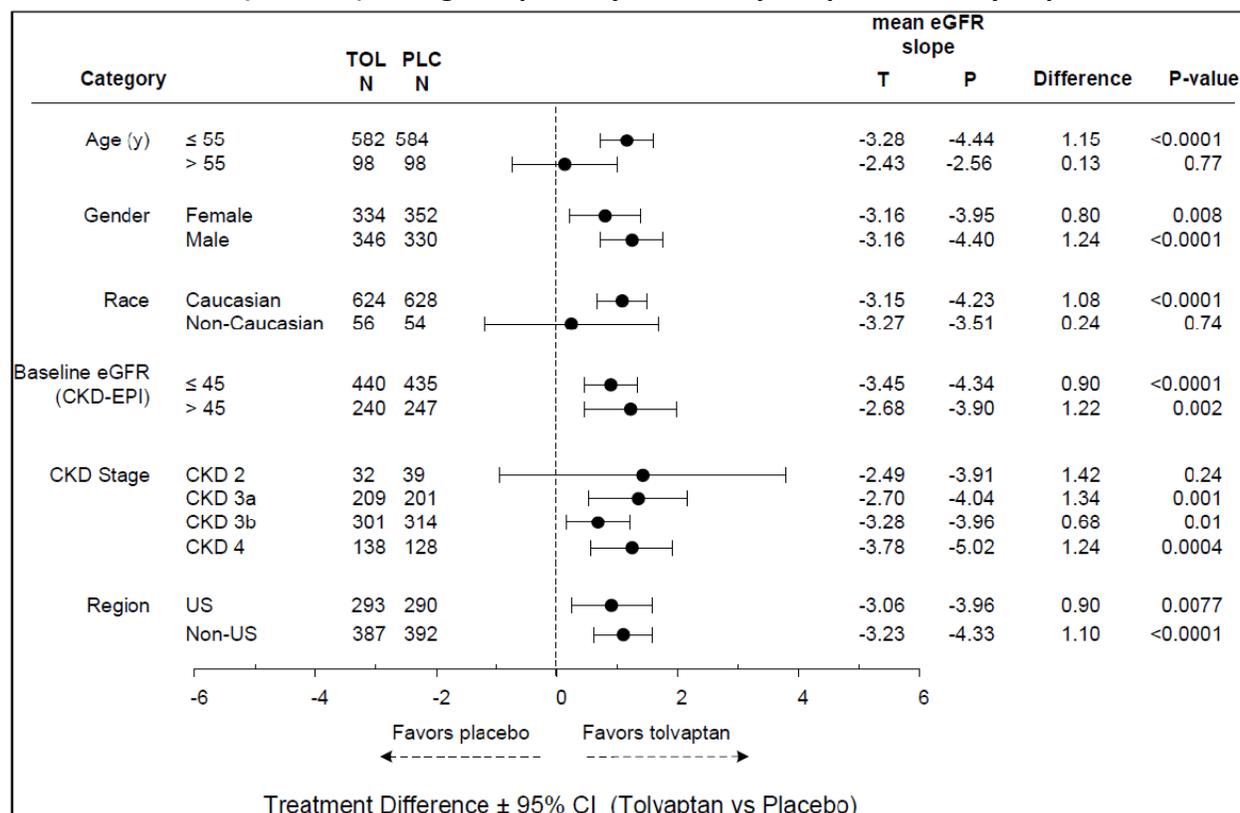
Source: p. 116, Clinical Study Report for Study 156-13-210

**Reviewer's Comments:**

*The results of this secondary slope-based analysis confirm the results of the primary efficacy analysis, i.e., that over one year time the difference in change in eGFR is ~ 1 mL/min.*

Subgroup analyses of the secondary endpoint were, not surprisingly, like the subgroup analyses of the primary efficacy endpoint. See Figure 7. Sensitivity analyses supported the robustness of the results.

**Figure 7: Subgroup Analysis of the Key Secondary Endpoint: Linear Mixed Effect Model of Annualized eGFR (CKD-EPI) Change Slope - Key Secondary Endpoint Efficacy Population**



**Exploratory Outcomes**

Shown in Table 10, an analysis of rates of first clinical events of interest was performed for the composite of 6 ADPKD outcomes (kidney pain, hematuria, nephrolithiasis, urinary tract infection, anemia, and significant drop in kidney function), and separately for the individual outcomes of hematuria, kidney pain, and urinary tract infection. None of these analyses showed a statistically significant difference between treatments. For the time to multiple event analyses, a nominally statistically significant difference was observed for the outcome of gross hematuria (p = 0.02), for which more events occurred in the tolvaptan arm; no other significant results were observed).

**Table 10: ADPKD Outcome Event Rates**

	Tolvaptan N=681	Placebo N=685	HR (95% CI)	P value
# of first ADPKD outcome event/ f.u. years; composite (kidney pain,	208 events/ 520.8 years	228 events/ 535.1 years		

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hematuria, nephrolithiasis, urinary tract infection, anemia, and significant drop in kidney function)				
First events per 100 f.u. years	39.9	42.6	0.93 (0.78, 1.13)	0.47
# of total ADPKD outcome events/ f.u. years; composite (kidney pain, hematuria, nephrolithiasis, urinary tract infection, anemia, and significant drop in kidney function)	341 events/ 625.1 years	347 events/ 664.2 years		
Total ADPKD outcome events per 100 f.u. years	54.6	52.3	1.0	0.65
# of first kidney pain events / f.u. years	138 events/ 554.1 years	157 events/ 575.2 years		
First kidney pain events per 100 f.u. years	24.9	27.3	0.91 (0.72, 1.14)	0.4
# of total kidney pain events / f.u. years	215 events/ 625.1 years	664.2 events/ 33.7 years		
Total kidney pain events per 100 f.u. years	34.4	33.7	1.1 (0.8, 1.3)	0.9
# of first gross hematuria events/ f.u. years	45 events/ 602.7 years	33 events/ 645.7 years		
First gross hematuria events per 100 f/u years	7.5	5.1	1.46 (0.93, 2.3)	0.1
# of total gross hematuria events/ f.u. years	63 events/ 625.1 years	38/ 664.2 years		
Total gross hematuria events per 100 f.u. years.	10.1	5.7	1.76 (1.1, 2.9)	0.02
# of first UTI events/ f.u. years	40 events/ 606.5 years	54 events/ 634.2 years		
First UTI events per 100 f/u years	6.6	8.5	0.77 (0.5, 1.2)	0.2
# of total UTI events/ f.u. years	51 events/ 625.1 years	64 events/ 664.2 years		
Total UTI events per 100 f.u. years.	8.2	9.6	0.8 (0.5, 1.3)	0.5

Source: Clinical Study Report for Study 156-13-210, p. 5112

*Reviewer's Comment: There were more gross hematuria events in the tolvaptan arm than in the placebo arm. See safety section 8.5.4 for further discussion.*

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### **Additional unplanned exploratory analyses**

Il conducted an analysis to rule out any worsening of ADPKD events of worsening kidney function in the tolvaptan group using the ADPKD dataset. For the event called “significant drop in kidney function”, there were 39 subjects (5.7%) with 360 total events in the post-randomization placebo group and 44 subjects (6.4%) with 329 total events in the post-randomization tolvaptan group labeled, respectively. There were 12 subjects (0.8%) with 77 events of “significant drop in kidney function” in the pre-randomization tolvaptan titration and run-in phase. There was no signal of acute kidney injury or prerenal renal failure in the AE dataset.

Also, using the ADPKD dataset, and selecting all events called, “dialysis”, only two subjects had dialysis, both in the placebo arm and the events occurred in the post-randomization period. One subject in the tolvaptan treatment group had transplantation in the post-randomization period

**Reviewer’s Comment:** There is no concern that tolvaptan causes “significant drop in kidney function” (an exploratory efficacy outcome measure), acute kidney injury, or prerenal renal failure.

### **Data Quality and Integrity**

No issues with data quality/integrity were found. The data in the datasets appeared to match that found in the CRFs. This application went through a Jumpstart, which is a service provided by the FDA’s Office of Computational Science that assesses the quality of the SDTM data and provides some assessments of the safety data. Jumpstart identified some minor issues with the data, however there was minimal impact on the ability to conduct the review. Specific issues with data are discussed in the specific safety section.

### **Efficacy Results – Secondary and other relevant endpoints**

Because the sponsor proposed in labeling to state, “TRADENAME is a selective vasopressin V<sub>2</sub>-receptor antagonist indicated to slow kidney function decline (b) (4) in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD),” (b) (4)

(b) (4) In the TEMPO trial, a statistically significant reduction in kidney cyst growth was shown, but this mostly occurred during the few weeks/months of treatment, and, it was unclear what if any clinical significance there was to this finding and whether it was a durable effect. To gain further insight into the durability of effect on cyst growth and TKV, I reviewed the extension study to TEMPO.

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Study 156-08-271, titled, “Multi-center, Open-label, Extension Study to Evaluate the Long-term Efficacy and Safety of Oral Tolvaptan Tablet Regimens in Subjects with Autosomal Dominant Polycystic Kidney Disease (ADPKD)”

### Studied Period:

Date of first patient first visit: 26 May 2010

Date of last patient last visit: 29 Feb 2016

**Study Design:** This trial was a multicenter, international, open-label, extension trial using oral tolvaptan tablets in subjects with ADPKD. More than 90% of the REPRISE completers were enrolled. All subjects were started on tolvaptan and followed for two years to determine any difference between the REPRISE arm that had originally been treated with tolvaptan (early-treatment) compared to the arm that had originally been treated with placebo (delayed-treatment).

**Enrollment Criteria:** To be included, subjects had to have successfully completed (protocol-defined completer without early termination) a phase 1, 2, or 3 tolvaptan ADPKD or renal impairment trial, have a confirmed diagnosis of ADPKD and have an eGFR by Modification of Diet in Renal Disease (MDRD)  $\geq 30$  mL/min/1.73m<sup>2</sup> within 45 days prior to the baseline visit (unless approved by a medical monitor). Subjects were to be enrolled within 6 months following previous ADPKD or renal impairment trial completion or trial site IRB approval, whichever was later.

Of the 1083 subjects enrolled in this open-label extension trial only 871 (80.4%) subjects from 156-04-251.<sup>22</sup> Only subjects from study 156-04-251 who were not in the Japanese sites in the first study were included in the primary efficacy analysis. The patients who had enrolled in study 156-04-251 and were in Japanese sites were excluded because there was a separate extension study for that population.

**Drug dosing and schema:** The tolvaptan daily doses used in this trial included 45/15 mg, 60/30 mg, or 90/30 mg, split-doses taken orally approximately 9 hours apart. Subjects were titrated to the highest dose tolerated unless an equivalent dose was not tolerated or was associated with a significant adverse event (AE) in a prior tolvaptan trial. Beginning at Month 1, subjects could titrate the dose levels up or down per investigator discretion with the goal of maximizing tolerability while attempting to keep morning trough urine osmolality  $\leq 300$  mOsm/kg. During

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<sup>22</sup> A double-blind, placebo-controlled phase 3 trial to evaluate the long-term safety and efficacy of tolvaptan for the treatment of ADPKD

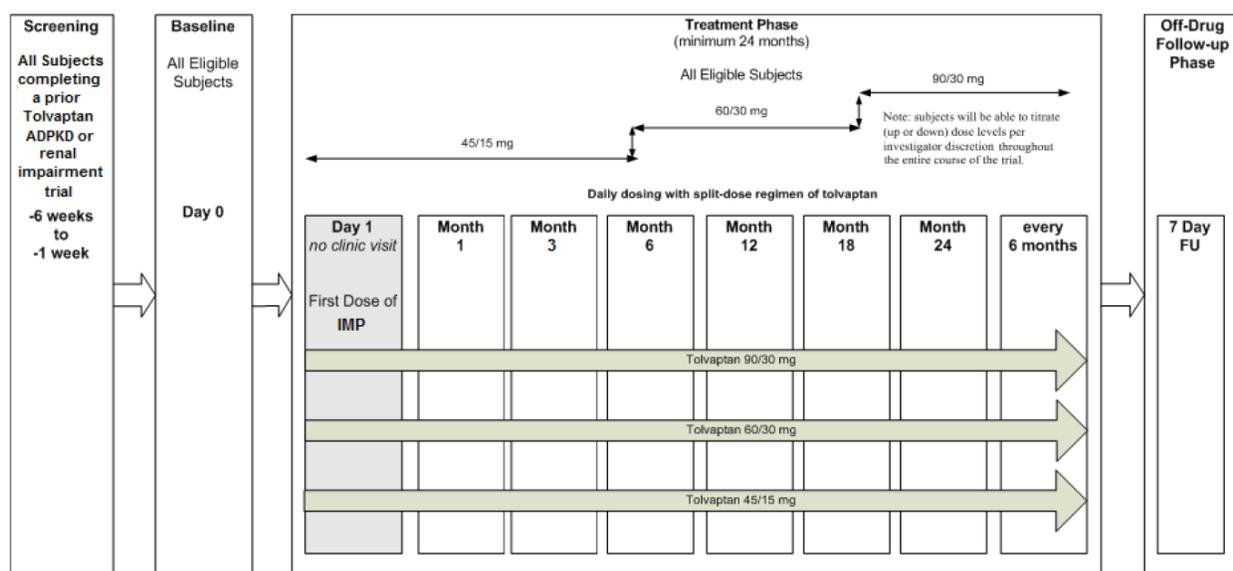
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the trial, dose levels could be increased, held, or decreased as appropriate. Treatment visits occurred on Months 1, 3, 6, and every 6 months thereafter. See Figure 8 for a schematic representation of the trial design.

### Duration of Treatment/ Schema

Patients were to be studied for at least 24 months. The longest duration of treatment was approximately 54 months. See Figure 8 for a schematic of extension study 156-08-271.

**Figure 8: General Trial Design Schematic for study 156-08-271**



Source: p. 52 of CSR Study 156-08-271

**Primary efficacy endpoint:** Change from the Study 156-04-251 baseline in TKV at Month 24 of Study 156-08-271. Primary efficacy analysis was planned to be conducted in subjects randomized to tolvaptan and placebo in Study 156-04-251 and enrolled and treated in Study 156-08-271 as early-treated and delayed-treated groups.

Statistical Test: Mixed-Effect Model Repeated Measures (MMRM) with factors of treatment group (the early-treated group and the delayed-treated group), visit (Study 156-08-271), treatment group visit interaction, region, Study 156-04-251 baseline hypertension status, creatinine clearance status, renal volume status, and covariate baseline (Study 156-04-251) with unknown variance covariance structure for the repeated visits. Comparison between the early-treated group and the delayed-treated group at Month 24 in Study 156-08-271 was to be made using the least squares (LS) means at Month 24 of the MMRM to test the superiority of early tolvaptan treatment. Log transformation of TKV was to be used in the analysis. The

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primary analysis was based on the Efficacy Sample with alpha level 0.05. The changes from Study 156-04-251 baseline at Study 156-08-271 baseline, Months 12, and 24 were to be included in the analysis.

### **“Key” Secondary efficacy endpoints (unordered, although in the statistical section they are referred to as the first, second and third key secondary endpoints):**

- Change from the Study 156-04-251 baseline in the estimated glomerular filtration rate (eGFR) (calculated using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation [eGFR<sub>CKD-EPI</sub>]) at Month 24 of Study 156-08-271.

The statistical analysis for this endpoint was identical to the primary efficacy endpoint analysis except that no log transformation was to be applied to the eGFR data.

- Slope of TKV in Study 156-08-271
- Slope of eGFR<sub>CKD-EPI</sub> in Study 156-08-271

Statistical test for the second and third key secondary endpoints: Model of random coefficient regression, with fixed effects of intercept, time, treatment group (the early-treated group and the delayed-treated group), treatment group time interaction, and random effects of intercept and time with unknown variance covariance structure, to the data collected in Study 156-08-271, from baseline to Month 24. Time was to be treated as a continuous variable and was defined as time spent from baseline to collection of the data. The 95% confidence interval (CI) based on a contrast between the early-treated group and the delayed-treated group and obtained from the treatment group time interaction, were to be used to test the noninferiority null hypotheses. For TKV, log-transformed data were to be used, and the noninferiority null hypothesis was to be rejected if the upper limit of the 95% CI was less than two-thirds of the treatment effect in slowing TKV (log-transformed) growth in Study 156-04-251.

### **Other Secondary efficacy endpoints (unordered):**

In prior placebo subjects enrolled from Study 156-04-251:

- Rate of change in annual TKV slope when crossing over from placebo to tolvaptan treatment
- Rate of change in annual slope of renal function (eGFR<sub>CKD-EPI</sub>) when crossing over from placebo to tolvaptan treatment

For all subjects enrolled in this trial:

- Change from baseline in TKV by exposure group
- Change from end of titration in renal function (eGFR<sub>CKD-EPI</sub>) by exposure group

### **Exploratory endpoints (unordered)**

- Polycystic kidney disease (PKD) outcomes (including onset of end-stage renal disease [ESRD]) and resource utilization.

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- Absolute change at each visit and change from baseline in European Quality of Life-5 Dimensions (EQ-5D) summary index using the 5-level version (EQ-5D-5L)
- Changes in ADPKD clinical progression events, including severe renal pain, and worsening renal function.

### **Efficacy Assessments:**

- MRI assessments, performed per the schedule of assessments: within 2 weeks prior to the baseline visit, within 2 weeks of the Month 12 and Month 24 visits (while the subject was still receiving study treatment), and ET/End of Study (EOS) visits if the previous MRI was taken more than 6 months prior to the ET/EOS visit. For subjects who terminated  $\geq$  24 months on study, an MRI was performed if the subject's last scan was performed  $\geq$  12 months prior to termination. Subjects with ferro-magnetic prostheses, aneurysm clips, severe claustrophobia or other contraindications or exclusions interfering with the MRI endpoint were excluded from the procedure and analysis. The parameter for primary efficacy analysis (using a central reader) was combined renal volume of both kidneys.
- Renal function assessments, all scheduled and unscheduled visits.
- Blood pressure and hypertension assessments
- Renal pain assessments (0-10 scale, 10 represented worst pain)
- Subject questionnaires

### **Sample Size and Power**

Assuming that the treatment differences in percent change from baseline in TKV ( $\pm$  SD) and change from baseline in eGFR ( $\pm$  SD) of the early-treated tolvaptan group and delayed-treated tolvaptan group at Month 24 of Study 156-08-271 are respectively 6 ( $\pm$  15)% and 2.4 ( $\pm$  10) mL/min/1.75m<sup>2</sup>, and assuming up to 900 subjects (600 early-treated and 300 delayed-treated) enrolled from Study 156-04-251, the trial had over 90% power to detect the treatment group difference at Month 24 in Study 156-08-271 for TKV and eGFR.

### **Subject Disposition (Efficacy set only)**

Trial Retention was good and most subjects completed the 24 months specified in the statistical analysis plan. More patients in the placebo group who crossed over to tolvaptan discontinued tolvaptan in < 24 months than the group who had previously been in the tolvaptan arm of study 156-04-251, mostly after AEs (11.1% vs. 2.9%). See Table 11 for a tabular description of the subject disposition.

**Table 11: Subject disposition**

Subjects	Tolvaptan (N/%)	Placebo (N/%)
Enrolled	557 (100)	314 (100)

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Completed 24 months	507 (91.0)	256 (81.5)
Discontinued < 24 months	50 (9.0)	58 (18.5)
Lost to follow up	7 (1.3)	3 (1.0)
AEs	16 (2.9)	35 (11.1)
Withdrawal Criteria Met	3 (0.5)	0
Withdrawal of Consent	21 (3.8)	18 (15.7)
Other	3 (0.5)	2 (0.6)
Discontinued IMP due to AE after 24 months	24 (4.3)	15 (4.8)
Analyzed for Primary Efficacy	557 (100)	312 (99.4)

Source: 156-08-271 CSR; p. 84.

### **Pertinent Demographic Information**

In the Extension Study 156-08-271, compared to REPRISE, there were more Caucasians (~96% in Extension Study 156-08-271 compared to ~84% in Study 156-04-251), fewer Asians (~0.6% in Extension Study 156-08-271 compared to ~12.7% in Study 156-04-251 and as expected, the mean age was higher (~42 compared to ~38 in in Study 156-04-251).

**Table 12: Baseline Demographics of study 156-08-271 (all subjects who came from Study 156-04-251)**

Parameter	Statistic	Study 156-04-251	
		Tolvaptan (N=557)	Placebo (N=314)
Race <sup>a</sup>			
Caucasian	n (%)	535 (96.1)	302 (96.2)
Black or African American	n (%)	9 (1.6)	2 (0.6)
American Indian or Alaska Native	n (%)	0	0
Asian	n (%)	3 (0.5)	2 (0.6)
Other	n (%)	10 (1.8)	8 (2.5)
Ethnicity <sup>a</sup>			
Hispanic/Latino	n (%)	24 (4.3)	19 (6.1)
Not Hispanic/Latino	n (%)	471 (84.6)	249 (79.3)
Unknown	n (%)	62 (11.1)	46 (14.6)
Age (years)	Mean (SD)	42.2 (6.9)	42.5 (7.2)
	Range	21–54	21–54
Height <sup>b</sup> (cm)	Mean (SD)	174.8 (10.3)	174.1 (9.7)
	Range	150–210	152–201
Weight (kg)	Mean (SD)	82.63 (18.40)	81.02 (17.30)
	Range	47.0–163.8	47.5–146.8

<sup>a</sup>Percentages are based on the number of randomized subjects.

Source: [CT-3.1.1](#).

Source: CSR of Extension Study 156-08-271, p. 89

Comparing certain tolvaptan –modifying baseline demographics at baseline of Study 156-04-251 to baseline of Extension Study 156-08-271 (Table 13) reveals expected post-randomization bias, i.e., baseline TKV, eGFR and ACR were lower in the early-treatment group than in the delayed treatment group in Study 156-08-271. Despite balanced male: female proportions in REPRISÉ between treatment groups, there were 18% more males in the early-treatment group compared to the delayed-treatment group in Study 156-08-271 (ratio of M/F; 1.19 [303/254] for early vs 1.01 [158/156] for delayed).

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To explore the effects of the off-treatment period (i.e., the interval between completion of Study 156-04-251 and initiation of Study 156-08-271) on the TKV endpoint, the duration of the off-treatment period was calculated. Overall the off-treatment period duration varied among subjects

(range: 13 - 829 days, mean = 80.8 days, median = 37 days), but was not significantly different between the early- and delayed-treated subjects.

**Table 13: Demographics of Subjects enrolled in Study 156-08-271 and comparison to their baseline in Study 156-04-251.**

Parameter	Study 156-04-251			Study 156-08-271		
	Tolvaptan (N=557)	Placebo (N=314)	p-value <sup>a</sup>	Early Treated Tolvaptan (N=557)	Delayed Treated Tolvaptan (N=314)	P-value <sup>a</sup>
Gender						
Male, n (%)	303 (54.4)	158 (50.3)	0.2467	303 (54.4)	158 (50.3)	0.2467
Female, n (%)	254 (45.6)	156 (49.7)		254 (45.6)	156 (49.7)	
Age, mean year (SD)	38.9 (6.9)	39.2 (7.3)	0.2959	42.2 (6.9)	42.5 (7.2)	0.3160
Height, mean cm (SD)	174.6 (10.4)	173.9 (9.8)	0.3217	174.8 (10.3)	174.1 (9.7)	0.3516
Weight, mean kg (SD)	80.49 (17.73)	79.22 (17.22)	0.3028	82.63 (18.40)	81.02 (17.30)	0.2261
TKV, mL (SD)	1706.28 (879.71)	1672.99 (889.10)	0.6029	1919.52 (1022.91)	2095.62 (1231.47)	0.0459
eGFR, mL/min/1.73 m <sup>2</sup> (SD)	82.17 (20.64)	83.54 (22.59)	0.5942	72.34 (24.46)	70.42 (25.00)	0.3835
Blood Pressure, mmHg						
Diastolic (SD)	82.6 (9.1)	82.7 (9.0)	0.9146	80.8 (8.6)	81.1 (8.8)	0.4060
Systolic (SD)	128.6 (13.2)	128.8 (13.2)	0.8619	126.6 (12.4)	127.0 (12.1)	0.6821
ACE/ARB use <sup>b</sup> , n (%)	401 (72.0)	223 (71.0)	0.7595	452 (81.1)	247 (78.7)	0.3761
ACR, g/mg (SD)	6.4060 (11.7454)	6.6475 (16.3084)	0.8545	6.0723 (12.4607)	7.6863 (19.2689)	0.0396
Copeptin, pmol/L (SD)	8.65 (10.03)	10.87 (25.49)	0.6991	-	-	-

<sup>a</sup>For continuous variables, the p-values were from Wilcoxon two-sample tests; for categorical variables, the p-values were from chi-square tests.

<sup>b</sup>Medications taken prior to start of IMP for progressing hypertension, with medication class = agents acting on the renin-angiotensin system and medication code ended in 'sartan' (ACE) or 'pril' (ARB).

Source: ST-4.1 and ST-4.2.

Source: p. 93 of CSR of Study 156-08-271

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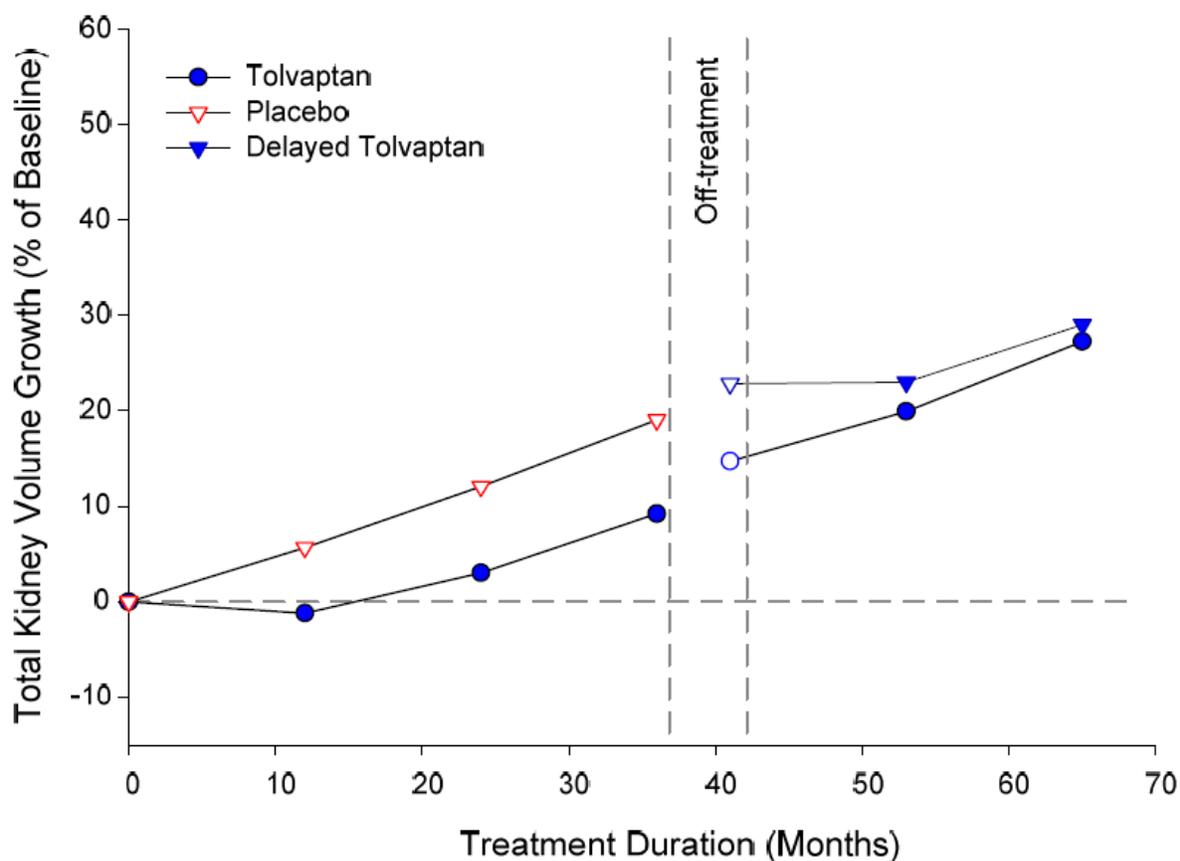
**Reviewer's Comment:** *While there are small differences in demographics between TEMPO and study156-08-27, I do not think that they affect the interpretability of the findings.*

## Efficacy Results

The results of this study are presented in Figure 9. The change from the Study 156-08-271 baseline at the end of Study 156-08-271 was 28.7% for the early treatment group and 30.6% for the delayed treatment group ( $p=0.36$ ), essentially no different. The delayed-treatment group's TKV had an average 12% growth in the first 2 years of Study 156-04-251 and this decreased by ~half to approximately ~6% growth in the next two-year period in the extension study. The growth rate of the early treatment group was ~ 12.5% growth during the extension study, similar to the growth seen in the placebo group in REPRISE. Figure 9 shows that the kidney size of the early treatment group essentially caught up to the kidney size of the delayed treatment group. This finding provides evidence that there is an early effect on kidney size with tolvaptan, but the effect does not continue to accrue over time.

A key secondary endpoint was eGFR at month 24. The difference was 3.15 mL/min/1.73 m<sup>2</sup> (1.46, 4.84) and the nominal p value was 0.0003. The difference between the early treatment group and the delayed treatment group persisted throughout the 2-year period and was ~ 2-3 mL/min/ 1.73 m<sup>2</sup> by the CKD-EPI calculation at each of the 3 pre-baseline and baseline measures and 10 baseline/post-baseline measurements and each value was nominally statistically significant. These results add confidence to the conclusion that the effect on eGFR persists throughout treatment.

**Figure 9: Annual Total Kidney Volume Percent Change from Study 156-04-251 Baseline to Study 156-08-271 Month 24 Visit (Least-square Mean Values)**



**Conclusions:** The results of the extension trial provide no evidence of a sustained effect on TKV. However, the effect on eGFR persisted, adding confidence to the conclusion that the effect on declining renal function is a durable effect.

## 7. Integrated Review of Effectiveness

### 7.1. Assessment of Efficacy Across Trials

In summary, the results of the REPRISE trial provide persuasive evidence of a small effect on decline in eGFR in patients with ADPKD who are at more advanced stages of disease than patients who participated in the first pivotal trial, TEMPO. Taken together the results of these

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two trials provide convincing evidence that tolvaptan has a clinically meaningful effect on renal function decline in patients with rapidly advancing ADPKD who have baseline eGFRs between normal values and 25 mL/min/1.73m<sup>2</sup>. If taken chronically, tolvaptan should slow the decline of renal function and delay the onset or reduce the incidence of ESRD in patients similar to the ones enrolled in TEMPO and REPRISE.

### 7.1.1. Primary Endpoints

TEMPO was successful on its primary endpoint, TKV, which because of type 1 error preservation allowed the analysis of the secondary endpoints and tertiary endpoints which the clinical review team considered to be more clinically relevant. The efficacy endpoint of primary interest in common to both pivotal trials, TEMPO and REPRISE, that was relied upon to establish substantial evidence of benefit, was a representation of the rate of renal function decline. Both trials showed similar tolvaptan treatment effect sizes, a reduction in the slope of 1/serum creatinine ([mg/mL]<sup>-1</sup> of ~1.0 (the tertiary efficacy endpoint in TEMPO and the secondary efficacy endpoint in REPRISE) AND a reduction in rate of eGFR decline of ~0.9-1.3 mL/min/1.73m<sup>2</sup>/year (in TEMPO and REPRISE, respectively) representing a 28% (TEMPO) to -36% (REPRISE) decrease in rate of decline in eGFR compared to placebo (primary efficacy endpoint in REPRISE and exploratory endpoint in TEMPO). All results were highly statistically significant with p values < 0.0001.

### 7.1.2. Secondary and Other Endpoints

In TEMPO, the key secondary composite endpoint (ADPKD progression) was time to multiple clinical progression events of: 1) worsening kidney function (defined as a persistent 25% reduction in reciprocal serum creatinine during treatment (from end of titration to last on-drug visit); 2) medically significant kidney pain (defined as requiring prescribed leave, last-resort analgesics, narcotic and anti-nociceptive, radiologic or surgical interventions); 3) worsening hypertension (defined as a persistent increase in blood pressure category or an increased anti-hypertensive prescription); 4) worsening albuminuria (defined as a persistent increase in albumin/creatinine ratio category). The relative rate of ADPKD-related events was decreased by 13.5% in tolvaptan-treated patients, (44 vs. 50 events per 100 person-years; hazard ratio, 0.87; 95% CI, 0.78 to 0.97; p=0.0095). The result of the key secondary composite endpoint was driven by effects on worsening kidney function and kidney pain events. In contrast, there was no effect of tolvaptan on either progression of hypertension or albuminuria. The effects of each of the composite endpoints will be shown in the label as events per 100 person-years, percentage of subjects with an event and HR, 95% CI.

### 7.1.3. Subpopulations

When looking at the subgroup efficacy analyses of TEMPO and REPRISE, the only subgroup where the effect of tolvaptan appeared to be neutral is the subgroup in REPRISE > 55 years old.

No such subgroup was studied in TEMPO (only enrolled patients 18- 50 years of age), but there were no age-related differences in TEMPO. The lack of age related diminishment of effect in TEMPO makes it less likely that the effect of tolvaptan diminishes by age. However, it is possible that other factors such as concomitant medical conditions (such as hypertension and diabetes) and medications could reduce effectiveness of tolvaptan and these conditions would be more common in the elderly; this subgroup finding is at most hypothesis generating.

#### **7.1.4. Dose and Dose-Response**

The dose was selected based on maximum V2-receptor blockade.

#### **7.1.5. Onset, Duration, and Durability of Efficacy Effects**

Durability of effectiveness on eGFR decline has been demonstrated over 5 years (TEMPO and TEMPO extension study) in patients with early ADPKD and over 1-year in patients with more advanced disease (REPRISE).

### **7.2. Additional Efficacy Considerations**

#### **7.2.1. Considerations on Benefit in the Postmarket Setting**

The clinical trials were enriched with patients who were at risk for rapid progression (by TKV in TEMPO and by historical rate of eGFR decline in REPRISE). It is likely that patients who are not rapidly progressing will consider taking tolvaptan. Regarding efficacy considerations, it is reasonable to assume that benefit will be conferred to a lower-risk population, but the risk-benefit balance could be offset somewhat. This would be off-label use.

Because of aquaretic effects, it is possible that doses in practice may be lowered below what was studied in the clinical trials or tolvaptan may be taken intermittently. Efficacy might be lessened if doses are reduced considerably or tolvaptan is taken intermittently. The label states that patients should be maintained on the highest tolerable dose.

Additionally, because of the drug's orphan status, there is no requirement to study tolvaptan in children. The label will state that, "Safety and effectiveness of JYNARQUE in pediatric patients has not been established." There is a study in children with ADPKD being conducted outside of US and was submitted to the IND.

#### **7.2.2. Other Relevant Benefits**

TEMPO suggested that there may be a reduction in renal pain events in addition to a slowing in decline of eGFR.

### **7.3. Integrated Assessment of Effectiveness**

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In TEMPO, TKV was measured at the beginning of the trial and every year thereafter. In the placebo group, TKV grew approximately 5.5% each year. In the tolvaptan group, TKV was approximately unchanged during the first year, but grew approximately 5.1% per year in each of the subsequent years. This comparison will be stated in the label in Section 14. The key secondary composite endpoint (ADPKD progression) was time to multiple clinical progression events of: 1) worsening kidney function (defined as a persistent 25% reduction in reciprocal serum creatinine during treatment (from end of titration to last on-drug visit); 2) medically significant kidney pain (defined as requiring prescribed leave, last-resort analgesics, narcotic and anti-nociceptive, radiologic or surgical interventions); 3) worsening hypertension (defined as a persistent increase in blood pressure category or an increased anti-hypertensive prescription); 4) worsening albuminuria (defined as a persistent increase in albumin/creatinine ratio category). The relative rate of ADPKD-related events was decreased by 13.5% in tolvaptan-treated patients, (44 vs. 50 events per 100 person-years; hazard ratio, 0.87; 95% CI, 0.78 to 0.97;  $p=0.0095$ ). The result of the key secondary composite endpoint was driven by effects on worsening kidney function and kidney pain events. In contrast, there was no effect of tolvaptan on either progression of hypertension or albuminuria. The effects of each of the composite endpoints will be shown in the label as events per 100 person-years, percentage of subjects with an event and HR, 95% CI. The third efficacy endpoint (kidney function slope) was assessed as slope of eGFR during treatment (from end of titration to last on-drug visit). There was an estimated difference in the annual rate of change of  $1.0 \text{ mL/min}/1.73 \text{ m}^2/\text{year}$  with a 95% confidence interval of (0.6, 1.4) between treatment groups. Because of the differential drop-out rate between treatment groups in TEMPO, there is less confidence in this finding.

In the randomized period of REPRISE, the change of eGFR from pretreatment baseline to post-treatment follow-up was  $-2.3 \text{ mL/min}/1.73 \text{ m}^2/\text{year}$  with tolvaptan as compared with  $-3.6 \text{ mL/min}/1.73 \text{ m}^2/\text{year}$  with placebo, corresponding to a treatment effect of  $1.3 \text{ mL/min}/1.73 \text{ m}^2/\text{year}$  ( $p < 0.0001$ ). The key secondary endpoint (eGFR slope in  $\text{ml}/\text{min}/1.73 \text{ m}^2/\text{year}$  assessed using a linear mixed effect model of annualized eGFR (CKD-EPI)) showed a difference between treatment groups of  $1.0 \text{ ml}/\text{min}/1.73 \text{ m}^2/\text{year}$  that was also statistically significant ( $p < 0.0001$ ). This information should be stated in the label.

## 8. Review of Safety

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### Safety Review Approach

This review presents the safety findings from trial 156-13-210, REPRISE. One purpose of REPRISE was to test a strategy to mitigate the risk of Drug Induced Liver Injury (DILI). The trial appeared to mitigate the risk, but shortly after the application was resubmitted, there was a post-marketing case of liver transplantation in a subject treated with tolvaptan. Thus, this

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review also examined the liver data collected since the 2013 review, including post-marketing data. All tables and figures in Section 8 refer to the REPRISE trial and were created by the reviewer, unless stated otherwise.

The reader should refer to the 2013 original review of this application for a discussion of the safety of tolvaptan in ADPKD, trial 156-04-251, the TEMPO 3:4 three-year trial, hereafter referred to as TEMPO. The original review also discussed the liver findings including the most important safety finding of three “Hy’s Law” cases in tolvaptan treated subjects.<sup>23</sup>

## 8.2. Review of the Safety Database

### 8.2.1. Overall Exposure

The safety database includes two phase 3 trials, 156-04-251 (TEMPO) and 156-13-210 (REPRISE), both of which have been discussed earlier in the efficacy section. Because of differences in design and duration, the data from the two trials were not pooled for safety analyses. The safety population was defined similarly in both trials (minimum of one tolvaptan dose), however, subjects in REPRISE had to tolerate a 5 week tolvaptan titration and run-in period (minimum 60/30 mg for 3 weeks during the run-in phase) before being randomized.

In Trial 156-04-251 subjects were randomized 2:1 (tolvaptan to placebo) and stratified by baseline hypertension, estimated creatinine clearance, and combined renal volume. Treatment was initiated at 45/15 mg twice daily, and then titrated weekly to 60/30 mg and then 90/30 mg, if tolerated, for three years. The dose could be down-titrated at any time, but subjects unable to tolerate the 45/15 mg dose were to be discontinued from IMP.

The trial employed a single blind period consisting of a 1 week placebo run-in phase, a 2 week tolvaptan titration phase, and a 3 week tolvaptan run-in phase prior to being eligible for randomization 1:1 into the 12-month double-blind treatment phase. This design was used to reduce the amount of missing efficacy data and better ensure that subjects enrolled in the randomized phase would be able to tolerate the drug and thus remain on therapy. Subjects were stratified by baseline eGFR, age, and total kidney volume if known.

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<sup>23</sup> <sup>23</sup> Dr. Hy Zimmerman noted that drugs causing hepatocellular injury and clinical jaundice lead to acute liver failure

**Table 14. Number of subjects treated in core placebo controlled trials in ADPKD**

Clinical Trial	Tolvaptan (n=1642)	Placebo (n=1168)	Exposed to tolvaptan for at least one year (n=1418)
Trial 156-04-151, TEMPO	961	483	836 <sup>1</sup>
Trial 156-13-210, REPRISE	681	685	582 <sup>2</sup>

1. Applicant's analysis: source CSR 156-04-251 CT-7.1
2. Reviewer's analysis: ex\exposure, dataset adex

Table 15 shows the exposure for all subjects in REPRISE. The median duration of tolvaptan exposure was 359 days during the randomized period, and 394 days during the entire trial (includes titration/run-in plus randomization period). The median duration of tolvaptan exposure for subjects treated with placebo during the tolvaptan titration/run-in period was 35 days.

*Reviewer comment: The applicant mistakenly reports in their Clinical Overview Resub document that a total of 654 subjects in REPRISE were treated with tolvaptan for at least 1 year. To clarify, 654 subjects completed the Month 12 visit, and 577 subject were treated with tolvaptan for at least 12 months, defined as "at least 371 days".*

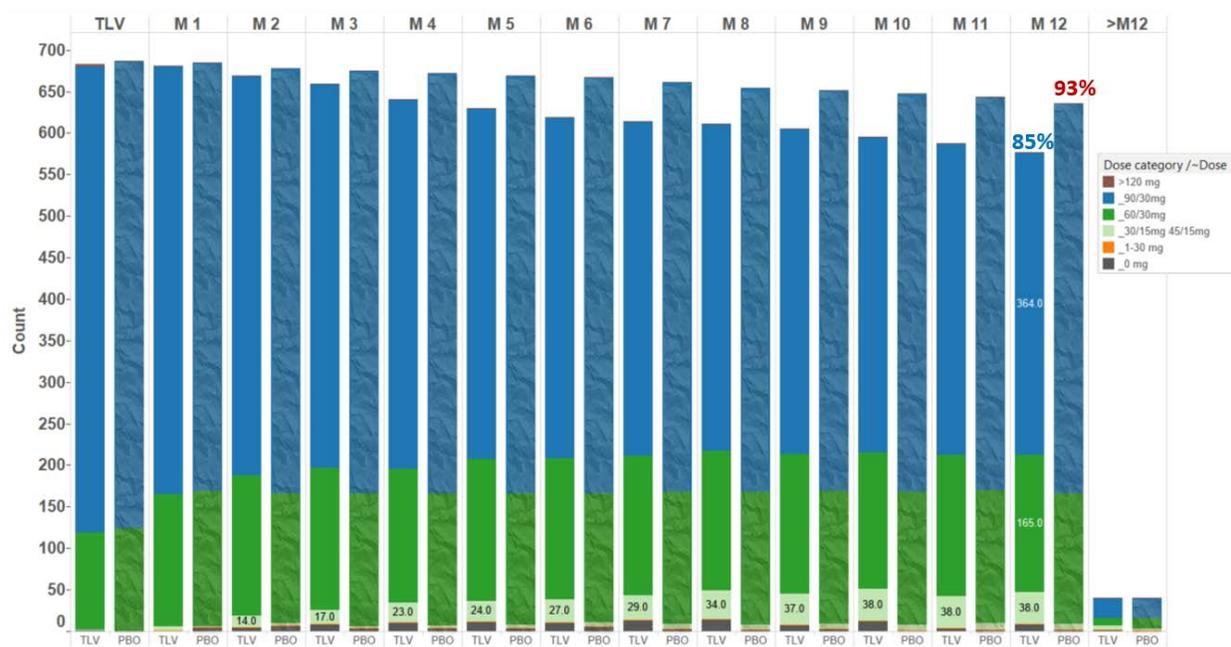
**Table 15. Subjects exposed to tolvaptan in REPRISE**

	Number of subjects exposed to tolvaptan				
	>= 1 dose	>=3 months	>=6 months	>=9 months	>=12 months
<b>Titration and randomized period</b>					
Subjects randomized and treated with tolvaptan	681 (100%)	663 (97.4%)	623 (91.5%)	606 (89.0%)	582 (85.5%)
<b>Randomized period</b>					
Subjects treated with tolvaptan	681 (100%)	645 (94.7%)	616 (90.5%)	595 (87.4%)	64 (9.4%)
Average modal dose	108.3 mg	108.7 mg	108.8 mg	108.6 mg	106.2 mg

Reviewer's analysis: ex\exposure. Dataset: adex  
 3 months=90 days, 6 months=180 days, 9 months=270 days, 12 months=365 days

Figure 10 shows the IMP exposure over time starting with the tolvaptan titration period. Subjects whose dose was held or interrupted during one month remained in the figure if they were subsequently dosed in the trial. Most subjects in the trial took the 90/30 mg dosage regimen. The figure also shows that there were subjects taking less than 60/30 mg daily. At Month 12, 85% of tolvaptan treated subjects were still on treatment; 364 (54%) subjects were taking 90/30 mg, 165 (24%) were taking 60/30 mg, and 38 (6%) were taking 30/15 mg or 45/15 mg.

**Figure 10. Exposure over time**



Reviewer's analysis, dataset: adex

TLV=tolvaptan, PBO=placebo, M=Month; first "TLV" across the top is the tolvaptan titration/run-in period.

Subjects whose dose was held or interrupted during one month remained in the figure if they were subsequently dosed later in the trial.

### 8.2.2. Relevant characteristics of the safety population

The safety population has 2 fewer subjects in each treatment arm compared to the efficacy population (See Table 5 for demographics of randomized population). Key demographic characteristics were similar in the two treatment arms.

### 8.2.3. Adequacy of the safety database

A total of 3,114 subjects were exposed to tolvaptan in the ADPKD program. The median exposure was  $\geq 18$  months and includes 744 subjects who have been exposed to tolvaptan for  $\geq 60$  months. The safety database from the two controlled trials in ADPKD includes 1,418 subjects exposed for at least one year (836 from TEMPO and 582 from REPRISE), and was generally adequate to characterize the safety. See also Section 8.5.1 Drug Induced Liver Injury (DILI) for more discussion of the database.

## 8.3. Adequacy of Applicant's Clinical Safety Assessments

### 8.3.1. Issues Regarding Data Integrity and Submission Quality

There are no substantial issues with data integrity or data quality that would preclude a timely

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review or approvability. The application data were evaluated in DataFit analyses in which the SDTM v 1.4 data were checked to conformance standards, the traceability of the SDTM to AdAM data were checked, and other potential data quality issues were checked. The applicant also provided reviewer's guides for the SDTM data, AdAM data, the resubmission, the safety update, and the REPRISE trial. These were generally helpful.

### 8.3.2. Categorization of Adverse Events

The applicant coded adverse event by system organ class and Medical Dictionary for Regulatory Activities (MedDRA) preferred term version 20.0. The definition of treatment emergent adverse events (TEAE) could not be found in the SAPs or protocols. The CSR defined TEAE as an AE that started after Investigational Medicinal Product (IMP), or an AE that was continuous from baseline and was serious, IMP related, or resulted in death, discontinuation, interruption or reduction of IMP treatment. Events were censored 7 days after the IMP end date. The applicant's primary TEAE tables are presented by Preferred Term within System Organ Class.

*Reviewer's Comment: The applicant's AE analyses and definition of TEAE are reasonable albeit it appears that TEAE was defined after the final protocol/SAP and differs from that used in TEMPO (albeit different study design).<sup>24</sup> Because of study design (tolerability run-in phase), the rates of TEAE in REPRISE will be lower than what would be expected when used in clinical practice, and should generally be lower per year than TEMPO. Multiple occurrences of a TEAE were counted only once per subject.*

*The applicant's translation of verbatim terms to preferred terms was acceptable.*

*Unlike the applicant, the reviewer grouped similar terms that occurred frequently into Custom MedDRA Queries (CMQ). These included terms related to aquaresis, liver injury/liver lab increases, and thirst. Because the reviewer grouped similar terms together, the reviewer's analyses are presented. MedDRA broad, narrow, and algorithmic SMQs were run and checked against the applicants, however the reviewer did not see the need to present those data in this review since the reviewer's CMQs captured the most common TEAEs. In addition, the reviewer examined all Preferred Terms that occurred less frequently.*

The applicant prespecified and analyzed two safety populations. The primary safety population

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<sup>24</sup> In TEMPO a TEAE was an event that started while on treatment plus 7 days after the last dose or if the event was continuous from baseline and was serious, related to treatment, or resulted in death, discontinuation, interruption, or reduction of treatment. A serious TEAE used a window of 30 days instead of 7 days. The AE data in TEMPO were coded to MedDRA version 14.1.

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(SAFFL=yes) included subjects who were randomized and took at least one dose of investigational medical product. The secondary safety population (SSAFFL=yes) included subjects who took at least one dose of IMP during the tolvaptan titration/run-in periods.

Adverse events were collected throughout the trial, from screening until 3 weeks after the end of treatment. See Section 6.1 for a schedule of assessments. To assess adverse events, the investigator was to ask the non-leading question, “How have you felt since your last visit?” Subjects that were run-in failures were to complete the End of Treatment visit assessments (see Section 8.3.3) and were to have a follow-up phone call after 7 days to record AEs. Subjects that completed the trial were to have follow-up for AEs up to 21 days after last dose. Any non-serious AE still ongoing at the last visit was to be noted on the eCRF.

Adverse event intensity was graded on a 3-point scale and defined as follows: mild – discomfort noticed, but no disruption to daily activity, moderate – discomfort sufficient to reduce or affect normal daily activity, and severe – inability to work or perform normal daily activity.

To assess tolerability, the investigator asked, “Can you tolerate this dose for the rest of your life?”

*Reviewer’s comment: This was a subjective question and did not specifically ask about any particular AE.*

Subjects with SAE were to be followed clinically until their health returned to baseline status, or until all parameters have returned to normal, or have otherwise been explained, or the subject is lost to follow-up. Any new SAE reported after the last scheduled contact and determined by the investigator to be reasonably associated with the use of the IMP should be reported to the Applicant. The Investigator was to follow the subject until the event resolved or the subject was lost to follow-up.

Any subject with a new liver test abnormality (AE or lab meeting the threshold), skin neoplasms or glaucoma was to have it immediately reported. These AE were all identified from TEMPO as potentially important AEs. See Section 8.5.1 for further discussion of liver tests.

### 8.3.3. Routine Clinical Tests

Table 16 shows the schedule of laboratory assessments. The testing appears adequate to characterize safety in the proposed population.

**Table 16. Schedule of vital signs and laboratory collection in REPRIS**

Assessment	Pre-randomization										Double-blind Randomized Treatment			Follow-up						
	Screening (2 weeks ± 1 day)		Placebo run-in (1 week ± 1 day) (Days -42 to -36)		Tolvaptan titration (2 weeks ± 1 day) (Days -35 to -22)					Tolvaptan run-in (3 weeks ± 1 day) (Days -21 to -1)			(Day 0)	Visits: monthly (± 2 days)	Month 12/ EoTx visit	3 weeks post-treatment				
	Days -56 to -43 <sup>a</sup>		Day -42	Day -39 ± 1 day	Day -36	Days					Days			Day 0	Months 1 to 11	Month 12 /EoTx	Days +7 to +21 post-final visit <sup>a</sup>			
Vital signs <sup>b</sup>	X	X		X					X				X		(X) <sup>b</sup>	X				X
<b>Clinical laboratory samples<sup>c</sup>:</b>																				
Hematology and coagulation	X																			
Urinalysis	X	X		X								X				X				
Serum Chemistry Panel	X															X				X
Liver Function Panel	X			X				X			X	X			X	X				X
Creatinine	X	X	X	X	X			X			X	X			X	X	X	X	X	X
Sodium	X	X		X	X			X			X	X			X	X	X			

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<sup>b</sup>The following visits (and all assessments required during those visits) should be performed in-clinic: screening, end of placebo run-in, end of tolvaptan titration, end of tolvaptan run-in, quarterly visits during the randomized, double-blind treatment period (eg, Months 3, 6, 9), Month 12/end of treatment (EoTx) visit, and the last follow-up visit. Vital signs at each of the above visits include sitting heart rate and blood pressure. Post-void body weight should be measured at the first screening visit and the Month 12/EoTx visit only. Height should be assessed at the first screening visit only. Either height or weight may be collected as an unscheduled measurement if its assessment was missed.

<sup>c</sup>The specifics and timing for clinical laboratory samples for central and local laboratory analyses are as follows:  
**Screening period:** Subjects will have 3 blood draws on separate days between Day -56 and Day -43. The subject's eligibility will be confirmed by the mean of eGFR calculated from the subjects' first 2 pre-treatment, central laboratory serum creatinine assessments.  
**Placebo run-in period:** Subjects will have 2 blood draws on separate days (at least 24 hours apart) between Days -42 to -36 with the last sample on Day -36.  
**Tolvaptan titration period:** Subjects will have 1 blood draw at the end of 2 weeks with the sample being obtained on Day -22.  
**Tolvaptan run-in period:** During the last 2 weeks of this period, blood will be drawn 2 times on separate days (at least 24 hours apart) with the last sample on Day -1.  
**Double-blind treatment period:** Samples will be collected for central lab analysis monthly and at the Month 12/EoTx visit. Local standard of care laboratory tests will be performed monthly per the subject's individual clinical management needs. Local liver function panel analyses will also be performed more frequently, if necessary.

Adapted from Applicant REPRIS CSR, Table 3.7-1

## 8.4. Safety Results

### Deaths

There were two deaths in the REPRIS trial, one in each treatment arm. Neither death was considered related to treatment; they are briefly described below.

Subject (b) (6) was a 35-year-old white male who died during the tolvaptan titration period (maximum dose of 90/30 mg), prior to randomization. He was hospitalized for pneumonia on Tolvaptan Day 31, and was subsequently found to be positive for Human Immunodeficiency Virus (HIV). He died on Day 60 from a pulmonary embolism (PE). The investigator assessed the SAEs of pneumonia, HIV, PE, and death as unrelated to tolvaptan.

Subject (b) (6) was a 43-year-old white male randomized to placebo who died from a traffic accident during the double-blind treatment period. He completed the trial with a last visit on Exposure Day 280, and last dose on Exposure Day 300. He died in a road traffic accident on

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Exposure Day 300.

#### 8.4.2. Serious Adverse Events

##### *Tolvaptan Titration/Run-in Period*

A total of 43 subjects had a serious TEAE during this period. The most frequently occurring SAEs were aquaretic effects (n=9, 0.6%), followed by increases in liver tests (n=8, 0.5%). The liver test AEs reported in this section are based on AE reported terms. See Section 8.5.1 for a more thorough analysis of liver tests AE combined with liver lab data.

**Table 17. SAE Custom MedDRA Queries and Preferred Term in ≥ 2 subjects, Titration Period**

Custom MedDRA Query/Preferred Term	Number of subjects	Proportion (%)
<b>Aquaresis CMQ</b>	<b>9</b>	<b>0.6</b>
Polyuria	4	0.3
Nocturia	3	0.2
Pollakiuria	2	0.1
<b>Liver test elevation CMQ</b>	<b>8</b>	<b>0.5</b>
Alanine aminotransferase increased	4	0.3
Drug-induced liver injury	1	0.1
Hepatic function abnormal	1	0.1
Liver function test abnormal	1	0.1
Transaminases increased	1	0.1
<b>Infection CMQ</b>	<b>6</b>	<b>0.4</b>
Renal cyst infection	2	0.1
Pyelonephritis	1	0.1
Pyelonephritis acute	1	0.1
Sinusitis	1	0.1
Urinary tract infection	1	0.1
<b>Preferred Terms in ≥ 2 subjects</b>		
Thirst & polydipsia	3	0.2
Acute kidney injury	2	0.1
Renal cyst hemorrhage	2	0.1
Renal cyst infection	2	0.1

Reviewer's analysis: MAED TLV titration serious. Dataset: adae  
 CMQ= Custom MedDRA Query. Preferred terms used for a CMQ are under the CMQ name.

##### *Randomized Period*

During the randomized period, serious TEAEs were reported in 85 (12.5%) tolvaptan treated subjects compared to 60 (8.8%) placebo treated subjects. The most common serious TEAEs

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were liver test elevations, 30 (4.4%) versus 4 (0.6%), tolvaptan versus placebo, respectively. TEAEs in the CMQ for infections were reported at a higher incidence in tolvaptan treated subjects, but the risk difference compared to placebo was only 0.7%. Table 18 shows CMQ whose incidence rate was higher in the tolvaptan arm compared to placebo (liver injury and infection) and preferred terms of interest. Not shown in the table are serious TEAEs that occurred in only one or two subjects.

Since AVP antagonists have been shown to cause small increases in circulating AVP concentrations, a potential clinical implication is enhanced platelet activation resulting in increased thrombotic events. (These events were infrequently observed in TEMPO.) The data from REPRISE are reassuring and do not suggest a risk of embolic events from tolvaptan.

There were 2 cancers reported (one was benign), both in the placebo arm.

**Table 18. SAE Custom MedDRA Queries and Preferred Terms, Randomized Period**

Custom MedDRA Query/Preferred Term	Tolvaptan (N=681) n=85 (12.5%)		Placebo (N=685) n=60 (8.8%)	
	Number of subjects	Proportion (%)	Number of subjects	Proportion (%)
Liver test elevations CMQ	30	4.4	4	0.6
Hepatic enzyme increased	11	1.6	1	0.2
Alanine aminotransferase increased	8	1.2	0	0.0
Liver function test increased	4	0.6	2	0.3
Aspartate aminotransferase increased	3	0.4	0	0.0
Liver function test abnormal	3	0.4	0	0.0
Liver injury	1	0.2	0	0.0
Gamma-glutamyl transferase increased	1	0.2	0	0.0
Infection CMQ	16	2.4	11	1.6
Urinary tract infection	3	0.4	0	0.0
Renal cyst infection	2	0.3	1	0.2
Bacteremia	1	0.2	0	0.0
Diverticulitis	1	0.2	0	0.0
Erysipelas	1	0.2	0	0.0
Gastroenteritis	1	0.2	1	0.2
Influenza	1	0.2	0	0.0
Klebsiella infection	1	0.2	0	0.0
Otitis media	1	0.2	0	0.0
Pneumonia	1	0.2	0	0.0
Pyelonephritis	1	0.2	3	0.4
Respiratory tract infection	1	0.2	0	0.0

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Sepsis	1	0.2	1	0.2
Upper respiratory tract infection	1	0.2	0	0.0
Appendicitis	0	0.0	1	0.2
Cellulitis	0	0.0	1	0.2
Cholangitis	0	0.0	1	0.2
Enterobacter bacteremia	0	0.0	1	0.2
Hepatic cyst infection	0	0.0	1	0.2
Rhinovirus infection	0	0.0	1	0.2
Urosepsis	0	0.0	1	0.2
<b>Embolic events</b>	<b>7</b>	<b>1.0</b>	<b>8</b>	<b>1.2</b>
Transient ischemic attack	2	0.3	1	0.2
Cerebrovascular accident	1	0.2	1	0.2
Intracranial aneurysm	1	0.2	1	0.2
Subarachnoid hemorrhage	1	0.2	3	0.4
Pulmonary embolism	2	0.3	0	0.0
Carotid artery aneurysm	0	0	1	0.2
Cerebral artery thrombosis	0	0	1	0.2
<b>Other Preferred Terms of interest</b>				
Rash pruritic	1	0.2	0	0.0

Reviewer's analysis: MAED ran serious. Dataset: adae

CMQ= Custom MedDRA Query. Preferred terms used for a CMQ are under the CMQ name.

Not all serious TEAE are shown. Most SAE occurred in only 1 or 2 subjects.

### 8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Subjects that discontinued IMP, but did not withdraw from the trial, were to have vital status, AEs, concomitant medications, ESRD status, and scheduled laboratory data (including serum creatinine) collected at scheduled monthly visit and at trial termination.

#### ***Tolvaptan Titration/Run-in Period***

During the tolvaptan titration and run-in period 126 (8.4%) out of 1496 subjects discontinued the trial and were not randomized. Five subjects never took tolvaptan. The most common reason for discontinuation was for an adverse event (n= 96, 6.4%) (See Table 19), of which "medication intolerability" was the most common adverse event (n=78, 5.2%) (See Section 8.3.2). To assess tolerability, the investigator asked the subject if they could take the medication for the rest of their life. Reasons why patients deemed the medication intolerable included aquaretic effects and events such as insomnia, thirst, rash, vomiting, fatigue, chapped lips, etc. Events such as insomnia, thirst, chapped lips and fatigue may have been related to the drug's aquaretic effect. (see Section 8.3.2)

Because of the potential for DILI, the threshold for discontinuation because of hepatic labs prior to randomization was low (ALT, AST, or total bilirubin > 2xULN). Ten (0.6%) subjects that were

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not randomized were either noted to have a hepatic lab value at threshold or a hepatic lab was the reason for discontinuation.

**Table 19. Reasons for discontinuation during tolvaptan titration period**

	Subjects, n/N 126/1496 (8.4%)	
AE	97	(6.5)
Medication intolerable	78	(5.2)
SAE	4	(0.3)
Hepatic lab <sup>1, 2, 3</sup>	10	(0.6)
Inclusion/Exclusion (excludes hepatic labs)	11	(0.7)
Trial burdensome	7	(0.5)
Unable to follow diet/fluid plan	3	(0.2)
Patient decision	5	(0.3)
Lost to follow-up <sup>2</sup>	4	(0.3)
Progression of disease leading to dialysis, transplantation or eGFR decline	2	(0.1)
Death	1	(0.1)

Reviewer's analysis: ds\dc\_pd1\_2\_runin.sas; Datasets: adae, adsl, liverf, ti

1. Three subjects counted in hepatic lab and in AE because they had other AEs (polyuria, thirst) also
2. One subject counted as lost to follow-up and hepatic lab because he had a rise in AST>2xULN before tolvaptan was stopped; ALT was rising, but was < 1 x ULN.
3. 2 out of 10 subjects had their rise in transaminase considered serious.

*Reviewer Comment: The subjects that discontinued (Table 19) were selected from the data in the ADSL dataset. The reasons for discontinuation from the ADSL dataset were cross checked with the adverse events and liver lab datasets. The later datasets provided information on the action taken with IMP (i.e., withdrawn, dose reduced, etc.) and liver labs around the time of discontinuation. The reviewer's Table 19 differs in presentation from the applicant's Table 10.1-2 (CT-1.1.1.2) which is also based solely on the ADSL dataset. This is because the reviewer also considered whether the reason given for discontinuation was mapped to a meaningful description.*

*The applicant reports 101 (6.8%) subjects with discontinuations because of an AE during the tolvaptan titration period based on the AE dataset using subjects that had an action of "Drug withdrawn", thus four additional subjects than shown in Table 19. In general, it is common for there to be differences between the disposition data and the AE data since different CRFs are used to collect these data and the different sources are not always checked for consistencies. The percent of subjects that discontinued because of an AE during the titration period is the same regardless of dataset used when rounded (7%).*

**Randomized Period**

During the randomized period, the most common reason for medication discontinuation was an adverse event.

**Table 20. Reasons for medication discontinuation during randomized period**

	Tolvaptan, n (%) N=681	Placebo, n (%) N=685
Permanently discontinued treatment	105 (15.4)	50 (7.3)
AE	80 (11.7)	18 (2.6)
Hepatic AE or hepatic lab abnormality	37 (5.4)	4 (0.6)
Medication intolerable	33 (4.8)	7 (1.0)
SAE	6 (0.9)	5 (0.7)
Other	11 (1.6)	13 (1.9)
Progression of disease leading to dialysis, transplantation or eGFR decline	7 (1.0)	6 (0.9)
Trial burdensome	4 (0.6)	4 (0.6)
Taking marketed product for tolvaptan	1 (0.1)	2 (0.3)
Lost to follow-up	1 (0.1)	4 (0.6)
Inclusion/Exclusion (excludes hepatic labs)	1 (0.1)	3 (0.4)

Reviewer’s analysis: ds\dc\_pd3\_ran; Datasets: adae, adsl, liverf, ti

In subjects that tolerated tolvaptan prior to randomization, by ~2 months after randomization, there starts to be more discontinuations in tolvaptan treated subjects compared to placebo. By the end of the trial, the number of subjects that discontinue treatment in the tolvaptan arm are more than twice the number in the placebo arm.

**8.4.4. Significant Adverse Events**

Most serious TEAEs were severe; however, most TEAEs were only mild in intensity (Table 21). There was a total of 5281 reported TEAE (2744 vs 2537, tolvaptan vs placebo, respectively), of which 4832 were unique TEAE per subject and severity.

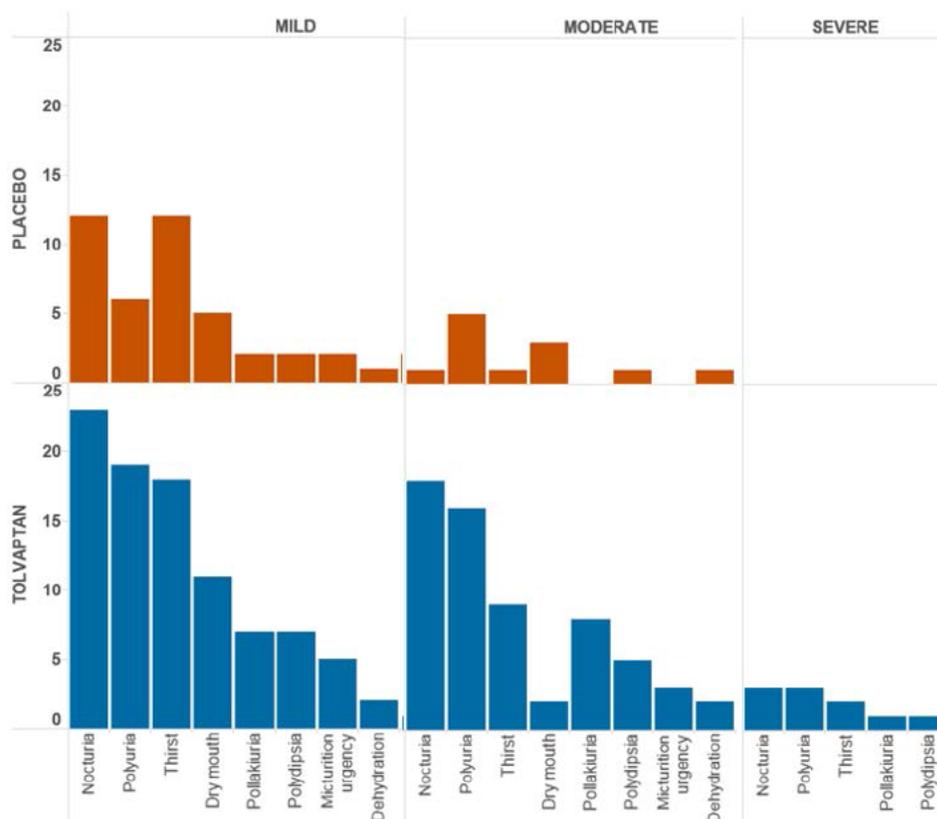
**Table 21. Severity of treatment emergent adverse events**

	Tolvaptan	%	Placebo	%
<b>Number of TEAE</b>	<b>2503</b>		<b>2329</b>	
<b>SAE</b>				
Mild	13	0.5	5	0.2
Moderate	42	1.7	34	1.5
Severe	51	2.0	41	1.8
<b>AE</b>				
Mild	1607	64.2	1544	66.3
Moderate	796	31.8	719	30.9
Severe	100	4.0	66	2.8

Reviewer's analysis: ae\ae\_severity. Dataset: adae  
 Multiple occurrences of AE are counted once per subject and severity. n=number of TEAE (not subject count).  
 Percent is % of number of TE adverse event by arm.

Analysis of intensity of some common adverse events are shown in Figure 11.

**Figure 11. Severity of select common TEAE**



Reviewer's analysis. Dataset ADAE

#### 8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

##### *Tolvaptan Titration/Run-in Period*

During this period 1051 (70.5%) subjects had a TEAE. The most common TEAEs were aquaresis and thirst/polydipsia. The preferred terms used for the CMQs of aquaresis, thirst/polydipsia, liver test increases, and infection (because this was commonly reported) are shown in Table 22.

**Table 22. Custom MedDRA Query/Preferred Term occurring >2% subjects, Titration Period**

<i>Custom MedDRA Query/Preferred Term</i>	<i>Number of subjects</i>	<i>Proportion (%)</i>
Aquaresis CMQ	652	43.6
Polyuria	475	31.8
Nocturia	308	20.6
Pollakiuria	70	4.7
Micturition urgency	6	0.4
Urine output increased	5	0.3
Enuresis	2	0.1
Polydipsia or thirst CMQ	575	38.4
Infection CMQ	129	8.6
Viral upper respiratory tract infection	47	3.1
Upper respiratory tract infection	21	1.4
Sinusitis	12	0.8
Influenza	11	0.7
Urinary tract infection	8	0.5
Renal cyst infection	4	0.3
Viral infection	3	0.2
Bronchitis	2	0.1
Cystitis	2	0.1
Lower respiratory tract infection	2	0.1
Prostatitis	2	0.1
Ear infection	1	0.1
Cellulitis	1	0.1
Diverticulitis	1	0.1
Erysipelas	1	0.1
Eye infection	1	0.1
Fungal infection	1	0.1
Fungal skin infection	1	0.1
Oral candidiasis	1	0.1
Oral fungal infection	1	0.1
Oral viral infection	1	0.1

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Onychomycosis	1	0.1
Pneumonia	1	0.1
Pyelonephritis	1	0.1
Pyelonephritis acute	1	0.1
Rhinovirus infection	1	0.1
Folliculitis	1	0.1
Keratitis	1	0.1
Lymphadenitis	1	0.1
<b>Liver enzyme increase CMQ</b>	<b>19</b>	<b>1.3</b>
Hepatic function abnormal	1	0.1
Liver function test abnormal	2	0.1
Liver function test increased	2	0.1
Blood bilirubin increased	1	0.1
Drug-induced liver injury	1	0.1
Alanine aminotransferase increased	7	0.5
Aspartate aminotransferase increased	5	0.3
Transaminases increased	3	0.2
<b>Other Preferred Terms</b>		
Fatigue	64	4.3
Headache	63	4.2
Blood creatinine increased	40	2.7
Constipation	40	2.7
Nausea	39	2.6
Renal pain	39	2.6
Dizziness	38	2.5
Hypertension	31	2.1
Decreased appetite	30	2.0

Reviewer's analysis: ae\MAED TLV titration, datasets: adsl, adae

CMQ=Custom MedDRA Query

Custom MedDRA Query and Preferred Term sorted by incidence in descending order

**Randomized Period**

Table 23 shows the adverse events with a risk difference of at least 1.5% greater in the tolvaptan treated subjects.

**Table 23. Treatment Emergent Adverse Events with Risk Difference  $\geq$  1.5%, randomized period**

Preferred Term	Tolvaptan (N=681)		Placebo (N=685)	
	Number of subjects	Proportion (%)	Number of subjects	Proportion (%)
Aquaretic CMQ	76	11.2	25	3.7
Polyuria	36	5.3	11	1.6
Nocturia	32	4.7	12	1.8
Pollakiuria	12	1.8	2	0.3
Micturition urgency	5	0.7	2	0.3
Liver enzyme increase CMQ	68	10.0	32	4.7
Alanine aminotransferase increased	25	3.7	9	1.3
Hepatic enzyme increased	17	2.5	3	0.4
Aspartate aminotransferase increased	15	2.2	11	1.6
Transaminases increased	10	1.5	5	0.7
Liver function test increased	7	1.0	3	0.4
Gamma-glutamyltransferase increased	6	0.9	4	0.6
Liver function test abnormal	4	0.6	0	0.0
Drug-induced liver injury	1	0.2	0	0.0
Liver injury	1	0.2	0	0.0
Hypertransaminasemia	1	0.2	1	0.2
Hepatic function abnormal	1	0.2	0	0.0
Blood bilirubin increased	0	0.0	2	0.3
<b>Other Preferred Term</b>				
Diarrhea	47	6.9	23	3.4
Thirst or polydipsia CMQ	39	5.7	16	2.3
Fatigue	46	6.8	24	3.5
Decreased appetite	17	2.5	5	0.7
Abdominal pain	25	3.7	15	2.2
Renal impairment	23	3.4	13	1.9

Reviewer's analysis: ae\MAED ran, datasets: adsl, adae

CMQ=Custom MedDRA Query

Sorted by CMQ risk difference in descending order, then by Preferred Term

Although the risk difference was not at least 1.5%, the anaphylactic SMQ occurred in more subjects treated with tolvaptan compared to placebo, 9 (1.3%) versus 4 (0.6%), respectively.

There were many common TEAE that occurred with similar frequency between tolvaptan and placebo; the most frequent included renal pain (17%), hypertension (11%), upper respiratory

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tract infection (9%), and headache (8%) (data shown for tolvaptan arm only, reviewer's analysis). Because these events occurred with similar frequency in both arms, and thus are unlikely to be due to tolvaptan, they will not be discussed further.

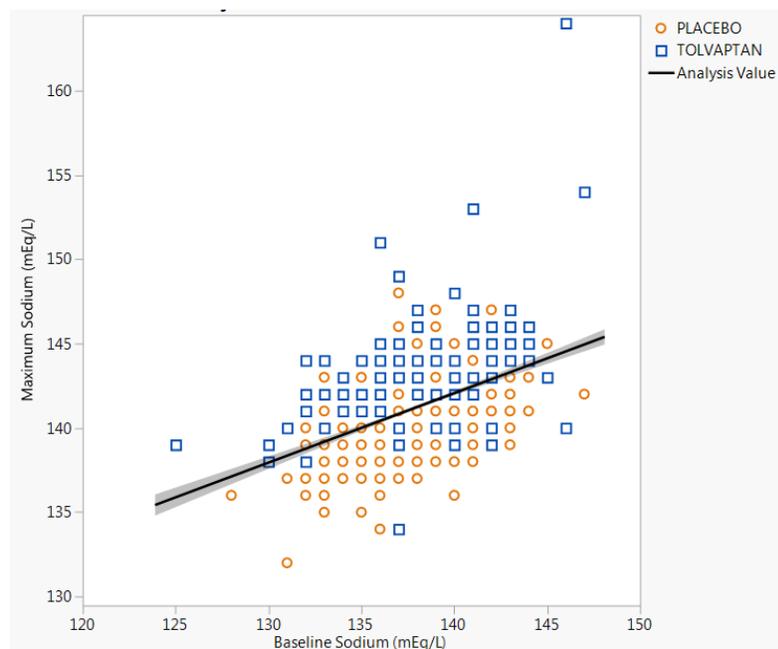
### 8.4.6. Laboratory Findings

See also Section 8.5 for a discussion of labs related to submission specific safety issues.

#### 8.4.6.1. Sodium

Tolvaptan raises serum sodium, and the protocol stipulated regular measurements as often as liver tests. Hypo- or hypernatremia were criteria for exclusion in France only. While most subjects were within normal range during the trial, there were a few subjects that had significant rises in serum sodium.

**Figure 12. Baseline versus maximum serum sodium**



Reviewer's analysis. Source: adlb

### 8.4.7. Vital Signs

Changes from baseline in vital signs were not clinically relevant (applicant CSR Section 12.5.2 vital signs). During the double-blind period, there were no differences between tolvaptan and placebo in vital sign changes. There were more subjects treated with tolvaptan with reports of hypotension [13 (1.9%) vs 6 (0.9%)] and orthostatic hypotension [3 (0.4%) vs. 1 (0.1%)],

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compared to placebo, respectively.

#### 8.4.8. **Electrocardiograms (ECGs)**

The applicant did not collect ECGs in REPRISE.

#### 8.4.9. **QT**

Reviewed previously. No effect on QTc interval.

#### 8.4.10. **Immunogenicity**

Not applicable.

### 8.5. **Analysis of Submission-Specific Safety Issues**

#### 8.5.1. **Drug Induced Liver Injury (DILI)**

##### *8.5.1.1. Background*

The first FDA clinical safety review of tolvaptan in ADPKD discussed the potential for DILI. In summary, following unblinding of the first trial 156-04-251 in April 2012, a higher proportion of subjects on tolvaptan had ALT elevations > 3xULN compared to subjects on placebo (4.1% versus 1.0%).<sup>25</sup> The sponsor convened an independent, blinded Hepatic Adjudication Committee (HAC) (Drs. Watkins, Lewis, Kaplowitz, and Alpers) to assess the causality of potential DILI cases in ADPKD, hyponatremia, and heart failure development programs.<sup>26</sup> (There were no prior signals of DILI from other development programs or in the postmarketing experience.) Three ADPKD subjects had severe hepatocellular liver injury, deemed Hy's Law cases, out of ~860 subjects with ADPKD treated over a 14-month period.<sup>27</sup> Two subjects were from the trial 156-04-251 and one subject was from its open label extension trial 156-08-271 (a subject that crossed over to tolvaptan after receiving placebo in the pivotal trial). All 3 subjects were female and were taking the highest dose of tolvaptan, 120 mg daily. The final causality

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<sup>25</sup> Liver lab monitoring was weekly for 3 weeks during titration, then every 4 months, and yearly in Trial 156-04-251; in its open label extension 156-08-271, liver monitoring was every 4 months.

<sup>26</sup> The HAC used the causality scale adopted by the United States Drug-Induced Liver Injury Network (Rockey DC 2010) See Appendix (13.3.4).

<sup>27</sup> The FDA DILI guidance defines a Hy's Law case as a subject with ALT >3xULN and total bilirubin > 2xULN, hepatocellular injury without initial findings of cholestasis, no other likely explanation for the liver injury, and a higher incidence of ALT elevations > 3xULN in the drug treated subjects relative to the comparator (assuming the comparator does not cause ALT elevations).

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assessments for the 3 Hy's Law cases were 2 "probable" and 1 "highly likely".<sup>28</sup> These subjects had initial symptoms of liver injury at 2.5 months, 5 months, and 7 months. There were no subjects that progressed to liver failure leading to transplantation or death. Based on Hy's Law, the rough incidence of liver failure was estimated as  $3/860 \times 10$ , or  $\sim 1$  in 3000 patients treated with tolvaptan, suggesting greater hepatotoxicity than some drugs withdrawn from the market for such toxicity.<sup>29</sup>

Risk mitigation strategies were implemented. Starting in November 2012 the applicant instituted monthly monitoring for the first 18 months of tolvaptan treatment, and every 3 months thereafter in all trials. Instructions on when to repeat liver testing, how to address abnormal liver lab values at screening and when to interrupt or discontinue IMP based on liver lab values or symptoms associated with liver injury were given. Global clinical databases were checked every two months (including REPRISÉ).

### 8.5.1.2. REPRISÉ

#### Liver Tests Monitoring

The schedule for liver tests is shown in Table 24. The number of actual liver tests paralleled subject participation in the trial (Figure 3, Figure 13). Testing will continue in the open-label extension trial 156-13-211 until subjects reach 18 months on tolvaptan, with subsequent liver testing every 3 months.

**Table 24. Liver test monitoring schedule in REPRISÉ**

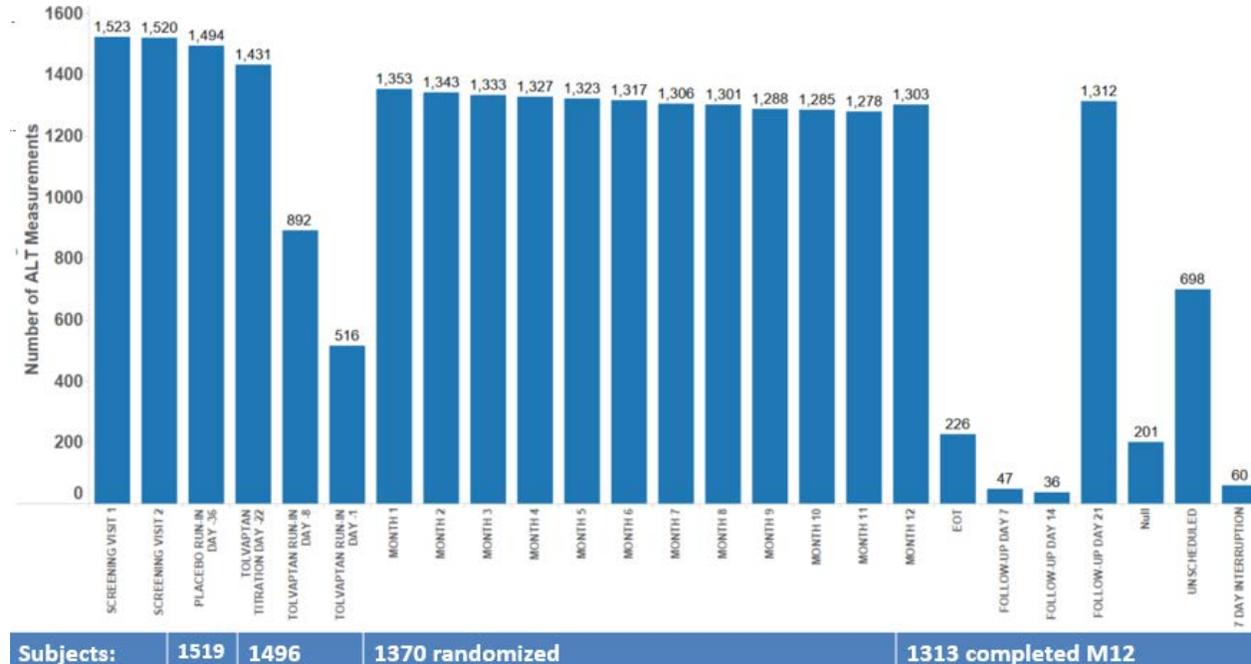
Period	Pre-randomization				Double-blind randomized period	Follow-up	
	screening	placebo run-in	tolvaptan titration	tolvaptan run-in			
Duration of period	2 weeks ± 1 day	1 week ± 1 day	2 weeks ± 1 day	3 weeks ± 1 day	12 months	3 weeks post-treatment	
Day relative to randomization	-56 to -43	-36	-22	-8	-1	Monthly	Day +7 to +21
Day relative to 1st tolvaptan dose	Baseline	Baseline	14	28	35	Monthly	Day +7 to +21

Reviewer's table. Adapted from Applicant 156-13-210 Protocol, Table 3.7-1. Schedule of assessments  
Liver tests included ALT, AST, alkaline phosphatase, and total bilirubin.

<sup>28</sup> "Probable" means 50-74% likelihood. The preponderance of the evidence supports the link between the drug and liver injury. "highly likely" means 75-95% likelihood. The evidence for the drug causing the injury is clear and convincing but not definite. See Appendix for complete causality scale.

<sup>29</sup> At the time, there were only a handful of marketed drugs with this incidence of liver injury (bosentan for pulmonary hypertension and isoniazid for tuberculosis). Most of the drugs withdrawn from the market for hepatotoxicity have caused death or transplantation at frequencies in the range of  $\leq 1$  per 10,000.

**Figure 13. ALT measurements over time, REPRISE**



Reviewer’s analysis. Applicant dataset liverf

IMP interruption that lasted ≥ 7 days was recorded as “7-day interruption” and the subject was to visit the clinic to begin EOT procedures. If the subject resumed IMP, then the 7-day interruption assessments were considered as “unscheduled”.

Prompt (within 72 hours) testing/retesting of hepatic function was to be done for any suspicious symptoms or signs of liver injury or any transaminase or bilirubin values exceeding 2xULN.<sup>30</sup> Testing was to be done at least weekly for the first month while values were in the abnormal range.

**Temporary or Permanent Medication Discontinuation**

The threshold for disqualification from randomization during the titration/run-in phase was any transaminase or bilirubin values exceeding 2xULN. There were 10 subjects not randomized that were noted to have a hepatic lab at or exceeding the threshold or the hepatic lab was cited as the reason for discontinuation. In 8 of the 10 subjects tolvaptan was stopped between days 1-17 (most were around 2 weeks). The other two subjects had medication stopped at day 30 and

<sup>30</sup> Subjects with liver lab abnormalities at screening or with a history of non-ADPKD related liver disease required further evaluation and completion of a special liver eCRF (see Section 13.3.3 Liver eCRF), additional testing to confirm stability of abnormality and eligibility for randomization.

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35 of tolvaptan treatment. (See also Section 8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects and **Description of REPRISÉ Liver Tests, page 93**).

During the randomized period, IMP was to be temporarily interrupted for a liver transaminase or bilirubin level of 2xULN, and only resumed after monitoring indicated abnormalities have resolved, were stable or were not rapidly increasing. Increased frequency of monitoring was required.

The protocol stated that “subjects would not typically be allowed to resume” IMP<sup>31</sup> if:

- the transaminase level was above 8xULN,
- the transaminase level was above 5xULN for more than 2 weeks, or
- concurrent elevations of transaminase > 3xULN and total bilirubin > 2xULN.

During the randomized period, 37 (5.4%) subjects treated with tolvaptan and 4 (0.6%) subjects treated with placebo discontinued treatment because of a liver lab or AE (see Table 20). Most of these subjects had liver lab changes without liver injury symptoms.

### Adjudication

The trigger for hepatic adjudication in the REPRISÉ trial was reasonable and included:

- A non-serious TEAE leading to discontinuation of IMP or any serious TEAE matching a lower level MedDRA term in any of the five hepatic SMQs or any of the following lab changes:
- ALT > 3xULN and total bilirubin > 2xULN
- AST > 3xULN and total bilirubin > 2xULN
- ALT > 3xULN
- AST > 3xULN

At the time of the NDA resubmission, the HAC adjudicated 70 cases from the REPRISÉ trial (see Table 25). For the 14 probable subjects, 7 were taking the 60/30 mg dose and 7 were taking the 90/30 mg dose. After learning about the post-marketing DILI liver transplant case, the Division requested adjudication data not included in the resubmission (June 01, 2017 to January 31, 2018). Twenty-five additional subjects from REPRISÉ and its open label extension were adjudicated after the NDA was resubmitted. All subjects were taking tolvaptan.

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<sup>31</sup> Subjects with these levels of abnormality may be rechallenged with IMP if abnormalities were adjudicated as having a < 50% likelihood of being related to IMP by the HAC and the investigator and medical monitor agree to intensive monitoring plan to mitigate risk. The subject also had to be willing to comply with these monitoring measures, be informed of the potential risk, and consent to IMP re-challenge.

**Table 25. Hepatic Adjudication Committee final causality assessments in REPRISE and extension study**

Final Causality	REPRISE cases up to 17 May 2017		REPRISE and Open Label extension cases 01 June 2017 to 31 Jan 2018
	Tolvaptan	Placebo	Tolvaptan
Highly likely	0	0	0
Probable	14	0	4
Possible	34	6	10
Unlikely	13	3	9
Insufficient data	0	0	2
<b>TOTAL</b>	<b>61</b>	<b>9</b>	<b>25</b>

Reviewer’s analysis, applicant dataset heparslt and hepaupdct (SN 0069). Includes error identified by reviewer and addressed in Submission Numbers 66 and 77.

*Reviewer comment: There is not a clear dose relationship with causality, although the design of REPRISE might have limited the ability to delineate a relationship between dose and causality. The first trial did not show a clear relationship either, however all three Hy’s Law subjects were taking the highest dosage regimen of tolvaptan, 120 mg.*

#### **Description of REPRISE Liver Tests**

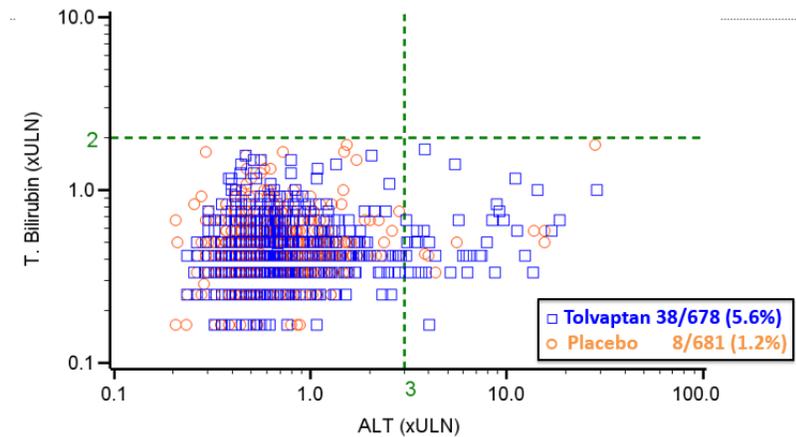
Figure 14 shows the maximum ALT and maximum total bilirubin per subject. Notably, there were no Hy’s Law subjects in the REPRISE trial, but like the first trial, there were more tolvaptan treated subjects with ALT>3xULN compared to placebo (5.6% vs. 1.2%), a characteristic of drugs that cause DILI.<sup>32</sup>

*Reviewer’s comment: Liver test elevations are also described in the Adverse Event sections (8.4.2 – 8.4.4). The number of subjects with “liver enzyme increase CMQ” were 68 (10%) vs. 32 (4.7%), tolvaptan versus placebo, respectively (Table 23). This is much higher than the numbers shown in the figure below that plots the maximum values. The numbers to rely upon are those shown in the figure below. The terms used for the CMQ are non-specific and may not indicate a clinically meaningful increase. Similarly, liver test increases are described during the titration phase. A more meaningful characterization of liver test increases are ones that led to medication discontinuation. There were very few subjects with actual “non-specific” liver injury symptoms such as rash, nausea, abdominal pain, etc.*

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<sup>32</sup> TEMPO trial ALT >3xULN, 40 (4.1%) versus 5 (1.0%) subjects treated with tolvaptan versus placebo, respectively. ALT is a sensitive, but not specific marker of a signal of hepatotoxic drugs. There are drugs that produce high ALT elevations, but have low risk of causing clinically important liver injury.

**Figure 14. Maximum ALT xULN and Total Bilirubin xULN, double-blind period**



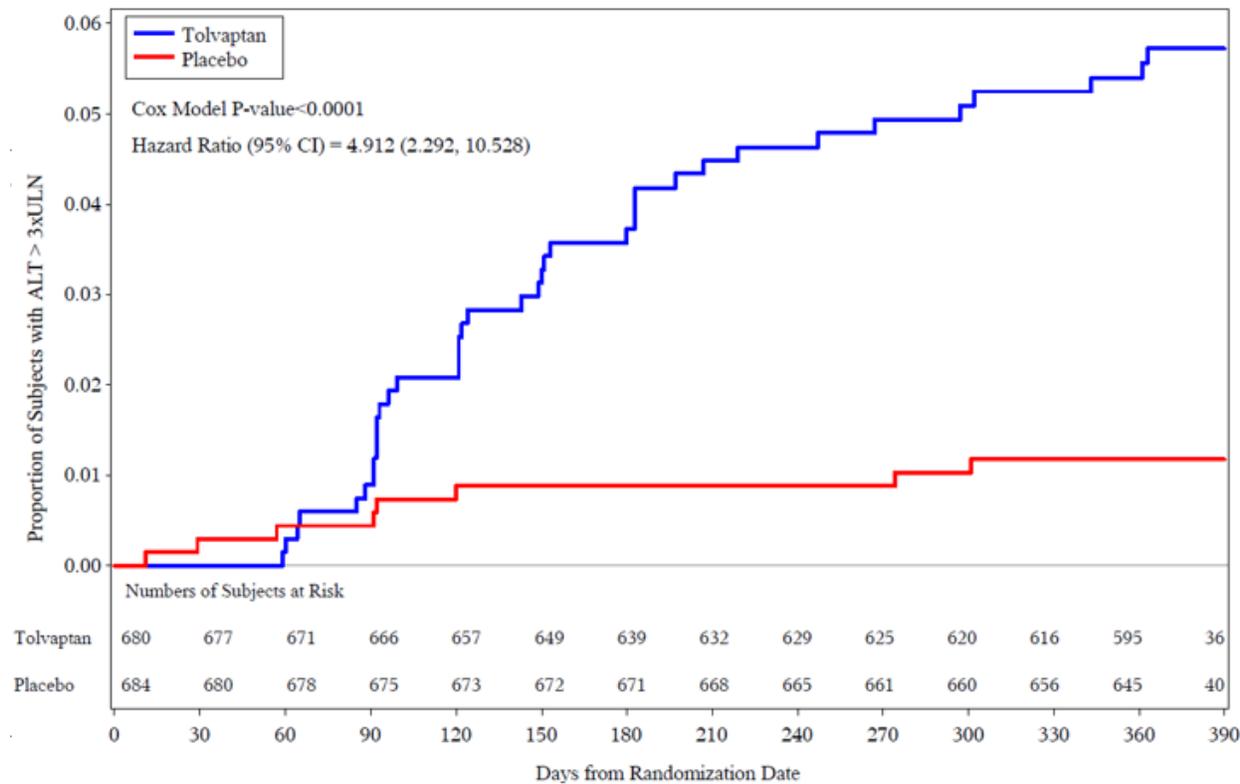
Reviewer's analysis: liver\TB\_ALT plot. Dataset: liverf

During the reviewer's analysis of the data to examine how quickly a subject could develop serious liver injury or how quickly the liver enzymes rise the reviewer examined a 56 year old female subject randomized to placebo that was almost in the Hy's Law quadrant, subject (b) (6). She had a rapid increase and high ALT and is represented in Figure 14 by the upper rightmost circle. A closer look at her shows that 4 weeks after starting tolvaptan in the titration period, her ALT started to rise, but was  $< 1xULN$ . Her last tolvaptan dose of 120 mg occurred one week later. She was then randomized to placebo. By her next scheduled lab, three weeks after her last tolvaptan dose, her ALT ratio was  $16xULN$ , and peaked at  $954 (28xULN)$  six weeks after her last dose of tolvaptan. Her total bilirubin peaked at  $2.2 (1.8xULN)$ , 8.5 weeks after her last dose. Her liver enzymes returned to normal after 3-4 months. The HAC adjudicated her case as "possible". Her ultrasound showed a complicated hepatic mass, and questionable new bleed into a cyst. The cause of the enzyme elevations was not entirely clear, but the reviewer thought that this was an important case that possibly highlights the magnitude and rate of rise. Dr. Lewis commented in his adjudication "important case – probably related if other causes excluded".

The time course of ALT elevations were examined to determine if there might be a window when drug effect is evident. Figure 15 shows the time to ALT elevation of greater than  $3xULN$  in all subjects treated during the randomized period. For subjects with a rise in ALT, it began around Month 2 and started to separate from placebo subjects by Month 3. The time of most of the elevations (the steepest) occurred between Month 2 to 6, however there were still subjects that had an elevation  $> 3xULN$  after 1 year. Subjects adjudicated as highly likely or probable have curves similar to all subjects with ALT elevations (source: applicant's safety update resub erratum-2, figure CF-2). The time course of ALT elevation in REPRISE and its open label extension is not that different from TEMPO and TEMPO's open label extension (see Figure

15, and Figure 20 and Figure 21 in the Appendix). The differences might be due in part by the difference in study design and longer exposure time in TEMPO (Figure 20).

**Figure 15. Time to ALT > 3xULN, double-blind period**

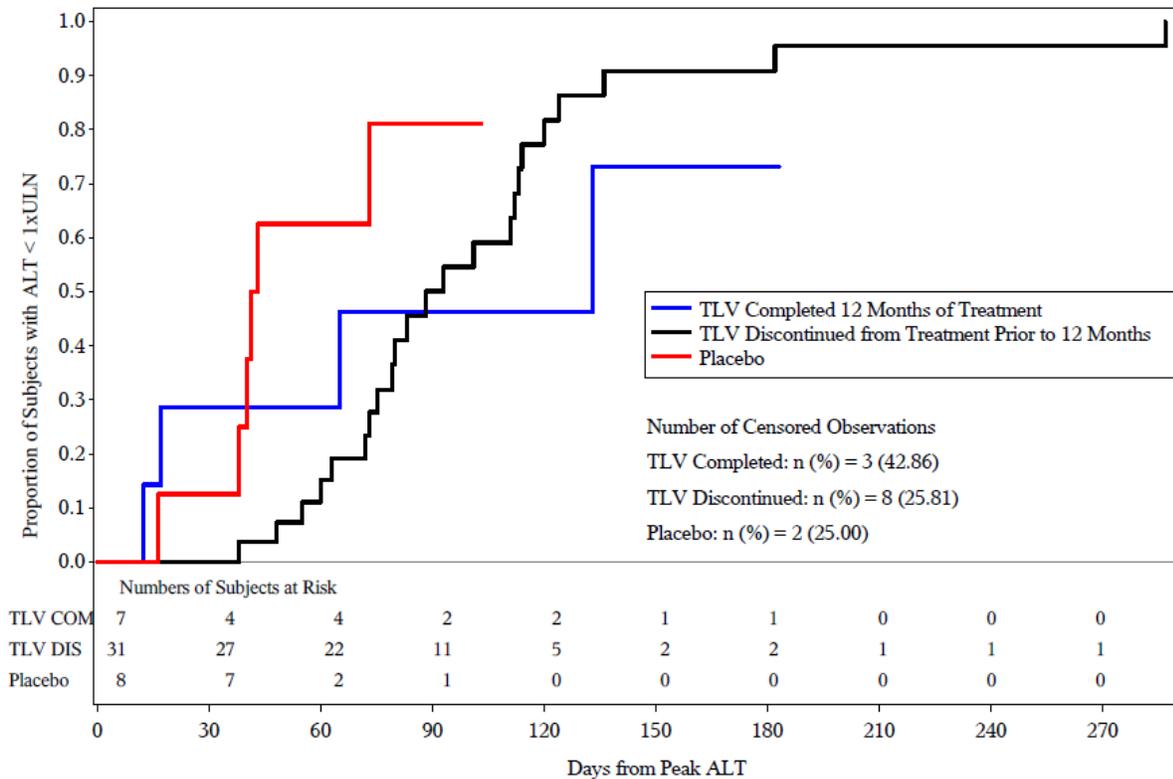


Source: REPRIS CSR, CF-10.1

*Reviewer comment: Although the randomized data indicate that the significant ALT elevations start around Month 2, the data in the titration period supports that the elevations can happen earlier than Month 2.*

Figure 16 shows the time for ALT to return to less than 1xULN in subjects that had an elevation of greater than 3xULN in the randomized period. There were seven subjects that completed 12 months of treatment, but most subjects discontinued treatment. In subjects that discontinued treatment, the time to return to baseline was mostly between 1-5 months.

**Figure 16. Time from peak ALT to < 1 xULN in subjects with ALT>3xULN, double-blind period**



Source: REPRIS CSR, CF-10.2.2

### Summary of REPRIS Liver Findings

The REPRIS trial had frequent liver testing and it appeared to mitigate the risk of irreversible liver injury. Most discontinuations were for liver enzyme elevations, not liver injury symptoms. There were no Hy’s Law subjects and the highest causality attributed to tolvaptan was “probable” in 18 subjects treated with tolvaptan (no “highly likely” or “definite”). There was not a clear dose causality relationship. Like other hepatotoxic drugs, there was an imbalance in ALT elevations > 3xULN (5.6% vs. 1.2%), tolvaptan versus placebo. Most ALT elevations of > 3xULN occurred from Month 2 to 6, but there were occurrences at Month 12. Return to < 1xULN occurred in most subjects by 1 to 5 months.

#### 8.5.1.3. Post-marketing case of serious liver injury resulting in liver transplant

During the review of this application, we became aware of the first case of what appeared to be irreversible tolvaptan-induced liver injury after ~ 6 months of tolvaptan treatment resulting in

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need for liver transplant at Month 8.<sup>33</sup> The patient was a 37-year-old Japanese female with a medical history significant for ADPKD x 2 years, hepatic cysts, tobacco use, urticaria, and alcohol use in her 20's. She denied taking other drugs, including over the counter medications. Her time course of events is shown in Figure 17.

*Reviewer's comment: The treating physician responded quickly to the patient's changes in liver injury tests. It is unknown if following the REPRISE protocol would have prevented the need to transplant. The physician reduced the dose before ALT reached 2xULN (albeit 9.9x her baseline, but there was no guidance based on the subject's baseline), and then stopped tolvaptan at her next visit which was 2 weeks later (earlier than 1 month) when ALT was 3.2xULN (20x her baseline). Notably, the patient had no symptoms when tolvaptan was stopped, total bilirubin was normal (but later rose to a maximum of 8.7xULN), and she had not met criteria for adjudication of a post-marketing event.*

Dr. John Senior, a hepatologist in the Office of Surveillance and Epidemiology at the FDA wrote in his consult review dated 13 March 2018 that "the information provided was incomplete, that other possible causes were at least reasonably excluded". The narrative of the histopathology report of the explanted liver states "the pathologic diagnosis to be acute liver injury with marked zonal necrosis... considered consistent even with changes caused by drug-induced liver disorder."

The HAC consensus causality agreement was "probable". Two of three HAC members adjudicated individual causality as "highly likely" because of the temporal relationship, pathology report, and work-up to exclude other causes.<sup>34</sup> The consensus comments on 20 Dec 2017 state that the "team provided that pathology report plus further metabolic disease workup and transplant follow up, all demonstrating no evidence for causes other than DILI. However acute liver failure from DILI is less common than idiopathic ALF, and in the absence of any prior cases of ALF attributed to tolvaptan, the reviewers all agreed that 'probable' was the best designation. Should another case of ALF occur in future that could be attributed to tolvaptan, then there would be a precedent for a more certain causality designation." With respect to causality, Dr. Senior states in his review, "still think that the liver failure in this patient was probably and very likely caused by tolvaptan."

*Reviewer's comment: This is the first known case of irreversible tolvaptan induced liver injury resulting in liver transplant.*

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<sup>33</sup> Case # JP-OTSUKA-2017\_021168, FAERS Case # 14032572

<sup>34</sup> Drs. David Alpers and James Freston adjudicated the case as "highly likely". Dr James Lewis adjudicated the case as "possible".

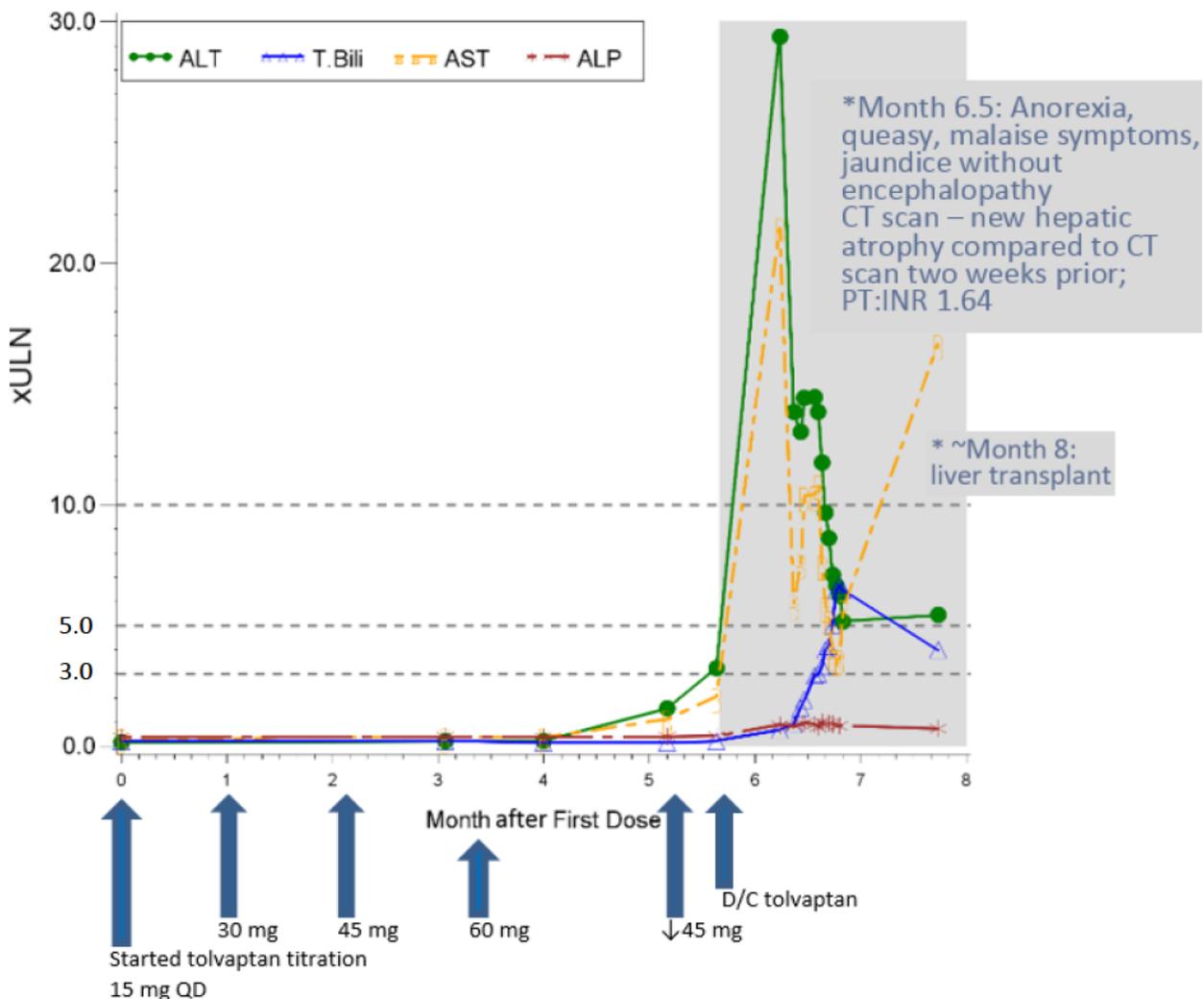
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Figure 17. Time course of events in subject that received transplant



Reviewer's figure based on applicant's response SN0068<sup>35</sup>

Grey shading indicates time when subject not taking tolvaptan.

<sup>35</sup> Acute liver failure is defined as a severe and sudden liver dysfunction able to induce encephalopathy and coagulopathy (prothrombin time:INR of > 1.5) within 26 weeks of the onset of symptoms in patients without previous liver disease.

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#### 8.5.1.4. Post-marketing adjudication

Tolvaptan is approved in ADPKD in Japan, Canada, European Economic Area, South Korea, Switzerland, Australia, and Hong Kong. From the time of the first NDA submission in 2012 until 31 January 2018, the HAC adjudicated 290 post-marketing cases.<sup>36</sup> Most of the “probable” and “possible” cases were in the ADPKD population. There was only one subject that the reviewer thought was DILI (discussed in the preceding Section). There were three other post-marketing cases of interest in subjects that had liver transplants, but review of those cases suggests that the transplant was not because of DILI.<sup>37</sup> In the HAC’s June 2017 report, they state that the post marketing “cases are consistent with the conclusions suggested from the clinical trial data that it is the length of treatment with tolvaptan, not the underlying indication, or even the dose, that provides the risk for DILI.”

*Reviewer comment: It is interesting that the HAC thinks that ADPKD does not play a role.*

**Table 26. Final causality assessments in post-marketing cases from 2012 to 31 Jan 2018**

Final Causality	Total	ADPKD total
Highly likely	0	0
Probable	15	14
Possible	96	86
Unlikely	143	6
Insufficient data	36	12
<b>TOTAL</b>	<b>290</b>	<b>118</b>

Reviewer’s table: liver\feb2018submission based on Applicant Safety Update Resub Erratum #2, SN 0077, dataset hepupdp. Cases identified from the time of the NDA submission in 2012 to 18 May 2017 and 01 Jun 2018 to 31 Jan 2018.

#### 8.5.1.5. Hepatic Adjudication Committee and Liver Injury

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<sup>36</sup> The triggers for adjudication of post-marketing events (ran monthly) included any AE in the five hepatic standardized MedDRA queries (SMQs) with subsequent liver laboratory and symptom screening; there were no laboratory triggers (see Appendix 13.3.2).

<sup>37</sup> FAERS case 13708088, Subject (b) (6), Subject (b) (6)

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Since the HAC first convened in 2012, they have adjudicated 214 cases from ADPKD trials.<sup>38</sup> The summary of causality in ADPKD trials is shown in Table 27. At the time of their last complete report (dated 28 June 2017) the first irreversible case of liver injury had not happened. The HAC state that “while the lack of Hy’s Law cases in this most current report of trial patients follows in time with the initiation of monthly testing for transaminase elevation, it is still too early to attribute a cause and effect relationship to the current risk management strategy.” In referencing that there were no new Hy’s law cases, the HAC stated that it was “encouraging for liver safety, but the experience is still limited. In addition, the data are still insufficient to assess the importance of underlying disease or tolvaptan dose in determining the risk of ALF”.

**Table 27. HAC Causality assessments of cases in ADPKD trials**

	Tolvaptan	Placebo
Highly likely	4	0
Probable	43	1
Possible	85	9
Unlikely	59	11
Insufficient data	2	0
<b>TOTAL</b>	<b>193</b>	<b>21</b>

Reviewer’s analysis: adjud table. Applicant datasets: dataset heparslt, hepupdct

*Reviewer’s comment: In efforts to understand how a probability of “highly likely” is decided over “probable”, I examined the 4 “highly likely” subjects. Three were from the original NDA submission, and lack of adjudication narratives made it difficult to determine the rationale for the HAC’s final adjudication. Subject (b) (6) was a Hy’s Law subject and had biopsy findings suggestive of DILI (other causes were ruled out). Subject (b) (6) had biopsy results that said “medicine induced acute hepatitis”. She was asymptomatic, and total bilirubin never increased. Subject (b) (6) had mild pruritis, bilirubin increased, but was not 2xULN. The “highly likely” subject from this resubmission is subject (b) (6). Her latency for ALT elevation was almost 1 year and she was asymptomatic. However, she had a positive dechallenge and a rechallenge. So, it appears that a positive dechallenge and rechallenge carries weight in causality. However, it was not possible to fully understand adjudication of causality.*

<sup>38</sup> All documents and datasets reviewed related to the HAC are described in Table 32 (Appendix). The numbers are based on the January 2018 quarterly update.

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Based on the latest HAC report that summarized the exposure data, dated 28 Jun 2017, the total number of patients exposed to tolvaptan for at least 18 months is 1940, this number comes from controlled trials in ADPKD. At the time of the NDA resubmission, there were no new Hy's Law cases. Based on the clinical trial data the HAC estimated the risk of ALF due to 18 months (the window of susceptibility) of tolvaptan to be 1/6,200.

*Reviewer's comment: My calculations to obtain the risk based on 3 Hy's Law subjects are shown below. The HAC's estimate is slightly more conservative.*

$$\frac{3 \text{ Hy's Law}}{1,940 \text{ exposed for 18 months}} = \frac{1}{650}, \text{ if 10\% go on to liver transplant or death then risk is } \frac{1}{6,500}$$

The signature clinical presentation that the HAC describes is:

- 1) Hepatocellular injury with R value > 5.0

$$R = \frac{\frac{ALT}{ALT \text{ ULN}}}{\frac{Alk \text{ Phos}}{ALK \text{ Phos ULN}}}$$

- 2) Onset between 3 and 18 months on treatment
- 3) Progressive rise in serum ALT/AST for several week after stopping treatment with tolvaptan followed by a return of these clinical chemistries to baseline over one to several months.

*Reviewer's comment: Liver enzymes were measured more frequently in REPRISE than in TEMPO, and REPRISE had a lower threshold for holding tolvaptan. Based on the discontinuation and liver enzyme data, there were three subjects that had a ALT/AST > 3 xULN in the first month (and did not get randomized).<sup>39</sup> Figure 15 shows that ALT > 3xULN starts by Month 2, however subjects that could not tolerate tolvaptan or who had elevations of 2xULN were discontinued and do not appear in that figure. The onset of significant rise starts at **1 month, not 3 months.***

### 8.5.2. Gout/increased uric acid

Decreased uric acid clearance by the kidney is a known pharmacodynamic effect of tolvaptan. TEMPO reported a higher incidence of uric acid increases greater than 10 mg/dL in the tolvaptan arm compared to the placebo arm (5.6% vs. 4.1%). "Gout" was also reported more

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<sup>39</sup> Reviewer's analysis: dc\_pd1\_2\_runin. Source adsl, liverf.

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frequently (2.9% vs. 1.4%) and increased use of antigout medicine was noted in the TEMPO trial. The data from REPRISÉ do not suggest a significant problem with gout or significant increases in uric acid. There were more subjects treated with tolvaptan taking antigout medications<sup>40</sup> [118 (17.3%) vs. 107 (15.6%)]. Use prior to the single blind period was balanced (14.5% vs 13.7%, tolvaptan vs. placebo).<sup>41</sup>

*Reviewer's comment: Because of tolvaptan's effect on urine osmolality, all subjects should have serum uric acid measured at baseline.*

**Table 28. Analysis of Gout/uric acid preferred terms**

Preferred Term	Tolvaptan (N=681)		Placebo (N=685)		Tolvaptan vs Placebo		
	Number of subjects	Proportion (%)	Number of subjects	Proportion (%)	RD (per hundred)	RD C.I. (lower bound)	RD C.I. (upper bound)
Gout CMQ	34	5.0	25	3.7	1.34	-0.81	3.5
Gout	21	3.1	20	2.9	0.16	-1.65	1.97
Blood uric acid increased	7	1.0	0	0.0	1.03	0.27	1.79
Hyperuricaemia	7	1.0	4	0.6	0.44	-0.5	1.39
Gouty arthritis	0	0.0	1	0.2	-0.15	-0.43	0.14

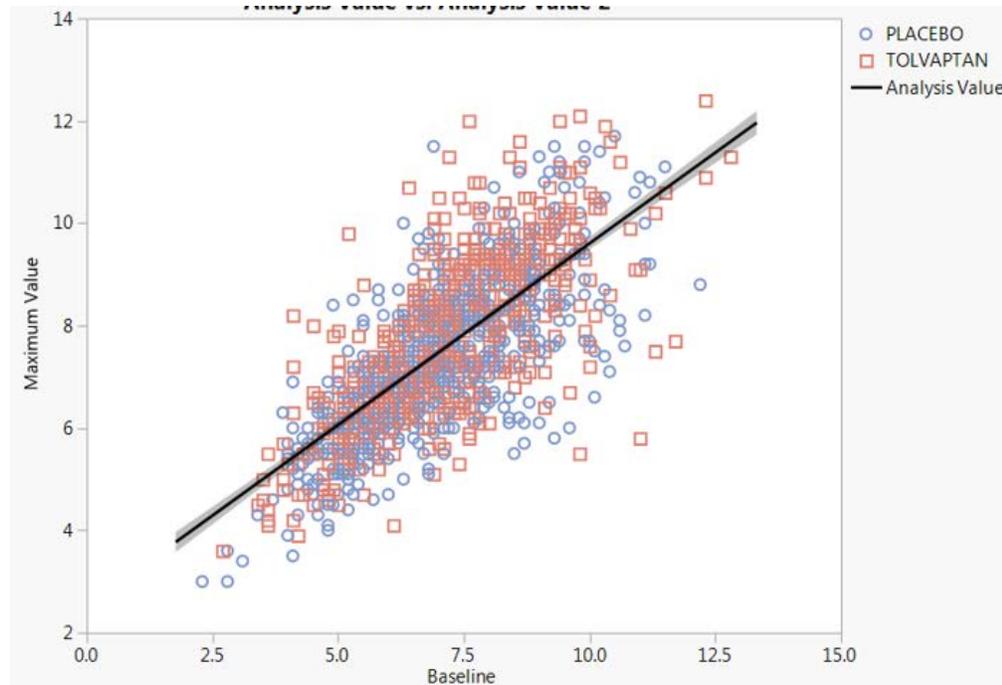
Reviewer's analysis: ae\MAED ae te durran\_CMQ, datasets: adsl, adae

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<sup>40</sup> Included allopurinol, colchicine, colchimax, and febuxostat. Source REPRISÉ CSR CT-4.1.4

<sup>41</sup> Source REPRISÉ CSR CT-4.1.1

**Figure 18. Baseline versus maximum uric acid**



Reviewer's analysis. Note that the colors for treatment arm are switched. Dataset: adlb

### 8.5.3. Hyperglycemia/Diabetes

An increase in circulating AVP may stimulate hepatic glucose production. Prior placebo-controlled trials in hyponatremia showed a 6-fold higher incidence of hyperglycemia in tolvaptan treated subjects compared to placebo. The first pivotal trial in ADPKD had inconclusive results.<sup>42</sup> Like the first trial, subjects with advanced diabetes (glycosylated hemoglobin (HgbA1c > 7.5 and/or glycosuria by dipstick) were excluded from REPRISE. Analysis of the REPRISE adverse event data do not show a concern for hyperglycemia or new onset diabetes in this population.

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<sup>42</sup> In trial 156-05-251 increased glucose concentrations were observed less frequently in tolvaptan treated subjects compared to placebo (5.5% vs 6.8%), but treatment emergent diabetes mellitus was greater in tolvaptan treated subjects (7 versus 0 subjects).

**Table 29. Hyperglycemia/Diabetes AE term Analysis, Randomized Period**

Preferred Term/Narrow SMQ	Tolvaptan (N=681)		Placebo (N=685)	
	Number of subjects	Proportion (%)	Number of subjects	Proportion (%)
Blood glucose increased	0	0	1	0.1
Type 2 diabetes mellitus	0	0	2	0.2
Diabetes mellitus	0	0	2	0.3
Hyperglycemia	3	0.4	5	0.7
Hyperglycemia/new onset diabetes mellitus Narrow SMQ	3	0.4	9	1.3

Reviewer's analysis: TEAE ran review. Dataset: adae  
 SMQ=Algorithmic search

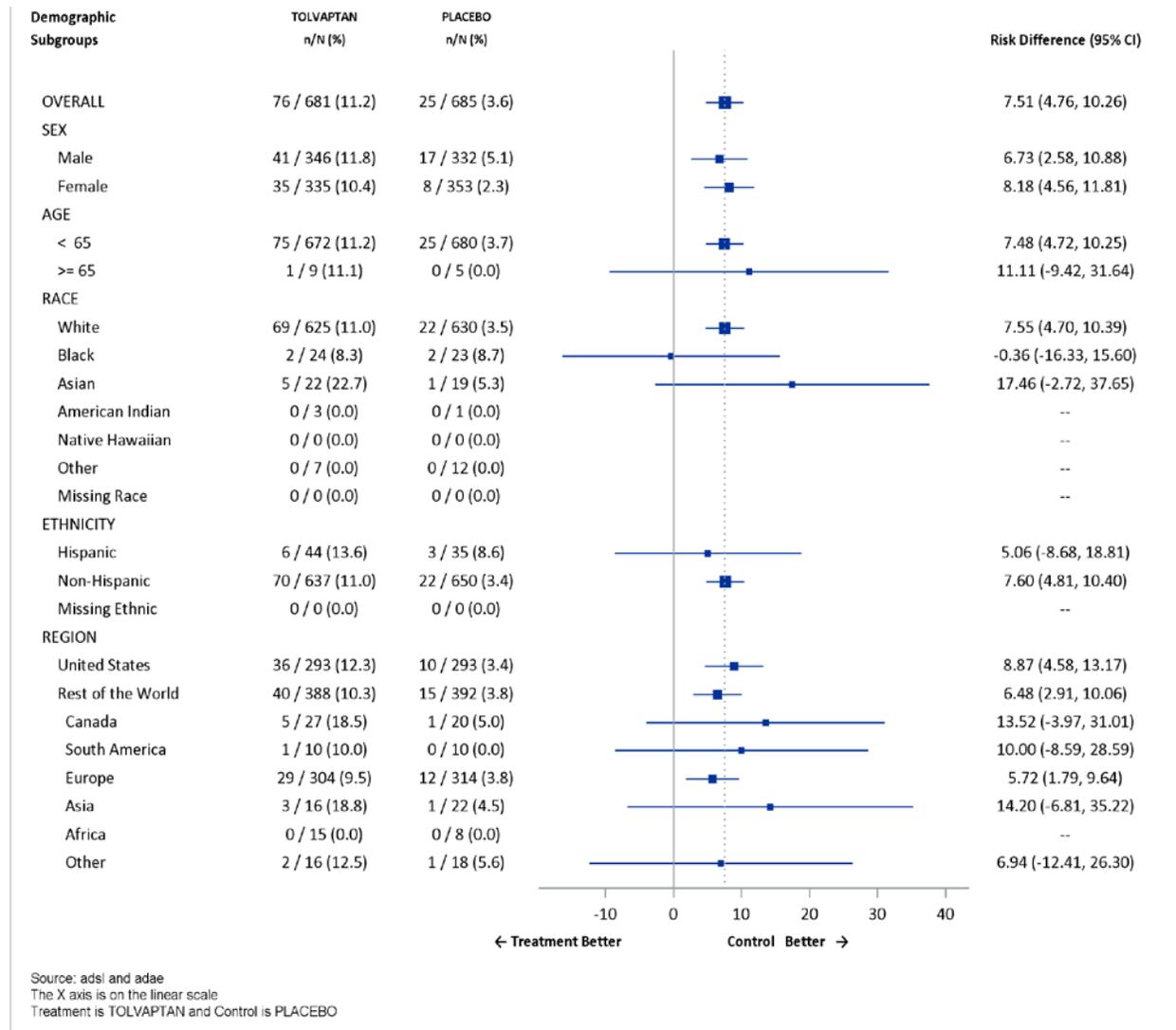
#### 8.5.4. Hematuria

An exploratory efficacy analysis on ADPKD outcome events (see Table 10) showed a numerically greater number of events of gross hematuria in the tolvaptan treatment arm. An analysis of hematuria and anemia events in the AE data did not suggest a signal. ADPKD can cause gross hematuria.

### 8.6. Safety Analyses by Demographic Subgroups

Subgroup analyses were explored for the common AE of aquaresis and thirst. For aquaresis, most of the risk difference for the subgroups centered around the overall risk difference of 7.5 (95% CI 4.8, 10.3) times greater with tolvaptan compared to placebo. Where there were differences in the risk difference compared to the overall, the subgroups appeared too small to make any generalizations. For thirst, the overall risk difference was 3.4 (95% CI 1.3, 5.5) times greater with tolvaptan compared to placebo. It appears that females have less risk for thirst, and have lower rates of thirst compared to males. Most subgroups were either too small to make any other generalizations or there did not appear to be large differences from the overall risk difference.

**Figure 19. Subgroup analysis of aquaresis**



Reviewer's analysis using Office of Computational Science Demographic tool. Dataset ADSL and ADAE

**Table 30. Subgroup analysis of aquaresis (continued)**

Subgroup	TOLVAPTAN N=681		PLACEBO N=685		Risk Difference (95% CI)
	n(%)	Total,N	n(%)	Total,N	
Safety Subgroup (AEDECOD in('Polyuria', 'Pollakiuria', 'Micturition urgen	76 (11.2)	681	25 (3.6)	685	7.51 (4.76, 10.26)
<b>STRATAGE</b>					
Age is greater than 55 years	10 (10.2)	98	1 (1.0)	99	9.19 (2.89, 15.50)
Age is less than or equal to 55 years	66 (11.3)	583	24 (4.1)	586	7.23 (4.19, 10.26)
Missing	0 (0.0)	0	0 (0.0)	0	--
<b>STRATTKV</b>					
Missing	0 (0.0)	0	0 (0.0)	0	--
TKV IS GREATER THAN 2,000 ML	6 (10.0)	60	6 (10.0)	60	0.00 (-10.74, 10.74)
TKV IS LESS THAN OR EQUAL TO 2,000 ML	9 (11.8)	76	1 (1.4)	72	10.45 (2.70, 18.20)
UNKNOWN	61 (11.2)	545	18 (3.3)	553	7.94 (4.91, 10.97)
<b>STRATEGF</b>					
EGFR IS GREATER THAN 45 ML/MIN/1.73M	25 (10.4)	241	8 (3.2)	248	7.15 (2.71, 11.58)
EGFR IS LESS THAN OR EQUAL TO 45 ML/MIN/	51 (11.6)	440	17 (3.9)	437	7.70 (4.20, 11.20)
Missing	0 (0.0)	0	0 (0.0)	0	--
<b>CKDSTGB</b>					
2	3 (9.4)	32	0 (0.0)	39	9.38 (-0.72, 19.47)
3a	27 (12.9)	209	9 (4.5)	201	8.44 (3.07, 13.81)
3b	30 (9.9)	302	10 (3.2)	314	6.75 (2.86, 10.64)
4	16 (11.6)	138	6 (4.7)	128	6.91 (0.43, 13.38)
Mi	0 (0.0)	0	0 (0.0)	0	--
Missing	0 (0.0)	0	0 (0.0)	3	--

Reviewer's analysis using Office of Computational Science Demographic tool. Dataset ADSL and ADAE

## 8.7. Specific Safety Studies/Clinical Trials

Not applicable.

## 8.8. Additional Safety Explorations

### 8.8.1. Human Carcinogenicity or Tumor Development

This was discussed in the first review of the three-year trial, TEMPO, which was of longer duration than REPRISE. In brief, there was a higher incidence of malignant tumors, in tolvaptan treated subjects compared to placebo in TEMPO [16(1.7%) vs 2 (0.4%), tolvaptan vs. placebo, respectively]. The difference was largely driven by skin neoplasms [10(1.0%) vs 1 (0.2%), tolvaptan vs. placebo, respectively]. After investigation of each case in TEMPO, no definitive conclusions could be made regarding the role of tolvaptan and the occurrence of neoplasms.

Skin neoplasms was an AE of special interest in REPRISE. In this one year trial, skin neoplasm SMQ was [3(0.4%) vs 5 (0.7%), tolvaptan vs. placebo, respectively]. The REPRISE data do not

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support a risk, but it was also a short trial.

*Reviewer comment: The applicant should continue to monitor for skin neoplasms through standard pharmacovigilance.*

### **8.8.2. Human Reproduction and Pregnancy**

This was reviewed previously. The safety of tolvaptan in pregnant women has not been studied, and pregnancy and lactation were exclusion criteria in the trials. Pregnancies were to be followed for a minimum of six months. The next table shows a summary of the pregnancies/pregnancy of partner in the ADPKD program.

Table 31. Listing of cases of pregnancy of trial participants or their partners treated with tolvaptan in the ADPKD development program

Trial Number	Subject ID	Event	Outcome
156-04-251		Pregnancy of partner	Live birth; no known defects
		Pregnancy of partner	Live birth; no known defects
		Pregnancy	Live birth; no known defects
		Pregnancy	Elective abortion
		Pregnancy	Elective abortion
		Pregnancy	Elective abortion
		Pregnancy	Spontaneous abortion
		Pregnancy	Elective abortion
156-08-271		Pregnancy	Live birth; no known defects
		Pregnancy	Live birth; no known defects
		Pregnancy	Missed abortion
		Gestational hypertension	Recovered; live birth; no known defects
		Pregnancy	Live birth; no known defects
		Pregnancy	Ectopic pregnancy
		Pregnancy	Still birth
156-10-003		Pregnancy	Live birth; no known defects
		Gestational hypertension	
		Pregnancy	Live birth; baby had neonatal jaundice which resolved; the relationship to IMP could be ruled out, per the investigator, since neonatal jaundice could commonly occur in newborns. Neonate had abnormality of bilateral renal cysts.
		Pregnancy of partner	Live birth; no known defects
		Pregnancy of partner	Live birth; no known defects
		Pregnancy of partner	Live birth; no known defects
		Pregnancy of partner	Live birth; no known defects
		Pregnancy of partner	Live birth; no known defects
156-13-210		Pregnancy	Spontaneous abortion
		Pregnancy	Elective abortion
		Pregnancy of partner	Spontaneous abortion

APPEARS THIS WAY ON ORIGINAL

<sup>a</sup> Subject (b) (6) had 2 pregnancies during the trial; 1 resulting in a missed abortion and 1 with gestational hypertension resulting in a live birth.

From Safety update resub, Table 5.4-1

The DPMH Maternal Health Team concluded that the risks of tolvaptan use in pregnancy, lactation, and reproduction cannot be determined due to insufficient evidence. The Maternal Health Team and the non-clinical review team concluded that use in pregnancy “may cause fetal harm”. Developmental toxicity did not occur in rats and rabbits at maternally non-toxic doses, however tolvaptan adversely affected embryo-fetal development at maternally toxic

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doses. Reproductive toxicity findings were observed in animals at exposure similar to the maximum dose of 120 mg a day.

The Maternal Health Team recommends that women not breastfeed during treatment with tolvaptan due to the potential serious adverse reaction in the breastfed infant.

### 8.8.3. Pediatrics and Assessment of Effects on Growth

[REDACTED] (b) (6)

The applicant is currently conducting the pediatric Trial 156-12-298 outside of the US with no plans to extend enrollment to the US.<sup>43</sup> Trial 156-12-298 is a one year randomized, double-blind, placebo-controlled trial followed by a two-year open label period. [REDACTED] (b) (4)

[REDACTED]

The Division of Pediatric and Maternal Health (DPMH) in OND was consulted regarding pediatric labeling recommendations, specifically recommendations for Section 8.4, to warn of the risk of acute liver failure and whether language should be included to discourage off label use in pediatric patients. Please refer to Dr. Elizabeth Durmowicz review from the DPMH dated 05 March 2018 for further information. DPMH concluded that the applicant's proposed labeling for pediatric use is acceptable unless the Division determines that the use of tolvaptan in pediatric patients or a subgroup with ADPKD would be ineffective or unsafe.<sup>44</sup> DPMH recommended some post marketing activities to monitor the risk in patients. DILI will be captured for every patient including pediatric patients because of the REMS.

### 8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

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<sup>43</sup> Applicant confirmed in communication SN 0078.

<sup>44</sup> Email communication with Dr. Durmowicz clarified that "unsafe" meant "use in the pediatric population or a subpopulation of pediatric patients would be more risky than use in the adult population."

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There were no overdoses in TEMPO. In REPRISE, 5 subjects reported an accidental overdose (4 received tolvaptan). One subject experienced polyuria and increased thirst on the same day as the accidental overdose. The other four subjects did not report any concomitant AEs. The expected AEs from an overdose of tolvaptan include a rise in serum sodium, polyuria, thirst, and dehydration/hypovolemia.

No cases of drug abuse were reported in any tolvaptan clinical trial. Tolvaptan is not a controlled substance and has not been studied in humans for its potential for abuse or physical dependence.

There did not appear to be withdrawal effects following tolvaptan discontinuation.

## **8.9. Safety in the Postmarket Setting**

### **8.9.1. Safety Concerns Identified Through Postmarket Experience**

See Dr. Paolo Fanti's (Division of Pharmacovigilance-I dated 06 March 2018) self-initiated memo that evaluates the FDA Adverse Event Reporting System (FAERS) cases of hepatic adverse events with the use of tolvaptan and Section 8.5.1. Drug Induced Liver Injury (DILI) for a discussion of the patient the developed liver injury resulting in liver transplant.<sup>45</sup> The reviewer did not find any additional cases of serious liver injury using Empirica Signal and FAERS that weren't already identified. The reviewer relied on the applicant's post-marketing reports for other AEs. Thirst was the most frequently reported preferred term. There were no additional safety concerns identified from the post-marketing experience that have not been described from the controlled clinical trials.

### **8.9.2. Expectations on Safety in the Postmarket Setting**

The registry will closely monitor for severe liver events.

### **8.9.3. Additional Safety Issues From Other Disciplines**

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<sup>45</sup> Dr. Fanti notes in his memo that the HAC did not adjudicate 3 FAERS reports that he identified, however those reports were all adjudicated (cases MCN# 2015\_004132, 2016\_007574, and 2017\_019752) as "possible"; Dr. Fanti escalated the cases to "probable". The 2017 case was reported after the close of data for the NDA resubmission, however in submission number 69, dated 06 February 2018, the applicant submitted an update of all cases adjudicated from the time of NDA resubmission to 31 January 2018.

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### *8.9.3.1. Non-clinical toxicology review of mechanistic hepatotoxicity studies*

Please refer to Dr. Gowra Jagadeesh review dated 27 Feb 2018 for more information on the three non-clinical mechanistic studies of tolvaptan induced hepatotoxicity that the applicant conducted. The studies suggest that oxidative stress, mitochondrial dysfunction, and alterations in bile acid transport (inhibition and or accumulation) are involved in tolvaptan induced hepatotoxicity. Tolvaptan and its metabolites inhibit several human hepatocytes involved in bile acid transport.

## **8.10. Integrated Assessment of Safety**

The clinical safety of tolvaptan in ADPKD was evaluated in two phase 3 placebo-controlled trials, a three-year trial 156-04-151 (TEMPO) and a one-year trial 156-13-210 (REPRISE). The safety database was adequate to evaluate the general safety of tolvaptan in ADPKD. As described in Section 8.2.1 these trials randomized a total of 1,642 ADPKD patients to tolvaptan of which 1,418 patients received tolvaptan for at least one year. TEMPO was reviewed in 2013. The second trial, REPRISE, was the primary focus of this review. As discussed in Section 6.1.1 REPRISE enrolled patients with more advanced renal disease than TEMPO. REPRISE had a 5-week titration run-in period prior to randomization, and so was designed to randomize subjects that could tolerate at least tolvaptan 60/30 mg and thus minimize treatment discontinuations. The median duration of exposure in the entire trial was 394 days, and the average modal dose at Month 12 was 106 mg daily. Most subjects in REPRISE took the highest dose of 90/30 mg daily. As shown in Figure 10, more subjects discontinued tolvaptan than placebo, and by Month twelve, 85% (577/681) of treated subjects were still taking tolvaptan while 93% (636/685) of treated subjects were on placebo.

The most important safety finding with tolvaptan is the risk of drug induced liver injury. As discussed in Section 8.5.1.1. tolvaptan's potential to cause DILI was not anticipated and was discovered after the first trial in patients with ADPKD was unblinded. The discovery of a higher rate of transaminase elevations (a sensitive signal of the potential to cause DILI, but not specific) in tolvaptan treated subjects compared to placebo (4.1% versus 1.0% in ALT, respectively) led Otsuka to convene an independent, blinded HAC to adjudicate the causality of potential cases of DILI in the ADPKD program as well as selected cases from the prior development programs in hyponatremia and heart failure. There were 3 Hy's Law cases out of 860 tolvaptan treated ADPKD subjects over a 14-month period. The cases were adjudicated as 2 "probable" and 1 "highly likely". Based on Hy's Law, the rough incidence of liver failure was estimated as 10 percent of 3/860 or ~ 1 in 3000 patients treated with tolvaptan. This was more hepatotoxic than some drug withdrawn from the market for hepatotoxicity which have frequency rates of liver transplant or death of  $\leq 1$  per 10,000.

One purpose of REPRISE was to test a strategy to mitigate the risk of serious liver injury. The intensive monitoring in REPRISE appeared to mitigate the risk; there were no Hy's Law cases in

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REPRISE, and most subjects that had IMP discontinued did not have clinical symptoms of liver injury. However, in the Fall of 2017, the first case of irreversible tolvaptan induced liver injury resulting in the need for liver transplant occurred in a patient with ADPKD. She took tolvaptan for ~six months in the post-marketing setting in Japan, which used a monitoring strategy similar to REPRISE. Despite a reasonable work up to exclude other causes and biopsy results read as hepatocellular injury from drug, the HAC was reluctant to 1) adjudicate causality any higher than “probable” and 2) label the case DILI. Instead the HAC characterized the case as “idiopathic ALF” citing that this is the first case and idiopathic ALF is more common than ALF from DILI. The FDA’s hepatotoxicity expert, Dr. John Senior also reviewed the case and stated that the “liver failure in this patient was probably and very likely caused by tolvaptan”. There are 3 Hy’s Law cases and one case of severe liver injury case requiring liver transplant among the clinical trials and post-marketing exposure.

The applicant has proposed a REMS to mitigate the risk of serious and fatal liver injury. We agree that a REMS is necessary given the gravity of the risk and potential long-term treatment of ADPKD. In addition to the REMS, we are recommending a postmarketing requirement (PMR) for a registry to determine the incidence and to describe the cases of irreversible liver injury, and to assess the adequacy of the proposed monitoring. Although not a PMR or post marketing commitment (PMC), the applicant will be asked to report severe liver cases as expedited (15 day) reports.

Labeling efforts to mitigate the risk of serious liver injury should include a box warning about the risk of serious liver injury, monitoring guidelines, warnings and precautions, and a contraindication in patients with signs or symptoms of liver injury or impairment.

Regarding other safety findings, most frequent AEs and top reasons for treatment discontinuation included the aquaretic effects, thirst and liver enzyme elevations (see Sections 8.4.2, 8.4.3, 8.4.5). The most common AE reason for medication discontinuation during the titration phase was intolerability, during the randomized phase it was liver enzyme elevations. Most common AEs were mild in intensity (see Section 8.4.4). Serious TEAEs occurred in 12.5% vs. 8.8%, tolvaptan vs. placebo, respectively, and liver enzyme elevations were the most common serious TEAE.

Other potential adverse effects include increases in serum sodium and uric acid, which were generally mild in nature. Subgroup analyses for aquaresis and thirst did not identify a subgroup that may be at greater risk for these two common AEs. The limited hepatotoxicity data suggests that females may be more susceptible to DILI.

In sum, tolvaptan can cause serious DILI. The proposed REMS is expected to mitigate the risk. The PMR will ascertain DILI as well as assess the adequacy of the monitoring schedule will aid in our understanding of the risk benefit.

## 9. Advisory Committee Meeting and Other External Consultations

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An Advisory Committee Meeting was held on 15 August 2013 (see Table 1). There was no need for an AC during this review cycle.

## 10. Labeling Recommendations

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### 10.1. Prescription Drug Labeling

Efficacy: The label should only include an indication for the slowing of kidney function decline in adults at risk of rapidly progressing ADPKD. There is insufficient evidence to support the proposed indication for [REDACTED] <sup>(b) (4)</sup>. Hence, this claim should be removed from the indication statement.

Safety: In addition to a boxed warning for serious liver injury, the label should recommend liver testing, medication interruption and plan of action similar to what was done in REPRISE.

### 10.2. Nonprescription Drug Labeling

N/A

## 11. Risk Evaluation and Mitigation Strategies (REMS)

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The applicant has proposed a REMS to mitigate the risk of serious and fatal liver injury.

Elements of the REMS consists of a Medication Guide, Communication Plan, and elements to assure safe use (ETASU) that include prescriber and pharmacy certification, liver monitoring, patient enrollment and education about risk and monitoring, documentation of safe use conditions and monitoring, an implementation system, and a patient registry. As part of the communication plan, the applicant will also send a healthcare Provider REMS letter to providers likely to prescribe tolvaptan.

Please see the Division of Risk Management's review (to be finalized) for specific details of the REMS.

## 12. Postmarketing Requirements and Commitments

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Because of the risk of serious liver injury and the uncertainty of the actual risk, the Division along with the Office of Surveillance and Epidemiology recommend a Post-Marketing Requirement (PMR) to establish the incidence of serious liver injury and describe the cases of serious liver injury via data gathered in the registry. Using these data, the incidence of severe liver injury in the post-marketing setting will be compared to that observed in the development program. The clinical information collected as part of the registry will also allow an assessment of the adequacy of monitoring in patients who experience a severe liver injury. Although not a PMR or PMC, the applicant will be asked to report severe liver cases as expedited reports. The Division of Pharmacovigilance will be monitoring the reports.

Refer to the PMR development template (not yet finalized) by Dr. Southworth for specifics.

## 13. Appendices

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### 13.1. References

### 13.2. Financial Disclosure

The financial disclosure information for TEMPO was provided in the first cycle tolvaptan NDA review. The financial disclosure information for REPRISE is provided in the table below. There are no concerns that financial incentives altered the outcomes of the clinical trials.

#### Study 156-13-210: REPRISE

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>833</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):  Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u>		

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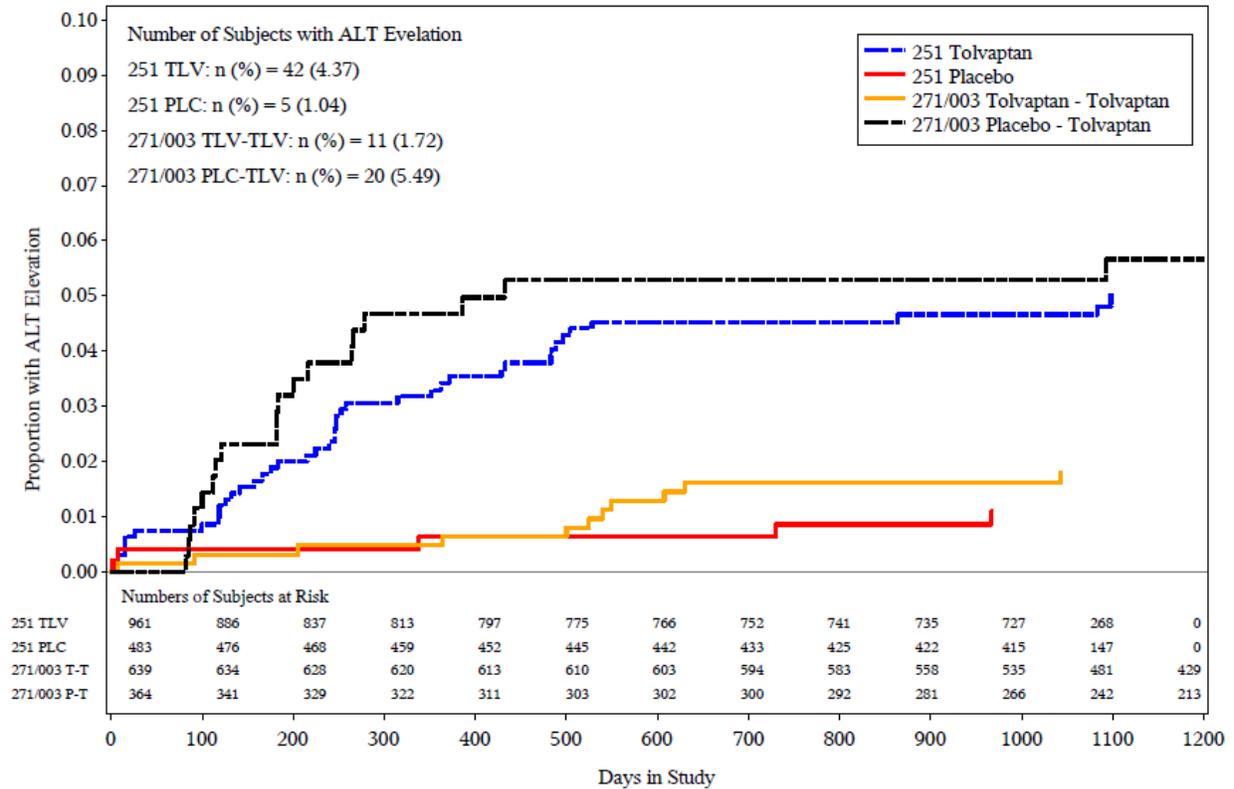
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Significant payments of other sorts: <u>0</u>		
Proprietary interest in the product tested held by investigator: <u>0</u>		
Significant equity interest held by investigator: <u>0</u>		
Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): <u>9</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

### 13.3. Additional Liver Information

#### 13.3.1. Kaplan-Meier time to first ALT $\times$ 3xULN in main trial and open label extension

Figure 20. Kaplan-meier time to first ALT $\times$ 3xULN in TEMPO and TEMPO open label extension



Applicant's safety update resub erratum-2, CF-6  
 TEMPO=251, TEMPO open label extension=271

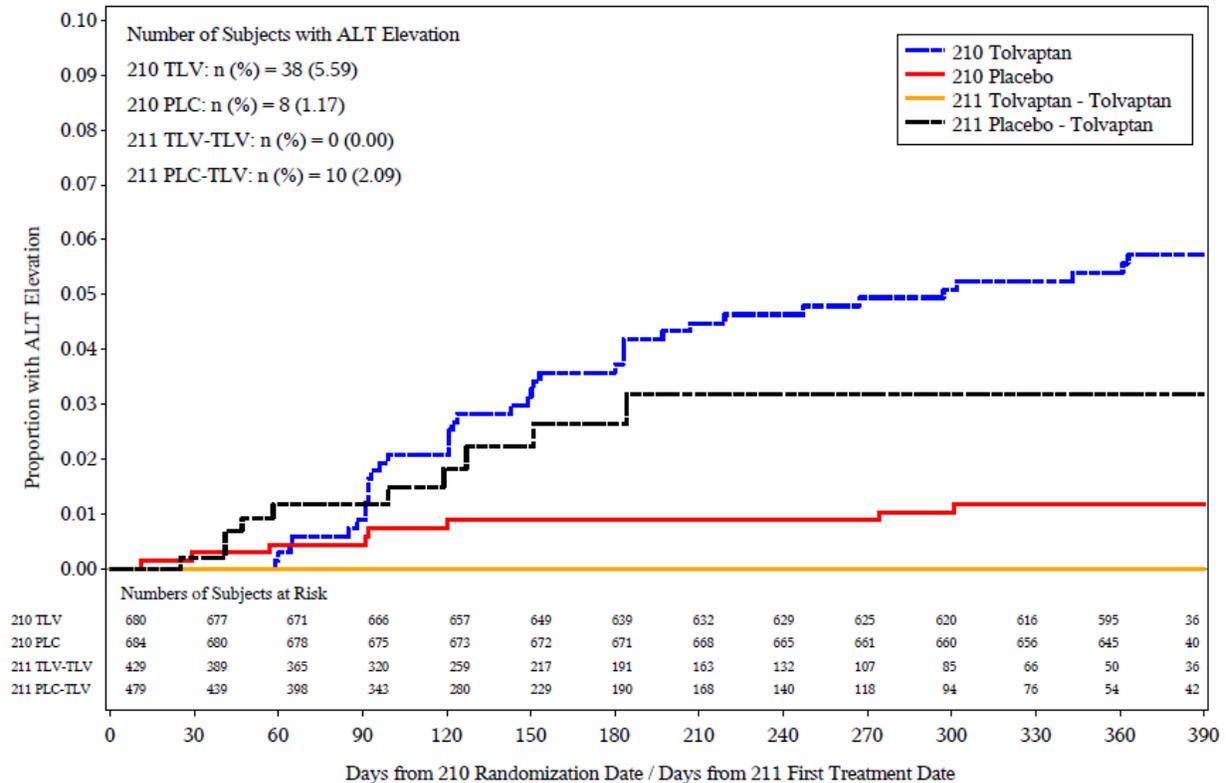
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**Figure 21. Kaplan-meier time to first ALT>3xULN in REPRISE and REPRISE open label extension**



Applicant's safety update resub erratum-2, CF-7.1

REPRISE =210, REPRISE open label extension=211

### 13.3.2. Trigger Criteria for Post-marketing events

Any AE matching a lower level MedDRA term in one of the five hepatic SMQs (MedDRA version 14.1) was a trigger for adjudication (ran monthly).

- 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

The results of these searches were further screened for cases meeting the following transaminase criteria:

- ALT or AST > 8xULN
- ALT or AST > 5xULN for more than 2 weeks
- ALT or AST > 3xULN and (total bilirubin >2xULN or INR > 1.5)
- ALT or AST > 3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

## Clinical Review

Nhi Beasley, Pharm. D., and Melanie Blank, M.D.

NDA 204441

Tolvaptan (JYNARQUE®)

- Patients with abnormal LFTs at baseline, and ALT or AST > 2 x ULN (or a doubling of baseline) of the highest abnormal liver enzyme.

Below were instructions given to investigators at the same time that monthly LFTs were instituted:

Confirm an increase of serum ALT or AST to >3x ULN by repeat testing (of ALT, AST, ALP, and BT) within 48 to 72 hours, i.e., do not wait a week or two, because levels can change rapidly and might become normal, leading to false conclusions.

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Evaluate relevant symptom data and history of concurrent diseases and also concomitant medications including nonprescription medications, herbal, and dietary supplements, alcohol use, recreational drug use, and special diets.

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Follow subjects closely if:

- ALT or AST becomes >3x ULN (for subjects with a normal baseline value, elevations <3x ULN are common and nonspecific)
  - ALT or AST becomes >2x ULN (for subjects with an elevated baseline value).
- 

Follow up with repeat LFTs 2 to 3 times per week (decrease to once per week if abnormalities stabilize or IMP has been interrupted and subject is asymptomatic) and perform other tests of liver function, as appropriate (e.g., INR).

---

Consider interruption of IMP in the following contexts (automatic interruption of IMP upon finding an ALT or AST elevation of >3x ULN may be unnecessary, i.e., transient rises and falls of ALT or AST are common):

- ALT or AST becomes >8x ULN (no rechallenge)
- ALT or AST becomes >5x ULN for more than 2 weeks (no rechallenge)
- ALT or AST becomes >3x ULN and BT is >2x ULN or INR is >1.5
- ALT or AST becomes >3x ULN with appearance of worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia

Follow until resolution and consider IMP reinitiation (rechallenge) if appropriate.

Source: HAC liver safety report 28 Jun 2017, Appendix A

### 13.3.3. Liver eCRF

The purpose of the liver disease eCRF was to facilitate review of each subject who presented with, or developed liver abnormality during REPRISÉ and to determine the probable cause of the abnormalities. The liver eCRF was to be completed for any subject who:

- Discontinued treatment due to a liver-related AE
- Reports a serious liver-related AE
- With normal screening levels developed ALT or AST levels  $\geq$  3x ULN, or total bilirubin  $\geq$  2x ULN

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 Tolvaptan (JYNARQUE®)

- With abnormal screening liver test level develops abnormalities in that test that are > 2 x UL of their highest screening value.

### 13.3.4. Hepatic Adjudication Committee – Other Information

**Table 32. Documents and datasets reviewed related to the HAC**

Document/dataset	Period covered	Sub date
Original liver safety report 28 Oct 2012- Watkins (HAC – Paul Watkins, Neil Kaplowitz, James Lewis, David Alpers)	28 Feb 2011 – 31 Mar 2012	First NDA
Addendum 1, report 08 May 2014 – Watkins, Kaplowitz, Lewis, Alpers	01 Apr 2012 – 28 Feb 2014	NDA resub
Addendum 2, report 23 May 2015 – Alpers, Kaplowitz	01 Mar 2014 – 31 Mar 2015	NDA resub
Addendum 3, report 01 Jul 2016 – Alpers, Kaplowitz, Lewis	01 Apr 2015 – 30 Apr 2016	NDA resub
Addendum 4, report 28 Jun 2017 – Alpers, James Freston, Lewis	01 May 2016 - 30 May 2017	NDA resub
Liver adjudication clinical package, dataset heparslt		NDA resub
Liver adjudication PM package, dataset heparspm		NDA resub
Datasets: liverf (clinical trial data)		
SN 0069 letter, HAC 01 Jun 2017 to 31 Jan 2018		2/6/18
3 <sup>rd</sup> quarter summary update (+ EU report same), 19 Dec 2017		2/6/18
4 <sup>th</sup> quarter summary update (+ EU report same), 09 Jan 2018		2/6/18
Safety adjudication packages Jun 2017 – Jan 2018		2/6/18
Dataset: hepupdpm (63 postmarketing adjudication, 01 Jun 2017 to 31 jan 2018)		2/6/18 SN 0069
Dataset: hepupdct (25 clinical trial adjudication, 01 Jun 2017 to 31 jan 2018) REPRISE and extension study		2/6/18 SN 0069

#### The Drug-Induced Liver Injury Network Scale

- **Definite:** >95% likelihood. The evidence for the drug causing the injury is beyond a reasonable doubt.
- **Highly likely:** 75%-95% likelihood. The evidence for the drug causing the injury is clear and convincing but not definite.
- **Probable:** 50%-74% likelihood. The preponderance of the evidence supports the link between the drug and the liver injury.
- **Possible:** 25%-49% likelihood. The evidence for the drug causing the injury is equivocal but present.
- **Unlikely:** <25% likelihood. There is evidence that an etiological factor other than a drug caused the injury.
- **Unassessable:** Insufficient information to assess causality

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/s/  
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BACH N BEASLEY  
04/19/2018

MELANIE J BLANK  
04/19/2018

ALIZA M THOMPSON  
04/19/2018



## DIVISION OF CARDIO-RENAL DRUG PRODUCTS

### *Divisional Memo*

**NDA:** 204441 Tolvaptan to slow progression of kidney disease in patients at high risk of progression of autosomal dominant polycystic kidney disease (ADPKD).

**Sponsor:** Otsuka

**Review date:** 26 August 2013

**Reviewer:** N. Stockbridge, M.D., Ph.D., HFD-110

**Distribution:** NDA 204441

This memo conveys the Division's decision to issue a Complete Response letter for tolvaptan to slow progression of kidney disease in patients at high risk of progression of ADPKD.

This application has been the subject of reviews of CMC (Dong, 7 July 2013), biopharmaceutics (Khairuzzaman, 10 July 2013), pharmacology/toxicology (Joseph, 15 July 2013), clinical pharmacology (Sahre & Li, 2 July 2013), medical (Beasley & Thompson, 7 July 2013), statistics (Lawrence, 25 June 2013), and hepatotoxicity (Senior, 29 June 2013). There is a comprehensive CDTL memo (Grant, 25 August 2013) with which I am largely in agreement. I also acknowledge verbal and written comments from the Advisory Committee (5 August 2013) and Drs. Temple and Unger.

The Establishment inspections were completed 26 August 2013 (acceptable).

A majority of the Advisory Committee did not support approval, and approval has not been recommended by the clinical/statistical review team, or by Drs. Grant, Temple, or Unger. All have somewhat different points that they emphasize; this memo provides my perspective.

The non-peptide vasopressin V2 receptor antagonist tolvaptan (Samsca) is approved for the treatment of hyponatremia.

Tolvaptan would be the first drug approved for the treatment of ADPKD, a heritable disease in which renal cysts form and enlarge throughout life, resulting variably in pain, hypertension, abdominal distension, and loss of renal function. Where progression reaches end stage renal disease, it is in one's fifties or later. The loss of renal function is thought to result from mechanical distortion of nephrons by cysts, but whether a therapy could slow progression by decompressing cysts or only by preventing cyst proliferation is not known, so the Agency has consistently denied effects on kidney volume as an adequate surrogate for progressive loss of renal function. On the other hand, it has been the applicant's belief that early treatment, decades before end stage, was necessary to impact renal function, creating a very difficult drug development scenario.

No one, including me, is entirely comfortable with the basis for approval that evolved over years of negotiations with the sponsor and the small community of physicians that specializes in this disease. Eventually, the Division agreed to an end point that was a composite of hypertension, renal pain, albuminuria, and decline in renal function, that allowed a subject to contribute multiple end point events to the analysis, and that would be satisfied by a single study with  $p < 0.01$ , despite most of the components being not at all irreversible morbidity.

In addition, the Division accepted a smaller decline in renal function as an “event” than it has previously for other chronic kidney diseases<sup>1</sup>. Even with that, the sponsor had to deal with the fact that, acutely and apparently reversibly, renal function declines a small amount on tolvaptan<sup>2</sup>. This would have been less problematic had there not been significant (and differential) loss to follow-up over the first few weeks.

(In retrospect, it probably would have been beneficial to have had a several-month run-in phase with everyone on drug to weed out subjects incapable of dealing with the 6.5-L daily fluid passage tolvaptan invoked, before randomizing subjects to tolvaptan or placebo.)

The sponsor tried to balance the need to show some clinical benefit against the perception that treating early was important, and they did so by enrolling subjects with total kidney volume >750 mL (mean of about 1.7 L; normal is about 150 mL apiece) but preserved renal function (required GFR<sup>3</sup> > 60 mL/min; actual mean was 81 mL/min/1.73 m<sup>2</sup> at baseline<sup>4</sup>).

Despite the mutual understanding reached on the nature of the regulatory basis for approval, the sponsor’s study had a primary end point of fractional change in renal volume, which is closely allied with the proposed mechanism of action. A finding of an effect on renal volume would be supportive, so I will return to it following discussion of the results on the composite end point.

By the sponsor’s analysis, the composite end point demonstrated a HR of 0.87 (95% CI 0.78-0.97) with p=0.0095<sup>5</sup>. Of the components, there appear to be effects on renal function (HR=0.39) and renal pain (HR=0.64)<sup>6</sup>.

In addition to controversy over whether the composite end point and alpha were reasonable, there are other issues with the interpretation of the study.

1. The order of secondary end points was set after about half of the end point events were acquired.
2. The first version of the statistical analysis plan was set after about 64% of events occurred.
3. Seven percent of subjects on tolvaptan and “few” on placebo withdrew in the first few weeks so they never had a post-titration baseline renal function assessment.
4. Overall, 23% of subjects on tolvaptan and 14% on placebo withdrew from treatment and follow-up.
5. By Dr. Lawrence’s analysis, which uses a different estimate of the variance, the p-value for the primary analysis is 0.012.

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<sup>1</sup> A 25% reduction in the reciprocal of the serum creatinine, about a 33% decrease in estimated GFR.

<sup>2</sup> The protocol reviewed under the Special Protocol Assessment had no such post-randomization baseline, and apparently the sponsor sought no particular reassurance regarding the amended protocol. (There never was a SPA Agreement.) The Division became conscious of the change at the time the SAP was being finalized—after half of the events had occurred—at which time our understanding (meeting minutes dated 17 June 2009) was that the post-randomization baseline was going to be used for a sensitivity analysis, not the primary one.

<sup>3</sup> Cockcroft-Gault.

<sup>4</sup> CKD-EPI.

<sup>5</sup> An analysis of time to first event, which counts each subject only once, gives HR=0.83; p=0.005.

<sup>6</sup> The latter effect is quite small. Only 3.6% of subjects were on medication for renal pain at baseline. The mean score at baseline was <1 on a 10-point Likert scale, so most subjects must have had zero scores.

6. Subjects were censored not when information was missing on any single component of the composite end point, but only when information was missing for all components. Censoring when the composite end point could not be assessed for lack of information on any component results in  $p=0.02$ .
7. The actual mean effect of tolvaptan on loss of renal function is small. The decline is about 3.7 mL/min/1.73 m<sup>2</sup>/year on placebo and 2.7 mL/min/1.73 m<sup>2</sup>/year on tolvaptan<sup>7</sup>. Projection of this effect over decades would lead one to predict a several-year difference in time to end stage renal disease for a patient in his 40's and a reasonable chance of never reaching ESRD for someone in his 20's treated for lifetime; this is no trivial matter, but it does require a constant treatment effect manifest for many times as long we have observed data.

Despite these concerns, Drs. Beasley and Thompson conclude there is adequate evidence of a treatment effect. Drs. Lawrence and Grant do not, and I agree with them. We offered a marginal basis for approval, and if you discount the sponsor's findings the least bit for late settlement of the analysis plan, any at all for missing data<sup>8</sup>, or any at all for the variance estimate procedure, then they do not meet the prespecified criteria.

Were there supportive findings on renal volume? Renal volume was assessed at randomization and annually. Over 3 years, renal volume increased by about 250 mL on placebo and by about 100 mL on tolvaptan, a difference of about 150 mL, or about the volume of one normal kidney or 9% over three years. However, the review team shows that this effect is mostly in the first year, and it is plausibly mostly in the first few weeks<sup>9</sup> (because of decompression of cysts). Unfortunately, there are no assessments of renal volume at three weeks post-randomization or at follow-up visits post-treatment. However, based on the changes in renal volume between years 1 and 3, the effect on renal volume that might plausibly have been a true fixed difference is more like 50 mL (3%) or less.

Is there a treatment effect here? I think so, but this feels more like a study with  $p\approx 0.05$  than  $p<0.01$ . Another is needed, and it ought to be conducted in patients with more advanced disease to demonstrate that treatment is likely to be effective over a significant fraction of the disease course. Steps need to be taken to minimize loss to follow-up and to disambiguate acute, reversible and fixed, anatomical effects on the kidney.

Because it is largely sections 1 and 14 in which labeling changes would be needed, there will be no labeling attached to the action letter.

The sponsor proposed a REMS program for management of the risk of hepatotoxicity, and the Division is largely in agreement on its terms. If, as seems likely, there is a substantial lag between the Complete Response and approval for ADPKD, the sponsor can complete negotiations on the REMS for hyponatremia.

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<sup>7</sup> CKD-EPI; you get a similar magnitude using CG.

<sup>8</sup> I do not think there is a huge problem with informative censoring here. The reason for differential withdrawal was surely mostly because of polyuria/polydipsia, not disease progression or perception of other clinical benefits. Nevertheless, it does not seem appropriate to be totally indifferent to so many people missing completely or partly from the critical analysis.

<sup>9</sup> In a phase 2 study, total kidney volume was reduced by tolvaptan by 1.9% in 8 days and by 3.8% over 21 days. Assessed again 21 days following last treatment, total kidney volume was partially recovered (1.6% reduction from baseline).

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/s/  
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NORMAN L STOCKBRIDGE  
08/26/2013

## Cross-Discipline Team Leader Review

<b>Date</b>	25 Aug 2013
<b>From</b>	Stephen M Grant
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA #</b>	204441
<b>Applicant</b>	Otsuka Pharmaceutical Development & Commercialization, Inc.
<b>Date of Submission</b>	1 March 2013
<b>PDUFA Goal Date</b>	1 September 2013
<b>Proposed Proprietary Name/ Established (USAN) name</b>	(b) (4) tolvaptan
<b>Dosage form/Strengths</b>	Immediate release tablet/ 15, 30, 45, 60, & 90 mg
<b>Proposed Indication</b>	To slow kidney disease in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease
<b>Recommended Action</b>	Complete Response

<b>Material Reviewed:</b>	<b>Names of discipline primary reviewers:</b>
<b>CMC</b>	Zedong Dong
<b>Biopharmaceutics</b>	Akm Khairuzzaman
<b>Pharmacology Toxicology</b>	Xavier Joseph
<b>Clinical Pharmacology</b>	Martina Sahre (clinical pharmacology) Fang Li (pharmacometrics)
<b>Clinical</b>	Aliza Thompson (efficacy) Nhi Beasley (safety)
<b>Statistical</b>	John Lawrence
<b>OSE/Hepatic Safety</b>	John Senior
<b>OSE/DRISK</b>	Kimberly Lehrfeld, Danielle Smith
<b>OSE/DMEPA</b>	Kimberly De Fronzo
<b>OSI</b>	Sharon Gershon
<b>Project Management</b>	Anna Park

OND = Office of New Drugs

OSE = Office of Surveillance and Epidemiology

DMEPA = Division of Medication Error Prevention and Analysis

DRISK = Division of Risk Management

OSI = Office of Scientific Investigations

## 1 Introduction

Tolvaptan is a selective vasopressin V2-receptor antagonist approved in May 2009 under NDA 22275 for the treatment of clinically significant hypervolemic and euvolemic hyponatremia and marketed as SAMSCA<sup>®</sup>. Otsuka Pharmaceutical Development & Commercialization, Inc. (Otsuka) has submitted NDA 204441 seeking authorization to market tolvaptan (proposed trade name (b) (4)) for the following indication:

(b) (4) (tolvaptan) is indicated to slow kidney disease in adults at risk of rapidly progressing ADPKD.”

To support the efficacy and safety of tolvaptan for this indication, the application relies on the results of a single randomized, placebo-controlled trial 156-04-251, “A Phase 3, Multi-center, Double-blind, Placebo-controlled, Parallel-arm Trial to Determine Long-term Safety and Efficacy of Oral Tolvaptan Tablet Regimens in Adult Subjects with Autosomal Dominant Polycystic Kidney Disease” (hereafter termed in this review as “study 251” but also referred to in other documents as “TEMPO”). The objective was to demonstrate that administration of tolvaptan to patients with ADPKD slowed the progression of the renal complications of autosomal dominant polycystic kidney disease (ADPKD). The primary endpoint was a comparison of change in total kidney volume (TKV) of tolvaptan to placebo subjects over a 36 month observation period. The Division’s consistent position was that TKV was an unproven surrogate whose relationship to a clinical benefit was unknown. The Division and Otsuka reached an understanding that the trial could provide adequate efficacy support to file an NDA only if the first secondary endpoint (hereafter referred to in this review as the efficacy endpoint but referred to elsewhere by a variety of terms), a composite of four events thought to be manifestations of worsening renal disease in ADPKD (worsening renal function, renal pain events, worsening in category of hypertension, and worsening in category of albuminuria), was successful at a p-value < 0.01. 1445 patients with no more than mild-moderate renal dysfunction but considered at high risk for suffering one or more of the consequences of ADPKD because of large TKV were randomized 2:1 to tolvaptan or placebo over about two years and followed for a fixed period of three years. After completion of the trial, the pre-specified analysis of the composite endpoint resulted in a p-value of about 0.01. Another pre-specified analysis to determine the effect of tolvaptan on the decline in glomerular filtration rate (GFR) indicated the decline was slowed by about 1 mL/min/1.73m<sup>2</sup> per year.

Despite the apparently statistically successful result, the review team has recommended that this NDA not be approved at the current time. The following concerns were raised during the review:

1. The baseline measurement used to determine the effect of tolvaptan on GFR was not collected at the time of randomization but rather about three weeks after randomization potentially introducing bias. If data collected at randomization are used as the baseline measurement, then tolvaptan does not appear to have any effect on the decline in GFR after 36 months at the end of the treatment period.
2. The protocol stipulated that subjects who discontinued study drug no longer were followed at an investigative site and so the occurrence of major efficacy outcomes was not collected. Nearly a quarter of tolvaptan subjects and an eighth of placebo subjects discontinued so confidence in the apparent results is lessened by the potential

bias introduced by the loss of subjects who might have had different outcomes had they remained in study 251. Sensitivity analyses meant to explore how robust the results of the efficacy (first secondary) endpoint analysis are to missing data from the subjects who discontinued study drug are not reassuring.

3. The outcomes measured in study 251 were not death or irreversible morbidity. A single trial with endpoints that do not include death and/or irreversible morbidity, does not provide adequate evidence for approval.
4. Otsuka and the reviewers agree that tolvaptan caused clinically significant but reversible hepatocellular injury in three ADPKD subjects in study 251 and its companion extension study. They further agree that based on historical data and in the absence of measures that reduce the risk, tolvaptan is likely to cause severe liver injury resulting in death or transplantation in 1 in 3000 patients. Despite a plan to mitigate this risk with monthly monitoring of serum transaminases, the demonstrated benefit is not commensurate with the risk.

## 2 Background

### 2.1 Tolvaptan

- Tolvaptan prevents binding of arginine vasopressin to the V<sub>2</sub>-receptor, thereby reducing the activity of vasopressin. It is selective for the V<sub>2</sub>-receptor with an affinity for binding about twice that of native arginine vasopressin and has much lesser affinity for the V<sub>1a</sub>-receptor.
- Antagonizing the effect of vasopressin at the V<sub>2</sub>-receptor causes an increase in free water clearance with a consequent decrease in urine osmolality. The increase in free water excretion results in polyuria/pollakuria and thirst, which limit tolerability.
- Tolvaptan exhibits dose proportional pharmacokinetics following single doses of 15 to 120 mg. Repeat doses given twice a day for 5 days also demonstrate proportional increases in exposure and little accumulation at steady state.
- Peak concentrations of tolvaptan are observed between 2 and 4 hours after oral dosing.
- Tolvaptan is eliminated entirely by non-renal routes and mainly, if not exclusively, metabolized by CYP 3A.

### 2.2 ADPKD

- ADPKD is a serious illness that results in kidney failure resulting in end-stage renal disease (ESRD) in approximately 50% of ADPKD patients, typically in the fourth to sixth decade of life. More than 2000 Americans with ADPKD begin dialysis each year and ADPKD is the reason for dialysis in 7 – 10% of patients on dialysis.
- While progression to ESRD takes decades, other renal manifestations appear earlier. Hypertension frequently develops during early adulthood (even during childhood). Pyelonephritis and renal-cyst infections can be serious problems requiring aggressive antimicrobial therapy. Other renal manifestations include pain, kidney stones, and hematuria.
- A review article (*NEJM 2008 359:1477*) states 300,000 to 600,000 Americans have ADPKD. However, FDA's Office of Orphan Drug products granted tolvaptan orphan

status for ADPKD because they concurred with Otsuka's assertion that the prevalence of clinically manifest ADPKD is less than 200,000 Americans.

*Reviewer's comment: Interestingly the author of the NEJM paper is the same person who provided the estimate upon which the Office of Orphan Products based its decision to grant tolvaptan orphan status.*

- ADPKD is caused by mutations in either of two genes encoding polycystin 1 (85% of cases) and 2 (15%), which regulate tubular and vascular development in kidneys or elsewhere. As the name indicates, ADPKD is inherited in an autosomal dominant fashion, arising as a spontaneous mutation in approximately 5% of cases. Disease expression can vary markedly even within families indicating that other mechanisms besides mutations in the genes encoding polycystin 1 and 2 are important to determining clinical outcomes.
- Affected patients have numerous fluid-filled cysts in the kidneys that multiply and enlarge over time with consequent massive kidney enlargement. Some authorities (*Nat Rev Nephro* 2011; 7:556) believe that the compression of renal architecture causing nephron loss by cysts is primarily responsible for the decline in glomerular filtration rate.

*Reviewer's comment: If true, then reducing growth of cysts and/or decreasing the rate of new cyst formation (which can be measured as a decrease in the rate of TKV expansion) should slow the progression of kidney dysfunction. However, TKV did not correlate with changes in kidney function in a clinical study (NEJM 2010; 363:830) in which 433 ADPKD patients were randomized 1:1 to everolimus or placebo for two years. TKV in everolimus subjects increased less (absolute difference of - 71 ml;  $p = 0.06$ ) but their decline in glomerular filtration rate was greater (absolute difference of + 1.2 ml/min/1.73 m<sup>2</sup>;  $p = 0.15$ ).*

### **2.3 Available Therapy**

ADPKD is a serious illness with unmet medical need. There are no drugs or other therapeutic products approved (or used significantly off-label) to slow kidney disease in adults with ADPKD. Patients with advanced ADPKD undergo dialysis and transplant to manage end-stage renal disease and symptomatic therapy for other manifestations.

*Reviewer's comment: NDA 204441 is the first NDA submitted for a product intended to slow the rate of progression of kidney dysfunction in patients with ADPKD. There was no precedent for the population studied, endpoints, and statistical persuasiveness required in the clinical trial.*

*The Division required that a single trial with this endpoint be successful at a  $p$ -value  $\leq 0.01$  to provide adequate support of efficacy for an NDA submission. Three of the four components for study 251, hypertension, albuminuria, and renal pain, are of much lesser clinical import than (b) (4) trial. Even the fourth component of study 251 is a smaller magnitude of increase in serum creatinine (100% vs. 33% in study 251). To date, the Division has never accepted avoidance of an increase in serum creatinine as small as 33% as the basis for approval of a drug for chronic kidney disease. Hence based on regulatory precedent, the Divisional requirement that*

*study 251 be successful at a p-value of < 0.01 to provide adequate evidence of efficacy for this NDA could be characterized as generous.*

## 2.4 Presubmission Regulatory Activity

Date and type	Important discussion/agreements/information
16 March 2005 Pre-IND meeting	<ul style="list-style-type: none"> <li>• “The Agency does not, at this time, agree that the rate of change in total renal volume is an acceptable endpoint for approval of the proposed indication. It would be necessary to show evidence of actual improvement (e.g., slowing rate of change in renal function) to be approved...”</li> </ul>
29 September 2005 No agreement SPA letter	<ul style="list-style-type: none"> <li>• Subjects withdrawn for any reason should be followed for outcomes until the end of the study.</li> <li>• The analysis of the primary endpoint will need a conservative plan for handling excess withdrawals from the tolvaptan treatment arm.</li> </ul>
15 November 2005 Meeting to discuss SPA letter	<ul style="list-style-type: none"> <li>• Otsuka proposed a composite endpoint consisting of hypertension, proteinuria, nephrolithiasis, and renal pain as a “key” secondary endpoint</li> <li>• “The Agency recommended that Otsuka encourage patients to continue with the monitoring and follow-up (including MRIs) as described in the protocol, even if they choose to discontinue study drug/placebo.”</li> </ul>
03 April 2006 Study 251 protocol submitted	<ul style="list-style-type: none"> <li>• Includes first secondary endpoint that is a composite of worsening renal function, renal pain events, worsening in category of hypertension, and worsening in category of albuminuria</li> <li>• Defines the baseline value for serum creatinine for the analysis of events of worsening of renal function as that obtained at baseline but does stipulate the end-of titration value as baseline for the analysis of change in GFR</li> </ul>
25 May 2007 First amendment to Study 251 protocol submitted	<ul style="list-style-type: none"> <li>• Defines the baseline value for serum creatinine for the analysis of events of the worsening of renal function as that obtained at end-of titration. The rationale for the change is discussed in “Modifications to Protocol” in a different section from the one actually changed. The cover letter indicates the changes made are minor and made in response to comments from the Division and does not mention that the baseline value for serum creatinine has been changed.</li> </ul>
10 June 2009 Meeting to obtain Divisional input into proposed SAP	<ul style="list-style-type: none"> <li>• The Division stated it was important to establish whether tolvaptan’s effect on the secondary endpoint events persists when treatment is discontinued noting “if the benefits persist, it would be easier to believe that tolvaptan therapy led to a change in the underlying renal anatomy/disease process” and proposes measuring key endpoints at a follow-up visit after subjects are off study medication. Otsuka agrees.</li> <li>• The Division stated and Otsuka accepted that the composite key secondary endpoint will need a p-value &lt; 0.01 to “provide convincing evidence of treatment benefit.”</li> </ul>
19 July 2012 Pre-NDA meeting	<ul style="list-style-type: none"> <li>• The Division reaffirmed that they consider the rate of change in total renal volume an unvalidated surrogate, so it would not play a role in the decision whether to approve tolvaptan for treatment of ADPKD.</li> </ul>
13 Nov 2012 IND submission	<ul style="list-style-type: none"> <li>• Otsuka proposes a risk mitigation plan that includes a report from a Hepatic Adjudication Panel, which concludes that tolvaptan administered to patients with ADPKD is likely to cause severe liver injury in ~1/3000 patients</li> </ul>

*Reviewer's comment: The important aspects of the presubmission regulatory activity can be summarized as follows:*

- 1. The Division consistently and repeatedly stated that change in TKV could not provide important support for the efficacy of tolvaptan for treatment of ADPKD because the relationship between change in TKV and clinical outcomes is unknown.*
- 2. The Division and Otsuka were aware that tolvaptan's effect on urine output and frequency would likely result in a substantial number of subjects randomized to tolvaptan in study 251 discontinuing study drug. Otsuka was urged to design and conduct study 251 so that all randomized subjects, not just those who remain on study drug, were followed in the same manner.*
- 3. Tolvaptan was known to cause an acute decrease in GFR that was thought not a result of irreversible kidney damage. However there was no explicit discussion of how to design study 251 so that the chronic effect of tolvaptan on ADPKD could be distinguished from its acute, and presumably reversible, effects. The original protocol for study 251 stipulated the worsening of renal function component of the efficacy (first secondary) endpoint be analyzed as change from baseline in serum creatinine. In the first amendment to the protocol Otsuka altered this analysis to change the "baseline" to the measurement obtained at end-of titration without bringing the change to the attention of the Division.*
- 4. Otsuka proposed a secondary endpoint composed of several events that occur as a consequence of ADPKD be used to demonstrate clinical efficacy. Otsuka appears not to have had information to use for predicting the incidence rates of these events in an untreated population or for estimating the size of the effect of tolvaptan on these events.*
- 5. In 2009 (i.e., well after study 251 was initiated) the Division and Otsuka agreed that this composite secondary endpoint would need to be successful at a p-value < 0.01 for the trial to provide adequate evidence to support an NDA based on a single trial. It is unclear how a value of 0.01 was chosen.*
- 6. Advice from the Division appears to have been predicated on the assumption that no new major safety concerns were likely to arise because tolvaptan had already been administered in several clinical studies during its development for hyponatremia.*

### **3 CMC**

The CMC reviewers concluded that the applicant's proposed manufacturing (and associated analytic methods) of the drug product and drug substance are acceptable. The overall EES status of the manufacturing sites is pending. Stability results support an initial expiry of 30 months for the 45-mg and 90-mg tablets.

#### **3.1 General product quality considerations**

The 15, 30, and 60-mg immediate release tablets were previously approved in NDA 22-275 so the only strengths reviewed were the two new strengths, 45-mg and 90-mg tablets. The formulation compositions of the two new strengths are proportional to the approved 60-mg tablet and the manufacturing process, equipment and in-process controls are similar. The specifications of the 45-mg and 90-mg tablets are similar to the other currently approved strengths. The analytical procedures for the 45-mg and 90-mg tablets are also the same as those for the approved strengths.

### **3.2 Facilities review/inspection**

The overall EES status of the manufacturing sites is pending at the time of this review.

## **4 Nonclinical Pharmacology/Toxicology**

The pharmacology/toxicology review concludes that there are no outstanding pharm/tox issues that preclude approval. The nonclinical pharmacology and toxicology studies were reviewed previously prior to the approval of marketing tolvaptan for treatment of hyponatremia under NDA 22275. A few pharmacology studies of the effects of tolvaptan in animal models of ADPKD were submitted and reviewed under the current NDA. Also, a six-week toxicity study of tolvaptan in juvenile rats was submitted and reviewed. This toxicity study was performed to support a clinical study of children with hyponatremia; therefore it is not pertinent to this NDA.

## **5 Clinical Pharmacology**

The clinical pharmacology reviewers conclude that there are no outstanding clinical pharmacology issues that preclude approval.

The clinical pharmacology of this drug has been previously reviewed under NDA 22275 and is summarized above in section 2.2. 10 new clinical pharmacology studies as well as clinical pharmacology data from study 251 were submitted in NDA 204441 and reviewed. In general these studies did not add significantly to what was previously known about the clinical pharmacology of tolvaptan. A single titrated dose regimen was tested in study 251, which confounded the pharmacometric analyses and so limited the utility of those analyses for exploring the relationship of dose to safety and efficacy. Two aspects of the clinical pharmacology program for ADPKD are important for this application and are reviewed below.

### **5.1 Acute Effect of Tolvaptan on GFR**

Otsuka states in the section detailing the rationale for study 156-09-284 that laboratory tests from previous clinical studies indicate that tolvaptan causes a “small but significant reduction in serum blood urea nitrogen levels with a concomitant increase in uric acid and a transient increase in serum creatinine concentrations.” It continues that “the reversibility of effects on renal hemodynamics after withdrawal of tolvaptan (is) unknown.” To assess the magnitude and reversibility of the effect of tolvaptan on GFR, in 2010-2011 Otsuka conducted study 156-09-284, in which ADPKD subjects with varying levels of renal function at baseline were titrated to a dose of 90 mg of tolvaptan in the morning and 30 mg in the afternoon over three weeks and then GFR was measured. Then tolvaptan was discontinued and renal function was assessed again three weeks later. The results are shown in the table below (adapted from study 156-09-284 CSR Table 9.3.3.1-1 as corrected by Dr. Sahre, the clinical pharmacology reviewer):

**Mean (SD) Measured GFR at Baseline, after 3 Weeks of Tolvaptan Treatment, and 3 Weeks after Treatment is Discontinued in Study 156-09-284**

	Subjects ≥ 60 mL/min/1.73 m <sup>2</sup> (N = 9)	Subjects ≥ 30 & <60 mL/min/1.73 m <sup>2</sup> (N = 9)	Subjects < 30 mL/min/1.73 m <sup>2</sup> (N = 9)
	Measured GFR (mL/min)		
Baseline	<b>112.3 (20.3)</b>	<b>66.3 (20.3)</b>	<b>29.3 (10.6)</b>
After 3 Weeks of Treatment	<b>104.3 (22.7)</b>	<b>60.1 (16.6)</b>	<b>28.6 (10.0)</b>
Change from Baseline	-8.0 (9.1)	-6.2 (6.2)	-0.7 (1.5)
Percent Change	-7.4 (8.7)	-8.4 (6.8)	-2.1 (5.5)
3 Weeks Post Treatment	<b>112.3 (23.1)</b>	<b>64.8 (18.1)</b>	<b>26.9 (9.3)</b>
Change from Baseline	0.1 (4.9)	-1.5 (4.0)	-2.4* (4.6)
Percent Change	-0.3 (4.8)	-1.4 (5.2)	-5.7* (4.6)

\* Reported in the CSR for study 156-09-284 as -1.2 and -2.6, respectively

*Reviewer's comments:*

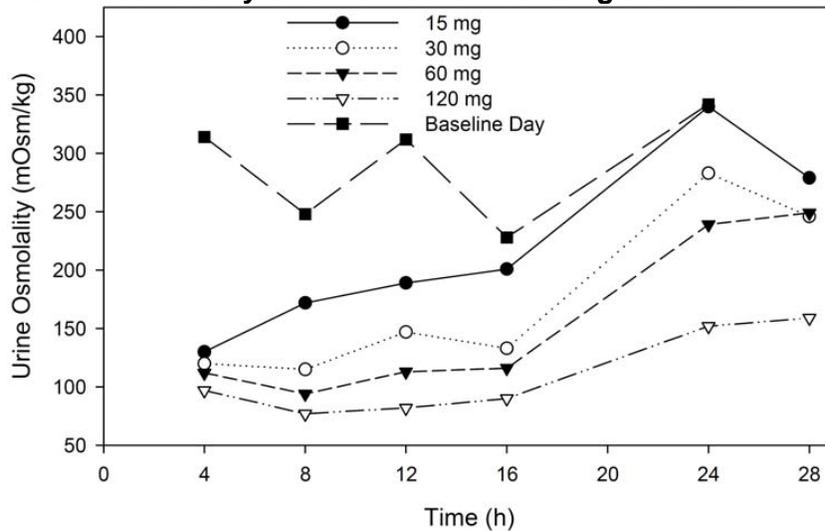
- The small numbers of subjects studied, the large standard deviations of the observed data, and the variability in outcomes among subjects with differing severities of renal dysfunction result in a fair amount of uncertainty about the significance of these observations.*
- The observed data from Study 156-09-284 are compatible with Otsuka's conclusion that on average administration of tolvaptan for a few weeks results in a small but reversible decrease in GFR in patients similar to those enrolled in study 251 (i.e., GFR ≥ 60 ml/min). However even if true, the applicability of this observation to effects caused by chronic administration of tolvaptan is unclear. For example, it is unclear if the effect changes over time and how the effect changes in the later stages of renal dysfunction. The acute reduction in GFR caused by tolvaptan may not be reversible in all stages of CKD caused by ADPKD.*

## **5.2 Dose Selection**

Otsuka presumed that to have a significant clinical effect in ADPKD vasopressin activity needed to be suppressed throughout the interdosing interval; they had some support for this hypothesis from studies in animal models of ADPKD. They further knew from the clinical studies previously conducted in patients with hyponatremia that tolerability was limited by polyuria/pollakuria. Hence they decided to test regimens in which a higher dose is administered in the morning and a lower dose in the afternoon so that patients' sleep will not be disturbed.

Otsuka conducted study 156-04-248 in Oct 2004 to determine the effect of single doses of tolvaptan on urine osmolality in patients with ADPKD to help select the total dose to be studied in ADPKD patients. Urine osmolality was used as a marker of vasopressin activity; a dilute (< 300 mOsm/kg) urine indicates reduced vasopressin activity. A figure taken from the Dr. Sahre's review displaying the results is shown below:

### Mean Urine Osmolality Over 28 Hours After Single Oral Doses of Tolvaptan



*Reviewer's comment: Not surprisingly the higher the dose of tolvaptan administered the longer the duration of suppression of vasopressin activity because suppression is concentration dependent. However, the data from 248 do not address the more important question of the degree and duration of suppression required to slow maximally the progression of renal dysfunction in ADPKD patients. The aquaretic effects of tolvaptan limit tolerability. If a lower dose is equally effective, it will provide better outcomes because more patients will be able to tolerate it.*

## 6 Clinical Microbiology

N/A

## 7 Clinical/Statistical- Efficacy

### 7.1 Design of Study 251

**Design:** International, “double-blind,” placebo controlled, parallel arm trial of administering a single regimen of tolvaptan or placebo to adult subjects with ADPKD

*Reviewer's comment: It is likely that many subjects and investigators were unblinded by the polyuria/pollakuria caused by tolvaptan. In study 156-09-284 ADPKD patients with no more than mild renal dysfunction administered the same regimen of tolvaptan tested in study 251 more than tripled their urine output from about 2 L/day to over 6 L/day. This magnitude of increase in urine output must have been perceptible as a change from normal.*

**Objective:** To provide such compelling evidence that tolvaptan slows the progression of the renal complications of ADPKD that as a single trial it provides adequate evidence of efficacy for approval to market tolvaptan for this indication

**Synopsis:** Up to 1500 adult subjects with ADPKD were randomized 2:1 to tolvaptan or placebo. In the first three weeks subjects were force titrated as tolerated to split doses of 90 mg in the morning and 30 mg about nine hours later. Subjects were followed for a fixed observation period of 36 months during which they were seen at the investigative sites about every four months for collection of adverse events and various efficacy measurements.

Subjects who discontinued taking study drug did not have site visits but were followed by phone contact and so could not contribute events to the analysis of the endpoint intended to show tolvaptan had a clinical benefit (i.e., the first secondary endpoint – see below). After the second protocol amendment in 2009, subjects had two site visits within 42 days after the end of the 36 months of study drug administration, primarily for collection of blood and urine to measure renal function.

*Reviewer's comment: Subjects who discontinued investigational product were not followed for major efficacy outcomes and so the resulting analysis is not ITT (i.e., does not include all outcomes for every subject based on randomized treatment assignment in the analysis). To avoid potentially biasing results, all subjects should be followed similarly even if they are no longer taking study drug. Unequal follow-up is especially problematic when drop-outs are likely to be higher in subjects randomized to the drug being tested, as was almost certainly going to be the case here.*

**Dosing:** Subjects were administered tolvaptan 45 mg qAM and 15 mg about nine hours later during the first week. They were then titrated to 60/30 mg the second week and to 90/30 mg the third week as tolerated. The intent was for subjects to remain on 90/30 mg for the remainder of the 36 month observation period but subjects could be down-titrated based on tolerability.

**Eligibility Criteria:** Notable eligibility criteria were the requirement for a total kidney volume of > 750 ml (volume of a single normal kidney ~ 150 ml) and GFR  $\geq$  60 ml/min estimated by the Cockcroft-Gault formula.

*Reviewer's comments:*

- 1. Progression of renal disease in ADPKD is correlated with kidney size so selecting patients with larger kidney sizes was an enrichment strategy meant to increase the probability that subjects will have endpoint events.*
- 2. Excluding patients with more than mild-moderate renal dysfunction may have had the perverse effect of enriching for patients less likely to have endpoint events and almost guaranteed that no subject would progress to ESRD. Based on advice from experts in ADPKD, Otsuka asserted that tolvaptan could not slow progression of renal disease in the later stages of ADPKD because the damage is so severe that it is self-perpetuating. The eventual data from study 251 suggest the effect of tolvaptan was similar in subjects with National Kidney Foundation stage 3 chronic kidney disease as in subjects with lesser degrees of renal dysfunction, suggesting such patients could have been included. Before the development of drugs that substantially reduce mortality in heart failure, some experts similarly hypothesized that drugs would not be effective in later stages of heart failure. This hypothesis was wrong and in fact angiotensin converting enzyme inhibitors were initially shown effective in reducing mortality in trials enrolling patients with advanced disease.*

**Primary Endpoint:** Change from baseline in TKV

*Reviewer's comments:*

- 1. The Division stated consistently and repeatedly that this endpoint measured a putative surrogate whose relationship to a clinical benefit was not known so that it could not provide much support for the efficacy of tolvaptan.*

2. *Retention of TKV as the primary endpoint resulted in a trial optimally designed to demonstrate that tolvaptan slowed the rate of increase in TKV but not optimally designed to demonstrate the clinical benefit required to support approval to market tolvaptan. For example, it necessitated periodic MRIs, which some individuals find unpleasant and so may have been a disincentive to enroll or to continue participation once enrolled.*

**Efficacy (first secondary) Endpoint:** A composite of four events thought to reflect progression of renal dysfunction in ADPKD:

1. Worsening in GFR measured as a 25% decrease in the reciprocal of serum creatinine (equivalent to about a 33% increase in serum creatinine),
2. Worsening in category of hypertension,
3. Worsening in category of albuminuria,
4. Events of renal pain requiring medical intervention.

*Reviewer's comment: Otsuka and the Division agreed that the first secondary endpoint could provide adequate efficacy support to file an NDA if successful at a p-value < 0.01. The four components of this endpoint differ greatly in clinical import. Decreasing the frequency of pain is a clinical benefit (although this component included events relieved by acetaminophen, so rather minor pain events were counted). On the other hand, albuminuria is really a biomarker and a delay in worsening of the category of albuminuria is not a clinical benefit or known to result in a clinical benefit. The clinical import of the events differed so greatly, they should not have been components of a single endpoint in the absence of any knowledge of their frequency and the effect of tolvaptan on each.*

**First Non-composite Secondary Endpoint:** Rate of change in GFR

**Analyses:**

- Analysis of the primary endpoint was a comparison of the change from baseline in TKV as measured by MRI in observed cases.
- Analysis of the efficacy (first secondary) endpoint was time to multiple events using the Andersen-Gill formulation of the Cox proportional hazards model method. The observation period for hypertension, albuminuria, and renal pain events was the entire 36 months of the double-blind study period. But for the worsening in GFR events the observation period was from the end of titration (approximately the end of week 3) to the end of the 36-month observation period. A pre-specified sensitivity analysis differed in that the end of titration period was used as baseline for all four components.

*Reviewer's comments:*

1. *Incredibly the original protocol for the trial was amended so that the analysis of the endpoint intended to demonstrate clinical efficacy was not ITT but rather, for the worsening in GFR events, based on data from a population that did not include all randomized subjects, i.e., included only those subjects who had taken either tolvaptan or placebo for three weeks after enrollment. Presumably Otsuka amended the original protocol to separate the acute but reversible increase in GFR caused by tolvaptan (as discussed in section 5.1 above) from the chronic effects. However, analyzing a post-randomization population altered by loss of subjects (and it was likely that many more tolvaptan than placebo subjects would discontinue study medication) and by three weeks of exposure to different study drugs was not an acceptable mechanism for separating these effects. A run-in period in which all subjects were titrated to maximum tolerated tolvaptan*

*with subsequent randomization would have excluded subjects unable to tolerate tolvaptan and would have provided baseline values for an ITT analysis.*

2. *Angiotensin converting enzyme inhibitors and angiotensin receptor blockers also cause an acute but reversible increase in GFR (of a greater magnitude than tolvaptan's effect). Nonetheless in the trials that demonstrated their utility for slowing the progression of diabetic nephropathy, the baseline values from the subjects as randomized were used in the analysis, not post-randomization values. So based on regulatory history alone, Otsuka should have sought the Division's input when they altered the original protocol.*

- Analysis of Second Secondary Endpoint was a comparison of change of rate of change in GFR from the end of titration to last on-drug visit using 1/serum creatinine as the measure for determining GFR.

## **7.2 Conduct of Study 251**

- 1445 subjects were randomized at 129 sites in 15 countries, including countries in North America and Europe as well as Argentina, Australia, and Japan. 379 subjects were enrolled in the United States, which was the country with the largest enrollment.
- Dates of major trial events:

Event	Date
First patient, first visit	01 Mar 2007
First protocol amendment	28 Mar 2007
Last patient randomized	05 Jan 2009
Second protocol amendment	10 Sept 2009
Last patient, last visit	23 Jan 2012
Final statistical analysis plan	02 Apr 2012
Data lock	12 Apr 2012
Unblinding	13 Apr 2012

- At the end of titration (about the end of the third week of the trial), almost 7% of subjects randomized to tolvaptan but few of the placebo subjects had stopped taking study drug.
- Of the 961 subjects randomized to tolvaptan, 221 (23%) did not remain on study drug for the entire 36 months and so by protocol were not being followed for components of the first secondary efficacy endpoint. Of the 484 subjects randomized to placebo 67 (14%) did not remain on study drug. The reason for discontinuing study drug was collected and mostly the reasons listed for tolvaptan subjects leaving the trial were symptoms attributable to intolerance of tolvaptan's aquaretic effects, i.e. polyuria/pollakuria and thirst.

### *Reviewer's comments:*

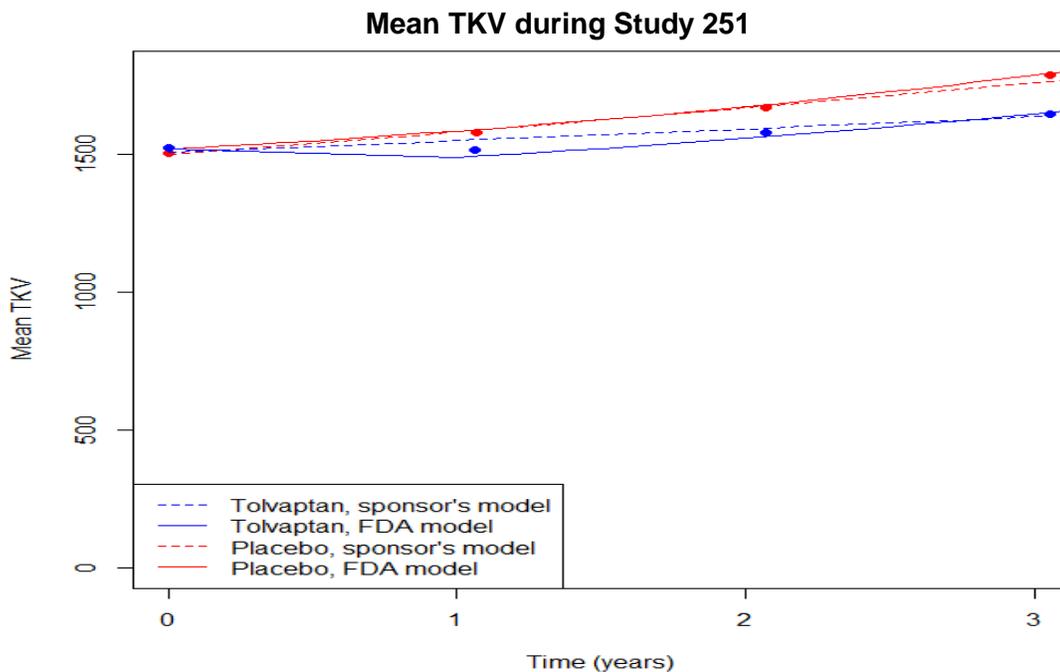
- *The reason for subject withdrawal can never be known with certainty and the contribution of lack of efficacy (especially in a trial that could not be well blinded) or another adverse effect not recorded cannot be excluded. Subjects who perceived a lack of efficacy may have been more likely to find the aquaretic effects intolerable. And the known intolerability of the aquaretic effects may have biased investigators to list them as the reason for*

*withdrawal even if subjects reported it as just one of more than one reasons for withdrawal.*

- *That almost 14% of the placebo subjects stopped taking study drug is striking and indicates that there was an inadequate effort to keep subjects in study 251 on assigned study drug. There do not appear to have been protocol-specified procedures intended to keep subjects on study drug. Placebo subjects did not have adverse events related to study drug, ADPKD is a serious condition, and there is no therapy (approved or unapproved) to prevent progression of kidney disease so there is no obvious reason for placebo subjects to discontinue study drug at such a high rate.*

### 7.3 Results in Study 251

**Primary Endpoint:** Study 251 demonstrated that administration of tolvaptan results in a statistically significant reduction in the rate of increase in TKV. Over three years tolvaptan reduced the percentage increase in TKV compared to placebo by about 9% so compared to placebo the mean absolute increase in TKV in tolvaptan subjects was about 150 ml less than in placebo subjects. Otsuka states that most of the difference is due to a decrease in kidney size in the first year (in the advisory committee meeting Otsuka asserted most of the decrease occurred in the first few weeks so presumably this was an acute and possibly reversible effect) but that a much smaller effect on slowing of the increase in kidney size was detectable in the second and third years. Dr. Lawrence (the statistical reviewer) demonstrates that the data are compatible with an acute effect during the first year with minimal effect after that. He estimates that of 150 ml difference in TKV, about 100 ml is an acute decrease in TKV with an about 50 ml smaller increase in TKV compared to placebo over the next two years; his analysis is shown in the figure below adapted from his review.



*Reviewer’s comments:*

1. *Dr. Lawrence’s analysis may overstate the chronic effect of tolvaptan on TKV. If the acute effect of tolvaptan is a reduction of TKV that occurs within the first few weeks of administration, then the slopes of the initial decline and subsequent rise in the tolvaptan subjects in the figure above should be steeper with perhaps a 100 ml decrease in the first month and a 50 ml smaller increase in TKV compared to placebo over three years (not two as shown above).*
2. *The effect of tolvaptan on the increase in TKV is not only small (no more than a 10% decrease in kidneys that are many times the normal size) but it is not sustained. A reduction of the increase in TKV over two or three years of only 50 ml does not support the hypothesis that upon which this development plan was based, i.e. tolvaptan has a significant effect on worsening of renal function via slowing the rate of increase in TKV.*
3. *Tolvaptan’s acute effect must be caused by a reduction in cyst volume and Otsuka does not supply data showing that having smaller cysts (as opposed to fewer cysts) is an important determinant of clinical outcomes. The report cited above (NEJM 2010; 363:830) demonstrates that administration of at least one drug to patients with ADPKD that slows the increase in TKV was observed to result in a greater decrease in GFR compared to placebo. Even a single failure of a putative surrogate endpoint to correlate with the anticipated clinical benefit undermines the persuasiveness of the endpoint as a surrogate. However, the correct conclusion may be that the effect on TKV observed in the everolimus study and study 251 were so small that they are not adequate tests of the hypothesis that TKV is useful as a surrogate.*

**Efficacy (first secondary) Endpoint:** The result of the prespecified analysis of the efficacy (first secondary) endpoint is that the trial was statistically successful at the agreed-upon p-value of < 0.01. However, the result is marginal; Otsuka asserts that the correct p-value is 0.0095. Dr. Lawrence asserts that a more appropriate calculation of the variance than that used by Otsuka results in a p-value of 0.012. The p-values for time to multiple events and time to first event using the prespecified analysis and the prespecified sensitivity analysis (which uses the end of titration period as baseline for all four components) are shown in the table (adapted from study 251 CSR CT-5.2.1.2.1, CT-5.2.1.1.2, & CT-5.2.1.2.2) below:

**Nominal P-Values for Time to Multiple and First ADPKD Events Using EOT as Baseline for GFR Worsening only or All Events in Study 251**

Baseline measurement	Time to multiple events	Time to first event
	nominal p-value	
EOT as baseline for GFR component only	<b>0.01</b>	<b>0.005</b>
EOT as baseline for all four components	<b>0.02</b>	<b>0.08</b>

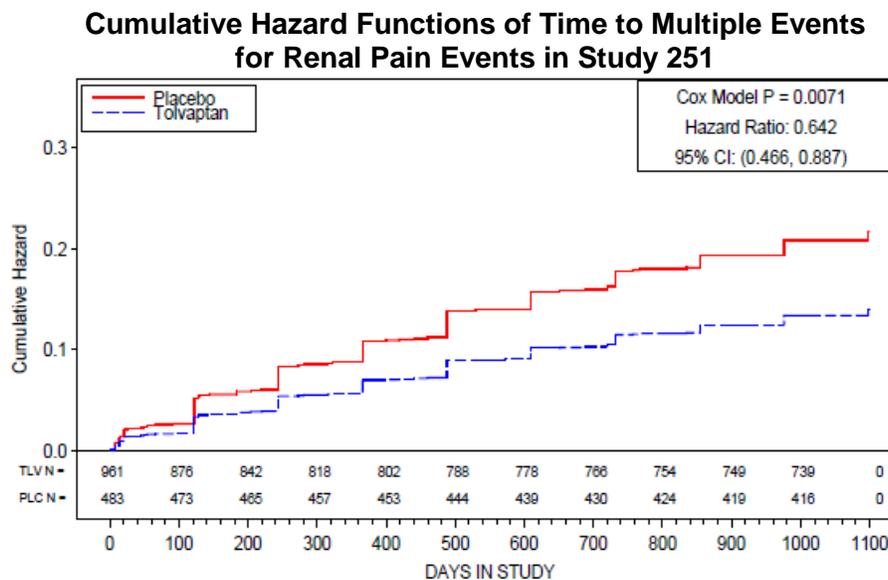
EOT = end of titration (about end of week 3)

Another sensitivity analysis performed by Otsuka to estimate the effect of missing data assumed that tolvaptan subjects who discontinued study drug had the same outcomes as placebo patients (i.e., returned to baseline but did not have worse outcomes, a not overly conservative assumption). The p-value for that analysis is 0.04.

*Reviewer’s comments:*

1. *Changing the observation period by three weeks in a well-conducted three year trial of a drug intended as chronic treatment for a chronic disease should not change the statistical significance much but it does here, especially the analysis of the time to first event.*
2. *It would be unreasonably stringent to require sensitivity analyses to meet the same p-values as the analysis being examined. But here the sensitivity analyses were prespecified and the p-values are much higher than the rather marginally significant p-value for the analysis being explored.*

The observed effect of tolvaptan on each of the four components of this endpoint varied considerably. Little or no effect was observed on events of hypertension or albuminuria. The analysis of renal pain events requiring medical intervention indicates that tolvaptan subjects had nearly 35% reduction in the risk for these events over the 3 years of study 251; the results are displayed in the figure below (from study 251 CSR fig 9.3.4-1):



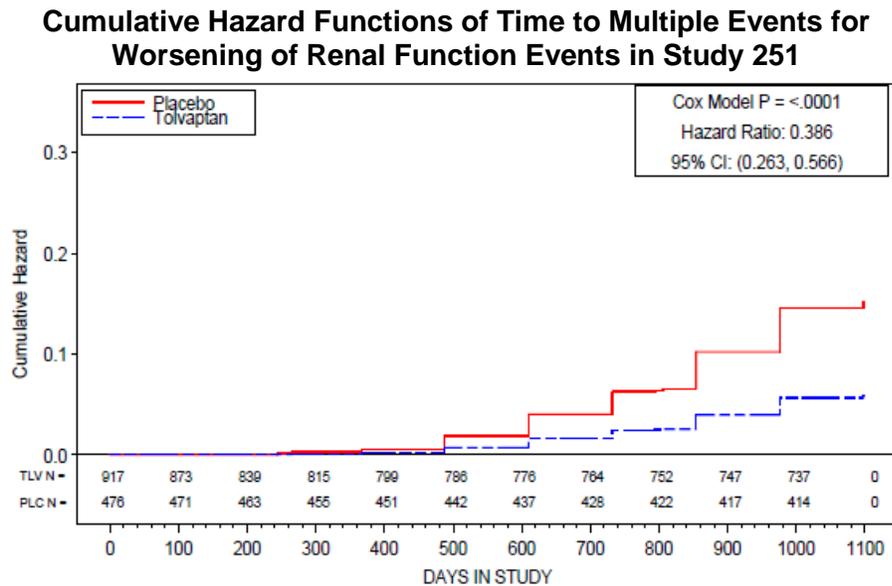
While statistically robust, the clinical significance of these findings is clouded by three issues:

- Although a 35% relative risk reduction sounds significant, the absolute difference in the number of moderate to severe pain events is small; about 1 event per 100 patient years. In table 16 of her review, Dr. Thompson, the clinical efficacy reviewer, categorizes five types of renal pain events based on what was required to relieve the pain. Of the 212 pain events, 114 were mild requiring only acetaminophen, another non-narcotic analgesic, or activity restriction for pain relief. Pain events necessitating a surgical or other procedural intervention or administration of a narcotic or tricyclic are clearly severer but there were only 10 and 88 of these events respectively observed in study 251. So the impressive sounding relative risk reduction results in a small absolute difference in moderate to severe renal pain events because moderate to severe pain was a relatively infrequent event in this trial. Supporting this finding is Dr. Thompson’s analysis in table 21 demonstrating that among the 96% not on pain medication at baseline, renal pain was not a significant problem at baseline (score of < 1 on a 10 point scale) and there was no change in this renal pain score during the course of the trial in either tolvaptan or placebo subjects.

- The concern that the differential loss of information between the treatment groups may have biased the observed results is particularly worrisome here because pain is a subjective endpoint. Subjects who stop taking study drug do so for subjective reasons such as intolerability of side effects and inconvenience. It is reasonable to believe that subjects intolerant of the side effects of tolvaptan would have been more likely to seek medical attention for pain had they remained in the trial. Because a high percentage of tolvaptan subjects stopped taking study drug, missing data from the tolvaptan subjects may have resulted in tolvaptan having a larger apparent treatment effect on pain than it actually does.
- The perception and reporting of pain are known to be affected by subjects' and/or investigators' knowledge of treatment assignment (investigators in study 251 decided if events were "medically significant" enough to be reported). The aquaretic effects of tolvaptan are likely to have unblinded considerable numbers of subjects and investigators.

*Reviewer's comment: As a single trial demonstrating tolvaptan reduces pain, study 251 provides minimal support for efficacy. The trial results suggest that tolvaptan prevents one moderate to severe renal pain event per 100 patient years but even that estimate of a small treatment effect is likely too high.*

Analysis of the final component, events of worsening of renal function, indicates that about 5% of tolvaptan subjects vs about 15% of placebo subjects had a 33% increase in serum creatinine (63% risk reduction) over the 3 years of study 251; the results are displayed in the figure below (from study 251 CSR fig 9.3.4-1):



While statistically robust, the clinical significance of these findings is made uncertain by several issues:

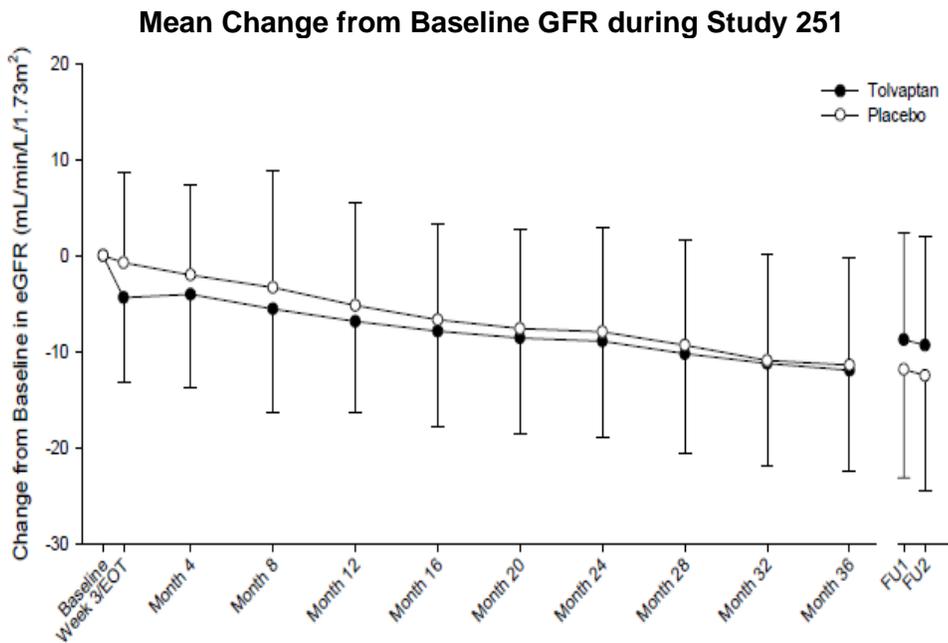
- The Division has accepted a doubling of serum creatinine as clinically meaningful in the treatment of chronic kidney diseases but to date has not accepted an increase as small as 33% as a primary endpoint or component thereof meant to support efficacy in an NDA.
- The analysis of this endpoint utilizes a post-baseline value as baseline and so is not ITT.
- Very few events occur before 500 days. By this time many subjects had discontinued study drug and so the outcomes for many randomized subjects are unknown, potentially biasing the results.

*Reviewer’s comment: This component (meant to capture worsening of renal function) is of unclear clinical significance and problematic to interpret. The analysis of the second secondary endpoint (discussed immediately below) results in a more easily interpreted estimation of the effect of tolvaptan on delaying worsening of renal function.*

**Second Secondary Endpoint:** The result of the prespecified analysis of the rate of change in GFR indicated that the decline in GFR per year calculated using the CKD-EPI formula was about 2.7 mL/min/1.73 m<sup>2</sup> in tolvaptan subjects vs. 3.7 in placebo. So the decline in GFR was about 1.0 mL/min/1.73 m<sup>2</sup> per year (95% CI 0.60 to 1.36) less in tolvaptan subjects than in placebo.

*Reviewer’s comment: While slowing the decline of GFR 1.0 ml mL/min/1.73m<sup>2</sup> per year does not sound large, there are no therapies that slow the decline in GFR in ADPKD. If that difference continues to accrue over decades, then tolvaptan would delay the progression to end-stage renal disease. On the other hand, translating the observed slowing of decline into the actual clinical benefit, delay in time to end-stage renal disease, is difficult (or impossible) to do. The design of study 251 was based on the hypothesis that tolvaptan would not be as effective (or effective at all) in patients with more than mild-moderate renal dysfunction so it is not clear that its effect will be maintained over decades of treatment. And nearly a quarter of the subjects in a clinical trial could not tolerate tolvaptan for three years, which suggests that tolerability will be a major problem if marketed; it is unclear if patients will be able to remain on tolvaptan for the decades required to attain the clinical benefit.*

The principal problem with the analysis is that the data upon which it is based may have been biased by using a “baseline” measurement not measured at the time of randomization but about three weeks later. The figure below (from study 251 CSR CT-6.1.4.6) shows the mean GFR of each treatment group during study 251:



The GFR’s of placebo and tolvaptan subjects were similar at baseline and at the end of 36 months; i.e. the difference in the rate of GFR decline between the two treatment groups during the protocol specified 36 months of observation is negligible. A difference in the rate of

decline is apparent only if the points chosen for analysis are 1) end-of-titration and end of the 36-month observation period (the pre-specified analysis) or 2) baseline and off-treatment follow-up.

*Reviewer's comments:*

- 1. The initial decline in GFR in the tolvaptan subjects may be the acute reversible decline identified in study 156-09-284 (see section 5.1 above). But there is no information internal or external to study 251 about the durability or significance of the acute effect over 3 years. Nor is there reliable information that explains why GFR increased in tolvaptan subjects after tolvaptan was discontinued. There may be many contributors to the change in GFR observed after discontinuation of treatment. For example, it is unclear how long it took subjects habituated to drinking several liters of water a day to return to normal fluid intake.*
- 2. The clinical relevance of an analysis that includes data from subjects who have discontinued tolvaptan is not clear. If marketed, patients are not expected to discontinue tolvaptan. Indeed the data presented in section 5.1 do not suggest an appreciable reversible effect in the later stages of renal dysfunction.*
- 3. 81 (8.7 %) of tolvaptan subjects and 14 (2.9%) of the placebo subjects did not have reliable serum creatinine measurements for the end-of-titration visit. By the end of the trial, about 24% of the tolvaptan subjects and almost 14% of placebo subjects were no longer having serum creatinine measurements. The potential for bias from this much missing data is concerning and no amount of data about the baseline characteristics and outcomes in the trial prior to leaving the trial of subjects lost to follow-up can fully alleviate this concern. Dr. Thompson's quote from The National Research Council's Panel on Handling Missing Data in her presentation to the advisory committee that "There is no 'foolproof' way to analyze data subject to substantial amounts of missing data; that is, no method recovers the robustness and unbiasedness of estimates derived from randomized allocation of treatments" is apposite here. In my opinion, the numbers lost and the disparity in numbers lost between the treatment arms in study 251 should significantly increase concern that the observed results may be biased.*

## **7.4 Efficacy Conclusions**

To have adequate evidence of efficacy to support approval of an NDA, FDA generally requires two trials both successful a p-value of  $\leq 0.05$ . The May 1998 Guidance "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" discusses situations in which a single study can be relied upon to provide adequate evidence of efficacy. It states that "reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality (or) irreversible morbidity....and confirmation of the result in a second trial would be practically or ethically impossible." It goes on to state the design and conduct of the study must be adequate. The outcomes of study 251 do not meet the standard for a single study approval.

- The results of the pre-specified analysis of the efficacy (first secondary) endpoint indicate that the trial was either statistically successful or nearly so at the agreed-upon p-value of  $< 0.01$ . However, sensitivity analyses performed by Otsuka meant to address the effects of

missing data and of using a post-baseline value for the worsening of renal function component do not provide much support.

- The components of the efficacy (first secondary) endpoint are not events of mortality or irreversible morbidity. In fact, only the renal pain component measures something that meets the conventional FDA definition of clinical benefit; i.e. something patients can directly perceive as a benefit such as longer life, better quality of life, or improved ability to function.
- The design of the trial was not adequate. The design made it impossible to analyze the results following the principles of ITT.
  - The protocol stipulated that subjects who stopped taking study drug were not followed for components of the primary or efficacy (first secondary) endpoints.
  - The “baseline” for analyzing events of worsening GFR was a post-randomization measurement. Randomization is meant to balance all the known and unknown factors in treatment groups so that outcomes are not biased by differences that are important determinants of outcomes between treatment groups or by exposure to the investigational product.
- The conduct of the study was not adequate. Nearly a quarter of the tolvaptan subjects and about one-eighth of the placebo subjects stopped taking study medication during the course of the trial. Outcomes for the four components of the efficacy (first secondary) endpoint were not known at the end of the 36-month observation period for these subjects. An analysis in which the tolvaptan subjects who stopped taking study medication had outcomes similar to placebo (based on the reasonable assumption that outcomes in subjects not taking tolvaptan were not better than the outcomes of placebo subjects) results in a nominal p-value of 0.04.
- The demonstration of clinical benefit does not appear to be either so large or so persuasive as to make another trial unethical (especially a study of ADPKD patients with greater degrees of renal dysfunction, who were not studied in study 251). The pre-specified analysis of rate of decline in GFR suggests that tolvaptan reduces this rate by about 1 mL/min/1.73m<sup>2</sup> per year. While clearly something is better than nothing, this clinical benefit is not large. Further, the observed difference between tolvaptan and placebo subjects in the rate of decline of GFR from baseline to the scheduled end of study drug administration is essentially zero. Accepting the accuracy of the pre-specified analysis depends on unverified assumptions about the effects of tolvaptan on GFR after years of administration and that a substantial amount of missing data is completely at random. Not accepting either of those assumptions leads to the conclusion that the trial data are consistent with no effect of tolvaptan on the rate of decline in GFR. The small effect of tolvaptan on TKV, the postulated mechanism of action, supports that conclusion.

## 8 Safety

### 8.1 *Tolvaptan-Induced Liver Injury*

Tolvaptan was found in study 251 to cause hepatotoxicity. The first subject in study 251 who developed hepatocellular liver injury (i.e., symptoms of liver injury with increased serum transaminases and concurrent increased serum bilirubin in the absence of an increase in serum

alkaline phosphatase) was reported in Spring 2008. Minutes of an open session of the DMC held on 6 January 2009 state:

“In late December 2008, members of the TEMPO IDMC received a letter from Dr. Frank Czerwiec, which stated, in part: A number of investigators in the TEMPO trial have reported seeing subjects with elevated liver function tests ... Additionally, 11 patients were identified from the TEMPO tables and listings compiled in August 2008 as having had potentially clinically significant increases in LFTs ...”

Dr. Czerwiec is an employee of Otsuka so Otsuka was apparently concerned that tolvaptan might cause liver injury and so notified the DMC of this concern. The DMC considered the available information and recommended to the steering committee for study 251 that the trial continue without modification. The DMC minutes show that the DMC was aware that there was a discrepancy between the treatment groups in the occurrence of significant transaminase elevations. They discussed seeking input from an expert in drug-induced liver injury but chose not to do so.

*Reviewer’s comment: Tolvaptan was being marketed for treatment of hyponatremia beginning in May 2009 so the question of whether tolvaptan was hepatotoxic was important for understanding the safety of a marketed drug not just for a drug whose safety and efficacy were being studied in a clinical trial. The DMC should have been more diligent in evaluating whether tolvaptan was a hepatotoxin.*

After data lock and unblinding it became apparent that two tolvaptan and no placebo subjects in study 251 had had significant but reversible hepatocellular injury and that significantly more tolvaptan subjects than placebo subjects had significant increases in serum transaminases. Otsuka convened an external panel of experts in drug-induced liver injury to evaluate data from study 251 and other clinical studies to determine whether tolvaptan had the potential to cause severe liver injury. That panel concluded “that in patients with ADPKD tolvaptan has the potential to cause liver injury capable of progression to liver failure.” They continued that “a rough incidence of liver failure can...be estimated as  $3/860 \times 10$ , or about 1:3000 patients (who) receive long term treatment with tolvaptan”. The clinical reviewers as well as the OSE hepatic safety consultant concur with that assessment.

## **8.2 Safety Conclusions**

A 1 in 3000 risk of liver failure resulting in death or liver transplantation is quite significant. The hepatic safety consultant to the review team indicates that only two drugs currently legally marketed in the USA, isoniazid and bosentan, have a similar risk of drug-induced liver injury and none have a higher risk. The FDA Guidance Drug-Induced Liver Injury: Premarketing Clinical Evaluation states “Most of the drugs withdrawn from the market for hepatotoxicity have caused death or transplantation at frequencies in the range of  $\leq 1$  per 10,000.” Otsuka asserts and the reviewers of this NDA agree that tolvaptan is likely to cause liver injury at a frequency about three times that identified in the Guidance as being so concerning that drugs with that frequency have been withdrawn from marketing. Therefore the benefit risk of treating ADPKD with tolvaptan cannot be positive unless either the demonstrated benefit(s) are substantial and/or the incidence of severe liver injury can be markedly reduced by risk mitigation measures.

## **9 Advisory Committee Meeting**

### **9.1 Main issues discussed**

The main points of discussion were about the size of the effect on worsening GFR and how that effect would translate to delaying progression to ESRD, how to interpret the efficacy data given the amount of missing data, use of a post-randomization value as baseline for measuring the effect of tolvaptan on worsening GFR, and the utility/appropriateness of the REMS for decreasing the incidence of severe tolvaptan-induced hepatotoxicity. There was also a discussion of the utility of TKV as a surrogate endpoint.

### **9.2 Open public hearing**

Several patients with ADPKD urged approval citing the immense burdens having ADPKD places on their lives and the distress that comes with a genetic disease without any treatment that is passed from parent to child.

*Reviewer's comments: The presentations were both moving and informative. It was clear that one aspect of ADPKD had been inadequately discussed in Otsuka's submissions and the Agency reviews of this NDA, i.e. the pain consequent to having kidneys of enormous size. It prompted this reviewer to review the effect of tolvaptan on TKV more carefully.*

*However to be complete, it should be noted that some of the consequences of having ADPKD cited at the public hearing were 1) events on which tolvaptan does not have an effect (e.g., hypertension), 2) events not specifically studied in study 251 (e.g., renal infections), and 3) events on which no drug can have an effect (e.g., inadequate evaluation of complications by health care providers).*

### **9.3 Vote on approval**

The committee voted 9-6 not to approve. Those voting not to approve indicated they were concerned that 1) the amount of missing data lessened the reliability of the effectiveness data, 2) the use of post-randomization value as baseline for measuring the effect of tolvaptan on worsening GFR may have biased the outcomes in ways that cannot be detected and are not quantifiable, 3) the size of benefit was not large, and/or 4) the risk of hepatotoxicity outweighed the demonstrated benefit. Those voting to approve indicated 1) the proposed REMS would adequately mitigate the risk of hepatotoxicity, 2) although small, the apparent benefit was adequate evidence of effectiveness for a serious illness with no available therapy, and/or 3) it is difficult to demonstrate benefit in a slowly progressive disease so any demonstration of benefit is adequate. The committee did not specifically discuss the acceptability of TKV as a surrogate but acceptability did not appear to have much, if any, support.

## **10 Pediatrics**

Tolvaptan for treatment of ADPKD has been designated an orphan product and so is not subject to the requirement to conduct pediatric studies under the Pediatric Research Equity Act.

## 11 Other Relevant Regulatory Issues

### 11.1 Risk Evaluation and Management Strategy

The Division of Risk Management (DRISK) in the Office of Surveillance and Epidemiology recommended a Risk Evaluation and Mitigation Strategy (REMS) if tolvaptan were to be approved for the treatment of ADPKD. The Food and Drug Administration Amendments Act of 2007 (FDAAA) authorizes the FDA to require a REMS if the FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh its risks. It was the conclusion of the review team as well as Otsuka that the 1 in 3000 risk that patients taking tolvaptan would develop liver failure resulting in death or liver transplantation required a REMS.

The intent of the tolvaptan REMS is to increase the probability that tolvaptan-induced liver will be detected at a time at which it is fully reversible if tolvaptan is discontinued. Otsuka and the review team agreed that a REMS that included four (out of a possible six) elements to assure safe use (ETASU) would be required to mitigate adequately the risk of hepatotoxicity. If tolvaptan is approved for treatment of ADPKD, the tolvaptan REMS would be one of the most stringent REMS ever adopted and so likely would be rather burdensome for health care providers, patients, and the health care system. An important part of the tolvaptan REMS is the requirement for a post-marketing registry to gather further information to characterize the frequency and time course of tolvaptan-induced liver injury.

The proposed tolvaptan REMS was presented to the REMS Oversight Committee, who concurred with it.

*Reviewer's comment: The proposed REMS is likely to reduce substantially the risk of tolvaptan-induced severe liver injury resulting in death or transplantation but there is not much information upon which to base a more precise estimate of the magnitude of reduction. As is noted in the February 2013 report from the Office of Inspector General of HHS ("FDA Lacks Comprehensive Data to Determine Whether Risk Evaluation and Mitigation Strategies Improve Drug Safety") "FDA has not identified reliable methods to assess the effectiveness of REMS." The only drug whose pre-marketing trials demonstrated hepatotoxicity with an incidence similar to tolvaptan is bosentan. Bosentan has an approved REMS whose goal, in part, is to minimize the risk of hepatotoxicity. The bosentan REMS has some of the same elements that are in the REMS proposed for tolvaptan (i.e., required monthly liver monitoring while on therapy). The bosentan REMS has been found to be effective in meeting its goals (last assessment April 2013). However, liver injury can be a consequence of the disease it is intended to treat (pulmonary artery hypertension) and so it is difficult to quantify the risk mitigation effect of the bosentan REMS.*

### 11.2 OSI consult

Five clinical investigator sites (four foreign, one domestic) were inspected. No regulatory violations were found during the inspections at two sites. Inspections of the remaining three sites were classified as VAI (voluntary action indicated) and OSI assessed the regulatory violations as minor and/or isolated and unlikely to impact data integrity. OSI concluded the "regulatory violations ...are unlikely to significantly impact the primary efficacy or safety analysis for this study. Therefore, the data generated by the sites inspected for this study may be considered reliable..."

### **11.3 Proprietary name**

Otsuka stated in the pre-NDA meeting with the Division on 19 July 2012 that they planned to seek approval for a dual proprietary name for tolvaptan tablets for treatment of ADPKD (SAMSCA<sup>®</sup> is the approved proprietary name for tolvaptan tablets for treatment of hyponatremia). Their rationale for this request was that “the dose, population treated, and outcomes are distinctly different” for each indication. In reviewing the request, the team was concerned about the possibility that approval of tolvaptan for ADPKD might require a REMS that imposed significant burdens on prescribers (e.g., a requirement that health care providers complete specific training to become certified to prescribe) to mitigate the risk of hepatotoxicity. If the product were being marketed under one proprietary name that had a REMS and another proprietary name without a REMS, then convenience might lead prescribers to choose to prescribe the product without the REMS for the indication requiring a REMS, thereby rendering the REMS less effective.

The review team shared this concern with Otsuka and indicated that further characterization of the liver injury risk would be required before a decision could be made regarding a dual proprietary name. Otsuka elected to withdraw their request for a dual proprietary name with the understanding they could resubmit it at a later time. Otsuka subsequently resubmitted the request for a dual proprietary name. Because the application is not approvable at this time, Otsuka will be asked to withdraw their pending proprietary name request after an action is taken on the application.

## **12 Labeling**

No review of the sponsor’s draft labeling has been performed because the application is not approvable at this time.

## **13 Recommendations/Risk Benefit Assessment**

### **13.1 Basis for Recommended Regulatory Action**

Study 251 as a single study clearly does not provide adequate evidence of effectiveness to support approval despite having met, or nearly met, the FDA specified p-value of < 0.01 for the composite efficacy (first secondary) endpoint. As discussed in section 7.4 the components of the composite efficacy (first secondary) endpoint are not death and/or events of irreversible morbidity, which are generally required for approval of an NDA based on results from a single trial. In fact, the only component that is a clinical benefit as usually defined is renal pain and the results for this component are not persuasive of much treatment effect. There were defects in design and conduct that seriously undermine confidence that the result of the pivotal pre-specified efficacy analysis was not biased. Finally and most importantly, analysis of the effect on tolvaptan on the decline in renal function using the baseline measurement of serum creatinine to the end of treatment is consistent with tolvaptan having no or minimal effect on the decline on renal function in ADPKD. These analyses probably bias the results of study 251 against tolvaptan because tolvaptan probably causes an acute but reversible decrease in GFR, at least in patients with no more than mild-moderate kidney dysfunction. However, the design and conduct of study 251 does not allow the acute effects of tolvaptan to be readily distinguished from its chronic effects. Any attempt to do so depends on unverified

assumptions about the effects of tolvaptan on GFR after years of administration and after patients' underlying kidney dysfunction has progressed.

Hence it is my conclusion that study 251 does not reliably demonstrate much if any effect of tolvaptan on the progression of renal disease in patients in ADPKD. An additional trial to provide evidence of tolvaptan's effect in ADPKD is not only ethical, but also is desirable so that patients with ADPKD will not be prescribed a drug of potentially little or no benefit. As a practical matter, if this NDA were approved at this time it would be impossible to use the results of study 251 to describe in any meaningful way the expected benefit of prescribing tolvaptan for treatment of ADPKD in the label.

In terms of safety, tolvaptan is, in the words of one of the experts in drug-induced liver injury who was a member of the advisory committee that considered this NDA, an "impressive" hepatotoxin. But the proposed REMS is so draconian that it is likely to decrease significantly the incidence of tolvaptan-induced liver injury progressing to death or transplantation (at least in the USA). I have some residual concern that marketing tolvaptan may result in the unfortunate but very rare patient developing severe irreversible liver injury, but that concern could have been outweighed by an unambiguous demonstration that tolvaptan provided an important clinical benefit in a serious illness without useful therapy.

*Reviewer's comment: My reason for recommending NDA 204441 not be approved at this time differs somewhat from those of the clinical reviewers. The clinical reviewers observe (I am not sure they actually conclude) "if tolvaptan's safety profile had been reassuring, we think the available data...might have been sufficient to support approval." My major concern is the lack of demonstrated efficacy and the residual concern about tolvaptan-induced hepatotoxicity did not weigh heavily in my conclusion that NDA 204441 is not approvable at this time.*

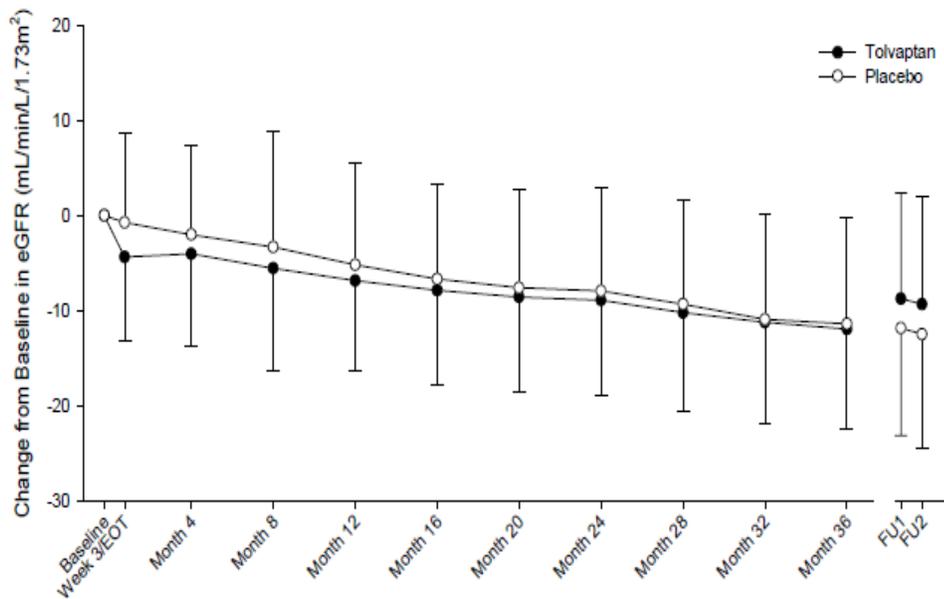
### **13.2 Recommended Comments to Applicant**

We have completed our review of your application to market tolvaptan to slow kidney disease in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD) and cannot approve it at this time. You and we agreed that as the sole study providing evidence of effectiveness to support approval of an NDA, study 156-04-251 would need to achieve a p-value < 0.01 for the first secondary efficacy endpoint, a composite of

- Events of worsening renal function events (about a 33% increase in serum creatinine),
- Renal pain events requiring medical intervention,
- Worsening in category of hypertension, and
- Worsening in category of albuminuria.

We conclude that the analysis specified in the final statistical analysis plan indicates the study was statistically successful, or nearly so. This outcome was driven principally by decreases in events of worsening of renal function and events of renal pain; there was no effect on the other two components. Your analysis of the second secondary endpoint assessing the effect of tolvaptan on the decline of glomerular filtration rate (GFR) suggests that tolvaptan reduces the worsening of GFR using the CKD-EPI formula by about 1 mL/min/1.73m<sup>2</sup> per year. However the following elements of study 156-04-251 lessen confidence in these results:

1. The protocol for 156-04-251 stipulated that subjects who discontinued study drug no longer were followed at investigative sites and so the information necessary to determine major efficacy outcomes was not collected. 23% of tolvaptan subjects and almost 14% of placebo subjects discontinued study drug so confidence in the observed results is lessened by the potential bias introduced by the loss of data from subjects who may have had different outcomes had they remained in study 156-04-251. Sensitivity analyses meant to explore how robust the results are to the data missing from subjects who discontinued study drug are not reassuring. An analysis of the secondary composite endpoint that imputes the outcomes of the placebo subjects to the tolvaptan subjects after they discontinued study drug (which we believe is not conservative) results in a p-value of 0.04.
2. The baseline value for serum creatinine used to identify events of worsening of renal function and to determine the effect of tolvaptan on GFR was not the value measured at randomization but rather the value measured at the end of the titration period, about three weeks after randomization. These analyses may be biased because the population analyzed was different from the randomized population: 1) some randomized subjects were not included in these analyses because they lack reliable values for serum creatinine at end of titration and the lack of reliable varies markedly by treatment assignment [81 (8.7 %) of tolvaptan subjects vs 14 (2.9%) of the placebo subjects] and 2) the subjects in each treatment group systematically differed because they had already taken either tolvaptan or placebo for three weeks. If the values for serum creatinine collected at randomization and at end of treatment are used as the baseline measurement for the analysis of decline in GFR, then tolvaptan does not appear to have much if any effect, as is shown in the following figure taken from your clinical study report for 156-04-251:



3. Reduction of pain is an important clinical benefit but the absolute reduction in pain events observed in 156-04-251 is small and likely a biased estimate of the treatment effect.

- a. 212 pain events were observed in 156-04-251, but 114 were mild requiring only acetaminophen, another non-narcotic analgesic, or activity restriction for pain relief. The absolute reduction in the number of moderate to severe pain events (i.e., those requiring a procedure or a narcotic or a tricyclic drug for pain relief) is only about 1 event per 100 patient years. Chronically administering a drug that is hepatotoxic and has intolerable side effects to prevent one moderate to severe pain event per 100 patient years is obviously problematic.
- b. Pain is subjective. Its perception and reporting are known to be affected if subjects and/or investigators are aware of treatment assignment. The aquaretic effects of tolvaptan are likely to have unblinded considerable numbers of subjects and investigators.
- c. The occurrence of renal pain events was not systematically collected from subjects who stopped taking study drug. Nearly a quarter of tolvaptan subjects stopped taking tolvaptan, generally because they were intolerant of side-effects (polyuria/pollakuria and thirst) that the subjects who continued to take tolvaptan were able to tolerate. It is reasonable to believe that the subjects who were intolerant of tolvaptan's side effects also would have been more likely to seek medical attention for pain had they remained in the trial. Hence the high percentage of subjects who stopped taking tolvaptan may have biased the observed reduction in pain events in favor of tolvaptan.

Additionally analysis of the primary endpoint in 156-04-251, change in total kidney volume (TKV) over a 36 month observation period, indicate that tolvaptan has a small or minimal chronic effect on slowing the increase in TKV. The data demonstrate an acute decrease in TKV of about 100 ml during the first year (you suggested during the advisory committee meeting that most of that may occur in the first few weeks of tolvaptan administration) with an about 50 ml smaller increase in TKV compared to placebo over the next two years. Hence, the effect of tolvaptan on the increase in TKV is not only small (no more than a 10% decrease in kidneys that are many times the normal size) but it is not sustained. Further, another clinical study of ADPKD patients (NEJM 2010; 363:830) was reported to show that another drug that slowed the increase in TKV was associated with a greater decrease in GFR compared to placebo. Even a single failure of a putative surrogate endpoint to correlate with the anticipated clinical benefit significantly undermines the persuasiveness of that endpoint as a surrogate.

We agree with the conclusion of your hepatic adjudication panel that in the absence of measures to mitigate the risk of hepatotoxicity tolvaptan can “ cause liver injury capable of progression to liver failure.... with “a rough incidence of liver failure ....estimated as 3/860 x 10, or about 1:3000 patients (who) receive long term treatment with tolvaptan.” However, we believe that the risk evaluation and management strategy that resulted from your discussions with us is likely to decrease significantly the incidence of tolvaptan-induced liver injury

progressing to death or transplantation (at least in the USA). We have some residual concern that marketing tolvaptan may result in the unfortunate but rare patient developing severe irreversible liver injury, but that concern could have been outweighed by an unambiguous demonstration that tolvaptan provided an important clinical benefit in a serious illness without useful therapy.

For this application to be approved, you need to conduct an additional efficacy trial that tests the hypothesis that tolvaptan slows the loss of GFR and is successful at a p-value < 0.05. This study could provide additional information about tolvaptan-induced hepatotoxicity and determine the effectiveness of a risk mitigation plan for identifying liver injury before it results in permanent morbidity. Because of the unmet medical need in this serious condition, we are anxious to work with you in the design of this trial.

*Acknowledgement: This review rests entirely upon the hard work that went into the excellent primary reviews of this NDA. Any errors in this review are mine and most if not all of the important observations are other's.*

*I wish to note that members of this review team conducted themselves in a professional manner, working energetically with each other to determine the facts of this application and resolving differences courteously. I was fortunate to have had the opportunity worked with this group of outstanding reviewers.*

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/s/  
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STEPHEN M GRANT  
08/25/2013

# CLINICAL REVIEW

Application Type	NDA
Application Number(s)	204441
Priority or Standard	Priority
Submit Date(s)	March 1, 2013
Received Date(s)	March 1, 2013
PDUFA Goal Date	September 1, 2013
Division / Office	Division of Cardiovascular and Renal Products/ODEI
Reviewer Name(s)	Nhi Beasley (Safety) Aliza Thompson (Efficacy)
Review Completion Date	July 7, 2013
Established Name	Tolvaptan
(Proposed) Trade Name	To be determined
Therapeutic Class	Vasopressin receptor antagonist
Applicant	Otsuka Pharmaceutical Company, Ltd.
Formulation(s)	15-, 30-, 45-, 60-, and 90 mg immediate release tablets
Dosing Regimen	Initial dose of 60 mg per day as a split-dose regimen of 45 mg/15 mg with titration up to a target dose of 120 mg per day (90 mg/30 mg)
Indication(s)	to slow kidney disease in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease
Intended Population(s)	Adults

Template Version: [March 6, 2009](#)

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

We do not recommend approval at this time.

### 1.2 Risk Benefit Assessment

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a serious disease with unmet medical need. The disease is characterized by the presence of numerous fluid-filled kidney cysts. Over time, patients may experience progressive loss of renal function leading to end-stage renal disease.

Tolvaptan is a vasopressin V2 receptor antagonist that targets cyst growth and formation. Because some experts believe that therapies that target renal cysts are unlikely to be effective if administered at later stages of disease, the applicant's phase 3 trial enrolled patients with relatively preserved renal function (an estimated GFR  $\geq 60$  mL/min as determined by the Cockcroft-Gault equation) deemed to be at high risk of progression (total kidney size  $\geq 750$  cc).<sup>1</sup> The trial demonstrated tolvaptan's effectiveness in slowing the loss of renal function in this population. However, because of missing data in a sizeable portion of the study population and particularly so in the tolvaptan arm, the size of the treatment effect is unclear. Treatment effects on other endpoints (kidney volume and renal pain events requiring medical intervention) were supportive of the drug's activity.

As previously noted, subjects enrolled in the phase 3 trial were for the most part remote from end-stage renal disease. As a consequence, treatment effects on this clinical outcome were not directly observed. In absolute terms, the effect on renal function observed in the phase 3 trial was small (an  $\sim 1$  mL/min/1.73m<sup>2</sup> difference between the two arms in the rate of change in renal function per year) and would not be considered clinically meaningful in itself. Nevertheless, this effect would be expected to translate into a benefit in delaying end-stage renal disease if it were to accrue over time.

Both the missing data as well as the lack of data in subjects with more advanced stages of disease make it difficult to project tolvaptan's likely benefit in delaying the onset of end-stage renal disease. Under the assumptions of Dr. Lawrence's model (see Dr. Lawrence's statistical review for additional details), one would predict an approximately 4 year delay in the time to a GFR  $< 15$  mL/min/1.73m<sup>2</sup> (essentially end-stage disease) in the trial population overall. In what might be considered a best case scenario- a patient at high risk of progression who starts therapy young with a relatively preserved GFR and remains on therapy, his model predicts that the need for dialysis some 40 years into the future would be prevented. While these projections provide a window into what might be possible, whether they are accurate is unknown.

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<sup>1</sup> See sections 2.5 and 5.3.2 for further discussion.

If tolvaptan's safety profile had been reassuring, we think the available data, despite the aforementioned limitations, might have been sufficient to support approval. However, tolvaptan's safety profile was not reassuring. Tolvaptan caused liver injury in patients with ADPKD. There were three subjects with hepatocellular liver injury judged to be at least probably due to tolvaptan ("Hy's Law" cases) out of ~860 subjects with ADPKD treated over a 14-month treatment period. These subjects did not progress to liver failure leading to transplantation or death, but the finding of two or more Hy's Law cases in a clinical trial safety database is a strong predictor of a drug capable of causing such injury. Based on Hy's Law, the rough incidence of liver failure can be estimated as  $3/860 \times 10$ , or ~ 1 in 3000 patients treated with tolvaptan.<sup>2</sup> There are only a handful of marketed drugs with this incidence of liver injury (bosentan for pulmonary hypertension and isoniazid for tuberculosis). Most of the drugs withdrawn from the market for hepatotoxicity have caused death or transplantation at frequencies in the range of  $\leq 1$  per 10,000.<sup>3</sup>

If one were confident that the period of risk was limited to a relatively short time window early in the course of therapy, it might be easier to mitigate the risk of severe liver injury in the postmarketing setting. According to experts in the field, "...as a general rule, drugs that cause serious liver injury will do so within the first year of treatment".<sup>4</sup> Available data on the latency of significant serum ALT elevations suggest a "signature period of risk" for tolvaptan with onset between 3 to 14 months after drug initiation. However the amount of data in subjects exposed to tolvaptan for an extended duration is limited (in the pivotal trial ~740 subjects were exposed for 36 months) and as experts have noted, "drugs with characteristic signatures may produce injuries without all of the characteristics of that signature".<sup>4</sup> Hence, at this time, it is unknown if the risk of severe drug-induced liver injury is limited to a finite period. Ongoing clinical trials may provide further insight into this issue. Should the drug be approved, the proposed patient registry should also be used to better characterize the incidence and time course of this risk (see section 1.3).

Given the expected frequency of liver injury requiring liver transplant or resulting in death, we are unlikely to understand the true nature of tolvaptan's risk until after it is approved and more widely used in patients with ADPKD. In contrast, additional efficacy data, such as evidence from the applicant's ongoing extension trials or possibly a new trial in patients with lower levels of renal function, could help reduce some of the residual uncertainty about the nature of tolvaptan's benefit. We believe such data would provide the information necessary for patients to make a properly informed decision about whether to use this therapy. We also believe it would place us in a better position for making decisions in the post-marketing setting about withdrawing the drug from the market should cases of severe liver injury be seen or possibly scaling back on the proposed measures to mitigate risk should the safety experience support the decision to do so.

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<sup>2</sup> While there is some uncertainty around the estimate for tolvaptan's risk of severe liver injury, FDA has not seen any false positive Hy's Law findings for a drug that was subsequently found not to cause severe drug-induced liver injury in a larger treatment population. (Source: FDA Guidance for Industry on Drug-Induced Liver Injury: Premarketing Clinical Evaluation dated July 2009)

<sup>3</sup> FDA Guidance for Industry on Drug-Induced Liver Injury: Premarketing Clinical Evaluation dated July 2009

<sup>4</sup> Hepatic adjudication committee report for tolvaptan

It is for these reasons that we do not recommend approval at this time. Others, however, may have a different interpretation of the data and we look forward to the discussion at the upcoming advisory committee meeting.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

If approved for the proposed indication, we think a REMS is necessary to ensure that the benefits of tolvaptan outweigh the risk of severe drug-induced liver injury.

The applicant has submitted a proposed REMS. The goals of the REMS are to inform and educate healthcare providers and patients about:

- The risk of hepatotoxicity associated with the use of tolvaptan
- Appropriate pre-treatment screening for liver disease
- Strategies to enhance early detection and intervention for hepatotoxicity including the need to:
  - Measure plasma hepatic transaminases and total bilirubin prior to initiation and continuing monthly for 18 months, and at regular intervals (e.g., every 3-6 months) thereafter for those patients maintained on therapy
  - Counsel patients on how to self-monitor and recognize signs and symptoms that may suggest liver injury, stop tolvaptan if they experience any signs or symptoms consistent with liver injury, and immediately report these to their healthcare provider

The proposed REMS contains a Medication Guide and elements to assure safe use (ETASU) including prescriber certification, documentation of safe use, pharmacy certification, and a registry. In brief,

- The Medication Guide will be dispensed with each prescription.
- Outpatient prescribers will be required to be certified and will agree or attest to REMS requirements.
- Prescribers will document that baseline liver tests were performed and every two months will document that liver testing has been ordered and reviewed.
- The applicant will ensure that tolvaptan is acquired and dispensed only through pharmacies that are specially certified.
- All outpatients will be required to enroll in the Tolvaptan REMS registry in order to receive tolvaptan in the outpatient setting. A Patient Enrollment Form will be used for enrolling patients into the registry and will include agreements by the patient that they: (1) have reviewed the Medication Guide with their prescriber; (2) understand the risk of hepatotoxicity; (3) understand the need for baseline and monthly bloods tests during treatment; (4) understand they will be enrolled in the Tolvaptan REMS program.

The registry will capture the frequency of Liver Function Test confirmations which can be used to estimate compliance with required monitoring. The registry will also capture the reason for discontinuation as solicited from prescribers by the specialty pharmacies.

Cases of severe liver injury will be evaluated and the registry will capture the frequency and timing of severe liver injury.

The Division of Risk Management was consulted on the applicant's proposal. Their review contains more detailed information on the proposed REMS and recommendations on revisions, along with supportive rationale. In brief, these recommendations include:

- Revisions to the Tolvaptan REMS Goal and Objectives:  
The goal of the Tolvaptan REMS is to mitigate the risk of serious outcomes associated with hepatotoxicity by:
  - 1) Informing healthcare providers about the risk of hepatotoxicity associated with the use of Tolvaptan
  - 2) Informing patients receiving outpatient Tolvaptan therapy about the risk of hepatotoxicity associated with its use
  - 3) Ensuring only patients who received education about how to recognize the signs and symptoms of hepatotoxicity and appropriate actions to take, if it occurs, will be prescribed Tolvaptan as outpatient therapy
  - 4) Ensuring compliance with monthly hepatic laboratory monitoring prior to outpatient Tolvaptan therapy and monthly during treatment
  - 5) Establishing long term safety and safe use of Tolvaptan through periodic review of hepatotoxicity events reported in patients enrolled in the Tolvaptan Patient Registry.
- Inclusion of a drug-induced liver injury specific Patient Education Tool.
- Monthly prescriber documentation that the monthly laboratory monitoring has been reviewed and is acceptable. Pharmacies will verify this documentation prior to dispensing any outpatient prescriptions for tolvaptan.
- Certification of all prescribers of tolvaptan regardless of healthcare setting.
- Pharmacy and prescriber agreement to mandatory reporting to the registry of any adverse events suggestive of liver injury associated with the administration of tolvaptan in the inpatient and outpatient setting. A standardized adverse event reporting form would be utilized to collect data on events suggestive of liver injury to enable the Agency to further characterize the risk of hepatotoxicity associated with tolvaptan and potentially refine recommendations to mitigate the risk.

Reviewer's conclusions: While the REMS is clearly burdensome and will likely restrict patient access, we do not think it unduly burdensome considering the serious nature of the risk being mitigated and the nature of the benefit established by the development program. As also noted in the Division's review, although the proposed REMS may mitigate the risk of serious liver injury, it will not prevent (and cannot be expected to prevent) all cases of drug-induced liver injury.

## 1.4 Recommendations for Postmarket Requirements and Commitments

We are not recommending approval at this time.

## 2 Introduction and Regulatory Background

### *Overview of disease*

Autosomal dominant polycystic kidney disease (ADPKD) is an inherited systemic disease caused by mutations in PKD1 and PKD2, genes encoding plasma membrane spanning proteins that regulate tubular and vascular development in organs including the kidney, liver, brain, heart and pancreas. The disease is characterized by the presence of numerous fluid-filled kidney cysts. The development and growth of these cysts over time is thought to lead to progressive loss of renal function as well as other complications.

While multiple bilateral renal cysts are thought to develop in all family members who inherit a defined mutation, the clinical course is variable even in settings where the mutation is characterized. In those with progress to end-stage renal disease, end-organ failure typically develops in the 50's; patients with mutations in PKD2 (approximately 15% of resolved cases) are reported to develop renal failure approximately 15-20 years later than patients with mutations in PKD1 (approximately 85% of resolved cases)<sup>5</sup>. Other renal-related clinical manifestations of the disease include urinary tract infections, visible hematuria, cyst hemorrhage and rupture and nephrolithiasis. Hypertension and renal pain (sporadic or chronic in nature) are common. Liver cysts develop in many patients and intracranial aneurysms occur in approximately 8% of patients.

The disease has been reported to affect 300 to 600,000 patients in the United States (1:500 to 1:1000). However, according to an expert in the field (information submitted by the applicant in support of orphan drug designation for tolvaptan for the treatment of ADPKD), this estimate does not differentiate between those who would be diagnosed in their lifetime due to the appearance of typical symptoms of ADPKD, those who come to diagnosis incidentally without symptoms or those who are diagnosed only at death. Thus, it appears that the prevalence of symptomatic disease is not well understood.

### 2.1 Product Information

Tolvaptan is a vasopressin V2 receptor antagonist that is currently approved as a treatment for clinically significant hypervolemic and euvolemic hyponatremia, including patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone. The proposed indication is to slow kidney disease in adults at risk of rapidly progressing ADPKD. The recommended starting dose is 60 mg per day as a split-dose regimen of 45 mg/15 mg (45 mg taken on waking and 15 mg taken 8 hours later). The dose should be titrated to 90 mg per day (60 mg/30 mg split dose regimen) then to a target of 120 mg per day (90 mg/30 mg split-dose regimen) as tolerated.

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<sup>5</sup> It is reported that in comprehensive studies, approximately 9% of cases remain unresolved. The type of mutation may also affect the phenotype in patients with mutations in PKD1.

## **2.2 Tables of Currently Available Treatments for Proposed Indications**

There are no approved products for slowing progression of kidney disease in patients with ADPKD. Existing therapies are used to treat complications of disease including pain, infections and hypertension.

## **2.3 Availability of Proposed Active Ingredient in the United States**

Tolvaptan is currently marketed in the United States under the trade name SAMSCA as a treatment for clinically significant hypervolemic and hypovolemic hyponatremia. Tablets are available in 15 and 30 mg strengths; a 60 mg strength is also approved but not marketed.

## **2.4 Important Safety Issues with Consideration to Related Drugs**

Conivaptan is an intravenous vasopressin V1a and V2 receptor antagonist approved for short term use in raising serum sodium in hospitalized patients with euvolemic and hypervolemic hyponatremia. The experience with conivaptan does not raise any new or important safety concerns as relates to the safety of tolvaptan for the proposed indication. No other vasopressin receptor antagonists are approved for use in the United States.

## **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

There were a number of interactions with the Agency over the course of development; a summary of key regulatory milestones, agreements and advice is provided in the table below. Discussions focused on suitable endpoints for approval and the evidence needed to support approval based on the findings of a single trial. A “No Agreement” letter was issued in response to a request for Special Protocol Assessment in 2005. Nevertheless, in light of the unmet need for treatments for this serious condition and lack of approved therapies, the development program was granted access to available programs (i.e., fast track status, rolling review and priority review) meant to speed review and facilitate development. The applicant also requested (and was granted) Orphan Drug Designation for tolvaptan for the treatment of ADPKD.

Table 1. Summary of key regulatory milestones, agreements and advice

Source (date of meeting or submission)	Advice from Agency
March 16, 2005 Pre-IND meeting	Sponsor requested meeting to discuss development plans and specifically, the use of total kidney volume as an endpoint for approval. Sponsor indicated that cysts grow over time and increase renal size whereas the decrease in renal function is relatively late. Sponsor also noted and that there was evidence that reducing kidney size would improve kidney function. Agency noted that “at this time” it did not agree the endpoint was acceptable. Agency encouraged the sponsor to consider other endpoints such as effects on renal function and also advised the sponsor to make a case in writing supporting the view that reducing cyst and kidney size alone would be a persuasive and clinically meaningful endpoint.
July 27, 2005	IND submitted
September 29, 2005 Request for Special Protocol Assessment (SPA)- No agreement letter	<p>Agency provided feedback on proposed phase 3 trial and responses to questions submitted by sponsor.</p> <p><i>Efficacy endpoints:</i> Rate of renal volume change proposed as the primary endpoint for the phase 3 trial. Agency acknowledged that if “the hypothesis that early treatment is necessary to affect outcome is correct” then it would be difficult to demonstrate effects on renal function. However Agency also noted that there was no intervention that altered renal volume that was known to affect renal function and so it was hard to accept as a surrogate. Agency also indicated that even if one thought the endpoint was “reasonably likely” to predict effects on renal function it seemed unlikely that subjects would remain on placebo once the drug was available. Agency advised the sponsor to craft a composite secondary endpoint that represented the serious manifestations of the disease; to establish efficacy, the development program would need to demonstrate a convincing effect on the composite. Agency also suggested “a possible sequential approach, keeping volume as the primary endpoint and the suggested composite as a needed endpoint that would be reviewed if the volume effect were favorable.”</p> <p><i>Findings needed to support approval:</i> Agency noted that further discussion was needed after agreement on a primary endpoint but thought that a single study with an alpha of 0.05 on a single endpoint was not likely to be acceptable.</p> <p><i>Other aspects of trial design:</i> Sponsor was advised that subjects withdrawn for any reason should be followed for outcomes until the end of the study. Agency also indicated that the proposed study population was acceptable.</p>
Follow-up meeting held on November 15, 2005	<p><i>Efficacy endpoints:</i> Sponsor proposed a key secondary composite endpoint consisting of hypertension, proteinuria, nephrolithiasis and renal pain.</p> <p><i>Findings needed to support approval:</i> Sponsor proposed that if the primary endpoint and composite key secondary endpoint were both statistically significant, and if the other specified endpoints were supportive, the data from a single phase 3 study would be sufficient to support an NDA approval for the proposed indication. Agency agreed.</p> <p>Sponsor was advised to submit the statistical analysis plan for review and</p>

Source (date of meeting or submission)	Advice from Agency
	<p>comments as soon as possible. Sponsor indicated plans to order the important secondary endpoints but, given uncertainty about incidence of particular events in the ADPKD population, proposed to establish the sequence after observing the frequency of events and/or magnitude of change from baseline based on blinded data. Agency agreed.</p> <p><i>Other aspects of trial design:</i> Sponsor asked whether their proposed outcome plan for subjects that “withdraw from the study for any reason” was appropriate. Division responded that the sponsor should encourage patients to “...continue with the monitoring and follow-up (including MRIs) as described in the protocol, even if they choose to discontinue study drug/placebo.”</p>
January 20, 2006	Fast Track Designation Granted
Phase 3 Protocol submitted on March 31, 2006	Phase 3 Protocol submitted. Primary endpoint is rate of renal volume change; secondary composite endpoint is a time to multiple event analysis for hypertension, severe renal pain, worsening albuminuria, and worsening renal function.
Type C meeting held June 6, 2009	<p>Meeting held at request of sponsor to obtain Agency’s input and concurrence on proposed statistical analysis plan.</p> <p><i>Further discussion of endpoints:</i> Agency advised sponsor to add post-therapy follow-up visits to assess effects on endpoints that might be susceptible to potential “hemodynamic effects”, and told that “ideally” such endpoints (including changes in serum creatinine) should be defined as the change from baseline to the post-therapy period when any potential “hemodynamic effect” had worn off. Agency advised sponsor to establish an adjudication committee for adjudication of secondary composite endpoint findings.</p> <p><i>Findings needed to support approval:</i> When asked about significance level that would be acceptable for approval based on a single study, Agency indicated that in order to provide convincing evidence of treatment benefit, the composite secondary endpoint would need a p-value &lt; 0.01.</p> <p>Agency stated that it did not consider changes in renal volume an “irrelevant endpoint” and commented that showing an effect of tolvaptan on renal volume would provide supportive data.</p>
April 6, 2012	Orphan Drug Designation granted by Office of Orphan Products Development

<b>Source (date of meeting or submission)</b>	<b>Advice from Agency</b>
Meeting Minutes PreNDA meeting (July 19, 2012)	<p>Agency agreed that results of phase 3 trial as summarized were adequate to support an acceptable NDA filing; emphasis would be placed on findings for key composite secondary endpoint.</p> <p>Sponsor was advised that key efficacy issues include the robustness of the findings for the renal pain and renal function components of the composite secondary endpoint, the amount of missing data, and the nature of the follow up of study subjects who prematurely discontinued study medication.</p> <p>Agency also interested in whether the data suggest that benefit continues to accrue over time and whether effects are seen across the spectrum of renal disease (defined by level of renal impairment and also by kidney size).</p> <p>Sponsor indicated that safety data, including liver-related safety findings, were being reviewed and would follow up regarding the need for a Risk Evaluation and Mitigation Strategy once the review was completed.</p>
November 9, 2012	Rolling Review Granted
November 13, 2012	Submission of proposed Risk Evaluation and Mitigation Strategy and findings of external expert review of hepatic safety

## 2.6 Other Relevant Background Information

None.

## 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

As a whole, the submission was well organized and sufficiently complete to support review of the application within PDUFA time frames.

### 3.2 Compliance with Good Clinical Practices

Clinical investigator sites are being inspected to assess the quality, integrity, and acceptability of the data submitted in support of the application and the adequacy of the protection of the rights and welfare of human research subjects. Five sites (domestic and international) were selected based on a high risk ranking as determined by the GCP Site Selection Tool; the results of these audits are not yet available. No single site is driving the efficacy findings and so removal of a single site from efficacy analyses (based on inspection findings) is unlikely to alter the regulatory outcome.

With regard to unblinding of subjects in the pivotal phase 3 trial, one site received an unblinded safety report for one subject during the trial because of an incorrect setting in the IVRS. Unblinded subject information for a total of 9 out of 1445 study subjects was also mistakenly distributed in Annual Safety Reports and unblinded Serious Unexpected Serious Adverse Reaction/CIOMS reports. In the aforementioned cases, the applicant appears to have taken appropriate corrective action. In addition, one investigator contacted the IVRS to obtain the treatment code for a subject who reported a positive pregnancy test and requested release of her treatment group assignment to her.

Seven subjects (3 assigned to tolvaptan, 4 assigned to placebo) had incorrect study medication dispensed for some period during the trial (e.g., randomized to tolvaptan and received placebo), as determined by a discrepancy between the expected kit number assignment per the IVRS and actual kit number dispensed as per the Study Drug Label case report form.

*Reviewer's comment: These cases do not raise significant concern about the integrity of the trial data.*

### **3.3 Financial Disclosures**

The applicant has adequately disclosed financial arrangements with clinical investigators in covered clinical studies. The applicant reported receiving statements from 218 investigators and 892 subinvestigators. Of those, 9 reported disclosable financial interests, and specifically “significant payments of other sorts...” The applicant addressed steps taken to minimize the potential for bias resulting from those interests and arrangements (i.e., the design of the pivotal trial as a randomized, double-blind, controlled trial and the fact that any individual site contributed a relatively small fraction of subjects to the overall trial population). The applicant was unable to obtain financial disclosure information for 8 subinvestigators participating in study 156-04-251. The submission contains a description of the process for collecting financial disclosure information, and, based on this description, the applicant appears to have acted with due diligence to obtain the required information. As previously noted, no single site is driving the efficacy results for the key composite secondary endpoint. Two of the sites that had an investigator reporting disclosable financial interests were selected for audited; the results of these audits are not yet available.

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Chemistry Manufacturing and Controls**

Five strengths of tablets (15-, 30-, 45-, 60-, and 90 mg) are proposed. Information on the new strengths (45- and 90 mg) is provided in the application. The CMC review is not yet complete.

To date, no significant issues have been identified that would affect the clinical interpretation of the safety or efficacy data.

## 4.2 Clinical Microbiology

Not applicable.

## 4.3 Preclinical Pharmacology/Toxicology

The application contains additional pharmacology studies that were conducted subsequent to the submission of NDA 22-275, the application supporting tolvaptan's hyponatremia indication. Juvenile animal toxicity studies, conducted to support pediatric development for the hyponatremia indication, are also provided in the application. The preclinical pharmacology/toxicology review is not yet complete. To date, no significant issues have been identified that would affect the clinical interpretation of the safety or efficacy data.

## 4.4 Clinical Pharmacology

The Office of Clinical Pharmacology has reviewed the clinical pharmacology and biopharmaceutics information. From a clinical pharmacology perspective, the NDA is acceptable. Section 5.1 of this review contains an overview of clinical pharmacology trials submitted in the current NDA. Clinical pharmacology attributes pertinent to the current application are highlighted below. For a discussion of the rationale supporting dose selection, see section 6.1.8.

### 4.4.1 Mechanism of Action

Tolvaptan is a selective vasopressin V2-receptor antagonist. Renal cysts in ADPKD are held to originate from the renal collecting duct where V2-receptors are found. Stimulation of the V2 receptor on cystic epithelial cells increases the intracellular level of adenosine 3', 5'-cyclic monophosphate (cAMP) which is thought to lead to cellular proliferation and cyst growth. Tolvaptan is thought to reduce cyst growth and/or formation by inhibiting vasopressin-stimulated cAMP production.

Tolvaptan also causes an increase in urine water excretion and decrease in urine osmolality by preventing vasopressin-mediated activation of aquaporin 2 water channels in the collecting ducts. Activation of these water channels increases the water permeability of the collecting ducts and thus the reabsorption of water into the systemic circulation.

### 4.4.2 Pharmacodynamics

Tolvaptan's blockade of the V2 receptor results in an increase in urine output and decrease in urine osmolality. Drug effects on urine osmolality were taken as an indicator of the adequacy of blockade of the receptor in renal cysts and are discussed in greater detail in sections 6.1.8 and 6.1.9.

*Urine volume:* In subjects with ADPKD and an eGFR > 60 mL/min/1.73m<sup>2</sup>, treatment with a 90/30 split-dose regimen of tolvaptan for up to 21 days resulted in a mean change from baseline in 24-hour urine volume of ~4.5 L and a mean (SD) 24-hour urine volume of ~6.5 (2.0) L. Lesser treatment effects were seen in subjects with an eGFR < 30 mL/min/1.73m<sup>2</sup>. The mean (SD) 24-hour urine volume in this population was ~5.0 (1.8) L, with a mean change from baseline of ~2.2 L.

*Kidney volume:* Tolvaptan causes an early and reversible decrease in kidney volume at the doses proposed for use. Following 8 days of tolvaptan treatment in 20 subjects, the mean (SD) percent change from baseline in total kidney volume was -1.9% (2.4). After up to 3 weeks of treatment with tolvaptan in 29 subjects, the mean (SD) percent change from baseline was -3.8% (3.1). Approximately 3 weeks post treatment in this study, total kidney volume had returned toward, but not to baseline levels (mean percent change from baseline of -1.6% with a SD of 2.9%).<sup>6</sup> The findings in these trials were consistent with the findings seen in the longer phase 3 trial.

*GFR:* An early and reversible decline in glomerular filtration was demonstrated in the short-term trials referenced above. In subjects with an eGFR > 60 mL/min/1.73m<sup>2</sup> and those with an eGFR between 30 and 60 mL/min/1.73m<sup>2</sup>, measured GFR as assessed using iothalamate clearance decreased by approximately 6-10%. In contrast, no obvious effect on measured GFR was observed in subjects with an eGFR < 30 mL/min/1.73m<sup>2</sup>, though the cohort was similar in size to the two cohorts with more preserved renal function. The clinical significance of this finding is not clear. According to the applicant, decreases in urine osmolality mediated by tolvaptan are thought to play a role in the acute decrease in GFR.

*AVP:* Plasma concentrations of AVP may increase during therapy (~2-9 pg/mL).

#### 4.4.3 Pharmacokinetics

Tolvaptan is >99% protein bound and is a substrate of CYP3A4 and MDR1 (P-gp). It is also an inhibitor of P-gp. The drug is mostly eliminated hepatically and has a terminal half-life of around 8-10 hours.

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

Tolvaptan's ADPKD development program consisted of a phase 3 randomized, double-blind placebo-controlled trial, uncontrolled extension studies and other "supportive trials" that were generally small in size and/or of short duration. The applicant's phase 3 trial (156-04-251) is described in section 5.3; other trials in subjects with ADPKD are shown in the tables below. In addition to these trials, the applicant submitted the results of: a PK and PD study in subjects

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<sup>6</sup> Results are from trials 156-06-260 and 156-09-284. For additional information on these trials, see section 5.1.

with varying degrees of renal impairment (156-09-282); a dose-strength equivalence and food effect study in healthy subjects (156-11-295); a relative bioavailability study comparing modified release and immediate release formulations (156-07-262); and a single dose PK-PD study in healthy male Korean subjects (156-KOA-0801).

Table 2. Phase 1 and 2 trials in subjects with ADPKD

<b>Trials</b>	<b>Period of enrollment; status of enrollment; number enrolled</b>	<b>Dose</b>	<b>Duration of exposure</b>	<b>Primary endpoint(s)</b>
156-04-248	Oct 2004; Completed Oct 2004; N=11	Tolvaptan: 15 mg, 30 mg, 60 mg, 120 mg	Single ascending doses of tolvaptan or matching placebo separated by 3-day washout	Tolvaptan PK parameters; urine osmolality
156-04-249	Nov 2004; Completed Mar 2005; N=37	Tablet: 15 mg BID, 30 mg am + placebo pm, 30 mg am + 15 mg pm, 30 mg BID	5 days	Tolvaptan PK parameters; urine osmolality
156-04-001 Japan/ Non-IND	Dec 2004; Completed May 2005; N=19	Tolvaptan Group I: 15 mg single dose, 30 mg single dose, 15 mg BID  Group II: 15 mg single dose, 30 mg single dose, 30 mg QD	Group I: Single ascending 15- and 30-mg doses, 15 mg BID for 5 days; Treatments separated by a 1-3 week washout  Group II: Single ascending 15- and 30-mg doses, 30 mg QD for 5 days, treatments separated by a 1-3 week washout	Urine osmolality
156-06-260	Mar 2007; Completed Feb 2010; N=20	Tolvaptan 45/15 mg split dose (am/pm)	8 days	Glomerular filtration rate, effective renal plasma flow, filtration fraction
156-09-284	Oct 2010; Completed Nov 2011; N=29	Tolvaptan 45/15 mg, 60/30 mg 90/30 mg, split dose (am/pm) (titrated)	21 days	Glomerular filtration rate, effective renal plasma flow, filtration fraction

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Trials	Period of enrollment; status of enrollment; number enrolled	Dose	Duration of exposure	Primary endpoint(s)
156-09-290*	Nov 2011; Ongoing; 180 planned	Tolvaptan : 60/30 mg split dose (am/pm)  Tolvaptan MR Capsule: 50 mg QD, 80 mg QD	8 weeks	Percent change from baseline in TKV at Week 3
156-09-285*	Nov 2010; Completed Jun 2011; N=25	Tolvaptan IR Tablet and MR Capsule (and matching placebo)  Group 1: 90/30 mg IR, 120 mg MR QD; and either 20 mg MR QD, or 20 mg MR BID, or 60 mg MR QD  Group 2: 20 mg MR QD, 20 mg MR BID, 60 mg MR QD	21 days (7 days for each regimen)	PK/PD

\* Studies related to the development of a MR formulation (conducted under IND 107847)

Table 3. Uncontrolled extension/long-term studies for efficacy and/or safety in patients with ADPKD

<b>Trials</b>	<b>Period of enrollment; status of enrollment; number enrolled</b>	<b>Dose</b>	<b>Duration of exposure</b>	<b>Primary endpoint(s)</b>
156-08-271  Subjects from 156-04-251, 156-04-250, 156-06-260, 156-09-284, 156-09-285, 156-09-290	May 2010; Ongoing; up to 1500	Tolvaptan: 45/15 mg, 60/30 mg, 90/30 mg split dose (am/pm)	24 months (minimum)	baseline (from trial 156-04-251) in total kidney volume and renal function
156-10-003  Non-IND (Japanese subjects from 156-04-251)	Oct 2010; Ongoing; up to 150 planned	Tolvaptan: 45/15 mg, 60/30 mg, 90/30 mg split dose (am/pm)	Until approval in Japan	Combined renal volume, renal function, urine albumin
156-09-003  Non-IND (subjects from 156-05-002)	Dec 2009; Ongoing; 15 planned	Tolvaptan: 15 mg BID	Until approval in Japan	AEs, vital signs, clinical laboratory tests, and ECGs
156-04-250  (includes subjects from 156-04-248 and 156-04-249)	Dec 2005; Completed Jun 2010; N=46	Tolvaptan Titration: 15/15 mg, 30/15 mg, 45/15 mg 60/30 mg, 90/30 mg split dose (am/pm) Fixed Dose: 45/15 mg or 60/30 mg split dose (am/pm)	Dose titration for up to 2 months followed by up to 36 months long-term treatment, with an optional 12-month extension	AEs, vital signs, clinical laboratory tests, ECGs, and physicalexams
156-05-002  Non-IND (includes subjects from 156-04-001)	Jun 2006; Completed Mar 2010; N=17	Tolvaptan 15 mg BID	Up to 36 months long-term treatment	AEs, vital signs, clinical laboratory tests, ECGs, and physical exams

## 5.2 Review Strategy

The Clinical Review focused on the design and conduct of and resulting data from protocol 156-04-251. Efficacy was reviewed by Dr. Thompson; safety was addressed by Dr. Beasley.

### 5.3 Discussion of Individual Studies/Clinical Trials

In support of the proposed indication, the applicant submitted the results of a single phase 3 trial titled “A Phase 3, Multi-center, Double-blind, Placebo-controlled, Parallel-arm Trial to Determine Long-term Safety and Efficacy of Oral Tolvaptan Tablet Regimens in Adult Subjects with Autosomal Dominant Polycystic Kidney Disease”. The trial was conducted at 129 sites in 15 countries.

*Protocol:* The protocol was originally issued on 31 March 2006. The protocol was amended twice- on 28 March 2007 (two months after the trial was initiated) and 10 September 2009; a regional protocol amendment was also issued in Japan in June 2007. Except where noted, the overview provided in section 5.3 is based on the protocol as amended in March 2007. A summary of the changes made in the 2009 protocol amendment and 2007 regional protocol amendment in Japan is provided at the end of section 5.3. A number of the changes implemented in the 2009 amendment were in response to Agency feedback at a June 2009 meeting (see section 2.5).

*Important Trial Dates:* The trial was initiated on 25 January 2007 (date of first signed informed consent). The first subject was randomized on 1 March 2007. The last patient’s last visit was on 23 January 2012. Database lock occurred on 12 April 2012 and the trial was unblinded on 13 April 2012.

#### 5.3.1 Study Design and Objectives

Protocol 156-04-251 was a randomized, placebo-controlled, multi-center study of a split dose regimen of tolvaptan (titrated from 45/15, 60/30, to 90/30 mg BID as tolerated) administered to adult patients with ADPKD for 36 months. The stated primary objective was to evaluate the long-term efficacy of tolvaptan in ADPKD as demonstrated by the rate of renal volume change (% change from baseline) for tolvaptan-treated compared to placebo-treated subjects. Stated secondary objectives included the evaluation of:

- long-term efficacy of tolvaptan in ADPKD as demonstrated by effects on a composite of ADPKD progression clinical markers (hypertension, renal pain, albuminuria and renal function)
- long-term efficacy of tolvaptan in ADPKD using non-composite clinical markers of ADPKD progression
- long-term safety of tolvaptan through standard clinical measures
- pharmacokinetic, pharmacodynamic and exploratory parameters for tolvaptan in ADPKD

#### 5.3.2 Study Population

Key enrollment criteria included: age 18 to 50 (age 20 to 50 for subjects enrolled in Japan), a diagnosis of ADPKD, an estimated GFR  $\geq 60$  mL/min within -31 days of randomization (using Cockcroft-Gault), and a “rapid estimated rate of renal volume increase” as defined by a total kidney size  $\geq 750$  cc by MRI at randomization.

*Reviewer’s comment:* By design, tolvaptan’s phase 3 trial enrolled patients with relatively preserved renal function. According to the protocol, entry criteria specified a GFR  $\geq 60$  because, “Beyond this level, less than 50% of functioning nephrons remain, but are already in a state of

*hyperfiltration and will likely succumb to the progression regardless of intervention.” This approach to studying patients with earlier stages of disease is not unique to the tolvaptan program.<sup>7</sup> Experts in the field have expressed the view that for therapies targeting early growth and expansion of cysts, “It may be futile to administer such agents late in the course of ADPKD, when a host of different processes have combined to produce the fibrotic end-stage kidney.” (Grantham et al, 2006)*

For the purpose of enrollment, ADPKD was defined by the presence of cysts in each kidney:

- 3 if by sonography or 5 if by computed tomography or MRI in those with a family history of ADPKD
- 10 cysts in each kidney by any radiologic method and exclusion of other cystic kidney diseases if there is no family history

Conditions that were to be excluded included: multiple simple renal cysts, renal tubular acidosis, cystic dysplasia of the kidney, multicystic kidney, multilocular cysts of the kidney, medullary cystic kidney and acquired cystic disease of the kidney.

*Reviewer’s comment: Subjects were not genotyped for the purpose of enrollment or during the course of the study.*

### 5.3.3 Procedures

*Randomization:* Patients were randomized by IVRS (2:1 tolvaptan to placebo) with stratification for baseline hypertension (systolic blood pressure > 139 and/or diastolic blood pressure > 89 mmHg or treatment for elevated blood pressure), estimated creatinine clearance (< 80 ml/min using Cockcroft-Gault) and combined renal volume (< 1000 cc). Centralized randomizations were to be performed in each region independently.

*Trial Treatments:* Study drug (administered as multiples of 15 and 30 mg tablets) was to be initiated at 45/15 mg twice daily and then titrated weekly (at scheduled office visits) to 60/30 mg and 90/30 mg if tolerated. Tolerability was to be assessed by asking subjects the following question: “Could you tolerate taking this dose of tolvaptan for the rest of your life, please answer only yes or no?”

Dose could be down-titrated at any time, “depending on their current dose”; subjects unable to tolerate the 45/15 mg dose were to be discontinued from investigational product. Dosing was to occur on waking and approximately 9 hours later, irrespective of meals.

*Schedule of study procedures (see section 7.2.4 for discussion of safety assessments):* During the titration phase, subjects were to be seen at weeks 1, 2 and 3/end of titration. Beginning month 4, subjects were seen to be seen every 4 months until month 36/early termination. During these visits, patients were to be assessed for efficacy events included in the composite

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<sup>7</sup> A phase 2 study of sirolimus in patients with ADPKD limited enrollment to patients with an estimated creatinine clearance of at least 70 ml per minute (Serra et al, 2010). A phase 2 study of everolimus included patients with an estimate GFR as low as 30 mL/min/1.73m<sup>2</sup>. However, in discussing the findings of their study, the manuscript authors noted that patients with advanced cystic disease may be unresponsive to therapies that could improve renal function, and concluded that “...future studies need to address the efficacy of mTOR inhibitors in patients with less-advanced disease.” (Walz et al, 2010)

secondary endpoint. MRI evaluations of kidney volume were to be performed at baseline, months 12, 24 and 36 (+/- 2 weeks)/early termination. The 2009 protocol amendment removed a 7 day follow up telephone contact and added two off study drug follow up clinic visits. Follow up visit #1 was to occur +7 (to +21) days after the month 36/end of treatment visit; follow up visit #2 was to occur +7 (to +21) days after follow up visit #1.

Subjects who discontinued investigational product for reasons other than non-compliance or lost to follow-up were to continue limited participation in the trial for further telephone/remote collection of information on “PKD outcomes”. This telephone/remote contact was to occur at normally scheduled trial visits. According to the protocol, these data were not to be used in the primary analysis, but might be utilized in exploratory analyses.

*Reviewer’s comment: The follow-up of subjects who discontinued study medication prematurely was different from the follow-up of subjects who remained in the trial on study medication. Because subjects who discontinued study medication prematurely were to be followed by telephone/remote contact, efficacy endpoint assessments such as serum creatinine levels, blood pressure, and kidney volume were not, per protocol, reliably captured in these subjects. Instead, investigators were to complete the “Polycystic Kidney Disease Outcomes” Case Report Form. This form asked investigators to check boxes indicating whether, since the last visit, the subject had a clinically significant event related to any of the following 13 “PKD related outcomes”: hypertension, kidney pain, hepatic cysts, hematuria, albuminuria, nephrolithiasis, urinary tract infection, anemia, colonic diverticuli, vascular/cardiac abnormalities, abdominal/inguinal hernia, other “cysts”, or a “significant drop in kidney function (eg, dialysis, transplant)”.*

#### 5.3.4 Endpoints

*Primary endpoint:* The primary endpoint in the phase 3 trial was the rate of renal volume (total, both kidneys) change (normalized as percentage) from baseline. Renal volume was assessed using a central reader. An imaging review charter specified the processes, roles and responsibilities of the imaging assessment service used to perform central readings.

*Secondary endpoints:* The first secondary endpoint was the time to multiple Investigator-reported ADPKD clinical progression events (progressing hypertension, severe renal pain requiring medical intervention, worsening albuminuria, worsening renal function). Efficacy assessments for and definitions of endpoint events are shown in the table below. In 2009, the protocol was amended to include an independent adjudication committee. These adjudicated events were to be used in a sensitivity analysis.

*Reviewer’s comment: All of the components of the composite captured manifestations of disease and perhaps could be viewed in aggregate as a measure of disease burden. However not all of the components of the composite endpoint carried the same clinical significance. It is unknown whether treatment effects on albuminuria will predict treatment effects on outcomes in this disease and the clinical significance of this component, when considered in isolation, is unclear.*

Table 4. Efficacy assessments and endpoint event definitions

Worsening renal function	
Assessments	Renal function was to be assessed using central serum creatinine measurements performed at screening, baseline, week 3 (or end of titration), month 4 and then every 4 months to month 36/end of treatment and at follow-up visits #1 and #2.
Definition of an event*	A “consistent” 25% reduction in the reciprocal serum creatinine from the valued obtained at week 3/ end of titration. “Consistent” was defined as “two consecutive visits separated by 2 weeks including unscheduled assessments”.
Severe renal pain	
Assessments	Subjects were to be asked the following question at screening, baseline, day 1, week 3(or end of titration), and month 4 and then every 4 months to month 36/end of treatment and at follow-up visits #1 and #2: “On a scale of 0 to 10, with zero representing no pain at all and 10 representing the worst pain you’ve ever experienced, what was the worst kidney pain you’ve experienced in the last 4 months?” If the latest assessment was less than 4 months prior, the question substituted “since your last visit” for “in the last 4 months”.  Clinical signs and symptoms that the pain originated in the upper urinary tract (e.g., flank tenderness, evidence of cystic expansion or hemorrhage, upper urinary tract infection, nephrolithiasis) were to be documented.
Definition of an event*	Endpoint events were based on the Investigator’s clinical judgment as to the need for medical intervention. Qualifying interventions included: prescription of narcotic pain relievers, tricyclic antidepressant medications for pain, surgical or invasive radiological procedures, work absence (or other similar limitation of activity) due to the pain, other “last resort” medications, over the counter or prescription analgesics (i.e., medications for which an individual subject might have other relative contraindications such as gastric erosion, bleeding, renal toxicities). Other types of events could qualify if after consultation with the Medical Monitor for the trial, they were judged to be medically significant.
Progressing hypertension	
Assessments	Brachial artery blood pressure measurements were to be made at screening, baseline, day 1, weeks 1, 2, and 3 (or end of titration), month 4, and then every 4 months to month 36/end of treatment and at follow-up visits #1 and #2. Measurements were to be made by a trained trial team member. Measurements were to be repeated at least twice; two additional measures were to be performed if either replicate varied by > 5 mmHg. The average of all valid (technically correct) measures (up to 4) was to be recorded in the CRF.

Definition of an event*	<p>An event occurred if a subject made a categorical increase in blood pressure over two consecutive visits (including an unscheduled visit) or one categorical increase at a visit and another categorical increase at the next consecutive visit (including unscheduled visit). The categories were as follows:</p> <ul style="list-style-type: none"> <li>• normotensive (dBp &lt; 80 and sBP &lt; 120 mmHg and off therapy)</li> <li>• low pre-hypertensive (sBP ≤ 129 and dBp ≤ 84 mmHg but not normotensive and off therapy)</li> <li>• high-pre-hypertensive (sBP ≤ 139 and dBp ≤ 89 mmHg but not normotensive/low-prehypertensive and off therapy)</li> <li>• hypertensive (sBP &gt;139 and/or dBp &gt; 89 mmHg or on anti-hypertensive therapy).</li> </ul> <p>The higher of the systolic or diastolic blood pressure was to determine category.</p> <p>Initiation of antihypertensive medication, increasing doses in anti-hypertensive medication, or introducing a new prescription of anti-hypertensive medication also qualified as an event.</p>
<b>Worsening albuminuria</b>	
Assessments	<p>Urine samples (provided as a mid-stream, clean catch sample) were to be collect at screening, baseline, week 3 (or end of titration), month 4 and then every 4 months until month 36/end of treatment and at follow-up visits #1 and #2. Samples were to be assessed using a central laboratory.</p>
Definition of an event*	<p>An endpoint event was counted when a subject increased from one albuminuria category to the next in 2 of 3 sequential observations (including unscheduled evaluations). A maximum of two albuminuria events was allowed for a subject. The following albuminuria categories were used:</p> <ul style="list-style-type: none"> <li>• A= "Normal" (urine albumin/ creatinine of &lt; 2.8 mg/mmol female or &lt; 2.0 mg/mmol male)</li> <li>• B= "microalbuminuria" (urine albumin/ creatinine of 2.8-28 mg/mmol female or 2.0-20 mg/mmol male)</li> <li>• C= "overt proteinuria" (urine albumin/ creatinine of &gt;28 mg/mmol female or &gt;20 mg/mmol male).</li> </ul> <p>The baseline category was to be determined by the first two (or three using the best 2 of 3, if first two were discordant) values. Values were considered invalid in the presence of gross hematuria or UTI.</p>

\*The 2009 Protocol Amendment added post-treatment assessments at follow-up visits #1 and #2 but specified that the primary composite endpoint analysis would only include events occurring during the double-blind treatment period. However, worsening renal function, albuminuria and hypertension observed at the end of treatment visit (i.e., the early termination visit or month 36 visit) could be confirmed as a clinical ADPKD progression event using the data collected at post-treatment follow-up visit #1.

Other secondary endpoints are shown below and were to be tested sequentially after the key composite secondary; these endpoints were re-ordered when the protocol was amended in 2009.

Table 5. Non-composite secondary endpoints

Secondary Endpoint	Order of testing	
	Protocol as amended in 2007	Protocol as amended in 2009
For subjects who are non-hypertensive at baseline, change from baseline for resting mean arterial pressure (MAP) at scheduled clinic visits up to point of exposure to anti-hypertensive therapy for any reason	1	2
For subjects who are non-hypertensive at baseline, time to progress to a) high-prehypertension (sBP > 129 and/or dBP > 84) or b) hypertension (sBP >139 and/or dBP >89 mm Hg) or c) requiring anti-hypertensive therapy	2	4
For subjects who are taking anti-hypertensive therapy at baseline, percentage with clinically sustained decreases of BP leading to a sustained reduction in antihypertensive therapy compared to baseline (while taking investigational product) at visit Months 12, 24 and 36 for hypertensive subjects	3	5
Rate of GFR change from post-dose baseline (End of Titration) to last on-drug trial visit (using the reciprocal of serum creatinine as the primary measure)	4	1
Change from baseline in kidney pain as assessed by 1-10 pain scale as average AUC between baseline and last trial visit or last visit prior to initiating medical (narcotic or tricyclic) or surgical therapy for pain	5	3

### 5.3.5 Study Sample Size and Power Considerations

Assuming an average progression of renal volume of 7% per year in the placebo arm, an average rate reduction of 20% with tolvaptan and a 20% withdrawal rate for the trial, ~600 subjects would be needed to compare the tolvaptan to placebo arm, at an overall alpha of 0.05 for the primary efficacy endpoint (controlling for two planned interim analyses) and targeting 85% power.<sup>8</sup> Approximately doubling this number would attain the power equivalent of two independent trials, and also improve the ability to evaluate tolvaptan's effect on the secondary composite endpoint (because of the lack of reliable information on the event rate of the secondary composite endpoint, the sample size needed for the secondary composite endpoint was not known/determined).

A blinded sample-size recalculation was to be conducted after 1000 subjects had been enrolled or 200 subjects completed their 12 month visit, whichever came first. This recalculation was to address sample size requirements/power considerations related to the primary endpoint and secondary composite endpoint. The recalculation showed that with a total sample size of 1400 and an alpha of 0.05, the trial should have at least 90% power to test a 20% reduction in the composite secondary endpoint.

<sup>8</sup> A protocol amendment in 2009 removed the two planned interim analyses.

### 5.3.6 Statistical Analysis Plan

The initial statistical analysis plan was issued on 10 January 2010; revised versions were issued on 1 April 2011 and on 2 April 2012. Database lock occurred on 12 April 2012 and the trial data were unblinded on 13 April 2012.

As might be expected given the dates of the various versions of the statistical analysis plan relative to the trial's completion date, a significant amount of study data had been amassed by the time the initial plan was issued and at the time of the subsequent revisions.

Table 6. Enrollment and endpoint events by statistical analysis plan date

Statistical Analysis Plan (SAP) Version	SAP date	Enrollment N (%)	Endpoint Events* N (%)
SAP Version 1	Jan 10, 2010	1445 (100%)	1122 (64%)
SAP Version 2	Apr 1, 2011	1445 (100%)	1644 (94%)
SAP Version 3	Apr 2, 2012	1445 (100%)	1758 (100%)

[Source: Response to Information Request, receipt date June 21, 2013; Table 1]

\*Counts are based on a comparison of event dates and statistical analysis plan finalization dates.

According to the applicant, the number of events available in the dataset at these dates would be expected to be "much less" since the trial used paper CRFs.

With regard to the 2011 and 2012 revisions, both added sensitivity analyses, specified additional computational details of key efficacy endpoint analyses (e.g., rules for mapping events to visits) and "clarified" text/terminology in the document. A late change with perhaps the greatest potential to affect efficacy results was a 2012 "clarification" on the window for inclusion of events/data in the key efficacy endpoint analyses. The 2010 version of the statistical analysis plan indicated that the primary endpoint and composite secondary endpoint analyses would be performed on events occurring during the "double blind treatment period". The 2012 revision specified that the double-blind treatment period would be defined as a period from the first dose of study medication to the end of a two-week window of the last dose of study medication; it also clarified that this window would be used in analyses of the non-composite secondary endpoints. The 2012 revision also added a sensitivity analysis including events beyond the two week window for the composite secondary endpoint, hence providing a potential means to address the impact of this late "clarification" on the composite endpoint findings.

*Reviewer's comment: The results of this analysis and an analysis of secondary composite endpoint events occurring before and after finalization of version 1 of the statistical analysis plan can be found in section 6.1.5.*

*Primary endpoint analysis:* The primary endpoint was the rate of total renal volume change (normalized as percentage) from baseline. The primary analysis was a linear mixed effect model (Laird and Ware) fitted to the log-transformed total renal volume repeated measures data. The primary analysis was to be performed on an observed cases dataset, i.e., only renal volume data observed at baseline and post-baseline visits during the double blind treatment period (including Month 36/early termination). The Wald test was to be used to test the treatment time interaction. A Mixed Model Repeated Measures (MMRM) analysis applied to the repeated measures of change from baseline in total renal volume (based on logarithm transformed data) was specified as a sensitivity analysis.

*Secondary composite endpoint analysis:* The key secondary composite endpoint was the time to multiple ADPKD clinical progression events (progressing hypertension, severe renal pain, worsening albuminuria and worsening renal function). Clinical ADPKD progression events occurring during the double-blind treatment period *from* 1) the date of first dose of study medication (for hypertension, albuminuria and kidney pain) or 2) the completion of the titration phase (for renal function) *to* the date of trial completion/early termination, or two weeks post last dose of study medication, whichever comes first, were included in the analysis.<sup>9</sup> An extended Cox model (the Anderson-Gill model/approach) was specified for the analysis.

The analysis excluded data from visits for subjects who withdrew from the investigational product administration but continued to have telephone contact for “PKD Outcomes”. Events of worsening renal function and albuminuria were to be derived from data considered reliable by investigators; data deemed unreliable by investigators were to be treated as missing values in the event derivation. If a subject had more than one event at a visit, the events were to be collapsed into one event for the purpose of the primary analysis. The statistical analysis plan also contained more detailed rules for counting/ranking events in the composite.

*Non-composite secondary efficacy endpoints:* The non-composite secondary endpoints were to be tested with a two-sided alpha level of 0.05 in the sequence in which they were listed in the protocol. The analysis of the first non-composite secondary efficacy endpoint (the rate of GFR change from the post titration baseline to a two-week window of the last dose of study medication) was to be similar to the analysis of the primary endpoint, except that the GFR value, instead of the log10 scale of the GFR value, was to be used in the slope analysis, with the baseline value used as a covariate in the model. The analysis was to be performed on observed values and was to exclude observations at Follow-up visits #1 and #2. Like the key composite secondary endpoint, creatinine measurements deemed unreliable by the investigator were to be excluded from the primary analysis but included in a sensitivity analysis. An MMRM analysis was specified as a sensitivity analysis.

The computational details of the other secondary endpoints were also addressed in the statistical analysis plan, but are not discussed in this review.

### 5.3.7 Adjudication Process

A Clinical Endpoint Committee was responsible for providing operational definitions for the adjudication of the clinical progression events and for adjudicating these events. An independent, parallel, blinded review process was used. Potential endpoint events were assigned to two reviewers for adjudication; for discordant decisions, a 3<sup>rd</sup> reviewer was used. Reviewers also had the option of requesting committee discussion of the event.

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<sup>9</sup> Though post-treatment assessments were made at follow-up visits #1 and #2, the primary composite endpoint analysis was limited to events occurring during the treatment period. Worsening renal function, albuminuria and hypertension observed at the end of treatment visit (i.e., the early termination visit or month 36 visit) could be confirmed as a clinical ADPKD progression event using the data collected at post-treatment follow-up visit #1.

Potential endpoint events were identified by triggers; an overview of these triggers is provided in the table below.

Table 7. Triggers for event adjudication

Potential endpoint event	Overview of triggers
Renal Function	Two consecutive-visits (at least 2 weeks apart) with at least a 25% reduction in reciprocal serum creatinine from post-titration baseline and any subsequent increase of this amount from a prior event; reductions from post-titration baseline at an early termination visit did not require confirmation
Renal Pain	Post-baseline prescribed surgical or invasive radiological procedures, introductions of new narcotic/tricyclic antidepressant medications and dose increases (excluding events occurring on Day 1 or Day 2 post-randomization), prescribed medical leave/activity restrictions/non-narcotic medication for renal pain
Hypertension	<p><i>Potential BP category events:</i> For patients not on anti-hypertensive therapy at baseline: two-consecutive-visits with higher categories compared to the baseline category, up to the first visit when a subject starts taking antihypertensive medication for treatment of hypertension; an increase in category compared to baseline at an early termination visit did not require confirmation</p> <p><i>Potential anti-hypertensive medication events:</i> Non-oral anti-hypertensive medications (whether acute or chronic), post-baseline introductions of new anti-hypertensive medications and all dose increases (excluding medication introductions or dose increases occurring on Day 1 or Day 2 post-randomization)</p>
Albuminuria	Three-consecutive-visits with higher categories compared to baseline at the first visit in the series and at least one of the second or third visits ; an increase in category compared to baseline at an early termination visit did not require confirmation

Though the CEC could not change the endpoint definitions in the protocol, it could provide clarifications to definitions. For hypertension events, the CEC charter specified that minor changes in blood pressure that resulted in a categorical change would not qualify as an endpoint event. Instead, a change in blood pressure of 10 mmHg systolic and /or 5 mmHg diastolic, at two consecutive visits, leading to above normal blood pressure, was needed as evidence of progression of hypertension. Similarly, for albuminuria events, minor changes that resulted in a categorical change would not qualify as an endpoint event. Instead, a minimum of doubling of the albumin/creatinine ratio (from baseline) in association with a categorical shift at 2 of 3 consecutive visits would be taken as evidence of progression of albuminuria.

### 5.3.8 Protocol Amendments

An overview of the 2009 protocol amendment and 2007 Japan regional protocol amendment is provided in the table below.

Table 8. Overview of protocol amendments

Japan Regional Amendment 1 18 June 2007	<ul style="list-style-type: none"> <li>For subjects in Japan, added monthly study site visits and required hospitalization for assessments performed on randomization day 1 and at 1 and 2 weeks after dose titration. These changes were made to address concerns that relatively few Japanese subjects had participated in tolvaptan trials and doses as high as 120 mg/day had not been used in this population</li> </ul>
10 September 2009 Protocol Amendment	<ul style="list-style-type: none"> <li>added two off study drug follow up clinic visits</li> <li>provided a more detailed definition of the composite endpoint and added an independent adjudication committee to review secondary composite endpoint events</li> <li>changed the order of testing non-composite secondary efficacy endpoints</li> <li>removed the interim analyses to evaluate the effect of tolvaptan on the primary endpoint and added information on the results of the blinded sample size re-calculation performed in October 2008</li> <li>specified that data collected after resuming study medication for subjects whose study medications were interrupted for at least 30 consecutive days in the study maintenance phase would be excluded from all efficacy analyses if the data fell in an interval starting from the beginning of the interruption period with the interval length equal to 2 times the interruption period<sup>10</sup></li> <li>added a MMRM analysis as a sensitivity analysis for the primary endpoint</li> <li>added sensitivity analyses for the secondary composite endpoint: (1) an analysis including all events observed from week 3/end of titration to the end of the double blind treatment period (2) analyses using the adjudicated data</li> <li>clarified that events of worsening blood pressure, albuminuria and reciprocal serum creatinine at early termination or the month 36 visit may be confirmed as endpoint events by using the data collected at post-treatment follow-up visit #1</li> <li>modified the exploratory endpoints</li> <li>added provisions for subjects who become unintentionally pregnant during trial participation</li> </ul>

## 6 Review of Efficacy

### Efficacy Summary

In support of the proposed indication, the applicant submitted the results of a single, randomized, double-blind, placebo-controlled phase 3 trial. The primary endpoint of the trial was the rate of total renal volume change, an endpoint not currently accepted by the Agency as a surrogate endpoint. The trial's first secondary endpoint was the time to multiple ADPKD clinical progression events (progressing hypertension, severe renal pain, worsening albuminuria and worsening renal function). From a regulatory perspective the trial's first secondary endpoint was considered the key efficacy endpoint.

<sup>10</sup> In response to this change, the Agency sent a follow-up letter advising the sponsor that "Primary analyses of key efficacy endpoints should be performed on an intent-to-treat population and events occurring concurrent with or proximate to a period of study medication interruption should not be excluded."

The trial was successful in establishing an effect on the primary endpoint and key composite secondary endpoint in the prespecified primary analyses. According to the applicant, the HR for the time to multiple ADPKD clinical progression events was 0.865 (95% CI 0.775 to 0.965,  $p = 0.0095$ ). According to Dr. Lawrence's statistical review, replacing the variance estimate used in the analysis with a more valid estimate resulted in a  $p$ -value of 0.02. Beyond this issue, there was a significant amount of missing data in the trial, raising concern about the reliability of efficacy findings. Treatment effects also varied greatly across the components of the composite further complicating interpretation of the endpoint results. Both of these factors are considered in greater detail below. In addition, tolvaptan has acute effects on renal function and kidney volume that differ from its chronic effects; Dr. Lawrence's review addresses the statistical implications of this issue.

Subjects who discontinued study medication prematurely were not followed for key efficacy outcomes after discontinuing therapy. Over the course of the trial, a sizeable portion of the study population discontinued study medication, particularly in the tolvaptan arm (23% of tolvaptan subjects compared to 14% of placebo subjects). Some of these randomized subjects never entered into efficacy endpoint analyses<sup>11</sup>; others contributed information for only a limited period of time. There is no satisfactory way to account for these missing data and the applicant's prespecified primary analysis of the composite secondary endpoint does not adequately address the problem. In an analysis assuming 100% of placebo risk once a tolvaptan subject discontinued from the trial (a plausible assumption), the  $p$ -value for the composite endpoint rose to 0.04. In an analysis assuming 110% of placebo risk once a tolvaptan subject discontinued from the trial (what might be viewed by some as a plausible assumption or possibly a reasonable penalty for the missing data), the  $p$ -value rose to 0.07.

While the  $p$ -value for the composite endpoint was not robust, it is also true that treatment effects varied greatly across the components. The HR for the worsening renal function component (defined as a consistent 25% reduction from a post-titration baseline in the reciprocal serum creatinine) was 0.39 with a nominal  $p$ -value  $< 0.0001$ . The HR for the severe renal pain component of the composite, defined as pain requiring medical intervention, was 0.64 with a nominal  $p$ -value  $< 0.01$ <sup>12</sup>. In contrast, analyses of the hypertension and albuminuria components of the composite did not suggest a treatment effect. Clearly, issues of multiplicity limit the interpretation of these HRs and  $p$ -values and it is important to consider these findings in the context of other trial data.

Other analyses supported the findings for the renal function component of the composite, and thus the conclusion that tolvaptan was effective in slowing the loss of renal function in the study population. A prespecified analysis of the next secondary endpoint in the testing chain, the rate of GFR change from the post-titration period to the last on drug trial visit, showed an  $\sim 1$  mL/min/1.73m<sup>2</sup> difference in the rate of change in renal function per year in the two treatment arms. An analysis of baseline factors including renal function, hypertension and kidney volume did not suggest that tolvaptan subjects with missing follow-up data had more severe underlying

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<sup>11</sup> See also discussion in Dr. Lawrence's review on the use of a post-randomization creatinine value as the "baseline value" in efficacy endpoint analyses.

<sup>12</sup> Causes of renal pain events were not systematically captured. Other data collected in the trial suggested a lower incidence of hematuria, urinary tract infections and, to some extent, nephrolithiasis in the tolvaptan arm relative to placebo.

renal disease than those who remained in the trial and sensitivity analyses addressing data missing not at random were also supportive of tolvaptan's efficacy in slowing the loss of renal function.

In contrast, an analysis looking at changes in renal pain scores over time in patients not on pain medication at baseline (~96% of study subjects) did not suggest an obvious benefit to treatment. The mean baseline pain score in this population was also low (less than one based on a Likert scale of 0-10 with zero representing no pain) and did not change significantly over time, suggesting that for many subjects in the trial, pain did not significantly impact day-to-day function. In addition, the endpoint was subjective, and because of the drug's aquaretic effects, it may have been difficult to maintain blinding. Subjects who discontinued study medication early also appeared to be more likely to have a history of renal pain, though this finding was more apparent in the placebo arm. Hence, while the findings for the renal pain component of the composite appear to be consistent with other data showing that tolvaptan targets cyst growth and formation, at this time it may be hard to support a conclusion beyond that.

Reviewer's conclusions on efficacy: In sum, the totality of the evidence indicates that tolvaptan has activity in treating the renal manifestations of the disease, and specifically, that tolvaptan was effective in slowing the rate of loss of renal function in the study population. Because of the missing data, the size of tolvaptan's effect on renal function remains unclear. Treatment effects on kidney volume and renal pain events requiring medical intervention were supportive of tolvaptan's effect on disease progression.

The clinical significance of tolvaptan's effect in slowing the rate of loss of renal function is discussed in section 1.2. If tolvaptan's safety profile had been reassuring, it would have been reasonable to consider approval.

## 6.1 Indication

The proposed indication is "to slow kidney disease in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease".

### 6.1.1 Methods

In support of the proposed indication, the applicant submitted the results of a randomized, double-blind, placebo-controlled phase 3 trial. The trial was conducted in 1445 adult patients with ADPKD and relatively preserved renal function (an estimated GFR  $\geq$  60 mL/min by the Cockcroft-Gault equation) who were felt to be at risk of rapid progression of their disease as indicated by a total kidney size  $\geq$  750 cc. The discussion that follows describes the efficacy findings in that study. For an overview of trial design, see section 5.3.

### 6.1.2 Demographics

Baseline demographics were similar in the two treatment arms (see tables below). The mean age of study subjects was 39 years (range of 18 to 51) and 52% were male. The mean estimated GFR was 82 mL/min/1.73 m<sup>2</sup> (CKD-EPI) and total kidney volume (TKV) was 1692 cc (height adjusted 972 cc/m). Approximately 79% of subjects had hypertension at baseline.

According to the sponsor’s classification, 84% of subjects were Caucasian, 13% Asian, and ~3% were Hispanic, Black or “Other”.

Table 9. Baseline demographics

Characteristic	Tolvaptan N=961	Placebo N=484
Male	51.5%	51.9%
Mean Age (range)	38.6 (18-51)	38.8 (18-50)
Stratification factor		
Hypertension	79.6%	78.9%
Estimated creatinine clearance <80 ml/min	25.2%	26.9%
Total kidney volume ≥ 1000 ml	79.5%	79.1%
Mean (SD) systolic blood pressure — mm Hg	129.3 (13.1)	130.1 (13.9)
Mean (SD) diastolic blood pressure — mm Hg	82.6 (9.6)	83.5 (10.0)
Mean (SD) TKV	1704.8 (921.3)	1667.1 (872.3)
Mean (SD) height-adjusted TKV	978.6 (514.8)	957.9 (482.8)
Mean (SD) CrCl — ml/min	104.0 (32.8)	103.8 (35.4)
Mean (SD) eGFR* — ml/min/1.73 m2	81.3 (21.0)	82.1 (22.7)
Race		
Caucasian	84.3%	84.3%
Asian	12.6%	12.8%
Black	1.7%	0.6%
Hispanic	1.4%	1.9%
Other	0.1%	0.4%

[Source: Reviewer’s analysis (Sponsor’s datasets=Dose0, mri0, vital0 and grf0; reviewer’s filename=demographics)] \*Calculated using CKD-EPI

The two treatment arms also appeared to be relatively well matched in other aspects of their disease.

Table 10. Other ADPKD-related medical history

	Tolvaptan N=961	Placebo N=484
Mean age at diagnosis	27.3	27.6
History of kidney pain	51.6	49.4
Presence of hepatic cysts	59.4	60.1
Nephrolithiasis	19.5	22.5
Upper urinary tract infection	30.2	33.9
Hematuria	35.2	33.9
Proteinuria	24.2	24.0

[Source: CSR, table 8.3-1 and Reviewer's analysis (Sponsor's dataset=kidpncm0; reviewer's filename=demograhpics) ; 1 placebo subject gave discrepant results at screening and baseline.

The majority of subjects were taking one or more antihypertensive medications at baseline (77% in both treatment arms) with 71% of tolvaptan and 72% of placebo subjects taking an agent that acts on the renin-angiotensin system. Analgesic use for kidney pain was reported in 5.1% and 5.8% of tolvaptan and placebo subjects, respectively. The most commonly used medication for kidney pain was paracetamol (approximately 2% of subjects in both treatment arms).

Twenty-six percent of study subjects were enrolled from sites in the U.S.; the percentage of subjects enrolled from other countries is shown below.

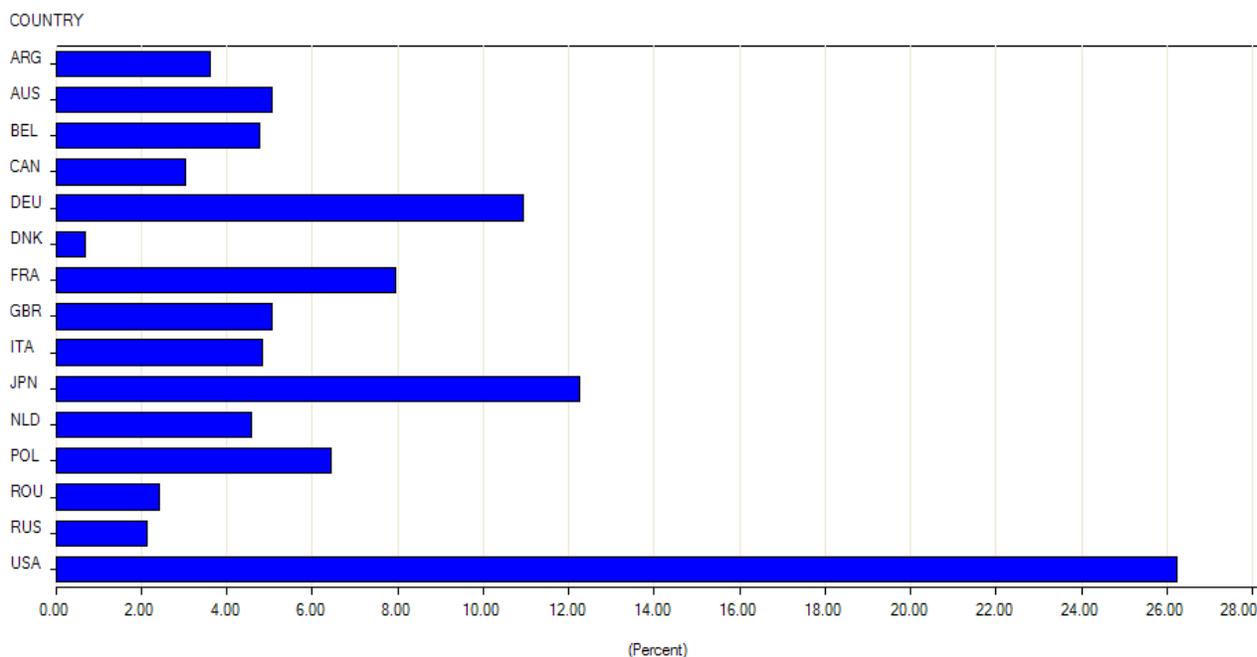


Figure 1. Enrollment by geographic region

[Source: Reviewer's analysis]

### 6.1.3 Subject Disposition

Of 2122 screened subjects, 667 (31.4%) were screen failures. According to the applicant, 78.6% of screen failures did not meet entry criteria: 370 subjects (54.7% of total screen failure) did not have a total renal size of 750cc by MRI at randomization and 119 subjects (17.6% of total screen failures) did not have an estimated GFR  $\geq$ 60 mL/min within -31 days of randomization. Other reasons given for screen failure were: subject withdrew consent to participate (6.6%), subject was withdrawn from participation by the investigator (2.5%) and “other reasons(s)” (12.6%).

A total of 1445 subjects were randomized; the disposition of these subjects is shown in the table below. Compared to the placebo arm, more subjects in the tolvaptan arm discontinued study medication prematurely. The most common reason for discontinuation of study medication in the tolvaptan arm was an adverse event. The incidence of discontinuations because of an adverse event was ~ 3-times higher in the tolvaptan compared to the placebo arm; other reasons for discontinuation of study medication were reported at a similar incidence in the two treatment arms. Subjects who discontinued study medication prematurely were to have telephone/remote collection of information for what was termed “PKD outcomes” (see section 5.3 for further description). Because these subjects were not required to return for the protocol specified efficacy endpoint assessments (e.g., serum creatinine measurements), follow-up information in these subjects is incomplete.

Table 11. Subject disposition

	Tolvaptan n (%)	Placebo n (%)
Randomized	961	484
Treated	961	483
Completed study on study medication	740 (77.0%)	417 (86.2%)
Discontinued study medication prematurely	221 (23.0%)	67 (13.8%)
Adverse event	148 (15.4%)	24 (5.0%)
Subject withdrew consent	50 (5.2%)	30 (6.2%)
Lost to follow up	15 (1.6%)	8 (1.7%)
Investigator withdrew subject	3 (0.3%)	4 (0.8%)
Subject met Withdrawal criteria	4 (0.4%)	0 (0%)
Protocol deviation	1 (0.1%)	1 (0.2%)
Discontinued study medication prematurely and followed for “PKD outcomes”*	102 (10.6%)	27 (5.6%)
Discontinued study medication prematurely and followed until month 36 for “PKD outcomes”*	70 (7.3%)	19 (3.9%)

[Source: Reviewer’s analysis (Sponsor’s datasets=ds and Dose0; reviewer’s filename=disposition) and tables CT 1.2 and 1.3 of CSR 156-04-251 Amendment 1]

\*Different from efficacy endpoints (see section 5.3 for further description)

The time course for discontinuation of study medication is shown in the figure below. By month 4, 10.3% of tolvaptan subjects and 2.3% of placebo subjects had terminated the trial based on vital signs data. In contrast, after month 4 the incidence was only slightly greater in the tolvaptan arm (~12.6%) compared to the placebo arm (~11.5%).

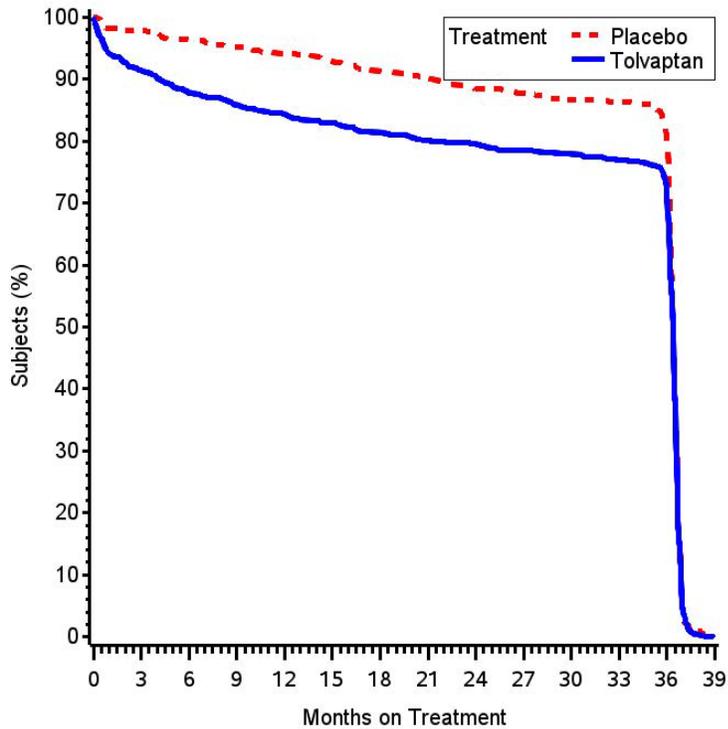


Figure 2. Time to discontinuation of study medication

[Source: Dr. Beasley]

A history of renal pain, reported at baseline, appeared to be more common in subjects who discontinued study medication prematurely compared to subjects who completed the study on study medication. Analyses of baseline GFR, kidney volume and history of hypertension did not suggest obvious differences in the severity of baseline renal disease between subjects who discontinued study medication and those who did not.

Table 12. Characteristics of subjects who discontinued study medication prematurely

	Completed		Discontinued	
	Tolvaptan N=737	Placebo N=415	Tolvaptan N=221	Placebo N=67
GFR, CKD-EPI				
Mean	80.8	81.7	83.2	84.6
Median	80.3	79.6	83.7	84.0
Total Kidney Volume				
Mean	1696.1	1653.6	1734.0	1751.3
Median	1480.2	1452.6	1440.5	1491.3
History of Hypertension	81.8%	78.4%	72.4%	82.1%
History of Renal Pain	50.4%	46.5%	55.7%	67.2%

[Source: Reviewer's analysis (Sponsor's datasets=Dose0, gfr0, mri0 and kidpncm0; reviewer's filename=demographics)]

#### 6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint was the rate of total renal volume change (normalized as percentage) over 3 years. The primary endpoint analysis, performed on an observed cases dataset, excluded ~14.8% of randomized subjects in the tolvaptan arm and ~5.4% of subjects on placebo. In those included in the analysis, the rate of change was 2.8% per year in the tolvaptan arm (n=819) and 5.5% per year in the placebo arm (n=458), a 49% reduction in slope. The p-value, derived from testing the time treatment interaction using a linear mixed model, was <.00001, however, as noted in Dr. Lawrence's statistical review, important assumptions of this model were violated.

In a mixed model repeated measures analysis, a prespecified sensitivity analysis meant to account for nonlinearity, a greater treatment effect on TKV was demonstrated in the first year compared to later years. While an increase in TKV of 4.62% was observed in the placebo arm at year one, the tolvaptan arm exhibited negative TKV growth (a decrease by 1.65%) over this time period. In subsequent years, TKV increased in both arms. The initial treatment effect persisted, however, relative to the first year, smaller incremental treatment effects on TKV were observed during the second and third years. The treatment effect in the first year was -6.3 % (tolvaptan minus placebo TKV growth). At months 24 and 36, the treatment effect was -8.2% and -9.2%, respectively. A model incorporating both acute and chronic treatment effects on TKV can be found in Dr. Lawrence's review. As noted in section 4.4.2, an early and reversible treatment effect on TKV was also observed in short-term trials of tolvaptan in patients with ADPKD.

#### 6.1.5 Analysis of Secondary Endpoints(s)

##### *Composite endpoint findings*

The first secondary endpoint was the time to multiple ADPKD clinical progression events (progressing hypertension, severe renal pain, worsening albuminuria and worsening renal function). Based on the prespecified analysis, there were 44 events per 100 follow up years in the tolvaptan arm compared to 50 events per 100 follow up years in the placebo arm. The

applicant calculated a HR of 0.865 (95% CI 0.78 to 0.97, p = 0.01). According to Dr. Lawrence’s statistical review, replacing the variance estimate used in the analysis with a more valid estimate results in a p-value of 0.02. The HR for the time to the first event also favored tolvaptan (HR of 0.83, 95% CI 0.72 to 0.94, p = 0.005). The findings in the U.S. were consistent with the findings seen in the population as a whole (HR of 0.85, 95% CI 0.66 to 1.08, p=0.18 for time to multiple events). An analysis of adjudicated events produced results that were similar to the results of the prespecified primary analysis of the composite secondary endpoint (HR=0.85, p-value=0.004).

Table 13. Time to multiple and first ADPKD clinical progression event(s)

	Time to multiple events		Time to first event	
	Tolvaptan N=961	Placebo N=483	Tolvaptan N=961	Placebo N=483
Number of events	1049	665	572	341
Events/100 follow up years	44	50		
HR	0.87		0.83	
95% CI	0.78, 0.97		0.72, 0.94	
p-value	0.01		0.005	

[Source: Clinical Study Report 156-04-251]

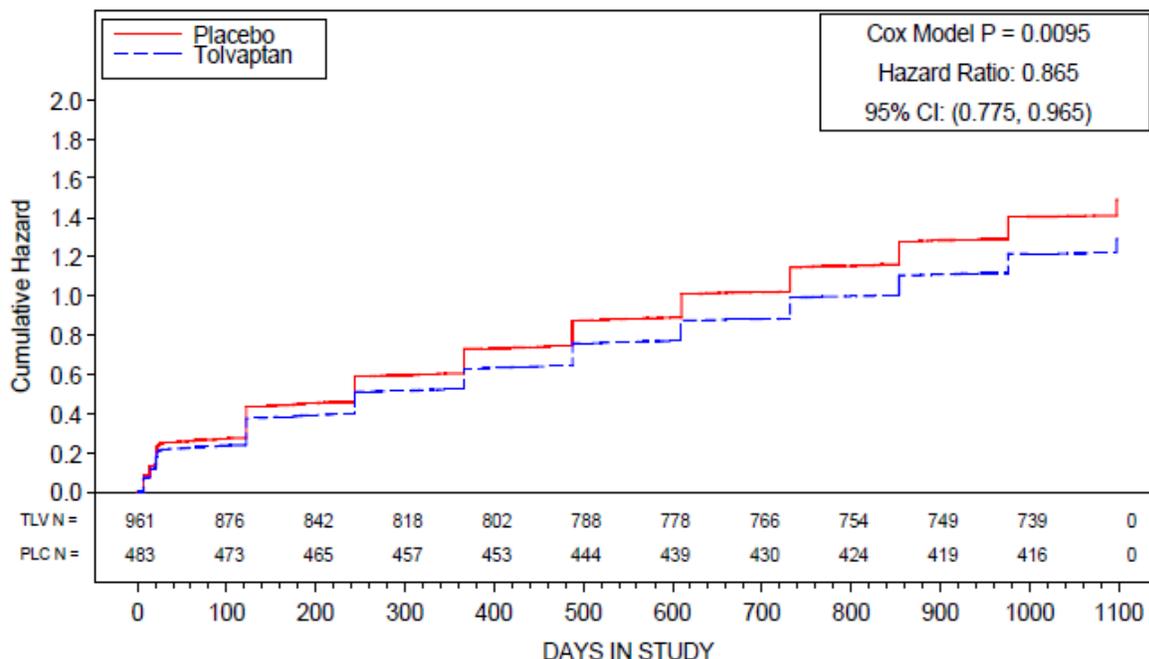


Figure 3. Cumulative hazard function of time to multiple ADPKD clinical progression events  
 [Source: Clinical Study Report 156-04-251, Figure 9.4.1]

As noted in section 6.1.3, follow up information to month 36 was missing in 23% of tolvaptan subjects compared to ~14% of placebo subjects. In an analysis assuming 100% of placebo risk once a tolvaptan subject discontinued from the trial (a plausible assumption), the p-value for the composite endpoint rose to 0.04. In an analysis assuming 110% of placebo risk once a tolvaptan subject discontinued from the trial (what might be viewed by some as a plausible assumption or possibly a reasonable penalty for missing data), the p-value rose to 0.07.

Table 14. Analyses under the assumption of data missing not at random: composite endpoint

Percentage of placebo risk imputed for tolvaptan subjects who discontinued	HR (95% CI)	p-value
100%	0.89 (0.79, 0.99)	0.04
105%	0.89 (0.80, 1.00)	0.05
110%	0.90 (0.81, 1.01)	0.07

[Source: Clinical Study Report 156-04-251; ST-2.7.3.1]

Other sensitivity analyses performed by the applicant showed the following:

- In an analysis including data collected off treatment up to month 36, the HR for the time to multiple events was 0.87 (95% CI 0.78 to 0.97, p=0.01). Including data collected off treatment up to month 36 and using week 3/end of titration as a baseline for event derivation for all events, the HR was 0.89 (95% CI 0.80 to 0.99, p=0.04).

- In an analysis of events (regardless of treatment period) occurring before and after finalization of version 1 of the statistical analysis plan in January 2010, the HR for events occurring before finalization of version 1 was 0.93 (95% CI 0.81 to 1.06, p=0.25) and for events occurring after was 0.79 (95% CI 0.67 to 0.93, p=0.01). The more favorable findings in the latter period was attributed to the increasing impact of renal function events which occurred late in the trial.
- In an analysis in which subjects could only contribute to the treatment group denominator at the last visit where an event occurred or where all 4 components were evaluated, the HR for the primary endpoint analysis was 0.88 (95% CI 0.79 to 0.98, p = 0.02).

*Components of composite endpoint*

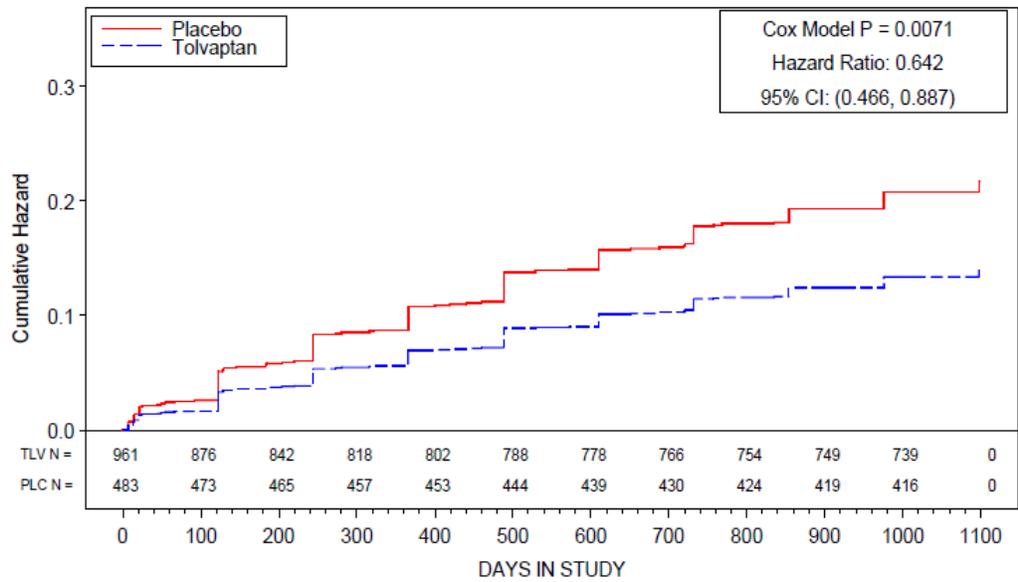
Of the composite components, events of progressing hypertension were reported in the greatest number of subjects and at the greatest frequency. During the double-blind treatment period, 426 tolvaptan subjects (44.3%) and 244 placebo subjects (50.5%) had one or more hypertension events. However tolvaptan did not appear to affect the time to multiple or first hypertension events. Rather, the difference between treatment arms was driven by effects on worsening renal function (HR of 0.39) and severe renal pain (HR of 0.64) - events that occurred at a considerably lower rate.

Table 15. Time to multiple events and first event for components of composite

	Time to multiple events		Time to first event	
	Tolvaptan	Placebo	Tolvaptan	Placebo
<b>Worsening Renal Function</b>	917	476	917	476
Number of events	44	64	42	61
Events/100 follow up years	1.85	4.84		
HR	0.39		0.37	
95% CI	0.26, 0.57		0.25, 0.55	
Nominal p-value	< 0.0001		< 0.0001	
<b>Renal Pain</b>	961	483	961	483
Number of events	113	97	95	78
Events/100 follow up years	4.73	7.30		
HR	0.64		0.65	
95% CI	0.47, 0.89		0.48, 0.88	
Nominal p-value	0.007		0.005	
<b>Hypertension</b>	961	483		
Number of events	734	426		
Events/100 follow up years	30.74	32.05		
HR	0.94			
95% CI	0.81, 1.09			
Nominal p-value	0.42			
<b>Albuminuria</b>	961	483		
Number of events	195	103		
Events/100 follow up years	8.17	7.75		
HR	1.04			
95% CI	0.84, 1.28			
Nominal p-value	0.74			

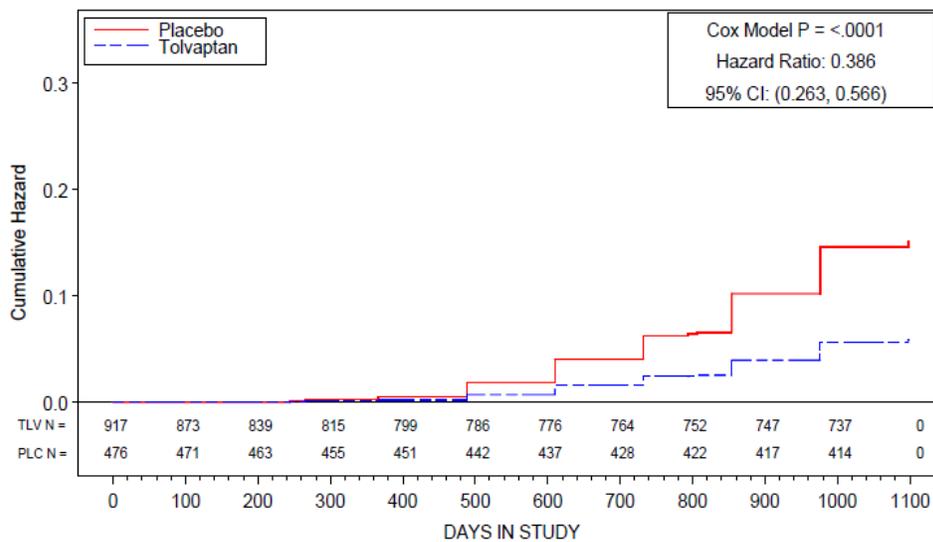
[Source: Clinical Study Report 156-04-251, Table 9.4.3-1, CT-5.2.4.2.1, CT-5.2.5.2]

As shown in the figure below, the treatment effect on the renal pain endpoint was observed relatively early in the course of therapy and appeared to increase over time. Effects on the renal function endpoint were more delayed, likely reflecting the more extended timeframe needed to develop a decline in renal function of this magnitude.



**Worsening Renal Pain**

Figure 4. Cumulative hazard function of time to multiple worsening renal pain events  
 [Source: Clinical Study Report 156-04-251, Figure 9.4.3-1]



**Worsening Renal Function**

Figure 5. Cumulative hazard function of time to multiple worsening renal function events  
 [Source: Clinical Study Report 156-04-251, Figure 9.4.3-1]

A breakdown of renal pain events by intervention category is provided in the tables below.<sup>13</sup> Across the intervention categories, the incidence of pain events appeared to be somewhat lower in the tolvaptan compared to the placebo arm. Of note, in 37 of the 212 pain events (~17%), the “significant intervention for relief of renal pain” consisted of a prescription for paracetamol (acetaminophen). An analysis excluding these paracetamol pain events from the key secondary composite endpoint, produced results that were consistent with analyses in which paracetamol events were included (HR=0.87, p=0.01).

Table 16. Interventions for relief of renal pain: events within the treatment period

	Tolvaptan	Placebo
Total Follow-Up Years	2387	1329
Surgical/Radiologic	5 (0.2)	5 (0.4)
Narcotic/Tricyclic	49 (2.1)	39 (2.9)
Medical leave or activity restriction	14 (0.6)	14 (1.1)
Non-narcotic excluding paracetamol	24 (1.0)	25 (1.9)
Paracetamol	22 (0.9)	15 (1.1)

[Source: Reviewer’s analysis (Sponsor’s dataset=nefren0; reviewer’s filename=efficacy)]

Including off-treatment data adds two narcotic events to the tolvaptan arm and one to the placebo arm and one addition surgical/radiologic event to the placebo arm

\*Table shows numbers of events and events per 100 follow-up years; see footnote in main text for discussion of total event counts

Table 17. Interventions for relief of renal pain: unique subjects with an intervention

	Within Treatment Period		At any time	
	Tolvaptan	Placebo	Tolvaptan	Placebo
Number of subjects	n=961	n=484	n=961	n=484
Surgical/Radiologic	2 (0.2)	5 (1.0)	2 (0.2)	5 (1.0)
Narcotic/Tricyclic	39 (4.1)	25 (5.2)	40 (4.2)	26 (5.4)
Medical leave or activity restriction	14 (1.5)	14 (2.9)	14 (1.5)	14 (2.9)
Non-narcotic excluding paracetamol	24 (2.5)	25 (5.2)	24 (2.5)	26 (5.4)
Paracetamol	22 (2.3)	15 (3.1)	22 (2.3)	15 (3.1)

[Source: Reviewer’s analysis (Sponsor’s dataset=nefren0; reviewer’s filename=efficacy)]

\*\*Table shows numbers of events and the percentage of subjects with an event; see footnote in main text for discussion of total event counts

Analyses of patient-reported pain scores (0-10 Likert scale) suggested that, in many cases, interventions were triggered by patient reports of increasing pain and that thresholds for intervening were similar in the two treatment arms. However, the table also suggests that some subjects without reported interventions for pain also had high pain scores during the recall period.

<sup>13</sup> Because of how individual renal pain events were counted in the renal pain component of the composite, the total counts shown in the tables differ somewhat from the counts shown elsewhere.

Table 18. Maximum change from baseline in renal pain scale (0-10) in subjects with post-baseline renal pain scale observations, within treatment period

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

[Source: Sponsor response to information request dated 16 May 2013, Table 1.2.4-2]

The renal component of the composite endpoint used a post-titration baseline. A Chi-squared test was also performed using the pretitration baseline and creatinine measurements at Follow-up Visits 1 and 2. A total of 56 of 679 subjects on tolvaptan (8.2%) and 59 of 383 subjects on placebo (15.4%) with measurement at these time points experienced a 25% reduction in 1/serum creatinine. The p-value derived from the chi-square test was 0.0003.

In a time to multiple events analysis for the renal function component of the composite addressing data missing not at random, the p-value rose above 0.01 imputing upwards of 160% of placebo risk once a tolvaptan subject discontinued from the trial and did not rise above 0.05 under the assumptions tested (up to 200% of placebo risk).

Table 19. Analyses under the assumption of data missing not at random: time to multiple worsening renal function events

Percentage of placebo risk imputed for tolvaptan subjects who discontinued	HR (95% CI)	p-value
100%	0.51 (0.36, 0.73)	<0.001
160%	0.63 (0.44, 0.90)	0.01
180%	0.66 (0.47, 0.94)	0.02
200%	0.70 (0.50, 0.97)	0.03

[Source: Clinical Study Report 156-04-251; ST-2.7.1.3]

Other sensitivity analyses of the worsening renal function and severe renal pain components (i.e., including data collect off treatment up to month 36 and using adjudicated events) produced similar results. The findings in the U.S. for these components were consistent with the findings seen in the study population as a whole. The HR for the time to multiple worsening renal function events for sites in the U.S. was 0.46 (95% CI 0.19 to 1.13, p value=0.09) and 0.60 (95% CI 0.32 to 1.1, p-value=0.1) for the time to multiple renal pain events.

*Non-composite secondary efficacy endpoints*

The non-composite secondary endpoints were to be tested with a two-sided alpha level of 0.05 in the sequence in which they were listed in the protocol. The first non-composite endpoint, the rate of GFR change (reciprocal serum creatinine) from the end of the titration phase to the end of a two-week window of the last dose of study medication excluding observations deemed unreliable showed a difference in the rate of change in renal function of ~1 mL/min/year between the two treatment arms. Sensitivity analyses including observations deemed unreliable and all available measurements showed similar results.

Table 20. Rate of change in renal function in subjects with at least 4 month follow-up, excluding observations deemed unreliable, within treatment period using a post-titration baseline

Endpoint	Tolvaptan N=842	Placebo N=464
<b>1/serum creatinine ([mg/mL]<sup>-1</sup>)</b>		
Mean rate of change per year	-2.6	-3.7
Estimated slope	-2.6	-3.8
Treatment effect (95% CI)	1.20 (0.62, 1.8)	
p-value	<0.0001	
<b>eGFR by CKD-EPI (mL/min/1.73m<sup>2</sup>)</b>		
Mean rate of change per year	-2.7	-3.6
Estimated slope	-2.7	-3.7
Treatment effect (95% CI)	0.98 (0.60, 1.36)	
p-value	<0.0001	

[Source: Clinical Study Report 156-04-251, Table 9.5.1.1-1]

A Kaplan-Meier plot of the time to last eGFR measurement used in the applicant's prespecified analysis, taken from Dr. Lawrence's review, gives a sense of both the number of subjects excluded from the analysis in the tolvaptan arm (~10% of subjects) and the further loss of follow-up information over time. Approximately 20% of subjects in the tolvaptan arm did not have a measurement beyond 1 year. The applicant performed an MMRM analysis in which data for subjects who did not have a post-baseline renal function measurement were imputed using the estimated placebo slopes for the respective renal function measurements. The analysis was consistent with the primary analysis (estimated treatment effect at Month 36 of ~3.4 mL/min/1.73 m<sup>2</sup> by CKD-EPI, p < 0.0001). The applicant reported similar results using a Wu-Bailey analysis to account for data missing not at random.

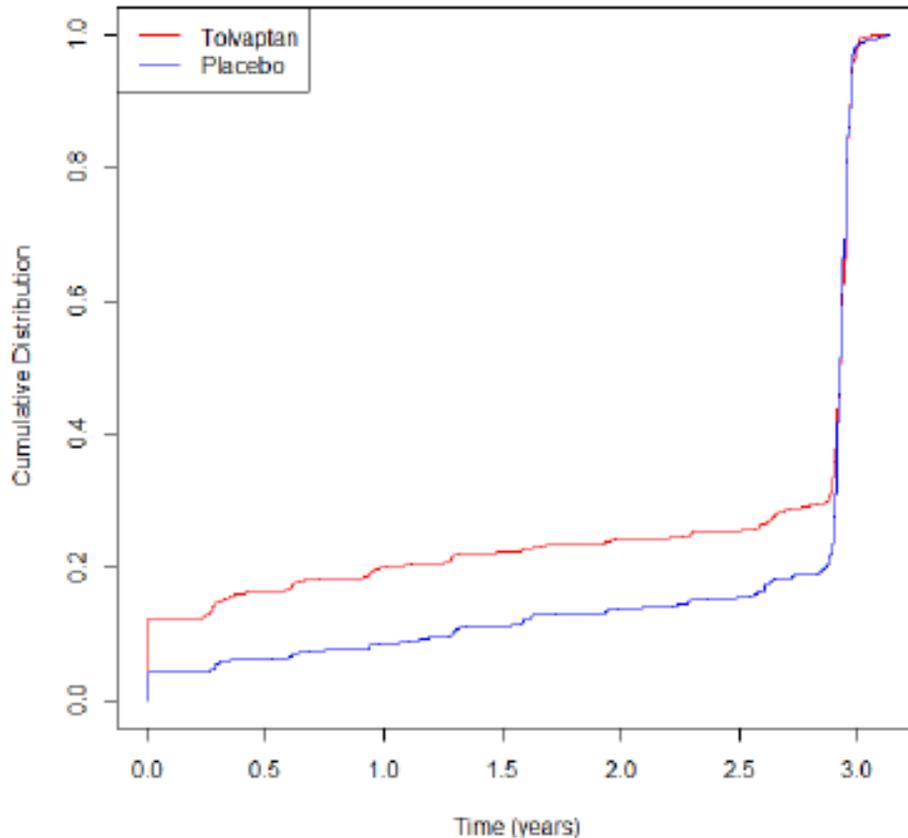


Figure 6. Kaplan-Meier plot of time to last eGFR measurement used in applicant's analysis of rate of GFR change

[Source: Dr. Lawrence's Statistical Review]

The next secondary endpoint in the sequence, the change from baseline for resting mean arterial pressure up to point of exposure to anti-hypertensive therapy in subjects who were non-hypertensive at baseline, failed (estimated treatment effect of -0.25 (95% CI -1.06 to 0.57, p-value=0.55). As noted in section 5.3, the remaining prespecified endpoints were to address effects on hypertension or renal pain. An exploratory analysis of the prespecified pain endpoint, the average AUC in renal pain score from baseline to the last visit prior to initiating pain medication did not suggest a benefit (results of ANCOVA analysis shown below). In both treatment arms, the mean baseline pain score was less than one (scale of 0-10 with zero representing no pain) and the change from baseline was close to zero. The data suggest that for many subjects in the trial, pain did not significantly impact day-to-day function.

Table 21. Time averaged AUC of change from baseline in renal pain score for subjects not taking renal pain medication at baseline

	Tolvaptan N=926	Placebo N=467
Mean baseline score (SD)	0.73 (1.6)	0.82 (1.7)
LS mean	0.0	0.08
Mean	0.06	0.09
Difference (95% CI)	-0.08 (-0.20, 0.03)	
Nominal p-value	0.16	

[Source: Clinical Study Report 156-04-251; Table 9.5.2-1 and Reviewer's analysis (Sponsor's dataset=eftmrp0; reviewer's filename=efficacy)]

\*Renal pain data censored once a subject starts pain medication

### 6.1.6 Other Endpoints

Exploratory analyses of PKD-related events reported on the PKD-outcomes CRF were also performed. Events of kidney pain, urinary tract infection, hematuria, anemia, and, to some extent, nephrolithiasis were reported at a lower incidence in the tolvaptan compared to placebo arm. The incidence of albuminuria events as reported on this CRF was inconsistent with and considerably lower than the incidence obtained via laboratory assessments (see key composite secondary endpoint findings). As discussed in section 6.1.3, less than half of the subjects who discontinued study medication prematurely were followed for these outcomes after discontinuation of study medication.

Table 22. Unique subjects with one or more PKD-related events

	Tolvaptan n=961	Placebo n=484
Hypertension	348 (36.2)	176 (36.4)
Kidney Pain	265 (27.6)	188 (38.8)
Hepatic Cysts	20 (2.1)	8 (1.7)
Hematuria	77 (8.0)	69 (14.3)
Albuminuria	7 (0.7)	8 (1.7)
Nephrolithiasis	21 (2.2)	17 (3.5)
Urinary Tract Infection	107 (11.1)	74 (15.3)
Anemia	25 (2.6)	22 (4.5)
Vascular/Cardiac Abnormalities	45 (4.7)	23 (4.8)
Abdominal/Inguinal Hernia	32 (3.3)	18 (3.7)
Other Cysts (e.g., pancreas, spleen, brain, uterus, ovary testicle)	15 (1.6)	10 (2.1)
Significant Drop in Kidney Function (e.g., dialysis, transplant)	9 (0.9)	6 (1.2)
Colonic Diverticuli	5 (0.5)	0

[Source: Reviewer's analysis (Sponsor's dataset=pkd0; reviewer's filename=efficacy)]

Like serum creatinine, plasma concentrations of cystatin C can be used as an endogenous marker of GFR. The pattern of changes in plasma cystatin C was, for the most part, consistent with the pattern seen for serum creatinine (see table below).

Table 23. Plasma Cystatin C Concentrations (mg/L)

		N	Value	Change from baseline
			Mean (SD)	Mean (SD)
Baseline	Tolvaptan	943	0.83 (0.22)	
	Placebo	483	0.83 (0.22)	
Week 3/end of treatment	Tolvaptan	906	0.88 (0.25)	0.05 (0.16)
	Placebo	470	0.84 (0.22)	0.01 (0.13)
Month 36	Tolvaptan	723	0.99 (0.34)	0.16 (0.21)
	Placebo	407	0.99 (0.38)	0.16 (0.24)
Follow-Up	Tolvaptan	724	0.97 (0.35)	0.14 (0.22)
	Placebo	396	0.99 (0.38)	0.16 (0.25)

[Source: Clinical Study Report for 156-04-251, Table 10.3.1-1]

### 6.1.7 Subpopulations

Though the trial excluded subjects with a CrCl < 60 mL/min by the Cockcroft-Gault equation, approximately 17% of subjects (163 tolvaptan and 85 placebo) who were enrolled had an estimated GFR < 60 mL/min/1.73m<sup>2</sup> using the CKD-EPI equation.<sup>14</sup> The mean GFR as estimated by the CKD-EPI equation in this subset of subjects was ~51 mL/min/1.73m<sup>2</sup> (both treatment arms). In the study population overall, only 43 subjects (3%) had a GFR less than 45 mL/min/1.73m<sup>2</sup> as estimated using the CKD-EPI equation.

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<sup>14</sup> The Cockcroft-Gault formula was used to determine patient eligibility because at the time the trial was initiated it was felt to have better accuracy around a GFR of 60 mL/min than other estimating equations (i.e., the MDRD equation). The CKD-EPI equation is thought to be more accurate than the MDRD equation at higher levels of GFR.

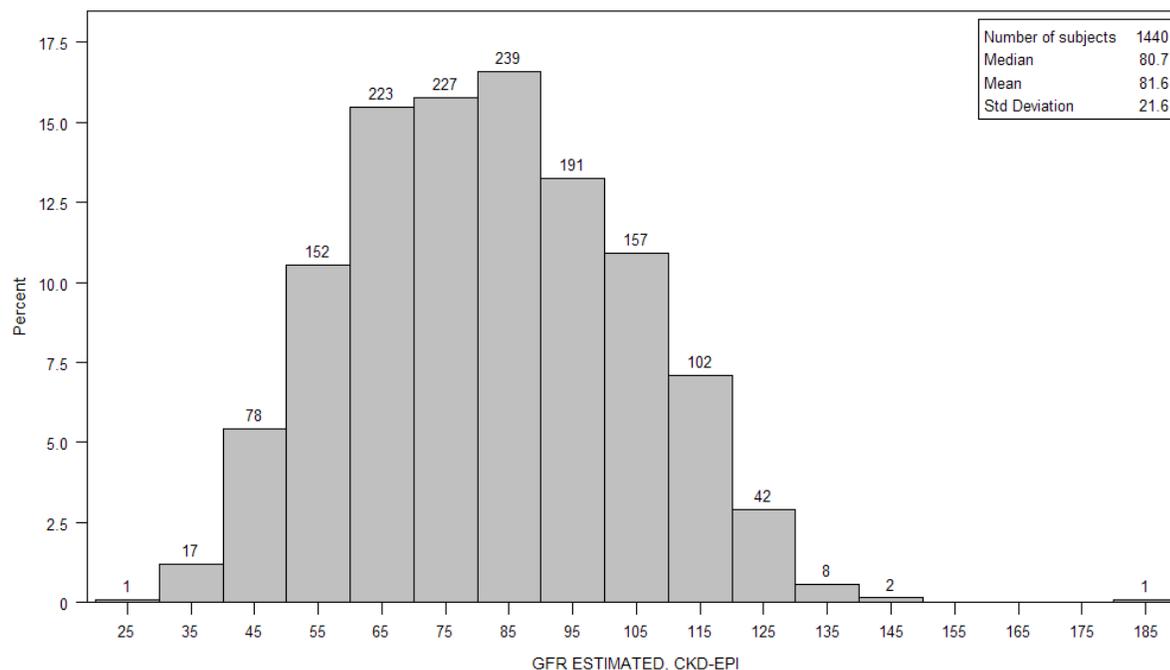


Figure 7. Distribution of baseline GFR by the CKD-EPI equation in the study population

[Source: Reviewer's analysis]

Of subjects with a GFR <60 mL/min/1.73m<sup>2</sup> by CKD-EPI, approximately 9% discontinued study medication prematurely in the placebo arm while approximately 20% discontinued study medication prematurely in the tolvaptan arm. Analyses conducted in this subset of subjects were consistent with the favorable findings seen in the study population overall.

- The HR for the time to multiple ADPKD events (regardless of treatment period) was 0.73 (95% CI 0.58 to 0.91, nominal p-value <0.01) and to the first event was 0.66 (95% CI 0.49 to 0.89, nominal p-value =.01).
- In an analysis of subjects who had serum creatinine measurements at pre-titration baseline and at both follow-up visits, 24% of tolvaptan subjects (28 of 117) and 46% of placebo subjects (32 of 70) had a one-third increase in creatinine (~25% reduction in the reciprocal of serum creatinine) from pre-titration baseline to both follow-up visits.
- An analysis of the rate of change in renal function (using the post-titration creatinine as baseline) also favored tolvaptan.

Table 24. Rate of Change in GFR by CKD-EPI, subjects with baseline eGFR < 60, regardless of treatment period

	Tolvaptan N=159	Placebo N=85
Mean rate of change per year (SD)	-4.3 (8.1)	-5.4 (4.1)
Slope*	-3.7	-5.4
Treat effect (95% CI)	1.7 (0.87, 2.52)	
Nominal p-value*	<0.001	

[Source: Response to Information Request, Response-7.3.2.1.2]

Uses end of titration/Week 3 value as baseline. \*Derived from testing the time treatment interaction using a linear mixed model in which both intercept and slope are fixed and random effects.

*Reviewer's comment: These findings support the conduct of trials in subjects with more advanced disease/lower baseline levels of renal function.*

At the time the phase 3 trial was initiated, it was understood that the Cockcroft-Gault equation would slightly overestimate GFR given the method used by the trial's central laboratory to measure serum creatinine levels. Differences in how the Cockcroft-Gault and CKD-EPI equations address weight may also account for the different renal function estimates provided by the two equations.<sup>15</sup> As shown in the figure below, the equations produced similar estimates in subjects in the lowest weight quartile but increasingly diverged at the higher weight quartiles. Consistent with this finding, the subset of subjects with an eGFR <60 mL/min/1.73m<sup>2</sup> by CKD-EPI appeared to be heavier than the overall study population (mean weight of 86.1 kg in the subset compared to 79.1 kg in the overall population).

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<sup>15</sup> The Cockcroft-Gault equation includes a term for weight; the CKD-EPI formula estimates GFR adjusted for body surface area.

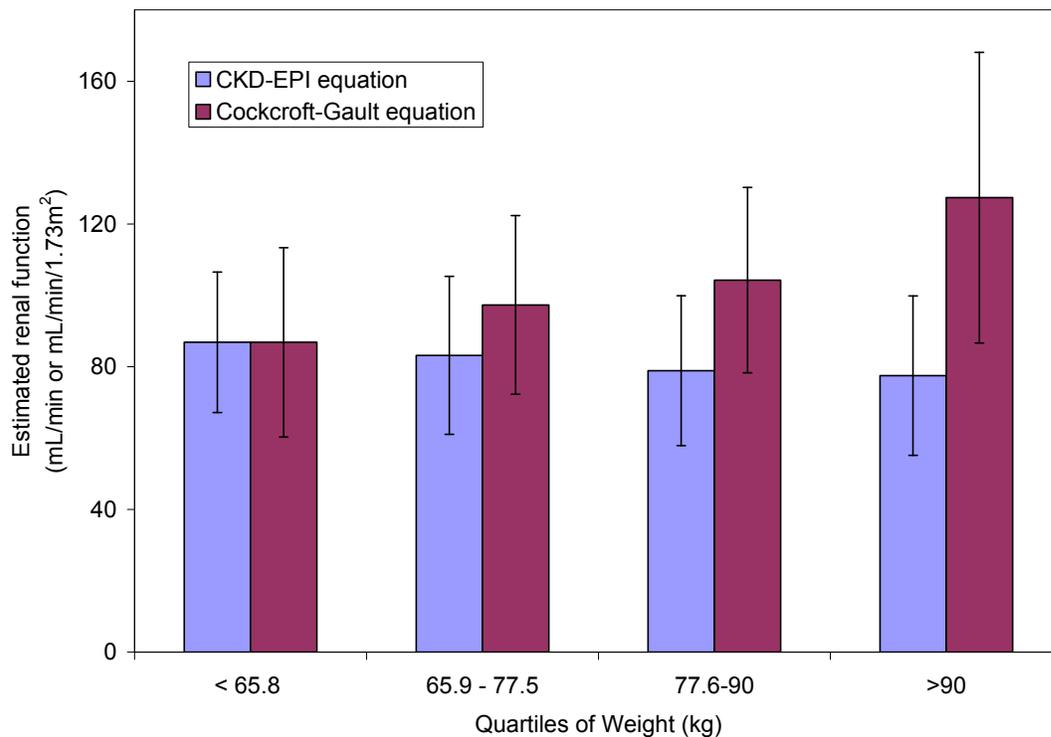


Figure 8. CKD-EPI and Cockcroft-Gault equation estimates of renal function by quartile of weight

Other subgroup analyses conducted by the applicant suggested favorable effects (as indicated by the point estimate) across the subgroups that were analyzed (subgroup analyses for the composite secondary endpoint and annualized change in renal function subgroup analyses shown below). In the composite secondary endpoint and annualized change in renal function subgroup analyses, effects were less pronounced in subjects without hypertension at baseline and those without microalbuminuria. What to make of this finding is not clear. Subgroup analyses for the time to worsening renal function component of the composite did not suggest lesser effects in these subgroups. As noted in Dr. Lawrence's review, the treatment effect on the composite endpoint was similar in subjects who were and were not on an ACEI/ARB at baseline.

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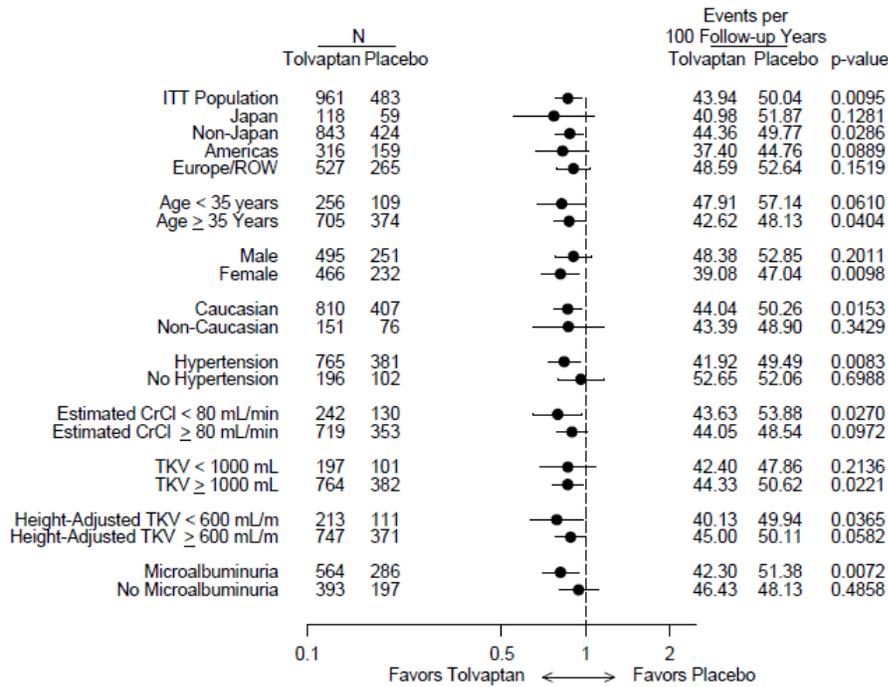


Figure 9. Subgroup analyses of time to multiple events of composite endpoint  
 [Source: Clinical Study Report 156-04-251, Figure 9.4.2-1]

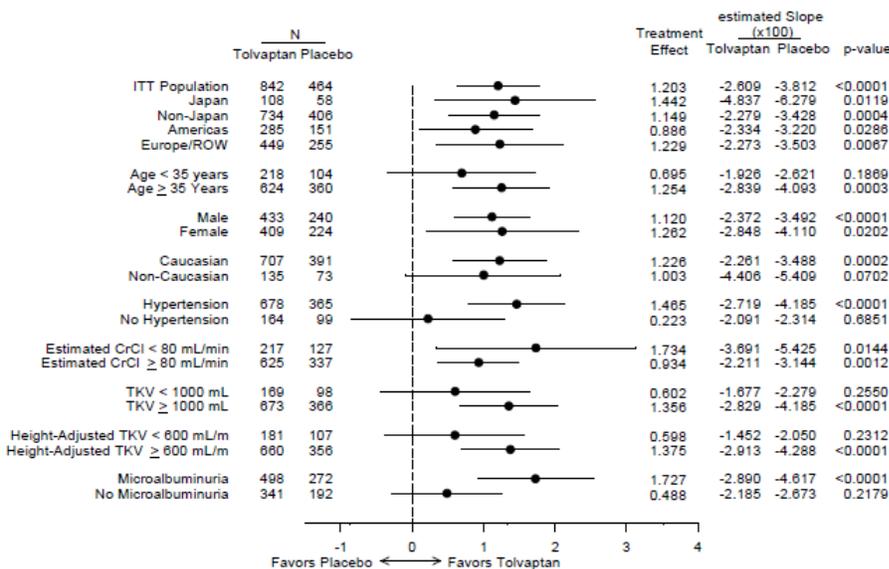


Figure 10. Subgroup analyses of annualized change in renal function (1/serum creatinine [mg/ml])

[Source: Clinical Study Report 156-04-251, Figure 9.5.1.3-1]

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Dose selection was guided by the premise that more constant and complete inhibition of the V2 receptor would result in greater efficacy and also by recognition that the ability to do so would be limited by tolerability. Urine osmolality was used as a surrogate of vasopressin V2 receptor inhibition; a trough urine osmolality below 300 mOsm/L was taken as evidence of effective receptor inhibition. As shown in the figure below, in a single dose study in subjects with ADPKD, increasing the dose of tolvaptan over the range of 15 to 120 mg prolonged the duration of the effect on urine osmolality. A multiple dose study in subjects with ADPKD compared the effect of a once daily, twice daily and split dose regimen on urine osmolality, however baseline differences in urine osmolality among the dosing groups made it difficult to interpret study results (see review by Drs. Sahre and Li).

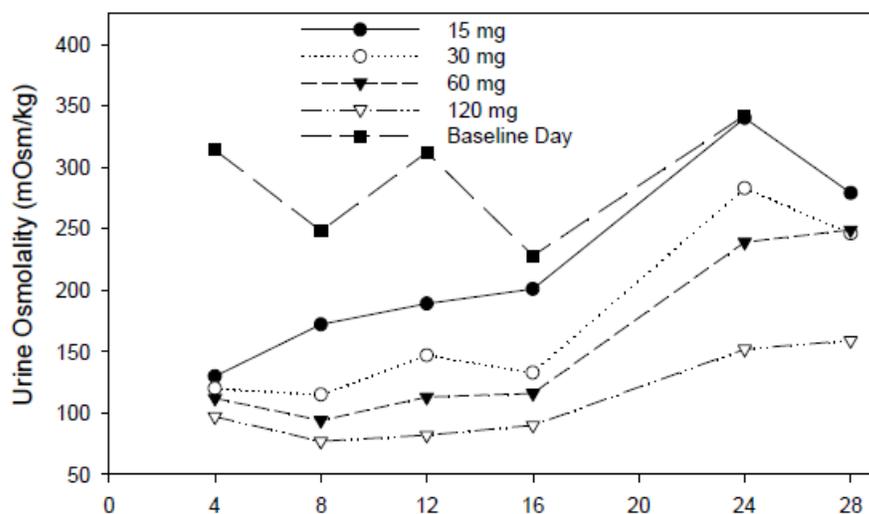


Figure 11. Mean urine osmolality at the end-time of the collection interval at baseline and following ascending single oral doses of tolvaptan

[Source: Clinical Study Report 156-04-248, Figure 9.3.3-1]

The dosing regimen used in the phase 3 trial was based on the preliminary findings from the forced titration phase of an ongoing open-label trial. In trial 156-04-250, subjects with ADPKD were initiated on a split dose of 30/15 mg and then titrated weekly, based on tolerability, to 45/15, 60/30 and 90/30 mg. Urinary osmolality was used as the pharmacodynamic endpoint. Tolerability was assessed by asking: “Could you tolerate taking this dose of tolvaptan for the rest of your life, please answer only yes or no?” Subjects who answered “no” were down-titrated to the previous dose (down titration to 15/15 was possible). Subjects who answered “yes” were up-titrated in dose to a maximum dose level of 90/30 mg.

As shown in the figure below, the proportion of subjects with a trough spot urine osmolality < 300 mOsm/L appeared similar at doses upwards of 45/15, however a marked decrease in tolerability was observed at doses of 60/30 mg and above. Because of variability in patient response as well as data suggesting activity at the lower doses, the decision was made to use a similar dose titration strategy in the phase 3 trial. Despite the use of this design, tolerability proved to be a problem for subjects. As discussed in section 6.1.3, 15.4% of subjects on

tolvaptan, compared to 5.0% of subjects on placebo discontinued study medication prematurely because of an adverse event.

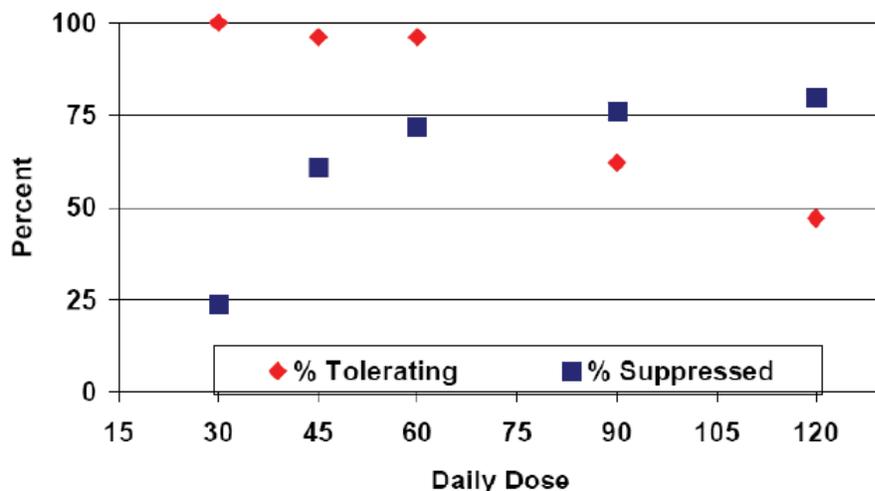


Figure 12. Percentage of subjects who tolerated dose and percentage with trough spot urine osmolality < 300 mOsm/L

[Source: Clinical Study Report 156-04-249, Figure 6.8-2]

\*Tolerating=answering “Yes” to the following question: “Could you tolerate taking this dose of tolvaptan for the rest of your life, please answer only yes or no?” Suppressed= trough spot urine osmolality < 300 mOsm/L

According to Dr. Sahre’s and Li’s review, analyses looking at the relationship between tolvaptan modal dose in the phase 3 trial and (1) total kidney volume, (2) percent change in estimated GFR and (3) events of worsening renal function (defined as a reproducible 25% decrease in the reciprocal serum creatinine from the week 3/end of titration visit) did not demonstrate a clear dose-response relationship. What to make of these findings is not clear given the trial’s dose titration design.

It is unknown whether a different dosing strategy, such as titrating to achieve a certain urine osmolality or urine osmolality reduction, would have been as or more effective than the dosing regimen used in the phase 3 trial. It is also unknown whether a different dosing strategy would have been as effective but more tolerable.

#### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Based on effects on urine osmolality, there does not appear to be significant loss of activity at the V2 receptor/development of tolerance over a three-year timeframe. Relative to placebo, tolvaptan treatment reduced trough urine osmolality by about 250 mOsm/kg at Week 3/end of titration and by about 190 mOsm/kg at Month 36 of the phase 3 trial (results based on ANCOVA model with treatment and covariate baseline as factors). At the second off-treatment follow-up visit, there was no difference between treatment arms (mean change from baseline ~ -70 mg/L in each arm). Data on renal function decline and total kidney volume suggest continued drug

activity during 3 years of treatment (see prior discussions of efficacy findings in phase 3 trial). Ongoing uncontrolled extension studies may provide further insight into long-term treatment effects, and specifically effects beyond 3 years.

#### 6.1.10 Additional Efficacy Issues/Analyses

As discussed in section 4.4.2, tolvaptan can cause an acute and reversible decrease in GFR. Because of expected changes in serum creatinine, the statistical analysis plan specified that the worsening renal function component of the composite endpoint would use the serum creatinine value obtained at Visit Week 3 (or the End of Titration Visit if a subject did not have a Week 3 Visit) as the subject's "baseline" for determining whether an endpoint event had occurred. The statistical analysis plan also specified that the first non-composite secondary endpoint, the rate of GFR change, would also be evaluated using this post-randomization assessment as the "baseline" value.<sup>16</sup>

*Reviewer's comment: It does not appear that this issue (the use of a post-randomization assessment as the "baseline" measurement for renal function-related endpoints) was discussed when the protocol was submitted to the Agency in 2006. However when the statistical analysis plan was submitted in 2009, the sponsor was advised to add post-therapy follow-up visits to assess effects on endpoints that might be susceptible to potential "hemodynamic effects", and told that "ideally" such endpoints (including changes in serum creatinine) should be defined as the change from baseline to the post-therapy period when any potential "hemodynamic effect" had worn off. The protocol was subsequently amended to include two off study drug follow up clinic visits. Follow-up visit #1 was to occur +7 (to +21) days after the month 36/end of treatment visit; follow-up visit #2 was to occur +7 (to +21) days after follow-up visit #1. In the applicant's NDA, data from these visits were used in a sensitivity analysis of the worsening renal function component of the composite endpoint (see section 6.1.4).*

During the review cycle a question arose as to whether tolvaptan might still be exerting a reversible pharmacodynamic effect on the serum creatinine level (either spuriously elevating or reducing the level) at Follow-up Visits 1 and 2. Additional analyses, described below, were performed to address this issue. These analyses did not suggest an obvious pharmacodynamic effect on creatinine levels at these follow-up visits.

- Subjects completing the phase 3 trial without early termination of study medication subjects were eligible for enrollment into long-term uncontrolled extension studies in which all subjects were treated with tolvaptan. An off-treatment baseline creatinine value was to be obtained prior to initiating tolvaptan in these extension trials. Though subjects enrolling into one of the extension trials were permitted to use a measurement obtained at a follow-up visit of the phase 3 trial as their baseline assessment, in the majority of subjects the

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<sup>16</sup> See also FDA's clinical pharmacology and statistical reviews for additional information on tolvaptan's acute effect on GFR. Dr. Lawrence's statistical review discusses the use of a post-randomization creatinine value as the "baseline value" in efficacy endpoint analyses and other statistical issue related to tolvaptan's acute effect on GFR).

measurement was made more than 8 weeks after the month 36 measurement (see figure below).

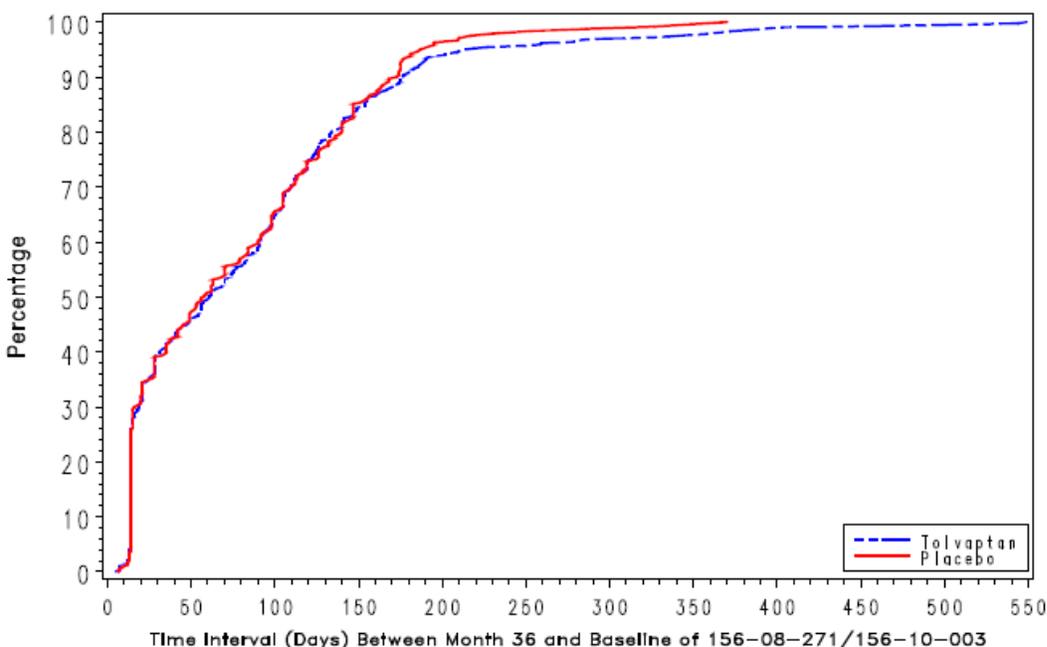


Figure 13. Distribution of the time interval between the month 36 visit in trial 156-04-251 and baseline value obtained for the extension studies (enzymatic assay used for assessments in all trials)

[Source: Response to Request for Information submitted to NDA on 17 June 2013; Figure 2]

The mean change in serum creatinine over time was determined for the 418 tolvaptan subjects and 242 placebo subjects who had serum, creatinine measurements at all of the following time points: baseline, month 36 and both follow-up visits in trial 156-04-251 and a baseline (off treatment) measurement in study 156-08-271 and 156-10-003. The difference between the two treatment arms in the mean change from the pre-treatment baseline creatinine to Follow-Up Visit 1, Follow-Up Visit 2, and the baseline visit for the extension trial were similar. However the ability of this analysis to address temporal changes in creatinine is somewhat limited because subjects could use a value obtained at their follow-up visit as the baseline value in one of the extension trial and because of the overlapping time window for Follow-up Visits 1 and 2.

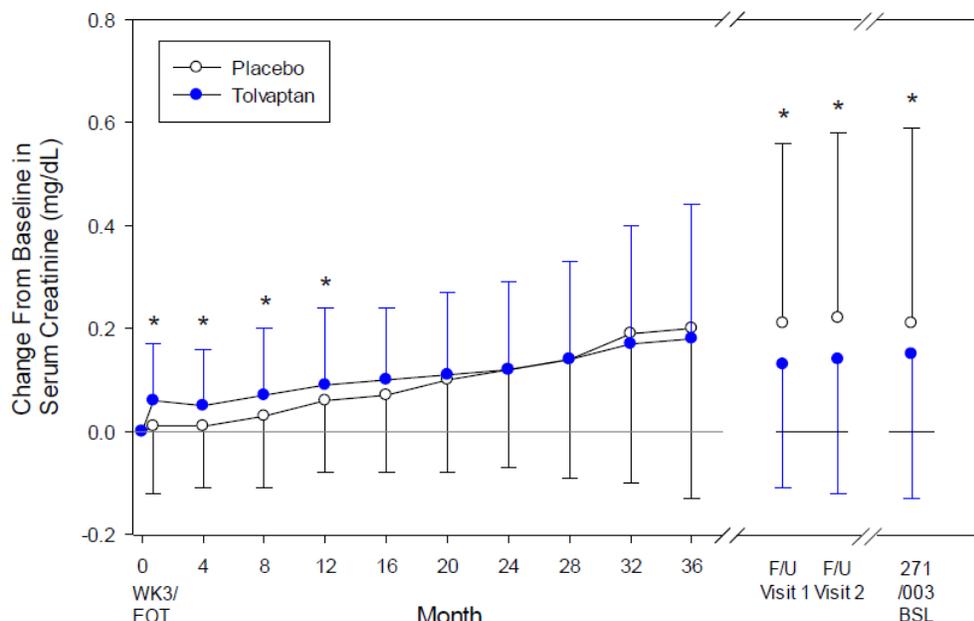


Figure 14. Mean (SD) change from pretitration baseline in serum creatinine in the phase 3 trial and as entering (baseline for) extension studies 156-08-271 and 156-10-003

[Source: Response to Request for Information submitted to NDA on 17 June 2013; Figure 1] 271/003 BSL=baseline value for extension studies; \*p<0.05 for difference between groups derived from an MMRM

- Changes in parameters that might be indicative of volume status or V2 receptor activity were also assessed.<sup>17</sup> As noted in section 6.1.9, at the second off-treatment follow-up visit, there was no difference between treatment arms in urine osmolality (mean change from baseline ~ -70 mg/L in each arm). With regard to other parameters, following initiation of therapy, there was a slight decrease in weight and increase in hematocrit and serum sodium in the tolvaptan arm. Serum sodium and hematocrit fell back to baseline levels by Follow-up Visits 1 and 2 (as indicated by the mean change from baseline at these visits). In contrast, weight rose in the tolvaptan arm following discontinuation of therapy, with both treatment arms showing a similar change from baseline in weight at off-treatment follow-up visits.

<sup>17</sup> Changes in urea nitrogen may not be a reliable indicator of changes in renal hemodynamics/volume status on tolvaptan and thus were not assessed for the purpose of this analysis. Serum urea nitrogen levels fall upon initiation of tolvaptan; it is thought that V2 receptor blockade and the subsequent decrease in urine osmolality may be affecting urea recycling from the collecting duct.

Table 25. Mean change from baseline in weight, hematocrit and serum sodium

	Tolvaptan			Placebo		
	N	Mean (SD)	Mean (SD) change from baseline	N	Mean (SD)	Mean (SD) change from baseline
<b>Weight</b>						
Baseline	961	79.7 (18.3)		483	78.5 (18.2)	
Week 1	938	79.0 (18.2)	-0.7 (1.3)	482	78.8 (18.3)	0.3 (1.4)
Month 36	727	80.6 (18.5)	1.3 (5.3)	409	79.4 (17.6)	1.7 (4.5)
Follow-up V1	731	81.0 (18.7)	1.9 (5.3)	406	79.5 (17.9)	1.6 (4.6)
Follow-up V2	735	80.9 (18.6)	1.8 (5.6)	405	79.4 (17.9)	1.5 (4.5)
<b>Hematocrit</b>						
Baseline	958	40.4 (3.8)		483	40.2 (3.7)	
Week 1	905	41.2 (3.8)	0.8 (2.0)	467	40.1 (3.7)	0 (1.9)
Month 36	702	40.8 (3.9)	0.5 (2.8)	395	40.4 (4.0)	0.3 (3.1)
Follow-up V1	693	39.8 (3.8)	-0.5 (2.9)	382	40.1 (4.1)	0 (3.0)
Follow-up V2	702	39.8 (3.8)	-0.5 (2.9)	380	40.2 (4.2)	0 (3.1)
<b>Sodium</b>						
Baseline	961	140.4 (2.1)		483	140.3 (2.0)	
Week 1	929	142.6 (2.6)	2.2 (2.5)	474	140.1 (2.2)	-0.2 (2.3)
Month 36	722	141.6 (2.6)	1.3 (2.8)	406	140.3 (2.3)	0 (2.6)
Follow-up V1	702	139.8 (2.2)	-0.5 (2.4)	401	140.4 (2.4)	0.1 (2.5)
Follow-up V2	730	140.1 (2.3)	-0.3 (2.6)	399	140.3 (2.3)	0 (2.6)

[Source: Clinical Study Report 156-04-251]

\*Decimals  $\geq 0.05$  rounded up; Follow-up V1 and V2 refer to Follow-up Visits 1 and 2, respectively.

## 7 Review of Safety

### Safety Summary

The safety database included 1432 subjects with ADPKD exposed to at least one dose of tolvaptan. In the pivotal phase 3 trial, a total of 961 subjects received at least 1 dose of tolvaptan, with 836 subjects exposed for at least 1 year, and 742 exposed for 3 years. At three years the average daily dose was 96.5 mg daily. Approximately 55% of subjects on tolvaptan were on a modal dose of 120 mg daily.<sup>18</sup>

The most important safety finding was drug-induced liver injury (DILI). A Hepatic Adjudication Committee (HAC) convened by the applicant to review potential cases of drug-induced liver injury concluded that there were three “Hy’s Law” cases in the tolvaptan arm, none in the placebo arm.<sup>19</sup> In addition, the pivotal trial showed a four-fold higher incidence of significant

<sup>18</sup> Since investigators could change the dose during trial 156-04-251, analyses of exposure were also conducted by modal dose (the most frequent dose taken during the entire trial).

<sup>19</sup> Dr. Hy Zimmerman noted that drugs causing hepatocellular injury and clinical jaundice lead to acute liver failure with a case fatality rate of ~ 10% (ranging from ~5 - 50%). Hy’s Law according to the FDA Drug-induced liver Injury guidance is defined as a subject with ALT > 3x ULN, total bilirubin > 2xULN and

ALT elevation for subjects on tolvaptan compared to subjects on placebo. The HAC concluded that “in patients with ADPKD tolvaptan has the potential to cause liver injury capable of progression to liver failure”. They state that the “rough incidence of liver failure can therefore be estimated as  $3/860 \times 10$ , or about 1 in 3000 patients” who “receive long term treatment with tolvaptan”.

Although no subjects progressed to liver failure leading to transplantation or death, the finding of two or more Hy’s Law cases in a clinical trial safety database is a strong predictor of a drug capable of causing progressive liver injury and failure (FDA Drug-Induced Liver Injury Guidance 2009). All major drug-induced liver injury registries have confirmed this minimal case fatality rate of ~10% from drug-induced jaundice (Andrade RL 2005, Bjornsson E 2005, Chalasani N 2008, Devarbhavi D 2010). There are only a handful of marketed drugs with this severity of liver injury. Bosentan for pulmonary hypertension had two Hy’s Law cases among 600 patients. Isoniazid for tuberculosis also has a high incidence of drug-induced liver injury. These drugs remain on the market, although bosentan has one of the most burdensome REMS programs to mitigate this risk. Other drugs with lower incidence of severe liver injury have either been withdrawn from the market or not approved (bromfenac, ximelagatran, dilevalol, tasosartan). Most of the drugs withdrawn from the market for hepatotoxicity have caused death or transplantation at frequencies in the range of  $\leq 1$  per 10,000. While there is some uncertainty around the estimate of severe liver injury for tolvaptan, the Agency has not seen any false positive Hy’s Law findings for a drug that was subsequently found not to cause severe drug-induced liver injury in a larger treatment population.

The characteristic onset of injury was between three and fourteen months of treatment with tolvaptan. The HAC state that “as a general rule drugs that cause serious liver injury will do so within the first year of treatment”, however they go on to say (and the applicant acknowledges) that “characteristic signatures may produce injuries without all the characteristics of that signature”. Until data suggest otherwise, the risk estimate of 1 in 3,000 should be assumed for the entire duration of treatment, not just the signature period of risk.

Other than drug-induced liver injury, other important safety findings included a greater incidence of skin neoplasms, glaucoma, hypernatremia, increased uric acid/gout, and dehydration. These adverse events are described briefly below. While these risks should be described in labeling, in this reviewer’s opinion, they do not pose a barrier to approval.

- Skin neoplasms: basal cell carcinoma in 0.8% of subjects on tolvaptan compared to 0.2% of subjects on placebo, malignant melanoma in 2 subjects on tolvaptan
- Glaucoma: 2.1% of subjects on tolvaptan compared to 1.0% of subjects on placebo
- Hypernatremia: 4.0% of subjects on tolvaptan compared to 1.4% of subjects on placebo with potentially clinically significant increased sodium levels (sodium > 150 mEq/L)

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1)hepatocellular injury without initial findings of cholestasis (i.e., serum alkaline phosphatase < 2 xULN or the R value (ratio of serum ALT xULN/alkaline phosphatase x ULN) ratio > 5.0, 2)there should not be a more likely explanation for the liver injury, and 3) there should be a higher incidence of ALT elevations > 3x ULN in drug treated subjects relative to control.

- Increased uric acid / gout: more subjects on tolvaptan compared to placebo used anti-gout medicine (8.2% versus 5.8%), had increases in serum uric acid (6.2% versus 1.7%), and had gout (2.9% versus 1.4%)
- Dehydration: 64.5% of subjects on tolvaptan versus 33.3% of subjects on placebo with potentially drug-related events suggestive of dehydration

Aquaretic effects including thirst, polyuria, nocturia, pollakiuria, and polydipsia were also reported at a higher incidence in tolvaptan treated subjects and these adverse events were a common reason for permanent treatment discontinuation in the tolvaptan arm in the trial overall (7.7% on tolvaptan versus 1.0% on placebo) and in the first 28 days of treatment.

## 7.1 Methods

The primary safety data come from the pivotal, randomized, double-blind, placebo-controlled trial 156-04-251. The applicant did not prepare an Integrated Summary of Safety. Since the other controlled studies were of much shorter duration ( $\leq 8$  weeks), this approach seemed reasonable. The applicant discussed important safety findings from other trials in relationship to the findings in trial 156-04-251.

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety evaluation focused on datasets, case report forms (CRF), narratives and the amended clinical study report for the pivotal placebo-controlled trial 156-04-251. There were no new safety concerns identified in the supportive trials that were not identified and characterized in the pivotal trial. The following items were also reviewed and/or analyzed:

- Clinical study report for the largest open-label ongoing trial 156-08-271
- Applicant's Summary of Clinical Safety (SCS) report (includes 13 completed trials, 3 ongoing open-label trials, and very limited data from 1 ongoing, blinded trial 156-09-290)
- Adverse event datasets from the five open label extension trials
- Liver data from all 17 trials (see Section 5.1) including:
  - Liver laboratory datasets (both central and local lab)
  - Medwatch reports for subjects with significant liver related adverse events
  - Narratives and CRFs for subjects identified for adjudication of causality of liver injury
  - Adjudication packages of subjects with possible Drug-induced liver injury
  - Independent report prepared by Hepatic Adjudication Committee (HAC)
- CRFs for all deaths, discontinuations due to an serious adverse events (SAE), "loss to follow-up", "investigator withdrew subject", "subject withdrew consent", and subjects who developed clinically significant hypernatremia
- Narratives for subjects with serious treatment emergent adverse events (TEAE)<sup>20</sup>
- Dr. John Senior's (FDA, Office of Pharmacovigilance and Epidemiology) consult review on the hepatic safety of tolvaptan dated 28 June 2013

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<sup>20</sup> The sponsor defined TEAE as an adverse event that started while on treatment plus 7 days after the last dose or if the event was continuous from baseline and was serious; related to treatment; or resulted in death, discontinuation, interruption, or reduction of treatment.

In the review of cases of interest for possible Drug-induced liver injury, all of the above sources were considered with more reliance placed on primary sources of data, and data collected closer to the time of the event.<sup>21</sup>

### 7.1.2 Categorization of Adverse Events

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 14.1 for presentation in the SCS.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

In general, adverse event data were not pooled across studies for reasons stated in Section 7.1. The liver laboratory data were pooled across 16 trials; liver data from the ongoing blinded trial 156-09-290 were analyzed separately since treatment assignments were unknown.

## 7.2 Adequacy of Safety Assessments

In general, the safety monitoring in trial 156-04-251 appeared adequate. In the pivotal trial, the applicant monitored safety data in accordance with Otsuka Standard Operating Procedures until the Independent Data Monitoring Committee (IDMC) was formed. The IDMC meetings were held approximately every 6 months. The independent Statistical Data Analysis Center (SDAC), which supported the IDMC, received monthly laboratory and clinical data transfers (including treatment codes). For a timeline of events related to liver safety findings, see the Appendix.

*Reviewer's comment: Following all SDAC reports, the IDMC recommended continuing trial 156-04-251 per protocol.*

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The safety database in the ADPKD program consists of 1581 subjects who have been exposed to at least 1 dose of immediate release tolvaptan, including 1432 subjects with ADPKD, 37 non-ADPKD subjects with varying degrees of renal function, and 112 healthy subjects. The next table shows that the majority of subjects with ADPKD were exposed to tolvaptan doses within the proposed range for ADPKD (60 to 120 mg daily taken as a split dose) with more than 90% exposed for at least 6 months and more than 70% exposed for at least 1 year.

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<sup>21</sup> A judgment call was made for some subjects because of inconsistent information reported between sources.

Table 26. Cumulative tolvaptan exposure in subjects with ADPKD by dose received

Cumulative Exposure	Tolvaptan, n (%)		
	15 to 45 mg (N = 53)	60 to 120 mg (N = 1412)	Total (N = 1432)
Any exposure	53 (100.0)	1412 (100.0)	1432 (100.0)
At least 2 weeks	17 (32.1)	1366 (96.7)	1383 (96.6)
At least 6 months	17 (32.1)	1275 (90.3)	1292 (90.2)
At least 12 months	15 (28.3)	1002 (71.0)	1017 (71.0)
At least 24 months	14 (26.4)	825 (58.4)	839 (58.6)
At least 36 months	13 (24.5)	788 (55.8)	801 (55.9)
At least 48 months	13 (24.5)	214 (15.2)	227 (15.9)
At least 60 months	11 (20.8)	26 (1.8)	38 (2.7)

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. Excludes ongoing blinded Trial 156-09-290.

Data cutoffs for exposure were 01 Dec 2011 for ongoing Trials 156-10-003 and 156-09-003, and 31 Mar 2012 for ongoing 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 IMP and/or ascending doses) may be counted in both dose categories. However, such subjects are counted only once toward the total exposed.

Source: SCS, Applicant's Table 2.7.4.1.2.1-2, CT-1.1

In the pivotal trial, 961 subjects with ADPKD received at least one dose of tolvaptan, with 836 subjects exposed for at least one year. The average daily dose of tolvaptan at month 36 was 96.5 mg (see next table).

Table 27. Cumulative exposure to treatment in trial 156-04-251

Cumulative Exposure	Tolvaptan (N = 961)		Placebo (N = 483)	
	n	Average Daily Dose <sup>a</sup> (mg)	n	Average Daily Dose <sup>a</sup> (mg)
Any exposure	961	95.29	483	110.02
At least 8 months	864	101.53	470	112.51
At least 12 months	836	99.60	462	112.36
At least 24 months	774	97.04	437	110.76
At least 36 months	742	96.45	418	110.55

Trial 156-04-251.

<sup>a</sup> Average daily doses are the cumulative average daily doses for treated subjects from the initial dose through the time point summarized.

Source: CSR 156-04-251 CT-7.1.

The next table and figure shows the exposure in the pivotal trial by modal dose, which is the most frequent dose that the subject took during the entire trial. Since the dose could be

increased or decreased during the maintenance phase, the reviewer also analyzed the data by modal dose. Of the subjects randomized to tolvaptan, ~55% took the targeted dose most frequently during the trial. The figure shows that subjects able to tolerate tolvaptan in the beginning of the trial were more likely to take the 120 mg dose the majority of the time; the curve for the 60 mg modal dose reflects the early treatment discontinuations during the titration phase.

Table 28. Exposure by modal dose in trial 156-04-251

<b>Modal dose, mg (split dose regimen)</b>	<b>N (%)</b>	<b>Subject-years<sup>1</sup></b>	<b>Median (months)<sup>1</sup></b>	<b>Subject-years<sup>2</sup></b>
Tolvaptan				
45	3 (0.2)	1.2	2.0	1.1
60 (45/15)	244 (16.9)	502.0	35.7	484.2
90 (60/30)	184 (12.7)	468.1	35.9	459.2
120 (90/30)	530 (36.7)	1411.7	36.0	1388.5
Total tolvaptan	961 (66.6)	2383.1	36.0	2332.9
Total placebo	483 (33.4)	1325.7	35.9	1304.6

Modal dose is most frequent dose during entire trial.

1 includes temporary drug interruptions; dataset liverf

2 excludes temporary drug interruptions; dataset dose0

Reviewer's analysis: \hep\s-years.sas

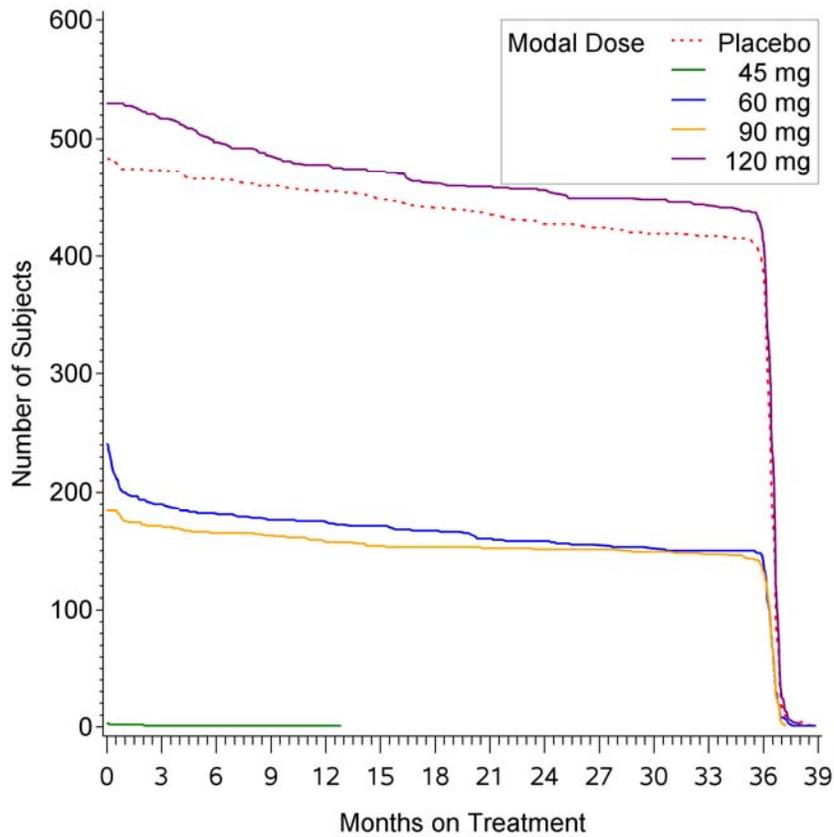
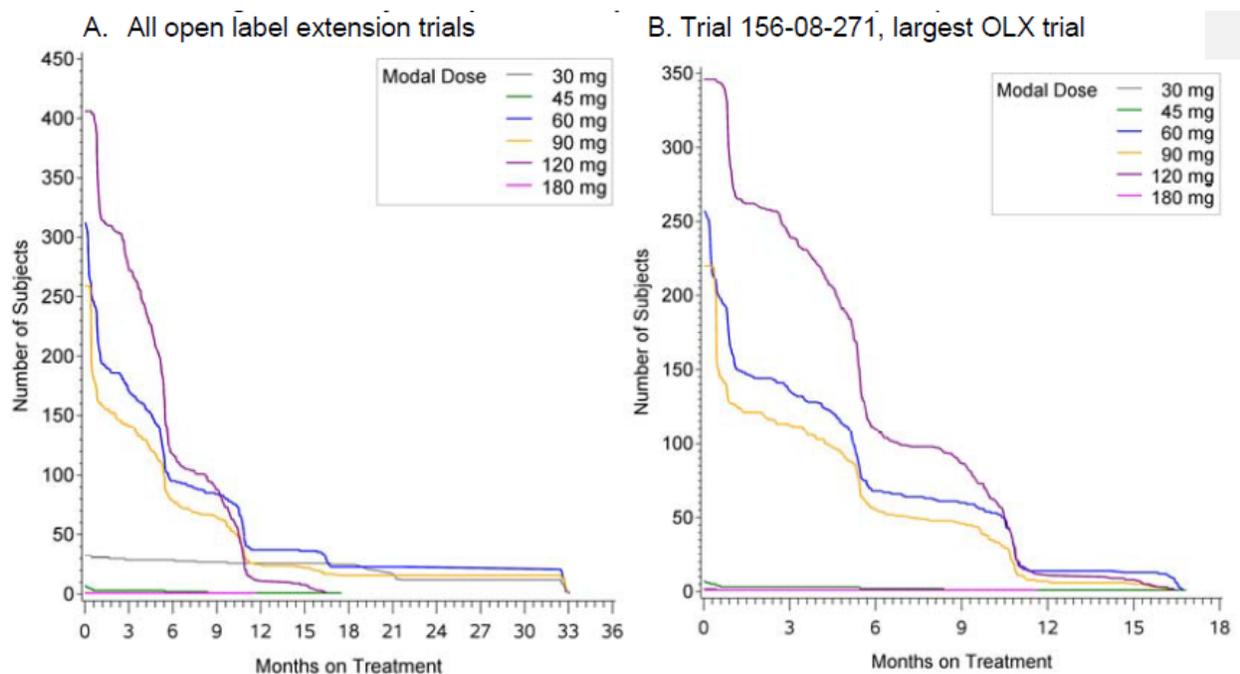


Figure 15. Exposure over time by modal dose in trial 156-04-251  
Reviewer's analysis: dose\modose days.sas, dataset liverf

Since the period of follow-up after drug discontinuation was at most ~42 days, the study duration (1341.1 subject years for placebo and 2417.0 subject years for tolvaptan) was not that much longer than drug exposure.

The next figure shows drug exposure by modal dose for all five open label extension trials and the largest open label extension trial 156-08-271. Of the subjects enrolled in trial 156-08-271 91% (823/904) were from the pivotal trial 156-04-251.



Reviewer's analysis: dose\modose days.sas, dataset liverf

Figure 16. Subject exposure over time by modal dose in open label extension trials

## 7.2.2 Explorations for Dose Response

See Section 7.2.1. See section 6.1.8 for discussion on effects on urine osmolality.

## 7.2.3 Special Animal and/or In Vitro Testing

The Pharmacology review has not yet been finalized. Chronic studies in rats and dogs at doses ~180x the human equivalent dose did not show any signs of liver toxicity (communication with Pharm-tox reviewer, Xavier Joseph). While this is a pertinent finding, preclinical data does not always reliably predict clinical hepatotoxicity.

#### 7.2.4 Routine Clinical Testing

Physical exams, assessments for adverse events, blood and urine labs for safety were done at the following study time points: optional screening up to 6 months prior to baseline, baseline (Day -31 to Day -14), randomization Day 1, Titration week 1, 2, 3 (end of titration), Month 4, 8, 12, 16, 20, 24, 28, 32, 36 (or early termination (ET)), follow-up visit #1 (7 to 21 days post Month 36/ET), and follow-up visit #2 (7 to 21 days post follow-up visit #1).

#### 7.2.5 Metabolic, Clearance, and Interaction Workup

These studies were conducted for NDA 22275 and labeling reflects those findings. See section 4.4.3 for additional information.

#### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Since tolvaptan had been studied in two other development programs, the applicant was aware of specific adverse events; their efforts to capture those events were adequate.

### 7.3 Major Safety Results

#### 7.3.1 Deaths

As of 31 March 2012, there were two reported deaths (one self-inflicted gunshot wound and one subarachnoid hemorrhage) in the ADPKD program. Both occurred in open-label extension trials, and both were assessed by the investigators as being unlikely related to tolvaptan.

At the end of trial 156-04-251, vital status was unknown in 199 subjects (151 on tolvaptan and 48 on placebo). The applicant attempted to determine vital status in these subjects (see next table). There were no additional reported deaths as of 21 Jan 2013.

Table 29. Vital status in trial 156-04-251 as of 21 January 2013

	Tolvaptan, N (%)	Placebo, N (%)	Total, N (%)
Randomized	961	484	1445
Alive	886 (92.2)	463 (95.7)	1349 (93.4)
Dead	0	0	0
Unknown	75 (7.8)	21 (4.3)	96 (6.6)
Vital Status could not be verified, Considered lost to follow-up	43 (4.5)	14 (2.9)	57 (3.9)
Status pending	32 (3.3)	7 (1.4)	39 (2.7)

Source: CSR 156-04-251, CT-1.1, SCS CT-7

### 7.3.2 Nonfatal Serious Adverse Events

Approximately 19% of subjects in each treatment arm experienced a serious treatment emergent adverse event (TEAE). The applicant defined TEAE as an AE that started while on treatment plus 7 days after the last dose or if the event was continuous from baseline and was serious; related to treatment; or resulted in death, discontinuation, interruption, or reduction of treatment. This reviewer analyzed the SAE data using various definitions including 1) applicant's TEAE + 30 days instead of 7 days, 2) on treatment + 7 days, and 3) on treatment +30 days. Results were consistent between definitions, so the SAE table below uses the applicant's definition.<sup>22</sup>

Serious TEAEs that occurred more frequently (a risk difference of  $\geq 0.5\%$ ) in tolvaptan subjects compared with placebo subjects included events suggestive of liver injury (2.2% on tolvaptan versus 0.6% on placebo), headache (0.6% on tolvaptan versus 0% on placebo), and fatigue (0.5% on tolvaptan versus 0% on placebo). Drug-induced liver injury is discussed in Section 7.3.5 Submission Specific Primary Safety Concerns.

Serious TEAEs that occurred more frequently in placebo subjects compared with tolvaptan subjects were generally related to ADPKD (see table below).

Table 30. Incidence of Serious TEAE occurring in  $\geq 3$  subjects in the tolvaptan arm in Trial 156-04-251

Preferred term	tolvaptan	%	placebo	%
<b>Total subjects</b>	<b>177</b>	<b>(18.4)</b>	<b>95</b>	<b>(19.7)</b>
ALT increased, AST increased, blood bilirubin increased, GGT increased, liver disorder, LFT abnormal, hepatitis, transaminases increased	21	(2.2)	3	(0.6)
renal cyst, renal cyst ruptured, renal pain, renal cyst hemorrhage, nephrolithiasis, renal cyst infection	13	(1.4)	16	(3.3)
urinary tract infection, kidney infection, pyelonephritis, urogenital infection	9	(0.9)	8	(1.7)
Inguinal hernia, intervertebral disc protrusion, hiatus hernia, umbilical hernia, abdominal distension, abdominal hernia obstructive	8	(0.8)	5	(1.0)
ankle fracture, clavicle fracture, fracture, hand fracture, multiple fractures, lumbar fracture, tibia fracture, wrist fracture, cartilage injury, ulna fracture	8	(0.8)	3	(0.6)
pollakiuria, polyuria, thirst, dehydration	6	(0.6)	3	(0.6)
Chest pain, palpitations	6	(0.6)	2	(0.4)
headache, migraine with aura	6	(0.6)	0	0.0
Intracranial aneurysm, subarachnoid hemorrhage, cerebral hemorrhage	5	(0.5)	2	(0.4)
fatigue, exercise tolerance decreased	5	(0.5)	0	0.0

<sup>22</sup> Reviewer's analysis: ae\sae review, SAE\_MAED analyses

Preferred term	tolvaptan	%	placebo	%
Acute myocardial infarction, coronary artery disease, myocardial ischemia, myocardial infarction, angina	4	(0.4)	2	(0.4)
breast cancer	4	(0.4)	1	(0.2)
Hematuria	4	(0.4)	1	(0.2)
Abscess limb, bartholin's abscess, liver abscess, perineal abscess	4	(0.4)	0	0.0
Uterine prolapse, uterovaginal prolapse	4	(0.4)	0	0.0
vertigo, dizziness, hypotension, orthostatic hypotension	4	(0.4)	0	0.0
Abdominal pain	3	(0.3)	3	(0.6)
depression, suicide attempt	3	(0.3)	2	(0.4)
Atrial fibrillation	3	(0.3)	1	(0.2)
menorrhagia, metorrhagia	3	(0.3)	1	(0.2)
diverticulitis, diverticulum intestinal	3	(0.3)	0	0.0
Pneumonia	3	(0.3)	0	0.0

Source: Reviewer's analysis: ae\sae review, sae\_spondef.xls, dataset AE0  
 Subjects counted only once in each grouping. Applicant's definition of TEAE used. Highlighted AEs indicate a risk difference of  $\geq 0.5\%$  in the tolvaptan group compared to the placebo group

Serious TEAEs reported in open-label trials generally aligned with those reported in the pivotal trial. In the largest open label extension trial 156-08-271, 6% of subjects had a serious TEAE (see next table). The percent of subjects with a SAE was slightly greater in subjects who had been previously treated with placebo (indicated by "delayed-treated tolvaptan" relative to subjects previously treated with tolvaptan (indicated by "early-treated" tolvaptan).

Table 31. Incidence of serious TEAE occurring in ≥ 2 subjects overall in Trial 156-08-271 by MedDRA System Organ Class and Preferred Term

SOC PT	Early-treated Tolvaptan (N = 530) n (%)	Delayed-treated Tolvaptan (N = 293) n (%)
Total subjects with ≥ 1 serious TEAE <sup>a</sup>	30 (5.7)	20 (6.8)
<b>Blood and lymphatic system disorders</b>		
Anaemia	2 (0.4)	0
<b>Infections and infestations</b>		
Diverticulitis	2 (0.4)	0
Pyelonephritis	1 (0.2)	1 (0.3)
Urinary Tract Infection	2 (0.4)	0
<b>Injury, poisoning and procedural complications</b>		
Joint Dislocation	1 (0.2)	1 (0.3)
<b>Investigations</b>		
Liver Function Test Abnormal	1 (0.2)	2 (0.7)
<b>Nervous system disorders</b>		
Cerebrovascular Accident	1 (0.2)	2 (0.7)
<b>Renal and urinary disorders</b>		
Renal Cyst Haemorrhage	1 (0.2)	1 (0.3)
Renal Failure Acute	0	2 (0.7)

APPEARS THIS WAY ON ORIGINAL

Source: Applicant CSR 156-08-271, CT-8.5.2.

### 7.3.3 Dropouts and/or Discontinuations

Approximately 23% of subjects on tolvaptan discontinued study medication prematurely compared to 13.8% on placebo. Most of the difference was because of discontinuations due to adverse events. (See also Section 6.1.3.)

#### Treatment Discontinuations due to adverse events

Adverse events resulting in treatment discontinuation occurred more frequently in tolvaptan subjects compared with placebo subjects (15.5% vs. 5.0%). The most frequently reported events where the risk difference was at least 0.5% on tolvaptan compared to placebo were those AEs related to aquaresis and potential liver injury (see table).

Table 32. Adverse events leading to treatment discontinuation in at least 2 subjects in Trial 156-04-251

Preferred Term	tolvaptan	%	placebo	%
<b>Total subjects</b>	<b>148</b>	<b>(15.4)</b>	<b>24</b>	<b>(5.0)</b>
thirst, pollakiuria, polyuria, nocturia, polydipsia, dry mouth, tongue dry, mucosal dryness	73	(7.7)	5	(1.0)
ALT increased, AST increased, blood bilirubin increased, hepatic enzyme increased, liver function test abnormal, hepatitis, GGT increased, hepatic function abnormal	17	(1.8)	0	0.0
Fatigue, malaise, asthenia, muscular weakness, anemia, myalgia, stress	12	(1.2)	4	(0.8)
renal pain, renal colic	5	(0.5)	4	(0.8)
abdominal distention, abdominal discomfort, gastritis, abdominal pain	5	(0.5)	0	0.0
hypertension	4	(0.4)	1	(0.2)
nausea, vomiting	3	(0.3)	2	(0.4)
blood creatinine increased	3	(0.3)	1	(0.2)
depression	3	(0.3)	0	0.0
insomnia	3	(0.3)	0	0.0
headache	2	(0.2)	3	(0.6)
paresthesia, pain, pain in extremity	2	(0.2)	2	(0.4)
dyspnea at rest, dyspnea	2	(0.2)	1	(0.2)
hypersensitivity, pityriasis, pruritis, hot flush	2	(0.2)	1	(0.2)
weight increased, edema	2	(0.2)	1	(0.2)
arthralgia	2	(0.2)	0	0.0
candidiasis, oral lichen planus	2	(0.2)	0	0.0
constipation	2	(0.2)	0	0.0
decreased appetite	2	(0.2)	0	0.0
intracranial aneurysm, cerebral hemorrhage	2	(0.2)	0	0.0

Reviewer's analysis<sup>23</sup>: \ae\dcae.sas, aedc\_teae.xlsx, dataset eos0 and ae0.

*Reviewer's comment: Investigators were only required to mark one AE as the reason for discontinuation on the AE CRF.<sup>24</sup> However, it is unclear if the treatment emergent AE marked*

<sup>23</sup> The additional 7 subjects in the above table compared to the applicant's AE resulting in DC table (CT-8.5.2 in CSR 156-04-251) is because the applicant's table was generated using dataset ae0 (created with the AE CRF). This table used dataset eos0 (created with the completion status CRF) and ae0. AEs starting more than 7 days after the last dose were not counted. All subjects in the table had TEAEs. For the 7 subjects without a selected AE leading to treatment discontinuation on the AE CRF (but marked as discontinued because of AE in the completion status CRF), the AEs that started within 30 days of treatment discontinuation were counted.

<sup>24</sup> Four subjects had more than one AE reason checked as the reason for drug discontinuation; all four subjects' reasons for discontinuation were elevations in both ALT and AST.

*as leading to drug discontinuation is permanent or temporary drug discontinuation. It was discovered late in the review cycle that some subjects noted to have discontinued treatment for an AE went back on treatment for a period of time. In these subjects the drug end date occurs much later (sometimes years later) than the date of the AE that was the reason for discontinuation. While this might be plausible in some subjects it does not appear that this can be true for all subjects. Other factors that complicated resolving this issue promptly included: incorrect AE start dates and case report forms and/or narratives not submitted to the NDA. The reviewers will resolve this issue with the applicant before the Advisory Committee Meeting.*

*This reviewer found that analyzing the actions (“dose interruption”, “dose reduced” or drug “discontinued”) done with the study drug due to an AE was unreliable and could be misinterpreted if the analysis was based solely on the “action” field of the AE CRF. There were cases when the action was listed as “none”, yet the AE start date and drug end date were the same indicating that drug was stopped on the same day that the AE started. This was likely due to the reporting requirements for the AE CRF.*

The next figure shows that subjects discontinued tolvaptan due to an AE early in the trial compared to placebo.

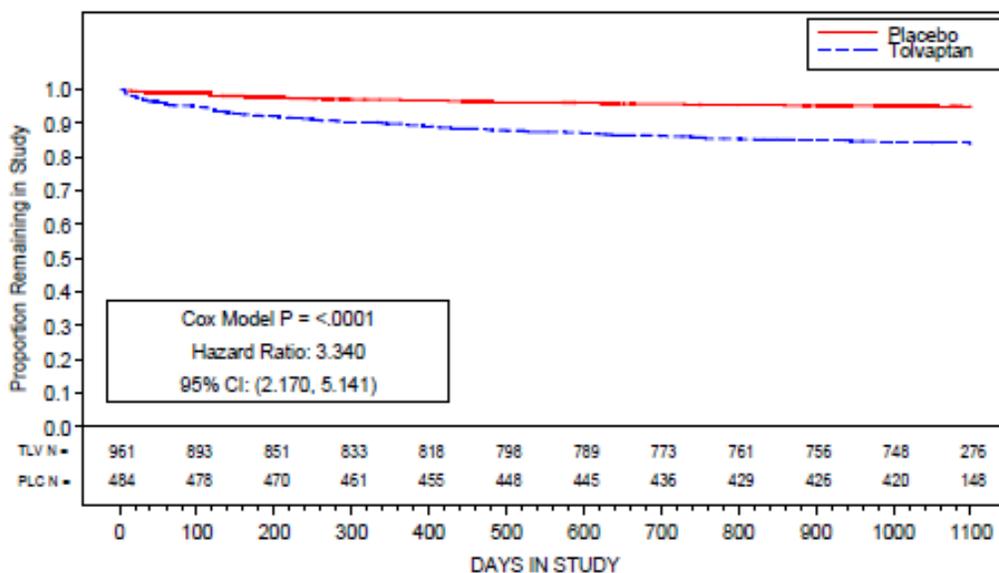


Figure 17. Time to treatment discontinuation due to AE

Source: Applicant’s CSR 251, CT-9.3

Examination of the first four weeks on treatment (includes the 3 week titration phase) shows early permanent treatment discontinuations were primarily due to AEs, consistent with the reason for treatment discontinuation in the trial overall. The most frequent AE was the aquaretic effects.

Table 33. Reason for permanent treatment discontinuation in first 28 days on treatment

Reason	Tolvaptan (n=961)	Placebo (n=483)
<b>Total subjects</b>	<b>56 (5.8)</b>	<b>10 (2.1)</b>
Discontinuing treatment due to AE	49 (5.1)	3 (0.6)
Subject withdrew consent	6 (0.6)	5 (1.0)
Protocol deviation	1 (0.1)	0
Lost to follow-up	0	1 (0.2)
Investigator withdrew	0	1 (0.2)

Reviewer's analysis: dc\dcae, dataset dose0

This analysis excludes periods of temporary interruptions, 28 days on treatment was arbitrarily chosen to examine early discontinuations.

The rate of discontinuation compared to placebo is higher in the beginning of the trial compared to overall.

Table 34. AEs in subjects who permanently discontinue treatment in first 28 days of treatment

Preferred Term	tolvaptan	%	placebo	%
Total subjects	49	(5.1)	3	(0.6)
thirst, pollakiuria, urine output increased, polyuria, nocturia, dry mouth, dysphagia, dehydration, polydipsia, dry skin	45	(4.7)	1	(0.2)
nausea, vomiting, vertigo, dizziness	8	(0.8)	0	0
fatigue, asthenia, stress, somnolence	8	(0.8)	1	(0.2)
hypertension	7	(0.7)	1	(0.2)
decreased appetite	6	(0.6)	0	0
insomnia	6	(0.6)	0	0
renal pain	6	(0.6)	0	0
Influenza, nasopharyngitis, cold sweat	5	(0.5)	0	0
headache	5	(0.5)	2	(0.4)
constipation	4	(0.4)	0	0
abdominal discomfort, abdominal pain, epigastric discomfort	3	(0.3)	0	0
diarrhea	2	(0.2)	0	0
myalgia	2	(0.2)	0	0
oral candidiasis, glossodynia, tongue coated, tongue disorder, oral lichen planus	2	(0.2)	0	0
palpitations, tachycardia	2	(0.2)	0	0
rash, pruritis, hot flush	2	(0.2)	0	0
weight decreased	2	(0.2)	0	0
hyperglycemia	1	(0.1)	0	0

Preferred Term	tolvaptan	%	placebo	%
albuminuria	1	(0.1)	0	0
angina	1	(0.1)	0	0
anxiety	1	(0.1)	0	0
deafness	1	(0.1)	0	0
hematuria	1	(0.1)	0	0
hepatic enzyme abnormal	1	(0.1)	0	0
kidney enlargement	1	(0.1)	0	0
muscle spasms	1	(0.1)	0	0
paresthesias	1	(0.1)	0	0
syncope	1	(0.1)	0	0
dyspnea	0	0	1	(0.2)
edema	0	0	1	(0.2)
weight increased, edema	0	0	1	(0.2)

Reviewer's analysis: ae\dcae, aedc\_early\_2.csv, dataset dose0, ae0, eos0

Subjects counted only once in each category. Preferred Terms grouped together in some categories. Analysis of subjects who discontinued for AE in Completion Status CRF

The most frequent TEAE that resulted in discontinuation of tolvaptan in the open label extension trials was polyuria. Subjects who previously received tolvaptan were less likely to discontinue tolvaptan due to a TEAE related to the aquaretic effects of tolvaptan.

#### 7.3.4 Significant Adverse Events

The applicant highlights AEs leading to treatment discontinuation as significant AEs (See Section 7.3.3). See also Section 7.4.1. Common AEs.

Administration of AVP antagonists has been shown to cause small increases in circulating AVP concentrations. Thus, a potential clinical implication of increased endogenous AVP is enhanced platelet activation, which could result in increased events related to thrombosis. Overall, TEAE related to arterial embolic, venous embolic or thrombotic events were infrequently observed in Trial 156-04-251.

Studies in subjects with cirrhosis observed an increased incidence of GI bleeding. This was not observed in the ADPKD program. Treatment emergent AEs related to hemorrhage were either reported less frequently or at a similar frequency in subjects treated with tolvaptan compared with placebo subjects.

An increase in circulating AVP may stimulate hepatic glucose production. Prior placebo-controlled trials in hyponatremia showed a 6-fold higher incidence of hyperglycemia in tolvaptan treated subjects compared to placebo. (Poorly controlled diabetics were excluded from Trial 156-04-251.) In Trial 156-04-251 increased glucose concentrations were observed less frequently in subjects on tolvaptan (5.5%) compared with subjects on placebo (6.8%).

Potentially significant decreases in glucose concentrations occurred at similar rates between treatment groups. Mean change from baseline to Month 36 were  $0.90 \pm 17.38$  mg/dL in the tolvaptan group and  $-0.36 \pm 17.36$  mg/dL in the placebo group. The reviewer's analysis of the change in glucose does not indicate a cause for concern either (see Section 7.4.2. Laboratory Findings). After removing thirst, polyuria, and polydipsia from the hyperglycemia/new onset diabetes mellitus Standardized MedDRA Queries (SMQ), there was no difference between treatment groups in hyperglycemia/new onset diabetes mellitus. Unsupportive of safety, however, was the report in 7 subjects treated with tolvaptan (versus zero in the placebo group) of TEAE diabetes mellitus. The applicant concludes that an association between tolvaptan and hyperglycemia/new onset diabetes cannot be excluded.

### 7.3.5 Submission Specific Primary Safety Concerns, Drug-Induced Liver Injury

The applicant conducted clinical trials of tolvaptan for the treatment of heart failure (HF) (IND 50,533) and for the treatment of hyponatremia (IND 54,200) in the mid 1990's to 2005. The randomized, placebo-controlled studies in hyponatremia were of short duration, so the HF studies provided the majority of the tolvaptan safety data.<sup>25</sup> Drug-induced liver injury was not identified as an adverse event in those applications. On 13 Apr 2012 trial 156-04-251 was unblinded, and the applicant discovered a higher proportion of subjects on tolvaptan with ALT > 3xULN compared to subjects on placebo. We reanalyzed the liver data in hyponatremia and HF (including new non-US IND data). There was not an imbalance between tolvaptan and placebo in elevations in liver test data, however many subjects were missing clinical narratives that are needed for determining the probable cause of significant ALT and total bilirubin elevations (TSI review#1332 filed May 17, 2013). Thus, DILI could not be excluded from prior development programs.

Unlike the data in hyponatremia and HF trials, the liver laboratory data in the ADPKD development program showed two characteristics seen with drugs that are known hepatotoxins, an imbalance of subjects in the potential Hy's Law<sup>26</sup> quadrant and in Temple's Corollary<sup>27</sup> quadrant. Figure A. shows that there are two subjects on tolvaptan (and no subjects on placebo) from the pivotal trial with liver tests suggestive of hepatocellular injury (Northeast Quadrant). Figure A. also shows that there is ~4x increase in ALT > 3xULN compared to placebo. Figure B. is a plot of the Northeast Quadrant showing all of the data from 17 trials. Three subjects, all

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<sup>25</sup> In the phase 3 placebo-controlled heart failure trial, 2603 subjects were exposed to tolvaptan 30 mg once daily for a median duration of 8 months. In the two phase 3 placebo-controlled hyponatremia trials, 223 subjects were exposed to tolvaptan 15-60 mg once daily, titrated to response, for ~30 days. An uncontrolled extension study (111 subjects) of the phase 3 hyponatremia trials also provided some data beyond 30 days; ~70% of subjects were exposed to tolvaptan for over a year; the average daily dose was 32.5 mg.

<sup>26</sup> Dr. Hy Zimmerman noted that drugs causing hepatocellular injury and clinical jaundice lead to acute liver failure with a case fatality rate of ~ 10% (ranging from ~5 - 50%). The potential Hy's Law quadrant is the Northeast quadrant.

<sup>27</sup> Dr. Robert Temple of FDA made the observation that drugs known to cause serious liver injury exhibit a higher incidence of ALT elevations > 3x ULN relative to a non-toxic comparator. Temple's Corollary quadrant is the Southeast Quadrant in Figure A.

females on the 120 mg tolvaptan dose, have liver test data suggestive of predominant hepatocellular injury.

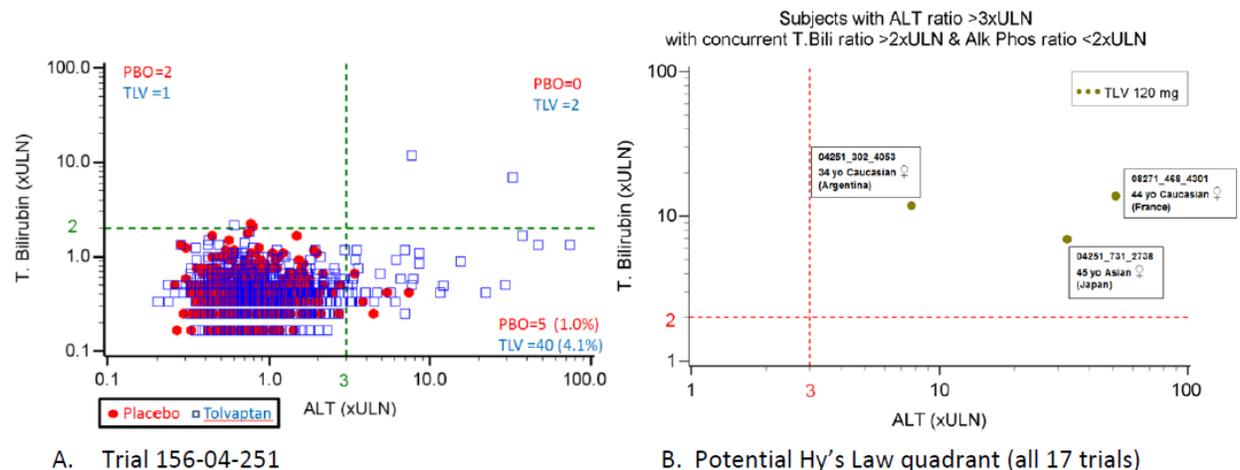


Figure 18. Peak ALT ratio with concurrent peak total bilirubin ratio (within 30 days after ALT) in treated subjects

Reviewer's analysis: hep\figcode\all quadrant ALT TB, datasets liverf (all 17 studies, last submission date 04/09/2013). Concurrent defined as within 30 days after peak ALT. Four subjects (on tolvaptan) are not included in Figure A because lab dates were prior to starting drug or more than 30 days after the last dose. Figure A depicts one point per subject. In Figure B only data in the Northeast Quadrant are shown.

Following the discovery of the imbalance in the proportion of subjects with elevated transaminases, the applicant formed a Hepatic Adjudication Committee (HAC) consisting of four hepatologists: Drs. Paul Watkins (chair), James Lewis, Neil Kaplowitz, and David Alpers. Using the causality scale adopted by the United States Drug-induced liver Injury Network (Rockey DC 2010) the committee blindly and independently adjudicated cases of interest as determined by comprehensive criteria set forth by Otsuka (see Appendix).

The three cases in the Northeast quadrant are discussed in the Appendix. The consensus causality adjudication for the two subjects (b) (6) in this quadrant from the pivotal trial was "probable" (50-74% likelihood. The preponderance of the evidence supports the link between the drug and liver injury). By unanimous agreement, subject ID (b) (6), also in the Northeast quadrant from the open label extension trial (previously on placebo for ~ 3 years in study 156-04-251) was adjudicated as highly likely (75-95% likelihood). The evidence for the drug causing the injury is clear and convincing but not definite). All three cases in the Northeast quadrant were called "Hy's Law" cases defined per the FDA DILI Guidance.<sup>28</sup>

<sup>28</sup> Hy's Law according to the FDA DILI guidance is defined as a subject with ALT > 3x ULN, total bilirubin > 2xULN and 1) hepatocellular injury without initial findings of cholestasis (i.e., serum alkaline phosphatase < 2 xULN or the R value (ratio of serum ALT xULN/alkaline phosphatase x ULN) ratio > 5.0, 2) there should not be a more likely explanation for the liver injury, and 3) there should be a higher incidence of ALT elevations > 3x ULN in drug treated subjects relative to control.

The HAC adjudicated 62 cases in the ADPKD program. The next table shows that most cases adjudicated as probable or higher were in subjects on tolvaptan (only one was on placebo).

Table 35. Hepatic Adjudication Committee consensus causality assessment of 62 cases of interest in ADPKD

	Highly likely	Probable	possible	Unlikely
Trial 156-04-251				
Tolvaptan	1	15	10	10
Placebo	0	1	2	8
Trial 156-08-271				
Tolvaptan	2	4	1	3
Trial 156-09-290				
Blinded	0	0	1	1
Trial 156-10-003				
Tolvaptan	0	2	0	1

Source: applicant dataset heparst.xpt

Since drugs capable of causing progressive hepatocellular liver injury generally do so with similar latency as they cause elevations in serum ALT, it is important to examine the time course of significant rise in ALT in attempts to identify the risk period (Lewis 2013). The next figure shows the time to first ALT elevation >3xULN. The y-axis range is fairly narrow, showing ~4% of subjects with elevations in ALT > 3xULN. A clear separation between tolvaptan and placebo is evident at the 4 month study visit. The rate steadily climbs until ~ Day 500 (~16 months) and then flattens and runs parallel with the placebo.

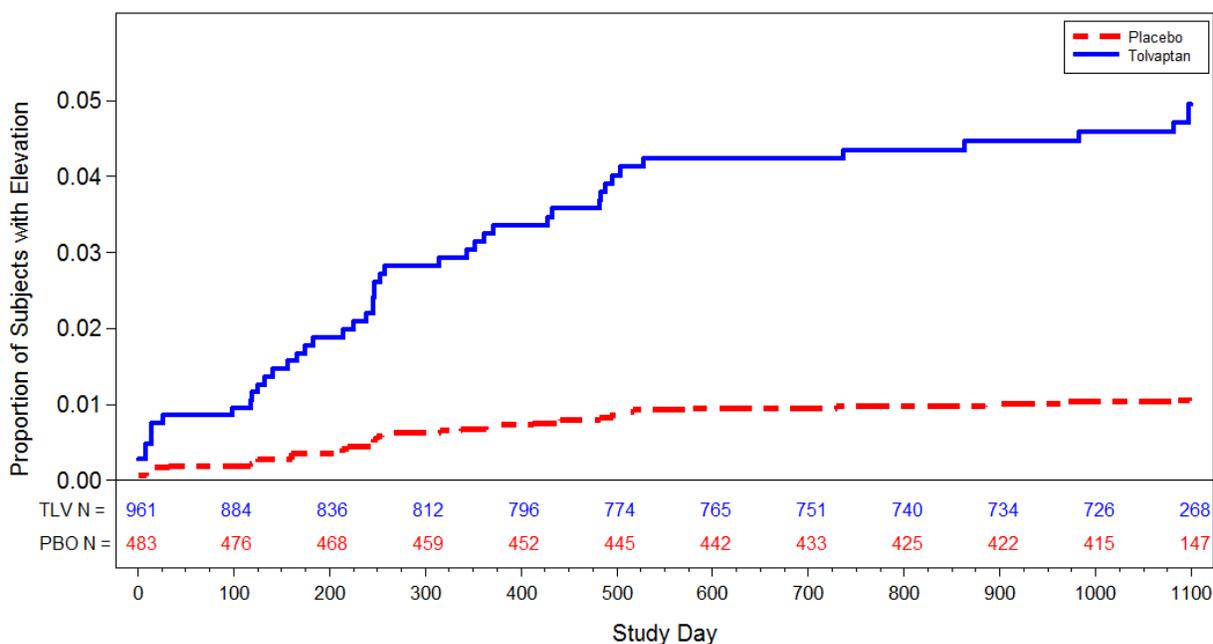


Table 36. Time to first ALT>3xULN, all subjects Trial 156-04-251

Reviewer's analysis: hep\km\tte\_alt\_jpn, dataset lablft0

The HAC show the time to ALT rise above 5x, and 10x the ULN for all subjects and for subjects adjudicated with “probable” or greater causality. The curves are not as steep for greater rises in ALT. The time course for subjects with “probable” and greater causality indicates a window of susceptibility between ~ 4 months to 14 months (see next figure). The HAC concludes that “the separation between tolvaptan and placebo treated subjects starts at 4 months (not earlier) and the slope differs until about 14 months (~400 days) on active treatment.” (Note that there were no scheduled blood draws between the Week 3/End of Titration visit and the 4 month visit.) The HAC conclude that the signature characteristic onset is “between 3 and 15 months of treatment”.

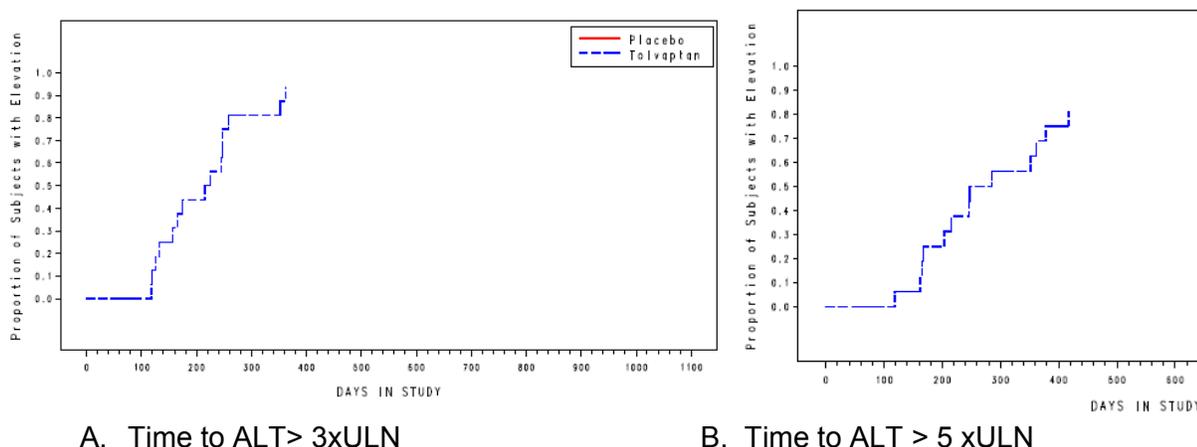


Figure 19. Time to first elevation in ALT in “probable” and “highly likely” cases of DILI

*Reviewer's comment: The AE dataset contains one subject who permanently discontinued treatment within 28 days on drug because of a “hepatic enzyme abnormal”. One of the Hy's Law cases, first had symptoms at 2.5 months. Albeit the numbers are small, there are cases in this clinical program that suggest the development of serious liver injury could happen sooner than 4 months. Indeed the HAC acknowledge that “drugs with characteristic signatures may produce injuries without all of the characteristics of that signature”.*

All subjects that were followed had resolution of ALT values. The figure below shows that for tolvaptan subjects who continued/resumed treatment after peak ALT was reached (21/35 subjects), resolution to  $\leq 3x$  ULN occurred within 4 months for ~80% of subjects. Resolution was faster in subjects who discontinued medication before peak ALT was reached or within 2 days of reaching peak ALT (14/35 subjects); resolution to  $\leq 3x$ ULN occurred within 40 days for 80% of subjects. The longest time to resolution was ~15.5 months after peaking for a subject who continued therapy and was ~ 19 months for a subject who discontinued treatment. Resolution to  $\leq 3x$ ULN was achieved within 20 days in all placebo subjects. The HAC describes the “signature” resolution of liver injury from tolvaptan as “the injury progresses by biochemical criteria for weeks after discontinuation of treatment, and resolves slowly over one to several months.”

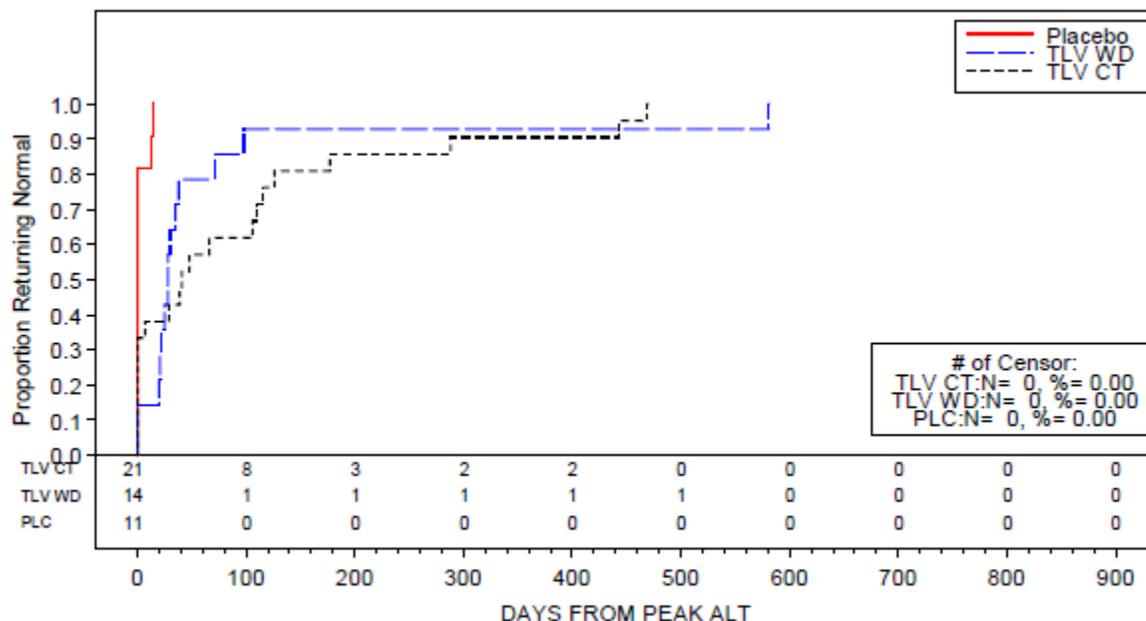


Figure 20. Time from peak ALT to less than 3x ULN, adjudicated subjects, trial 156-04-251

Source: applicant’s CSR 156-04-251, Figure 11.8.1.6.7.3.1-1

Trial design issues complicate the analysis and interpretation of whether there was a clear dose response. Available data suggests that there could be a relationship between dose and ALT (see next table). Whether this translates into risk of severe liver injury is unknown; all three Hy’s Law subjects were taking tolvaptan 120 mg at the time of their liver injury.

Table 37. Dose in 47 subjects with ALT >3xULN, Trial 156-04-251

Dose	Count based on dose prior to peak ALT measurement	Count based on modal dose during the trial
placebo	5/483 (1.0%)	5/483 (1%)
Tolvaptan 60 mg	11/961 (1.1%)	14/244 (5.7%)
Tolvaptan 90 mg	11/961 (1.1%)	7/184 (3.8%)
Tolvaptan 120 mg	20/961 (2.1%)	21/530 (4.0%)

Source: reviewer’s analysis ALT dose analysis, dataset liverf

There were seven subjects in the tolvaptan arm whose dose was stopped prior to their peak ALT measurement. In these subjects, the tolvaptan dose prior to stopping drug was counted.

There were two subjects of interest that upon rechallenge at lower doses experienced almost immediate rises in ALT relative to the latency of their initial rise in ALT. These subjects are discussed in detail in the Appendix. These cases support the involvement of the adaptive immune system. Also supportive of this mechanism is the progression and prolonged resolution observed after discontinuing tolvaptan.

Although the exact mechanism of tolvaptan Drug-induced liver injury cannot be determined, it would be helpful if the applicant could determine if a specific genetic determinant placed subjects at higher risk for severe liver injury. Other genetic studies have found adaptive immunity to be involved in the mechanism of DILI for ximelagatran, lumiracoxib and lapatinib. Specific HLA alleles have been identified as patient risk factors for DILI due to these drugs. (Kindmark 2007, Singer 2010, Spraggs 2011)

Analysis using baseline characteristics to identify an at-risk population was limited because the at-risk cohort was small. The applicant conducted exploratory analysis of the “highly likely” and “probable” cases compared to subjects adjudicated as “possible” and “unlikely” in attempts to identify a population most at risk (see table). Tolvaptan subjects in the “highly likely” and “probable” group were older, with a higher proportion being female, Asian, and with a lower mean body weight than those subjects adjudicated as “possible” and “unlikely” and those in the nonadjudicated group. The numbers in these comparisons are small and conclusions based on these analyses cannot be definitively made. The applicant was unable to find an association between increased risk of liver injury with dose, exposure, age, and gender.

Table 38. Demographic and baseline characteristics for subjects meeting criteria for event adjudication by adjudication category

Characteristic	Tolvaptan (N = 961)			Placebo (N = 484)		
	Highly Likely and Probable (N = 16)	Possible and Unlikely (N = 19)	Nonadjudicated (N = 926)	Highly Likely and Probable (N = 1)	Possible and Unlikely (N = 10)	Nonadjudicated (N = 473)
Age, years						
N	16	19	926	1	10	473
Mean (SD)	41.3 (6.3)	39.6 (5.9)	38.5 (7.1)	42.0 (–)	41.5 (6.9)	38.8 (7.2)
Min, max	29, 50	28, 50	18, 51	42, 42	25, 48	18, 50
Sex, n (%)						
Male	5 (31.3)	12 (63.2)	478 (51.6)	1 (100.0)	3 (30.0)	247 (52.2)
Female	11 (68.8)	7 (36.8)	448 (48.4)	0	7 (70.0)	226 (47.8)
Race, n (%)						
Caucasian	11 (68.8)	14 (73.7)	785 (84.8)	1 (100.0)	10 (100.0)	397 (83.9)
Black	0	1 (5.3)	15 (1.6)	0	0	3 (0.6)
Hispanic	0	0	13 (1.4)	0	0	9 (1.9)
Asian	5 (31.3)	4 (21.1)	112 (12.1)	0	0	62 (13.1)
Other	0	0	1 (0.1)	0	0	2 (0.4)
Region, n (%)						
Americas	5 (31.3)	6 (31.6)	305 (32.9)	1 (100.0)	7 (70.0)	151 (31.9)
Japan	5 (31.3)	4 (21.1)	109 (11.8)	0	0	59 (12.5)
Europe/ROW	6 (37.5)	9 (47.4)	512 (55.3)	0	3 (30.0)	263 (55.6)
Height, cm						
N	16	19	925	1	10	472
Mean (SD)	168.1 (13.3)	176.6 (10.6)	173.6 (10.3)	168.0 (–)	171.9 (13.8)	173.6 (9.6)
Min, max	145, 198	162, 200	143, 210	168, 168	150, 201	150, 201
Weight, kg						
N	16	19	926	1	10	473
Mean (SD)	73.61(20.39)	81.77 (15.95)	79.52 (18.27)	82.50 (–)	80.59 (31.12)	78.46 (18.01)
Min, max	46.6, 105.0	52.5, 110.0	40.6, 160.6	82.5, 82.5	46.0, 151.8	46.5, 136.2
eGFR <sub>CKD-EPI</sub> , mL/min/1.73m <sup>2</sup>						
N	16	19	923	1	10	471
Mean (SD)	76.4 (22.0)	74.7 (16.9)	81.6 (21.1)	91.3 (–)	80.4 (18.1)	82.2 (22.9)
Min, max	35.7, 108.2	49.0, 105.1	32.3, 132.8	91.3, 91.3	58.4, 106.0	26.4, 186.8
Concomitant Medication, n (%)						
ACE inhibitor/ARB	12 (75.0)	17 (89.5)	753 (81.3)	1 (100.0)	10 (100.0)	385 (81.4)
Statin	2 (12.5)	4 (21.1)	119 (12.9)	0	1 (10.0)	61 (12.9)
Allopurinol	0	3 (15.8)	62 (6.7)	0	0	25 (5.3)
Vitamin D	1 (6.3)	2 (10.5)	64 (6.9)	0	2 (20.0)	28 (5.9)

Max = maximum; Min = minimum.

Source: ST-1.23.

Source: CSR 156-04-251, Table 11.8.1.6.8.2.1.1-1

The reviewer examined the rate of ALT rise to > 3 xULN in the Japanese compared to the rest of the world. Subjects in Japan (only one was Caucasian, the rest were Asian) appear to have a faster rate of incline compared to the rest of the world. The Japanese made up about ~11% of the population in the pivotal trial. The small number of subjects limits definitive interpretation.

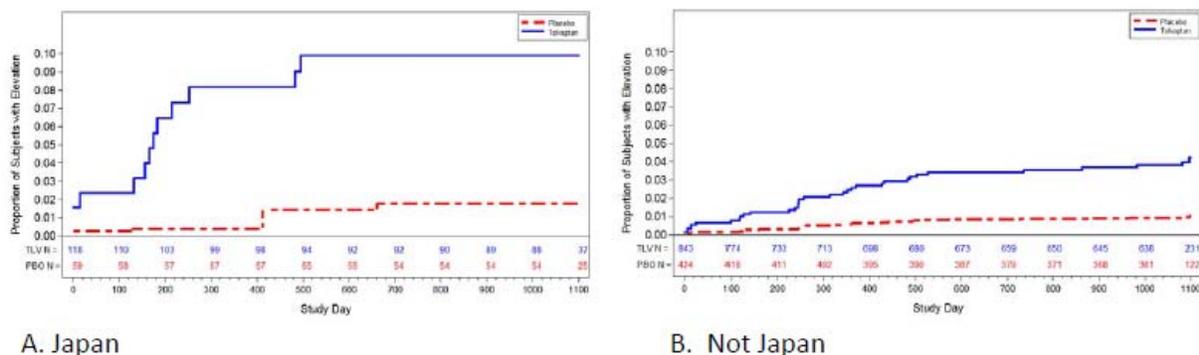


Figure 21. Time to ALT > 3xULN in Japan compared to the rest of the world  
 Source: reviewer's analysis: hep\km\l\l\l\alt\_jpn, data dos0 lablft0

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

Thirst, dry mouth, pollakiuria, polyuria, and nocturia were common adverse events that were reported at a higher incidence in the tolvaptan arm. These events occurred early following initiation of treatment and were generally mild to moderate in severity. Dizziness was also reported at a higher incidence on tolvaptan relative to placebo. In contrast, hypotension was reported at a similar rate in the two treatment arms. To further explore effects on AEs related to dehydration a number of terms suggestive of dehydration were pooled by the applicant. While this analysis showed a higher incidence of potentially drug-related events suggestive of dehydration in the tolvaptan arm (64.5% of subjects on tolvaptan versus 33.3% of subjects on placebo), the incidence of serious adverse events related to dehydration was low (see Section 7.3.2).

Other adverse events that were reported at a higher incidence in the tolvaptan arm, including constipation and skin dryness/irritation, may have been related to tolvaptan's aquaretic effect. Tolvaptan's effects on hypernatremia, uric acid and gout are discussed in Section 7.4.2. Laboratory Findings.

Table 39. Incidence of treatment emergent AE in at least 2% of subjects in any group by MedDRA system organ class and preferred term

SOC PT	Tolvaptan (N = 961) n (%)	Placebo (N = 483) n (%)	Total (N = 1444) n (%)
Total <sup>a</sup>	941 (97.9)	469 (97.1)	1410 (97.6)
<b>Blood and lymphatic system disorders</b>			
Anaemia	27 (2.8)	24 (5.0)	51 (3.5)
<b>Cardiac disorders</b>			
Palpitations	34 (3.5)	6 (1.2)	40 (2.8)
<b>Ear and labyrinth disorders</b>			
Vertigo	24 (2.5)	18 (3.7)	42 (2.9)
<b>Gastrointestinal disorders</b>			
Abdominal Discomfort	29 (3.0)	10 (2.1)	39 (2.7)
Abdominal Distension	47 (4.9)	16 (3.3)	63 (4.4)
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)
Diarhoea	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)
Gastroesophageal Reflux Disease	43 (4.5)	16 (3.3)	59 (4.1)
Nausea	98 (10.2)	57 (11.8)	155 (10.7)
Toothache	10 (1.0)	12 (2.5)	22 (1.5)
Umbilical Hernia	21 (2.2)	7 (1.4)	28 (1.9)
Vomiting	79 (8.2)	40 (8.3)	119 (8.2)
<b>General disorders and administration site conditions</b>			
Asthenia	57 (5.9)	27 (5.6)	84 (5.8)
Chest Pain	42 (4.4)	12 (2.5)	54 (3.7)
Fatigue	131 (13.6)	47 (9.7)	178 (12.3)
Malaise	24 (2.5)	10 (2.1)	34 (2.4)
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)
<b>Hepatobiliary disorders</b>			
Hepatic Cyst	13 (1.4)	10 (2.1)	23 (1.6)
<b>Immune system disorders</b>			
Seasonal Allergy	26 (2.7)	10 (2.1)	36 (2.5)
<b>Infections and infestations</b>			
Bronchitis	58 (6.0)	33 (6.8)	91 (6.3)
Cystitis	11 (1.1)	12 (2.5)	23 (1.6)
Ear Infection	22 (2.3)	7 (1.4)	29 (2.0)
Gastroenteritis	54 (5.6)	21 (4.3)	75 (5.2)
Gastroenteritis Viral	20 (2.1)	6 (1.2)	26 (1.8)
Influenza	75 (7.8)	38 (7.9)	113 (7.8)
Nasopharyngitis	211 (22.0)	111 (23.0)	322 (22.3)
Pharyngitis	16 (1.7)	16 (3.3)	32 (2.2)
Renal Cyst Infection	9 (0.9)	13 (2.7)	22 (1.5)
Rhinitis	14 (1.5)	11 (2.3)	25 (1.7)
Sinusitis	53 (5.5)	23 (4.8)	76 (5.3)
Upper Respiratory Tract Infection	82 (8.5)	42 (8.7)	124 (8.6)

(continued)

SOC PT	Tolvaptan (N = 961) n (%)	Placebo (N = 483) n (%)	Total (N = 1444) n (%)
Urinary Tract Infection	81 (8.4)	61 (12.6)	142 (9.8)
Viral Infection	21 (2.2)	13 (2.7)	34 (2.4)
<b>Injury, poisoning and procedural complications</b>			
Ligament Sprain	14 (1.5)	11 (2.3)	25 (1.7)
<b>Investigations</b>			
Alanine Aminotransferase Increased	39 (4.1)	17 (3.5)	56 (3.9)
Aspartate Aminotransferase Increased	36 (3.7)	16 (3.3)	52 (3.6)
Blood Creatinine Increased	135 (14.0)	71 (14.7)	206 (14.3)
Blood Urea Increased	10 (1.0)	12 (2.5)	22 (1.5)
Blood Uric Acid Increased	<b>24 (2.5)</b>	<b>6 (1.2)</b>	<b>30 (2.1)</b>
Gamma-glutamyl Transferase Increased	23 (2.4)	11 (2.3)	34 (2.4)
Weight Decreased	46 (4.8)	16 (3.3)	62 (4.3)
Weight Increased	46 (4.8)	19 (3.9)	65 (4.5)
<b>Metabolism and nutrition disorders</b>			
Decreased Appetite	<b>69 (7.2)</b>	<b>5 (1.0)</b>	<b>74 (5.1)</b>
Dehydration	18 (1.9)	11 (2.3)	29 (2.0)
Gout	<b>28 (2.9)</b>	<b>7 (1.4)</b>	<b>35 (2.4)</b>
Hypercholesterolaemia	26 (2.7)	12 (2.5)	38 (2.6)
Hyperglycaemia	6 (0.6)	10 (2.1)	16 (1.1)
Hypernatraemia	<b>27 (2.8)</b>	<b>5 (1.0)</b>	<b>32 (2.2)</b>
Hyperuricaemia	37 (3.9)	9 (1.9)	46 (3.2)
Polydipsia	100 (10.4)	17 (3.5)	117 (8.1)
<b>Musculoskeletal and connective tissue disorders</b>			
Arthralgia	69 (7.2)	28 (5.8)	97 (6.7)
Back Pain	133 (13.8)	88 (18.2)	221 (15.3)
Flank Pain	11 (1.1)	10 (2.1)	21 (1.5)
Muscle Spasms	35 (3.6)	17 (3.5)	52 (3.6)
Musculoskeletal Pain	37 (3.9)	17 (3.5)	54 (3.7)
Myalgia	50 (5.2)	16 (3.3)	66 (4.6)
Neck Pain	25 (2.6)	12 (2.5)	37 (2.6)
Pain In Extremity	42 (4.4)	27 (5.6)	69 (4.8)
Tendonitis	16 (1.7)	10 (2.1)	26 (1.8)
<b>Nervous system disorders</b>			
Dizziness	109 (11.3)	42 (8.7)	151 (10.5)
Dysgeusia	21 (2.2)	7 (1.4)	28 (1.9)
Headache	241 (25.1)	121 (25.1)	362 (25.1)
Hypoaesthesia	15 (1.6)	12 (2.5)	27 (1.9)
Migraine	22 (2.3)	10 (2.1)	32 (2.2)
Paraesthesia	19 (2.0)	13 (2.7)	32 (2.2)
<b>Psychiatric disorders</b>			
Anxiety	30 (3.1)	8 (1.7)	38 (2.6)
Depression	42 (4.4)	21 (4.3)	63 (4.4)
Insomnia	55 (5.7)	21 (4.3)	76 (5.3)
Stress	9 (0.9)	10 (2.1)	19 (1.3)

(continued)

SOC PT	Tolvaptan (N = 961) n (%)	Placebo (N = 483) n (%)	Total (N = 1444) n (%)
<b>Renal and urinary disorders</b>			
Haematuria	75 (7.8)	68 (14.1)	143 (9.9)
Nephrolithiasis	15 (1.6)	14 (2.9)	29 (2.0)
Nocturia	<b>280 (29.1)</b>	<b>63 (13.0)</b>	<b>343 (23.8)</b>
Pollakiuria	<b>223 (23.2)</b>	<b>26 (5.4)</b>	<b>249 (17.2)</b>
Polyuria	<b>368 (38.3)</b>	<b>83 (17.2)</b>	<b>451 (31.2)</b>
Renal pain	260 (27.1)	171 (35.4)	431 (29.8)
<b>Respiratory, thoracic and mediastinal disorders</b>			
Cough	77 (8.0)	38 (7.9)	115 (8.0)
Dyspnoea	22 (2.3)	6 (1.2)	28 (1.9)
Oropharyngeal Pain	46 (4.8)	18 (3.7)	64 (4.4)
<b>Skin and subcutaneous tissue disorders</b>			
Dry skin	<b>47 (4.9)</b>	<b>8 (1.7)</b>	<b>55 (3.8)</b>
Eczema	<b>19 (2.0)</b>	<b>3 (0.6)</b>	<b>22 (1.5)</b>
Pruritus	33 (3.4)	13 (2.7)	46 (3.2)
Rash	<b>40 (4.2)</b>	<b>9 (1.9)</b>	<b>49 (3.4)</b>
<b>Vascular disorders</b>			
Hypertension	310 (32.3)	174 (36.0)	484 (33.5)
Hypotension	30 (3.1)	15 (3.1)	45 (3.1)

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.

<sup>a</sup> Subjects with TEAEs in multiple SOCs were counted only once toward the total.

Source: CSR 156-04-251, Table 11.3.1-1

#### 7.4.2 Laboratory Findings

##### Sodium

Because of its mechanism of action tolvaptan can cause an increase in serum sodium levels. The incidence of potentially clinically significant increased sodium levels (sodium > 150 mEq/L) was higher in the tolvaptan group (4.0%) compared with the placebo group (1.4%). The applicant reports the mean increase from baseline after the titration period was ~2.2 mEq/L on tolvaptan compared to ~0.02 mEq/L on placebo. The next figure of baseline serum sodium compared to minimum and maximum values in trial 156-04-251 shows that there were subjects on tolvaptan with significant elevations in serum sodium (as high as 163 mEq/L). There were no reported serious TEAE of hyponatremia.

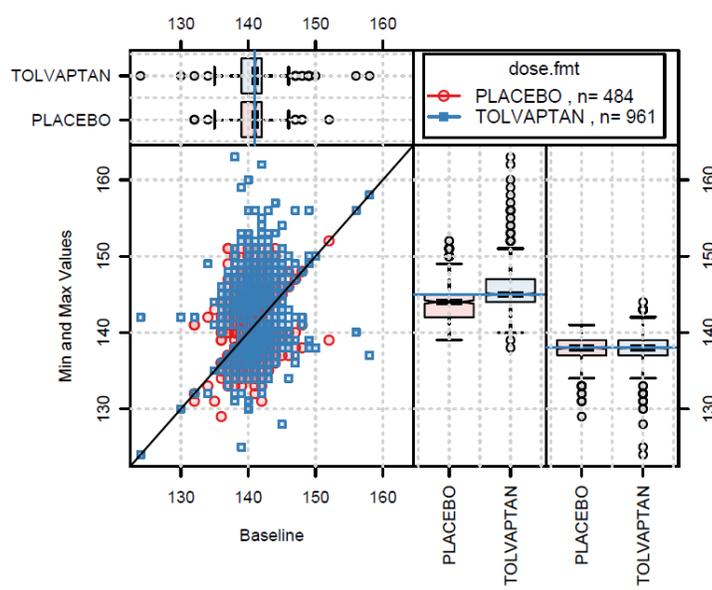


Figure 22. Serum sodium at baseline and minimum and maximum values in trial 156-04-251 (reviewer's analysis)

### Potassium

The applicant reports that the incidence of TEAE in the hyperkalemia customized MedDRA query (CMQ) was similar between treatment groups (5.8% tolvaptan versus 5.0% placebo) (source CSR 156-04-251, ST 1.8.35.1). In both treatment groups the most frequent TEAE was muscle spasm, reported by 3.6% of tolvaptan subjects and 3.5% of placebo subjects. There were no serious TEAE in the hyperkalemia CMQ reported by subjects in trial 156-04-251.

Laboratory analysis of potassium data at baseline and of values during the trial does not suggest a concern (see figure). There were subjects in both arms with very high potassium concentrations.

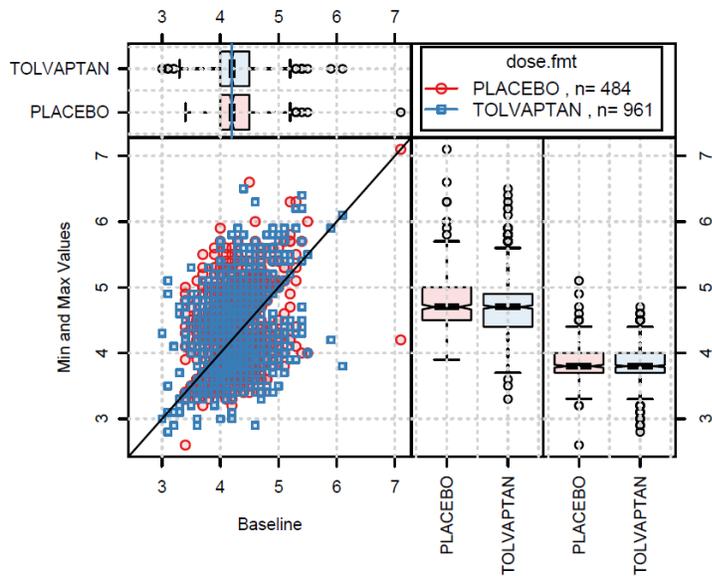


Figure 23. Serum potassium at baseline and minimum and maximum values in trial 156-04-251 (reviewer's analysis)

### Glucose

Analysis of laboratory data did not suggest clinically important effects on glucose levels. For discussion see also Section 7.3.4.

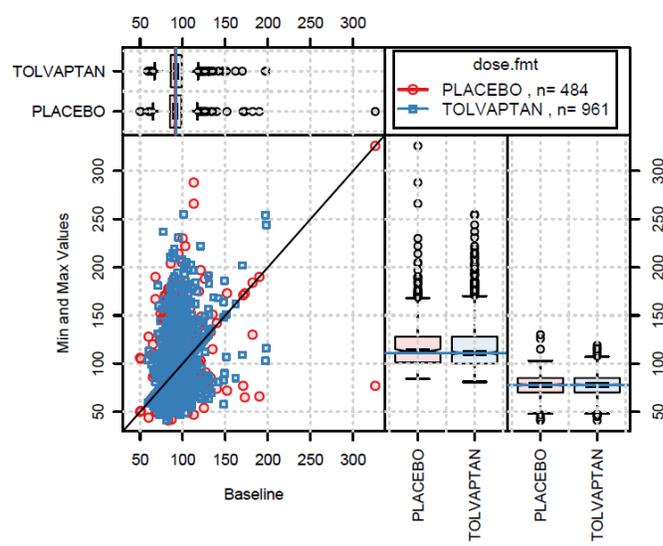


Figure 24. Glucose at baseline and minimum and maximum values in trial 156-04-251 (reviewer's analysis)

Uric Acid/Gout

Increased plasma uric acid concentrations, due to decreased uric acid clearance by the kidney, is a known effect of tolvaptan. Potentially clinically significant increases in uric acid, reports of gout, and use of anti-gout medication were all higher in tolvaptan treated subjects compared to placebo treated subjects (see table). Effects on uric acid and gout were not reported as severe or serious and did not result in treatment discontinuation.

Table 40. Incidence of potentially clinically significant abnormalities uric acid and reports of gout

	<b>Tolvaptan (N=960 treated)</b>	<b>Placebo (N=483 treated)</b>
Anti-gout medication use	79/961 (8.2%)	24/484 (5.8%)
Increase in serum uric acid	59/953 (6.2%)	8/481 (1.7%)
Gout	28/960 (2.9%)	7/483 (1.4%)

The next figure shows that maximum uric acid concentrations were higher than placebo, but the changes in uric acid concentration are confounded by use of anti-gout medication.

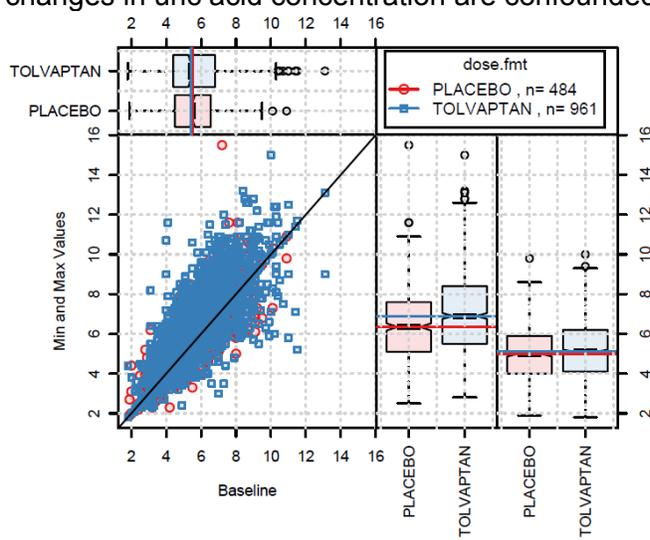


Figure 25. Uric acid at baseline and minimum and maximum values in trial 156-04-251 (reviewer's analysis)

BUN

The next figure shows the expected decrease in BUN in trial 156-04-251. Post treatment BUN rebounded in tolvaptan subjects, but levels remained ~ 1 mg/dL below placebo at follow-up visit 2 (applicant report CSR 156-04-251).

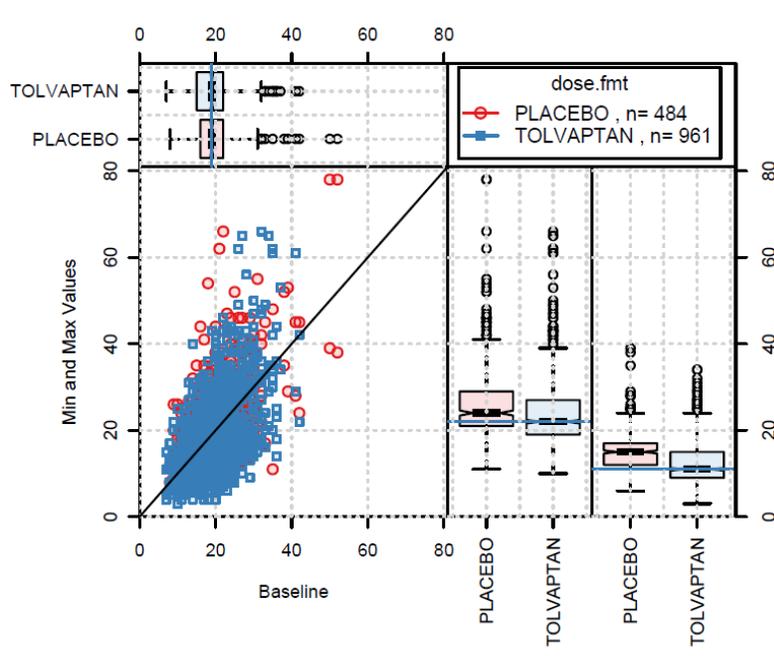


Figure 26. BUN at baseline and minimum and maximum values in trial 156-04-251 (reviewer's analysis)

#### 7.4.3 Vital Signs

Tolvaptan's effect on blood pressure was assessed in the composite secondary endpoint (see section 6.1.5). Tolvaptan's effect on weight is discussed in section 6.1.10. Compared to placebo, there were no clinically meaningful changes in HR or SBP in Trial 156-04-251 (reviewer's analysis).

#### 7.4.4 Electrocardiograms (ECGs)

A maximum dose of 300 mg/day for 5 days in a thorough QT study did not result in QTc prolongation.

#### 7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted in support of the proposed indication.

#### 7.4.6 Immunogenicity

Not applicable.

## 7.5 Other Safety Explorations

### **Glaucoma**

In prior trials of tolvaptan TEAEs related to glaucoma were reported in 7/3294 subjects on tolvaptan versus 0/2738 subjects on placebo. There were no reports of open angle glaucoma or increased intraocular pressure (IOP). (While raised IOP is a risk factor for glaucoma, it is not an absolute precondition.) The relationship between AVP and IOP is unclear; AVP increased IOP in some studies, and decreased IOP in other studies. Most studies suggest that vasopressin antagonists decrease IOP, but the mechanism is unknown.

In Trial 156-04-251, TEAEs in the glaucoma SMQ were reported in 2.1% (20/961) subjects in the tolvaptan group and 1.0% (5/483) subjects in the placebo group. A more focused analysis of the 3 most specific terms to glaucoma (Glaucoma, Open Angle Glaucoma, and Intraocular Pressure Increased) resulted in incidences of 0.7% (7/961) in the tolvaptan group versus 0.4% (2/483) in the placebo group.

Otsuka engaged an external independent expert in ophthalmology (Dr. Richard Lewis) to complete a blinded review of the 7 cases. He found no clear and consistent pattern that would attribute these events to tolvaptan. Although there is no direct evidence for a causal association between tolvaptan and glaucoma, the possibility cannot be excluded.

### **Arrhythmia-related disorders**

Arrhythmia-related investigations, signs and symptoms occurred more frequently in subjects on tolvaptan (7.4%) compared to subjects on placebo (4.6%). This difference was primarily due to a higher incidence of palpitations and syncope in the tolvaptan group (all were mild to moderate in severity). Four tolvaptan subjects experienced serious TEAEs in the arrhythmia-related investigations, signs, and symptoms SMQ (1 with palpitations, 1 with palpitations and syncope, and 2 with loss of consciousness) compared with 1 placebo subject (bradycardia). None of the events in this analysis resulted in IMP discontinuation. According to the applicant these reports may have occurred in association with volume depletion. The applicant concluded that tolvaptan was not associated with an increase in clinically relevant arrhythmia-related events in subjects with ADPKD; however the findings reinforce the importance of maintaining adequate hydration.

*Reviewer's comment: I agree with the applicant's assertion.*

### **Immune-mediated reactions**

Serious TEAEs in the anaphylactic reaction SMQ were reported in 1.0% of subjects on tolvaptan and 0.2% of subjects on placebo. Reported TEAEs in the angioedema SMQ were comparable in the tolvaptan (13.5%) and placebo (14.7%) groups. Treatment-emergent AEs in the anaphylactic shock SMQ were rare and comparable between the 2 treatment groups. Two tolvaptan subjects (0.2%) and 1 placebo subject (0.2%) experienced serious TEAEs. Reported event terms in the 2 subjects on tolvaptan were anaphylactic shock and respiratory failure. The one placebo subject experienced serious acute renal failure. The case of anaphylactic shock on tolvaptan was reported 3 to 6 months after the initiation of treatment and was moderate in severity; the case of respiratory failure was also moderate and occurred after Month 33. The applicant concludes that tolvaptan was not associated with a clinically meaningful increase in potential immune-mediated reactions, but they have the potential to occur.

*Reviewer's comment: I agree with this conclusion.*

#### 7.5.1 Dose Dependency for Adverse Events

See section 7.3.5 on drug-induced liver injury.

#### 7.5.2 Time Dependency for Adverse Events

See section 7.3.5 on drug-induced liver injury.

#### 7.5.3 Drug-Demographic Interactions

See section 7.3.5 on drug-induced liver injury.

#### 7.5.4 Drug-Disease Interactions

See section 7.3.5 on drug-induced liver injury.

#### 7.5.5 Drug-Drug Interactions

Refer to the approved drug label for the hyponatremia indication.

### **7.6 Additional Safety Evaluations**

None.

#### 7.6.1 Human Carcinogenicity

The results of the malignant tumor SMQ indicate a higher incidence in the tolvaptan arm compared to placebo (see table). The difference is largely driven by skin cancer.

Table 41. Incidence of treatment emergent adverse events in the neoplasms SMQs by MedDRA system organ class and preferred term

MedDRA Query PT	Tolvaptan (N = 961) n (%)	Placebo (N = 483) n (%)	Total (N = 1444) n (%)
Malignant tumors SMQ, Total <sup>a</sup>	16 (1.7)	2 (0.4)	18 (1.2)
Basal Cell Carcinoma	8 (0.8)	1 (0.2)	9 (0.6)
Breast Cancer	3 (0.3)	1 (0.2)	4 (0.3)
Cervix Carcinoma Stage 0	1 (0.1)	0	1 (0.1)
Chronic Myeloid Leukaemia	1 (0.1)	0	1 (0.1)
Kaposi's Sarcoma	1 (0.1)	0	1 (0.1)
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 (0.2)	1 (0.1)
Tumors of unspecified malignancy SMQ, Total <sup>a</sup>	0	1 (0.2)	1 (0.1)
Thyroid Neoplasm	0	1 (0.2)	1 (0.1)

Note: Subject (b) (6) reported separate TEAEs of Basal Cell Carcinoma and Squamous Cell Carcinoma. Subject (b) (6) reported separate TEAEs of Malignant Melanoma In Situ and Malignant Melanoma (Table 11.8.1.7.2-2).

<sup>a</sup>Subjects with TEAEs in multiple SOCs were counted only once toward the total.

Source: ST-1.8.44.1 and ST-1.8.54.1.

#### Skin cancer

Eight tolvaptan subjects were diagnosed with basal cell carcinoma in Trial 156-04-251. Seven of these subjects had a history of sun exposure sufficient to cause skin damage, ranging from multiple truncal nevi to multiple prior diagnosed skin cancers. All 7 subjects developed basal cell carcinoma on sun-exposed areas of the skin. The subject on placebo entered the trial with a past medical history of multiple skin cancers. Two subjects treated with tolvaptan were diagnosed with melanoma, one of whom was also diagnosed with melanoma in situ, a premalignant condition. Both subjects had early stage disease, presumed cured by surgical excision.

#### Breast cancer

Three subjects on tolvaptan (0.3%) and 1 subject on placebo (0.2%) in this trial were diagnosed with early stage breast cancer, all of whom were treated by surgical therapy with curative intent. All diagnosed breast cancers were early stage and presumed cured by surgery and adjuvant therapy. Breast cancers 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.

#### Cervical Neoplasm

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.

#### Kaposi's Sarcoma

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.

#### Leukemia

One subject on tolvaptan (0.1%) was diagnosed on Day 1088 with Philadelphia chromosome-positive chronic myelogenous leukemia. The subject had no known prior radiation exposure.

#### Thyroid Neoplasm

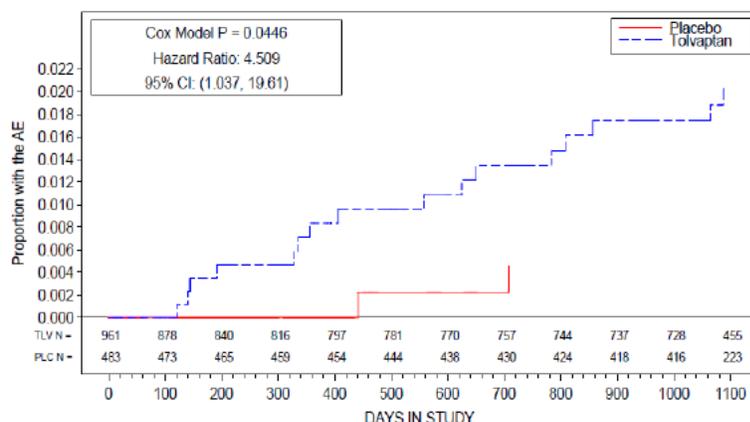
One subject on placebo (0.2%) was diagnosed with a thyroid neoplasm. It was unknown at the time of the report whether the neoplasm was benign or malignant.

*Reviewer's comment: Most of the cancers were either premalignant or occurred after a relatively short time (ranging from 121 days to approximately 3 years) suggesting that it was unlikely that tolvaptan played a role (see next figure of time course of occurrence). In carcinogenicity studies, there was no increase in mortality or tumors in tolvaptan treated animals compared to controls.*

The applicant asserts that tolvaptan's pharmacologic mechanism and observed effects have no identified link to carcinogenesis or promotion of malignant neoplasms. Published literature provides no clear evidence regarding the effects of AVP on either development or progression of malignant neoplasms. In vitro genotoxicity and rodent carcinogenicity testing revealed no evidence that tolvaptan is either mutagenic or carcinogenic. There was also no evidence of an increased incidence of malignant neoplasm diagnoses in subjects treated with tolvaptan in prior randomized clinical trials.

The imbalance in cancers was driven largely by neoplasms of the skin. Given the small number of observed events, chance may have played a role in the observed difference. Likewise, given the higher incidence of skin and subcutaneous tissue disorder TEAEs (e.g., rash) reported in tolvaptan subjects compared with placebo subjects (22.7% vs. 16.8%; source: applicant's CT-8.2.1), as well as the skin dryness and irritation that are known effects of aquaresis, more careful skin examinations in these subjects may have contributed to the increased reporting of basal cell carcinoma and other skin cancers observed in the tolvaptan group. Based on the data from this trial, no definitive conclusion can be made regarding the role of tolvaptan in the occurrence of neoplasms. The applicant's plan includes monitoring for cancers in tolvaptan clinical trials and postmarketing experience.

Figure 27. Time to first treatment emergent AE in the malignant tumor SMQ



Source: CSR 156-04-251, Figure 11.8.1.7.2-2

### 7.6.2 Human Reproduction and Pregnancy Data

Pregnancy was an exclusion criterion for trial participation. Pregnancies were reported as serious AEs only if there was an abnormality or complication associated with the event. Reporting of partner pregnancies during the trial was not required, because nonclinical results showed that tolvaptan had no effect on sperm. Eight female subjects and 3 partners of male subjects became pregnant during the trial. The data suggest that the safe use of tolvaptan during pregnancy has not been established. Its use during pregnancy is not recommended (see table).

Table 42. Listings of cases of pregnancy of trial participants or their partners

Subject ID	Gender	Randomized Treatment	Event	Outcome
(b) (6)	Male	Tolvaptan	Pregnancy of partner	Live birth
	Female	Placebo	Pregnancy	Spontaneous abortion
	Female	Placebo	Pregnancy	Elective abortion
	Male	Tolvaptan	Pregnancy of partner	Live birth
	Male	Placebo	Pregnancy of partner	Live birth
	Female	Tolvaptan	Pregnancy	Live birth
	Female	Tolvaptan	Pregnancy	Elective abortion
	Female	Tolvaptan	Pregnancy	Elective abortion
	Female	Tolvaptan	Pregnancy	Elective abortion
	Female	Tolvaptan	Pregnancy	Spontaneous abortion <sup>a</sup>
	Female	Tolvaptan	Pregnancy	Elective abortion <sup>a</sup>

<sup>a</sup>There was a serious TEAE reported in association with the pregnancy event.

Source: CSR 156-04-251, Table 11.9-1.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

Adolescents and children were not studied. The Pharm-tox review is not yet finalized, but a six week study in juvenile rats with doses up to 1000 mg/kg/day (~180x the human equivalent dose) showed a significant increase in liver weight and total bilirubin concentrations in rats treated with tolvaptan compared to controls (communication with Pharm-tox reviewer, Xavier Joseph).

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

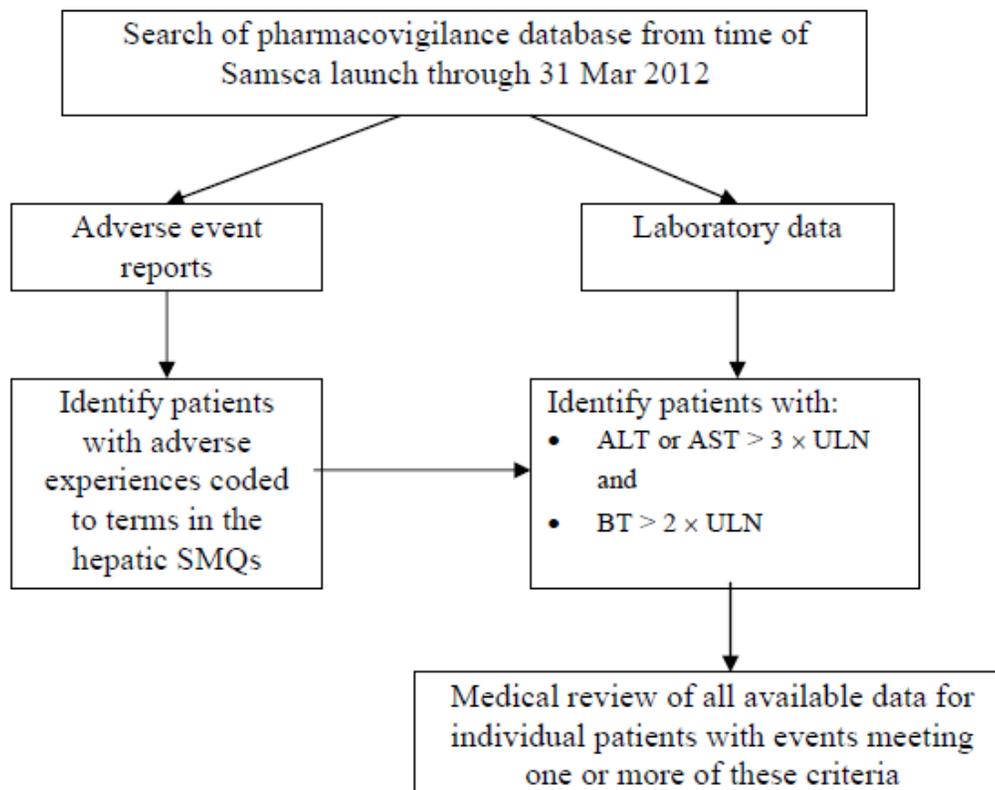
There were no reports of overdose or abuse.

## 7.7 Additional Submissions / Safety Issues

The 120-day safety update was not submitted in time to be included in this review. An addendum will be filed if the data contained in this submission significantly alter the safety findings/conclusions given in this review.

## 8 Postmarket Experience

Otsuka searched their pharmacovigilance database from the time of Samsca launch through 31 March 2012 for potential cases of drug-induced liver injury as shown in the figure below.



**Figure 2.7.4.6.3-1 Process Map for Screening of Postmarketing Surveillance Data**

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BT = total bilirubin;  
MedDRA = Medical Dictionary of Regulatory Activities; SMQ = standardized MedDRA query.  
Note: The following 5 hepatic SMQs were used for selection of events: 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; or liver-related coagulation and bleeding disturbances.

Figure 28. Otsuka's process screening for post marketing cases of liver injury

A total of 494 cases with 939 events were received during the search period. Of these, there were 53 events reported for 35 patients that met the hepatic standardized MedDRA query. Of the 35 patients, 4 patients in Japan were referred for review and evaluation by the HAC. A fifth patient with an AE of increased AST was also forwarded for adjudication and was retrospectively found to have been enrolled in postmarketing study 156-09-101. The HAC adjudicated all six subjects as "unlikely" related to Drug-induced liver injury. A sixth subject identified by laboratory data was reviewed by the applicant as having another plausible cause and transaminase values were elevated prior to taking tolvaptan.

## 9 Appendices

### 9.1 Literature Review/References

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## 9.2 Labeling Recommendations

We are not recommending approval at this time.

## 9.3 Advisory Committee Meeting

An Advisory Committee meeting is scheduled for August 5, 2013.

## 9.4 Timeline of events related to the development of awareness of hepatic abnormalities

<b>Date</b>	<b>Observation/Action</b>
01 Mar 2007	First subject randomized.
02 Nov 2007	First IDMC meeting: <ul style="list-style-type: none"><li>• Chairman identified and development of charter initiated.</li></ul>
22 Feb 2008	Monthly data transfers to SDAC began.
22 Apr 2008	First hepatic serious TEAE reported to Otsuka (Subject (b) (6)); initial report of nonserious liver dysfunction beginning on Day 129 resulted in hospitalization on Day 223 for liver biopsy, IMP was interrupted and later discontinued after rechallenge).

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02 May 2008	CIOMS report for first hepatic serious TEAE submitted to FDA (also submitted to other appropriate regulatory agencies around the same time).
03 May 2008	IDMC meeting: <ul style="list-style-type: none"> <li>• IDMC reported “no safety concerns”.</li> <li>• IDMC recommended continuing the trial according to the protocol.</li> </ul>
09 May 2008	First discontinuation of IMP due to a hepatic TEAE (Subject (b) (6) discontinued IMP due to a TEAE of Increased Liver Function Tests).
27 Jun 2008	First communication from FDA to Otsuka regarding hepatic safety. FDA requested additional information related to safety reports for Subject (b) (6).
03 Jul 2008	Otsuka provided additional information for Subject (b) (6) results of liver biopsy and gastroenterology consultation were pending.
10 Jul 2008	Otsuka submitted liver biopsy and gastroenterology consultation report results for Subject (b) (6) in an updated safety report to FDA.
August 2008	Otsuka observed PCS increases in LFTs for 11 blinded subjects in the trial during internal review of tables and listings.
06 Nov 2008	IDMC meeting: <ul style="list-style-type: none"> <li>• IDMC reported “no safety concerns”.</li> <li>• IDMC recommended continuing the trial according to the protocol.</li> </ul>
23 Dec 2008	Otsuka submitted LFT data for 19 subjects (the 11 mentioned above and 8 additional subjects) to the IDMC, requesting that the IDMC evaluate and provide conclusions and recommendations.
05 Jan 2009	Last subject randomized.
06 Jan 2009	SDAC provided an initial, closed report on LFT elevations (including, but not limited to, the 19 subjects referenced above) to the IDMC (by treatment group) and a blinded report to Otsuka.
26 Jan 2009	SDAC provided an updated closed report on LFT elevations to the IDMC (updates involved more current data than the 06 Jan 2009 report). (Note that both this and the previous report included information on more than the 19 subjects identified by Otsuka). The report was made available to the IDMC on 26 Jan 2009, but was dated 28 Jan 2009 (the planned date of the teleconference).
28 Jan 2009	Ad hoc IDMC meeting (a portion of the meeting was an open-session teleconference with Otsuka, and a portion of the meeting was a closed session teleconference to discuss the report provided by SDAC on 26 Jan 2009 as well as other information provided by Otsuka): <ul style="list-style-type: none"> <li>• IDMC recommended continuing the trial according to the protocol.</li> <li>• IDMC requested that Otsuka provide information regarding laboratory alert values for LFTs, the mechanism by which sites were notified of elevations, and a summary of actions to be taken when an alert was issued.</li> </ul>
17 Feb 2009	Information regarding the process for monitoring and surveillance of LFTs was provided to the IDMC by Otsuka.
27 Feb 2009	Second communication from FDA to Otsuka regarding hepatic safety. The FDA requested dates of the IDMC meetings, a copy of all information and documents provided to the IDMC, and trial enrollment information. Otsuka confirmed that the FDA would only receive blinded data.
06 Mar 2009	Otsuka provided the requested information to FDA.

Date	Observation/Action
13 Mar 2009	<p>IDMC meeting: closed session teleconference to discuss additional material provided by Otsuka (eg, responses to the outstanding questions from the IDMC regarding the monitoring and surveillance of LFTs for subjects in the trial and details regarding Japanese subjects with elevated LFTs).</p> <ul style="list-style-type: none"> <li>• IDMC recommended continuing the trial according to the protocol.</li> <li>• IDMC requested patient history profiles for subjects with clinically significant LFT elevations for future meetings.</li> <li>• IDMC requested that all local laboratory data be collected and made available to SDAC throughout the remainder of the trial.</li> </ul>
16 Apr 2009	<p>Response received from the FDA regarding the information provided by Otsuka on 06 Mar 2009. The agency stipulated the following:</p> <ul style="list-style-type: none"> <li>• The sponsor should forward reports of serious AEs related to hepatic safety resulting in liver biopsy, hospitalization, or death to the IDMC and agency in an expedited manner.</li> <li>• The sponsor should provide copies of serious AE reports related to liver injury/LFT abnormalities or narratives of these events to committee members at future IDMC meetings pertaining to hepatic safety.</li> <li>• Following any future IDMC meeting pertaining to hepatic safety, the sponsor should submit to the agency a copy of the background information that was provided to the committee members as well as a copy of their conclusions/recommendations.</li> </ul>
23-24 Apr 2009	<p>Informal communication between Otsuka and FDA to clarify that, pursuant to the third bullet point above in the entry for 16 Apr 2009, only safety data prepared for the IDMC that pertained to liver-related AEs needed to be provided to the agency.</p>
22 May 2009	<p>IDMC meeting:</p> <ul style="list-style-type: none"> <li>• IDMC recommended continuing the trial according to the protocol.</li> <li>• IDMC recommended that any additional information regarding LFTs not included in the central laboratory database be made available to SDAC for analysis. Once additional laboratory data were received, the IDMC was to review an updated LFT report.</li> </ul>
10 Jun 2009	<p>Type C meeting with the FDA regarding SPA.</p>
July 2009	<p>FDA guidance issued: Drug-induced Liver Injury (DILI), Premarketing Clinical Evaluation.</p>
10 Jul 2009	<p>Per 22 May 2009 IDMC request, SDAC released the first specific LFT report to the IDMC (unblinded) and to Otsuka (blinded) summarizing the data. No meeting was held.</p>
24 Jul 2009	<p>Tolvaptan Investigator's Brochure updated (Edition 15). A paragraph was added to the Precautions (Section 6.2) to Summary of Guidance to Investigators regarding these events occurring in this ongoing, blinded trial, including recommendations for monitoring liver functions.</p>
29 Jul 2009	<p>IDMC teleconference: open-session teleconference wherein Otsuka updated the IDMC on the meeting with the FDA and the upcoming protocol amendment addressing efficacy.</p>
30 Jul 2009	<p>IDMC meeting summary recommendations with Hepatic Safety Data updates (initiated in May) submitted to FDA (for 22 May 2009 meeting).</p>
18-19 Sep 2009	<p>Investigator booster meeting held for sites in North and South America to discuss monitoring for hepatic safety and management of subjects with liver abnormalities (instructions given to investigators regarding Drug-induced Liver Injury, Premarketing Clinical Evaluation guidance are summarized in <a href="#">Table 11.8.1.6.2-2</a>).</p>

Date	Observation/Action
25-26 Sep 2009	Investigator booster meeting held for sites in the EU to discuss monitoring for hepatic safety and management of subjects with liver abnormalities (instructions given to investigators regarding Drug-induced Liver Injury, Premarketing Clinical Evaluation guidance are summarized in <a href="#">Table 11.8.1.6.2-2</a> ).
28 Oct 2009	IDMC meeting: <ul style="list-style-type: none"> <li>IDMC recommended continuing the trial according to the protocol.</li> </ul>
21 Dec 2009	The Product ICF was updated to include language regarding reports of abnormal liver function tests in subjects participating in blinded ADPKD trials.
23-24 Jan 2010	Investigator booster meeting held for sites in Japan to discuss monitoring for hepatic safety and management of subjects with liver abnormalities (instructions given to investigators regarding Drug-induced Liver Injury, Premarketing Clinical Evaluation guidance are summarized in <a href="#">Table 11.8.1.6.2-2</a> ).
29 Jan 2010	Protocol ICF was updated to include language regarding reports of abnormal liver function tests in subjects participating in blinded ADPKD trials.
01 Mar 2010	Per 28 Oct IDMC request, SDAC issued LFT report (no meeting).
03 Mar 2010	IDMC meeting summary recommendations with Hepatic Safety Data update submitted to FDA (for 28 Oct 2009 meeting).
08 Apr 2010	Otsuka issued version 4 of the trial Operations Manual, which was revised to include information on DILI and information on hepatic IREs (the occurrence of elevated ALT or AST > 3 × ULN [or the subject's screening value] AND elevated bilirubin > 2 × ULN [or the subject's screening value] was to be reported as an IRE regardless of seriousness) ( <a href="#">Section 17.7.1.1</a> ).
01 Jun 2010	Clarification memo sent to the sites regarding Hy's laboratory criteria and requirements for reporting IREs ( <a href="#">Section 17.7.1.2</a> ).
02 Jun 2010	IDMC meeting: <ul style="list-style-type: none"> <li>IDMC recommended continuing the trial according to the protocol.</li> <li>IDMC recommended increasing the frequency of monitoring of LFTs in the recently initiated open-label extension trial (156-08-271) from every 6 months to every 3 months.</li> </ul>
18 Jun 2010	Tolvaptan Investigator's Brochure updated (Edition 16). No related updates.
13 Jul 2010	Volume 12 of the site newsletter contained an article focusing on the update of the IRE definition to include potential DILI ( <a href="#">Section 17.7.1.3</a> ).
26 Aug 2010	IDMC meeting summary recommendations with Hepatic Safety Data update submitted to FDA.
21 Nov 2010	IDMC meeting: <ul style="list-style-type: none"> <li>IDMC recommended continuing the trial according to the protocol.</li> </ul>
21 Dec 2010	IDMC meeting summary recommendations with Hepatic Safety Data update submitted to FDA (for 21 Nov 2010 meeting).
07 Jun 2011	IDMC meeting: <ul style="list-style-type: none"> <li>IDMC recommended continuing the trial according to the protocol.</li> </ul>
23 Jun 2011	IDMC meeting summary recommendations with Hepatic Safety Data update submitted to FDA (for 07 Jun 2010 meeting).
12 Jul 2011	Tolvaptan Investigator's Brochure updated (Edition 17). No related updates.
09 Nov 2011	IDMC meeting: <ul style="list-style-type: none"> <li>IDMC recommended continuing the trial according to the protocol.</li> </ul>
11 Jan 2012	IDMC meeting summary recommendations with Hepatic Safety Data update submitted to FDA (for 09 Nov 2011 meeting).
12 Apr 2012	Clinical trial database locked.
13 Apr 2012	Clinical trial data unblinded.

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11 Jan 2012	IDMC meeting summary recommendations with Hepatic Safety Data update submitted to FDA (for 09 Nov 2011 meeting).
12 Apr 2012	Clinical trial database locked.
13 Apr 2012	Clinical trial data unblinded.

Date	Observation/Action
21 Jun 2012	Background Package submitted for Pre-NDA Meeting, which included description of frequencies of LFTs of treatment group and several cases meeting "Hy's Law" laboratory criteria, but pending formal adjudication. During the preparation of this document, Otsuka initiated meetings with hepatic experts who recommended the formation of a Hepatic Adjudication Committee.
16 Jul 2012	Tolvaptan Investigator's Brochure updated (Edition 18). Updated to indicate the unblinded imbalance in frequency of transaminase elevations (tolvaptan > placebo) in ADPKD and with the causality evaluation ongoing.
19 Jul 2012	FDA Pre-NDA Meeting (included hepatic events discussion).
26 Jul 2012	Charter finalized for the Hepatic Adjudication Committee in order to standardize the evaluation of differential diagnosis of hepatic events meeting certain criteria identified from the ADPKD program and other tolvaptan populations (ie, hyponatremia and heart failure).
10 Aug 2012	Meeting of hepatic expert advisory board to receive recommendations on the best approach to evaluating the hepatic safety signal. Charter was modified in accordance with recommendations.
05 Oct 2012	IDMC meeting to discuss post-unblinded results and recommendations by hepatic advisory board. Recommendations for increased (ie, monthly) liver function monitoring were made for Trial 156-08-271.
28 Oct 2012	Final Hepatic Adjudication Committee report (Watkins) <sup>91</sup> available. Recommended more frequent liver chemistry monitoring, (ie monthly, between months 3 and 14 of exposure).
01 Nov 2012	Steering Committee endorsed Hepatic Adjudication Committee recommendation for more frequent liver chemistry monitoring to establish monthly monitoring between 3 and 14 months of exposure.
03 Nov 2012	Data including imbalances in transaminase elevations and occurrence of 2 cases meeting "Hy's Law" laboratory criteria were published online in the New England Journal of Medicine. <sup>92</sup>
13 Nov 2012	Draft REMS Proposal including summary of Hepatic Adjudication Report submitted to FDA.

LFT = liver function test; PCS = potentially clinically significant; REMS = risk evaluation and mitigation strategy; SPA = special protocol assessment.

Source: Applicant's CSR 156-04-251, Table 11.8.1.6.2-1

## 9.5 Instructions provided to sites for hepatic monitoring and management

Table 11.8.1.6.2-2 Instructions to Investigators	
1.	Confirm an increase of serum ALT or AST to $> 3 \times \text{ULN}$ by repeat testing (of ALT, AST, ALP, and BT) within 48 to 72 hours, ie, do not wait a week or two, because levels can change rapidly and might become normal, leading to false conclusions.
2.	Evaluate relevant symptom data and history of concurrent diseases and also concomitant medications including nonprescription medications, herbal, and dietary supplements, alcohol use, recreational drug use, and special diets.
3.	Follow subjects closely if: <ul style="list-style-type: none"> <li>• ALT or AST becomes <math>&gt; 3 \times \text{ULN}</math> (for subjects with a normal baseline value, elevations <math>&lt; 3 \times \text{ULN}</math> are common and nonspecific)</li> <li>• ALT or AST becomes <math>&gt; 2 \times \text{ULN}</math> (for subjects with an elevated baseline value).</li> </ul>
4.	Follow up with repeat LFTs 2 to 3 times per week (decrease to once per week if abnormalities stabilize or IMP has been interrupted and subject is asymptomatic) and perform other tests of liver function, as appropriate (eg, INR).
5.	Consider interruption of IMP in the following contexts (automatic interruption of IMP upon finding an ALT or AST elevation of $> 3 \times \text{ULN}$ may be unnecessary, ie, transient rises and falls of ALT or AST are common): <ul style="list-style-type: none"> <li>• ALT or AST becomes <math>&gt; 8 \times \text{ULN}</math> (no rechallenge)</li> <li>• ALT or AST becomes <math>&gt; 5 \times \text{ULN}</math> for more than 2 weeks (no rechallenge)</li> <li>• ALT or AST becomes <math>&gt; 3 \times \text{ULN}</math> and BT is <math>&gt; 2 \times \text{ULN}</math> or INR is <math>&gt; 1.5</math></li> <li>• ALT or AST becomes <math>&gt; 3 \times \text{ULN}</math> with appearance of worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia</li> </ul> Follow until resolution and consider IMP reinitiation (rechallenge) if appropriate.

INR = international normalized ratio; LFT = liver function test.

Source: CSR 156-04-251

## 9.6 Criteria for case selection for blinded causality assessment

1. Subjects who had serious adverse events and non-serious treatment emergent adverse events that led to discontinuation of study drug due to hepatic or liver function test abnormality adverse events and reported by the investigators. The adverse event terms included are the MedDRA preferred terms included in the following 5 Standardized MedDRA Queries (SMQs), MedDRA version 14.1.

- Cholestasis and jaundice of hepatic origin (SMQ)
- Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ)
- Hepatitis, non-infectious (SMQ)
- Liver related investigations, signs and symptoms (SMQ)
- Liver-related coagulation and bleeding disturbances (SMQ)

2. Subjects who had alanine aminotransferase (ALT) elevations > 3x upper limit of normal (ULN) and Total Bilirubin > 2x ULN, even if these two values were not concurrent, but no adverse events were reported. To be included for adjudication, subjects from Group 2 and Group 3 should meet the following criteria:

- ALT>3 X ULN and Total Bilirubin > 2 X ULN, even if the two values were not concurrent.

3. Subjects meeting the FDA set criteria ALT or AST > 5x ULN or TBL > 2x ULN.

Note: In cases when the ULN for ALT cannot be obtained from the investigators, 40 IU/L will be used as the ULN. In cases when the ULN for total bilirubin cannot be obtained from the investigators, 1 mg/dL or 17 µmol/L will be used as the ULN.

## 9.7 DILI network causality scale

**Definite:** >95% likelihood. The evidence for the drug causing the injury is beyond a reasonable doubt.

**Highly likely:** 75%-95% likelihood. The evidence for the drug causing the injury is clear and convincing but not definite.

**Probable:** 50%-74% likelihood. The preponderance of the evidence supports the link between the drug and the liver injury.

**Possible:** 25%-49% likelihood. The evidence for the drug causing the injury is equivocal but present.

**Unlikely:** <25% likelihood. There is evidence that an etiological factor other than a drug caused the injury.

**Unassessable:** Insufficient information to assess causality.

## 9.8 Reviewer comments on select liver cases

These cases have all been reviewed in detail by Dr. John Senior at FDA and the HAC.

### 9.8.1 Subject (b) (6), first Hy's Law case

Subject (b) (6) was a 45 year old Asian female (Japan) who was hospitalized for worsening nausea after ~ 7 months on tolvaptan.

History of Present Illness (HPI): She complained of of nausea and stomach indisposition starting ~ 5 months (30 Oct 2008) on tolvaptan (per CRF). Accompanying symptoms included a loss of appetite, nausea, and stomach discomfort for almost a month. She said she did not have enough food and drink due to a busy lifestyle, and the Investigator prescribed rabeprazole (a proton pump inhibitor) and follow-up every 2 weeks. Her symptoms persisted despite continual improvement of AST and ALT [Day 176 and Day 190] (see figure). The nausea worsened and prompted hospital admission on Day 202 (b) (6) and cessation of tolvaptan.

Course: Other AEs occurring during this event included anorexia, nausea, stomach discomfort, abdominal pain, abdominal distension, pruritis, vomiting, choleplania, pollakiuria, thirst, hemorrhoids, constipation, palpitation, headache, pharyngodynia, proctoptosia, and worsening hypertension. (Note that jaundice was not reported, despite the significant rise in bilirubin

during her hospitalization.) She received corrective treatments, prednisolone, and fresh frozen plasma (see figure).

An abdominal CT showed multiple cystic lesions in the liver and both kidneys. Content fluid of the cystic lesions was considered to be hemorrhagic. Abdominal ultrasound showed that hepatic parenchyma was composed of almost normal appearance despite many cysts. There were no significant intrahepatic bile duct dilatation and no significant space-occupying lesion.

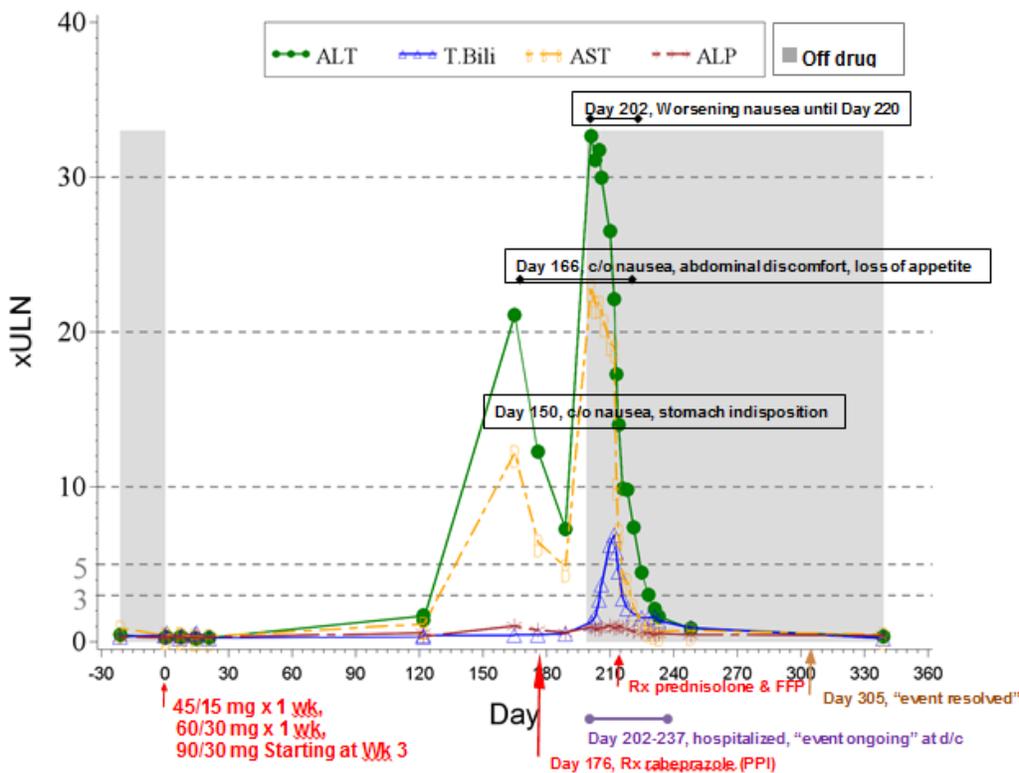
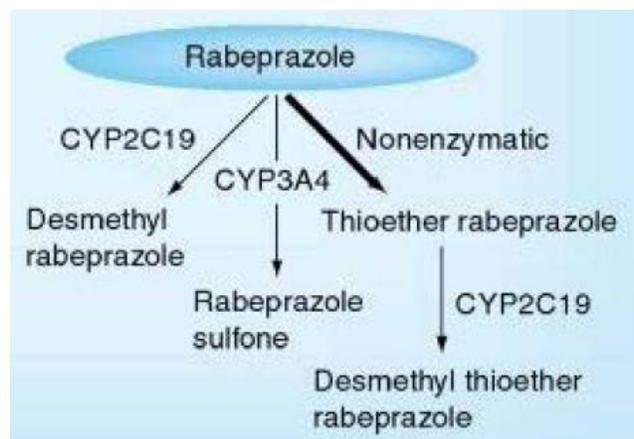


Figure 29. Subject (b) (6): time course of liver tests

The investigator assessed the event as severe in intensity and definitely related to tolvaptan. The HAC judged this event as probable (50-75% likely) due to tolvaptan and called this a Hy's Law case.

*Reviewer's comment: There are a few possible theories regarding this case and the time course of liver tests. This warrants review of rabeprazole metabolism (see figure). Note that rabeprazole was only mentioned in the Medwatch report (not in the CRF, narrative, adjudication document, or HAC report).*

Figure 30. Rabeprazole metabolism



*Rabeprazole primarily undergoes non-enzymatic reduction to thioether rabeprazole which is then metabolized by CYP2C19; less common pathways of metabolism include CYP2C19 and CYP3A4. Desmethyl thioether rabeprazole is metabolized by CYP3A4 to (R) & (S) rabeprazole.*

Hagymasi K, et al. Update on the pharmacogenomics of proton pump inhibitors. *Pharmacogenomics*. 2011; 12(6): 873-888.

The subject took rabeprazole, a potent inhibitor of CYP2C19 and p-gp inhibitor, from Day 177 to Day 190 (08 Dec 2008). The possible theories of what might have happened include:

- Rabeprazole increased tolvaptan concentrations via p-gp.
- Thioether rabeprazole inhibits CYP2C19, 2C9, 2D6, and 3A4. Thioether rabeprazole increased tolvaptan concentrations via CYP3A4.
- Rabeprazole increased tolvaptan concentrations via CYP3A4. However, other interaction studies of tolvaptan with drugs that are also metabolized by CYP3A4 show “small effects” on tolvaptan concentration.
- Poor metabolizer (PM) theory: ~ 15-22% of Asians are PM of CYP2C19. She could have been a PM of CYP2C19. If she could not metabolize thioether rabeprazole, then more of it was around to inhibit the metabolism of tolvaptan via CYP3A4, thereby increasing tolvaptan concentrations.

*This subject also had a fairly rapid (30 days) return to baseline relative to the “signature” decline described for tolvaptan.*

### 9.8.2 Subject (b) (6), second Hy’s Law case

Subject (b) (6) was a 34 year old Caucasian female (Argentina) who presented with pronounced jaundice at her 8 month routine study visit (b) (6), Day 246) prompting cessation of tolvaptan 90/30 mg due to this SAE.

HPI: She reported nonserious nausea and vomiting for 15 days up until her study visit. She stated that she took Augmentin (amoxicillin/clavulanate) 8 gm in one day for a toothache about 3 months prior to her visit.

Course: Concurrent AE included vomiting and nausea. She did not receive corrective treatments. An abdominal ultrasound reported liver without discernible parenchymatous lesions, polycystic kidneys, otherwise the abdominal ultrasound was within normal limits. See

figure for time course of liver labs. Other pertinent labs included negative viral serology on Day 252. Autoantibodies and a liver biopsy were not done.

Laboratory tests on Day 265 showed decreases in serum transaminases and bilirubin. She started feeling better off drug and never returned for follow-up after Day 266.

The investigator assessed the event to be mild in intensity and probably related to tolvaptan.

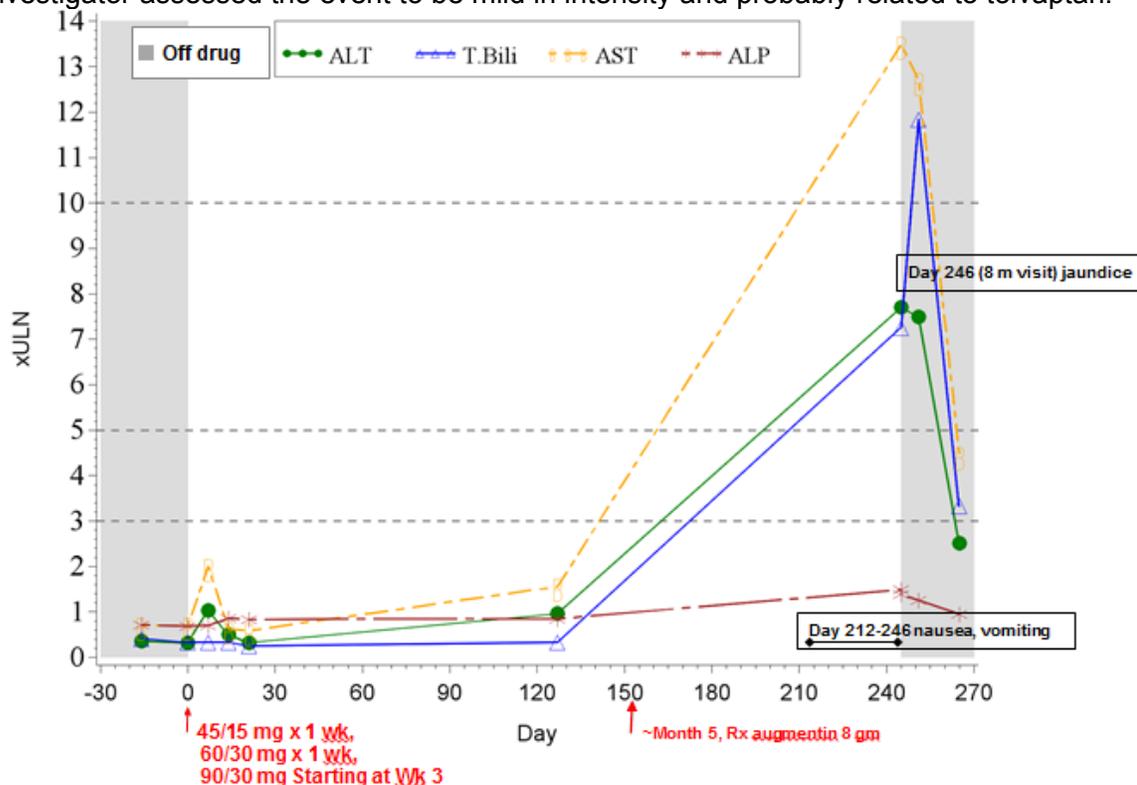


Figure 31. Subject (b) (6): time course of liver tests

The HAC noted that augmentin characteristically presents as a mixed hepatocellular/cholestatic injury. Hepatocellular injury is less common, but is more frequently observed in patients less than 45 years. They further note that to their knowledge, there have been no reports of augmentin causing clinically important liver injury after a single dose (albeit an overdose). The latency to presentation in this case was longer than usual for augmentin (usual being after 1-2 months of treatment).

The HAC noted that the timing of the event was consistent with the signature presentation, but the resolution was more rapid than has been characteristic. They adjudicated the event as “probable” (50-75% likelihood) and called this a Hy’s Law Case.

### 9.8.3 Subject (b) (6), third Hy’s Law case

Subject (b) (6) was a 44 year old Caucasian female (France) found to have elevated liver enzymes at her 3 month study visit (09 Jan 2012) prompting tolvaptan cessation on Day 90

(b) (6). She had no other reported signs or symptoms at this visit, but reported nausea, vomiting and abdominal pain in the right hypochondrium (per Medwatch report) in the weeks leading up to her clinic visit (~month 2.5).

Course: She had completed the pivotal trial 156-04-251 (placebo arm), and rolled over to open label tolvaptan (extension trial 156-08-271). See figure for time course of liver tests. Notably, all liver tests were normal during her ~33 month participation in the pivotal trial. At her 1 week follow-up (Day 98) visit her liver tests had decreased, but remained significantly elevated. She also reported hot flushes, an increase in right hypochondrium pain, and dark urine and pale stools. On Day 106 she took paracetamol 100 mg for right hypochondrium pain. On Day 107 she experienced “emergence of jaundice with elevated liver function test” and was hospitalized for 13 days for an SAE of acute cytolytic hepatitis and cholestatic hepatitis (not severe), with jaundice but without encephalopathy”. Corrective treatments were not given.

An abdominal ultrasound showed no blood vessel abnormality, no hepatic or portal vein abnormality. An MRI reported multiple cysts disseminated in the parenchyma, an enlargement of the main bile duct at 10mm 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 on Day 120 reported cytolytic and cholestatic hepatitis with moderate centrilobular necrosis, ductal neogenesis, and centrilobular inflammation consistent with drug-induced hepatitis. 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 she had old immunity. She was diagnosed with acute cytolytic and cholestatic hepatitis (factor V limit at 71% (50-150%)) with jaundice but without encephalopathy.

She was discharged on Day 120 (still jaundiced and with elevated liver enzymes) and was to follow-up with frequent LFT monitoring for the next month. She 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.

The Investigator assessed the event as drug-induced hepatitis, moderate intensity and related to tolvaptan. The HAC adjudicated this case as “highly likely” (75-95% likelihood) related to study drug.

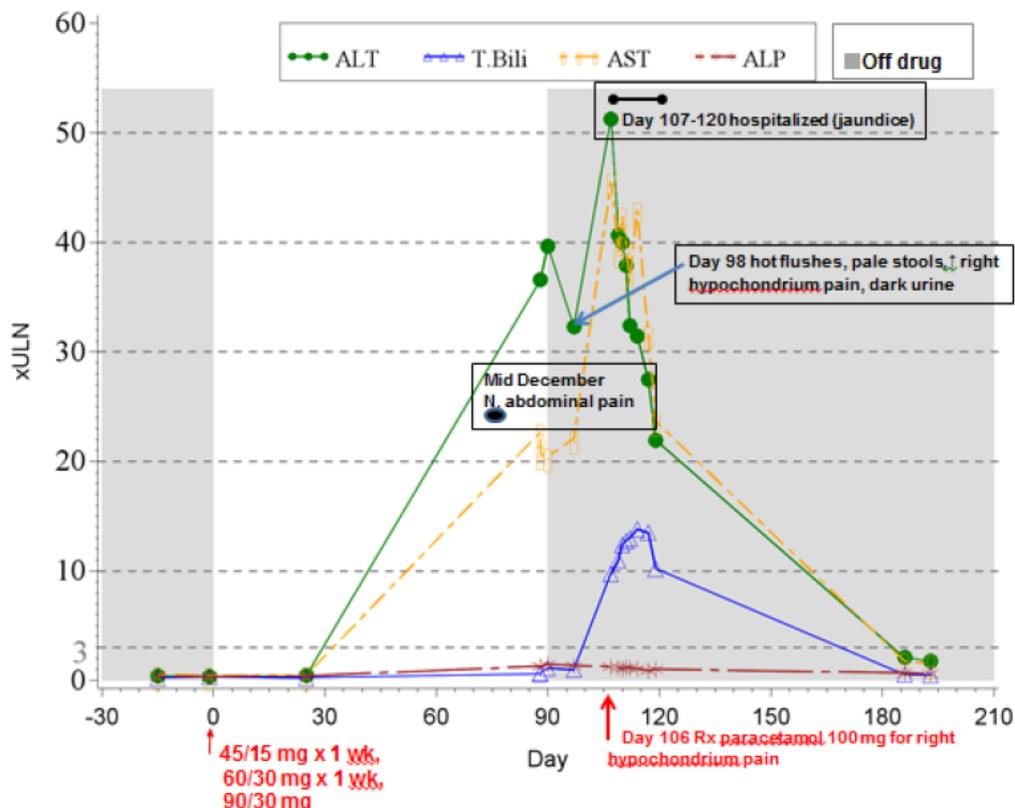


Figure 32. Subject (b) (6): time course of liver tests

#### 9.8.4 Subject (b) (6), rechallenge case

This was the first hepatic serious TEAE (received 22 April 2008). Subject (b) (6) was a 50 year old Asian female who had an initial report of non serious liver dysfunction on Day 129 (see figure). Tolvaptan was interrupted from Day 162- 273 (b) (6). Because of persistent elevation of transaminases, she was hospitalized on Day 223 (b) (6) for a liver biopsy (thus the serious TEAE).

Course: Other AEs ongoing in parallel to this event included musculoskeletal back pain, urticaria, eczema, and right hypochondralgia. She received corrective treatments while in the hospital and was discharged after one day.

Histopathology report was as follows: 1) Lobular architecture changed in shape due to shedding of liver cells and portal-central bridging; 2) Sporadic focal necroses were observed in hepatic parenchyma; also, intensive inflammation was shown especially in central vein range; due to the shedding, D-PAS (periodic acid-Schiff) positive macrophage was aggregated in some parts; and 3) Although there was fibrous enlargement slightly in portal tracts, inflammatory cell invasion was mild; immature cholangiocyte protruded into a part of the hepatic parenchyma. **The histological diagnosis was DILI.**

After the SAE resolved (Day 274), tolvaptan was restarted at a lower dose. However, transaminases quickly rose, prompting study discontinuation on Day 288. The investigator assessed the event as moderate in intensity and probably related to tolvaptan. No viral serology tests were performed to rule out viral hepatitis. No autoantibodies were tested to rule out autoimmune hepatitis. No further imaging studies were done.

The HAC states that “the rechallenge confirmed that the event was due to tolvaptan”. Their expert consensus was “probable”.

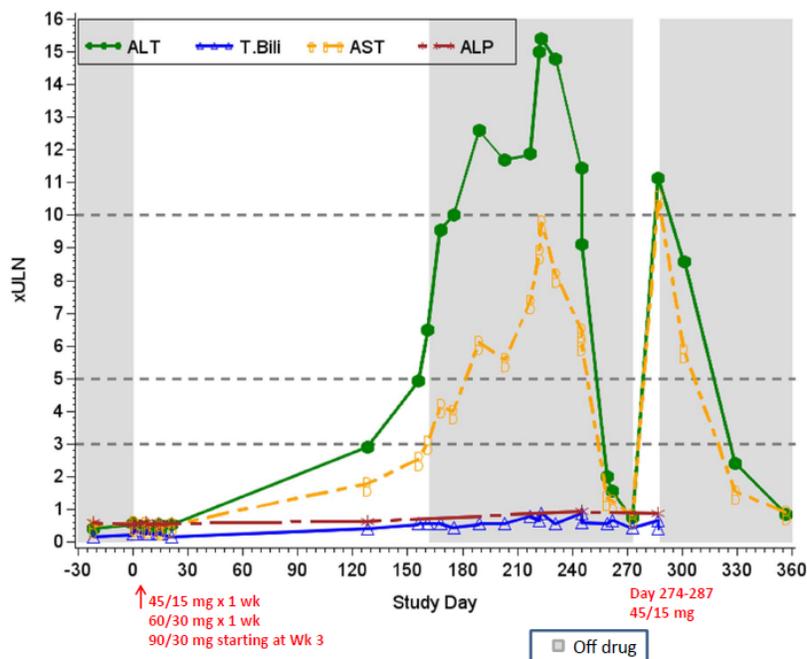


Figure 33. Subject (b) (6): time course of liver tests

Reviewer’s analysis: hep\figcode\line graph\_2401, dataset liverf

*Reviewer’s comment: The Medwatch report, narrative, and CRF were searched looking for other possible causes. There were two medications that stood out. At some point in time (unclear exactly when) she was taking pravastatin for hyperlipidemia. There is a note in the Medwatch report that this was discontinued. Another medication, anzelidipine (a calcium channel blocker, metabolized by CYP3A) was prescribed at the time of the initial tolvaptan discontinuation. Concomitant drugs metabolized via the same pathway as tolvaptan do not appear to significantly effect tolvaptan concentrations. Given that rechallenge with tolvaptan resulted in an immediate rise in transaminases, these other factors seem less important. This is not a typical “Hy’s Law” case in that her bilitubin was not clinically elevated.*

### 9.8.5 Subject (b) (6), rechallenge case

This is a 49 year old Caucasian female who had an SAE on Day 352 of a fall resulting in right flank pain and rib fracture. She was given paracetamol/codeine and a lidocaine patch for the

pain. An abdominal ultrasound reported no evidence of liver injury, multiple tiny cysts within the liver without significant change. An abdominal CT reported similar findings.

Because of significant elevations in liver tests shortly after the injury, tolvaptan was interrupted from Day 359 (01 Nov 2008) to Day 467. She had no other gastrointestinal complaints.

The following tests were negative: autoimmune liver disease screening (mitochondrial antibody, smooth muscle antibody, and liver kidney microsomal antibody), hepatitis C virus RNA, and hepatitis B surface antigen. On 14 Nov 2008, a hepatologist concluded that the elevation in liver enzymes was secondary to the fall, and medications were not likely the cause. Another CT in December reported stable findings of PKD that also involved the liver.

About 4 months later her liver enzymes returned to normal, and tolvaptan was restarted at a lower dose. Liver tests increased almost immediately resulting in study discontinuation. A liver biopsy revealed chronic inflammation in the portal triads. The pathologist commented the etiology and clinical significance of the chronic inflammation in the portal triads were not determined, it could represent nonspecific reaction to the liver cysts, and chronic hepatitis could not be excluded based purely on morphology.

The investigator assessed the event as moderate severity and probably related to the study medication. The HAC states that the rechallenge confirms that the event was due to tolvaptan. Their consensus causality assessment was “probable”.

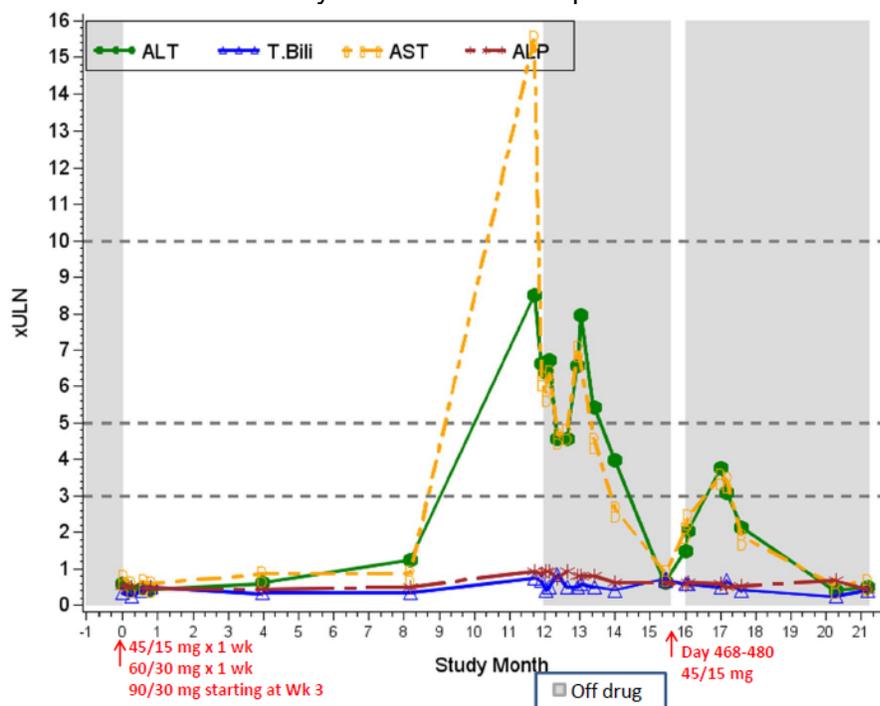


Figure 34. Subject (b) (4) time course of liver tests

*Reviewer's comment: The dose and duration of the paracetamol (another likely cause of DILI) is unclear.*

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/s/  
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ALIZA M THOMPSON  
07/07/2013

BACH N BEASLEY  
07/07/2013