FDA Briefing Document

Cardiovascular and Renal Drug Advisory Committee Meeting

August 5, 2013

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought tolvaptan to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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FOOD AND DRUG ADMINISTRATION

Center for Drug Evaluation and Research

Tolvaptan Advisory Committee Meeting

DRAFT POINTS TO CONSIDER

The Advisory Committee is asked to opine on the approvability of tolvaptan, a vasopressin V2 receptor antagonist, to slow kidney disease in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD). In support of the proposed indication, the applicant submitted the results of a single, randomized, double-blind, placebo-controlled phase 3 trial conducted in 1445 subjects with ADPKD and 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 because of the size of their kidneys. The primary endpoint of the trial was the rate of total renal volume change. 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).

1. Please comment on the design of the trial including:
    a. patient population enrolled
    b. use of a post-randomization measurement to assess tolvaptan's effect on renal function
    c. follow-up of subjects who discontinued study medication prematurely

2. Please comment on the conduct of the trial. Was follow-up for endpoint events adequate?

3. Please comment on the analysis of the trial's findings. Do the prespecified analyses of the ADPKD clinical progression endpoint and first non-composite secondary endpoint, the rate of change in renal function, adequately account for missing data? How should tolvaptan's effects on renal function be assessed given missing post-titration creatinine values?

4. Please comment on effectiveness. Did the phase 3 trial demonstrate a significant effect of tolvaptan on…
    a. …reducing ADPKD clinical progression events?
    b. …slowing the loss of renal function?
    c. …reducing severe renal pain events?

    If you answered in the affirmative for any of the aforementioned items, please provide a quantitative estimate of the benefit and its clinical impact.

5. Please comment on tolvaptan's risk of drug-induced liver injury and whether you think the proposed risk mitigation strategy is…
    a. … sufficient to mitigate the risk of severe liver injury should the drug be approved.
    b. …overly burdensome.

6. VOTE: Considering the risks and benefits of therapy, should tolvaptan be approved to slow kidney disease in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease?

7. If additional studies are needed to support approval, please discuss the design of those studies. In particular, should outcomes in patients with more advanced disease/lower levels of renal function be required?

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

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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 ≥ 60 mL/min as determined by the Cockcroft-Gault equation) deemed to be at high risk of progression (total kidney size ≥ 750 cc).[1] 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 ~ 1 mL/min/1.73m^2 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^2 (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.

[1] 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 x10, or ~ 1 in 3000 patients treated with tolvaptan.[2] 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 ≤ 1 per 10,000.[3]

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".[4] 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".[4] 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.

[2] 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)
[3] FDA Guidance for Industry on Drug-Induced Liver Injury: Premarketing Clinical Evaluation dated July 2009
[4] 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)[5]. 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 1:000). 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.

[5] 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	Agency provided feedback on proposed phase 3 trial and responses to questions submitted by sponsor. *Efficacy endpoints:* 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." *Findings needed to support approval:* 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. *Other aspects of trial design:* 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.
Follow-up meeting held on November 15, 2005	*Efficacy endpoints:* Sponsor proposed a key secondary composite endpoint consisting of hypertension, proteinuria, nephrolithiasis and renal pain. *Findings needed to support approval:* 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. Sponsor was advised to submit the statistical analysis plan for review and

Source (date of meeting or submission)	Advice from Agency
	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. *Other aspects of trial design:* 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."
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	Meeting held at request of sponsor to obtain Agency's input and concurrence on proposed statistical analysis plan. *Further discussion of endpoints:* 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. *Findings needed to support approval:* 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 < 0.01. 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.
April 6, 2012	Orphan Drug Designation granted by Office of Orphan Products Development

Source (date of meeting or submission)	Advice from Agency
Meeting Minutes PreNDA meeting (July 19, 2012)	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. 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. 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). 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.
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^2, 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^2. 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%).[6] 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^2 and those with an eGFR between 30 and 60 mL/min/1.73m^2, 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^2, 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

[6] 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

Trials	**Period of enrollment; status of enrollment; number enrolled**	**Dose**	**Duration of exposure**	**Primary endpoint(s)**
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

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

Trials	Period of enrollment; status of enrollment; number enrolled	Dose	Duration of exposure	Primary endpoint(s)
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 ≥ 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 ≥ 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 ≥ 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.[7] 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

[7] 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^2. 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*	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: • normotensive (dBP < 80 and sBP < 120 mmHg and off therapy) • low pre-hypertensive (sBP ≤ 129 and dBP ≤ 84 mmHg but not normotensive and off therapy) • high-pre-hypertensive (sBP ≤ 139 and dBP ≤ 89 mmHg but not normotensive/low-prehypertensive and off therapy) • hypertensive (sBP >139 and/or dBP > 89 mmHg or on anti-hypertensive therapy). The higher of the systolic or diastolic blood pressure was to determine category. Initiation of antihypertensive medication, increasing doses in anti-hypertensive medication, or introducing a new prescription of anti-hypertensive medication also qualified as an event.
Worsening albuminuria	
Assessments	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.
Definition of an event*	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: • A= "Normal" (urine albumin/ creatinine of < 2.8 mg/mmol female or < 2.0 mg/mmol male) • B= "microalbuminuria" (urine albumin/ creatinine of 2.8-28 mg/mmol female or 2.0-20 mg/mmol male) • C= "overt proteinuria" (urine albumin/ creatinine of >28 mg/mmol female or >20 mg/mmol male). 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.

*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

	Order of testing	
Secondary Endpoint	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.[8] 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.

[8] 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.[9] 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 3rd reviewer was used. Reviewers also had the option of requesting committee discussion of the event.

[9] 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	*Potential BP category events:* 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 *Potential anti-hypertensive medication events:* 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)
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	• 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
10 September 2009 Protocol Amendment	• added two off study drug follow up clinic visits • provided a more detailed definition of the composite endpoint and added an independent adjudication committee to review secondary composite endpoint events • changed the order of testing non-composite secondary efficacy endpoints • 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 • 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[10] • added a MMRM analysis as a sensitivity analysis for the primary endpoint • 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 • 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 • modified the exploratory endpoints • added provisions for subjects who become unintentionally pregnant during trial participation

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.

[10] 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[11]; 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[12]. 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 ~1 mL/min/1.73m^2 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

[11] 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.
[12] 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 ≥ 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 ≥ 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^2 (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 gfr0; 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.

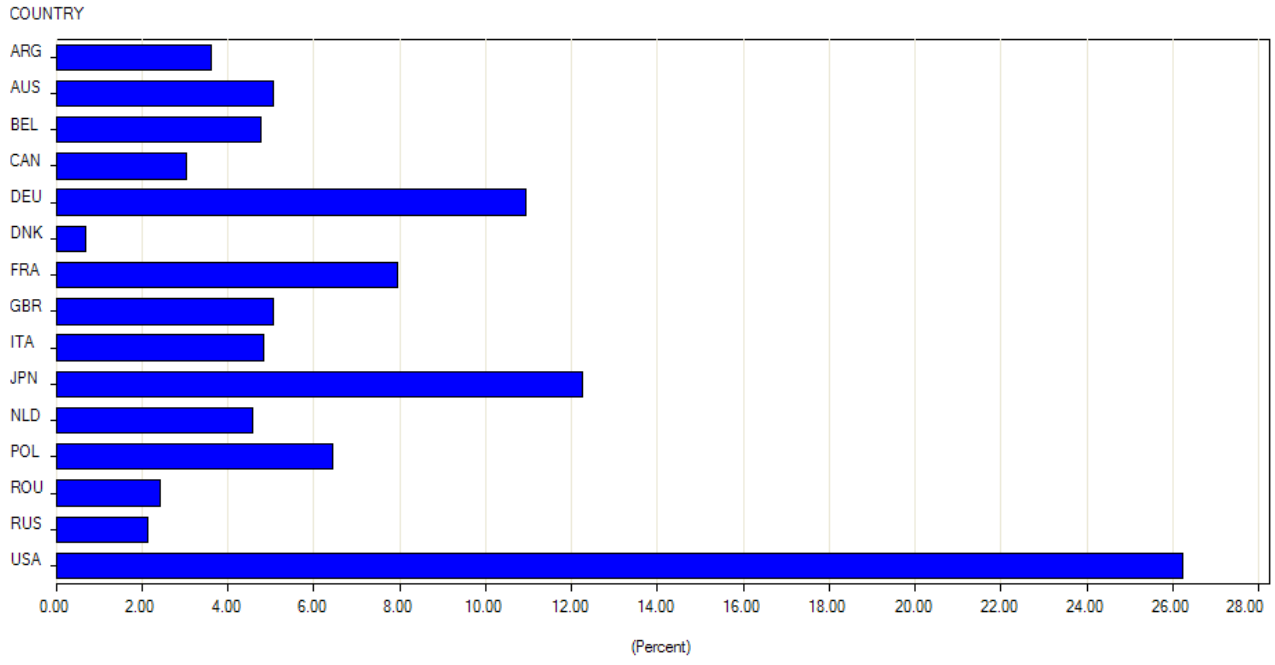


Figure 1. Enrollment by geographic region

[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 ≥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%).

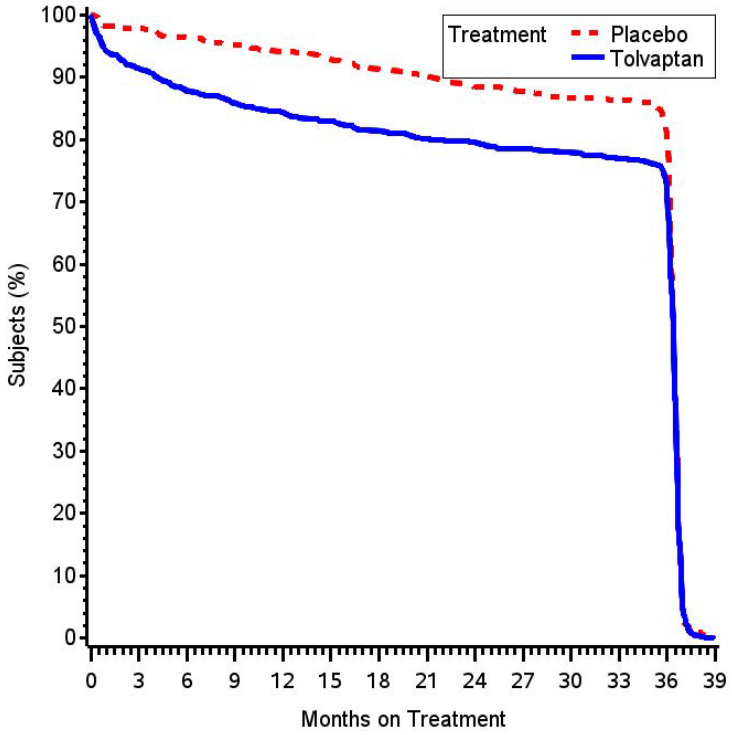


Figure 2. Time to discontinuation of study medication

[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]

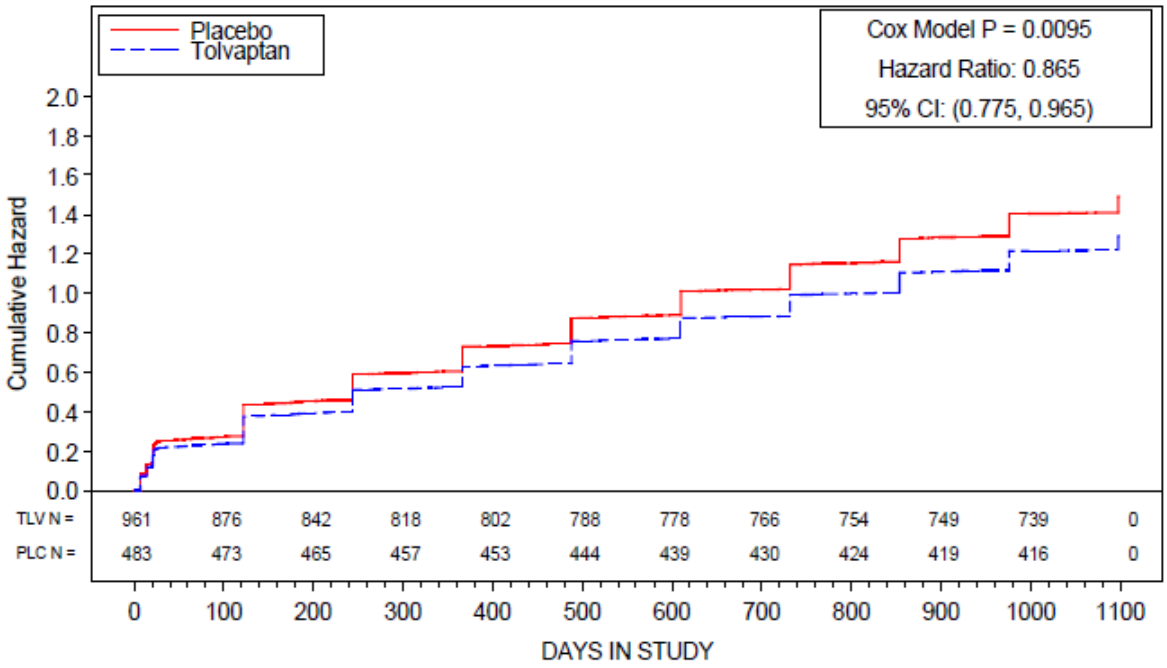


Figure 3. Cumulative hazard function of time to multiple ADPKD clinical progression events

[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
Worsening Renal Function	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	
Renal Pain	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	
Hypertension	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			
Albuminuria	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.

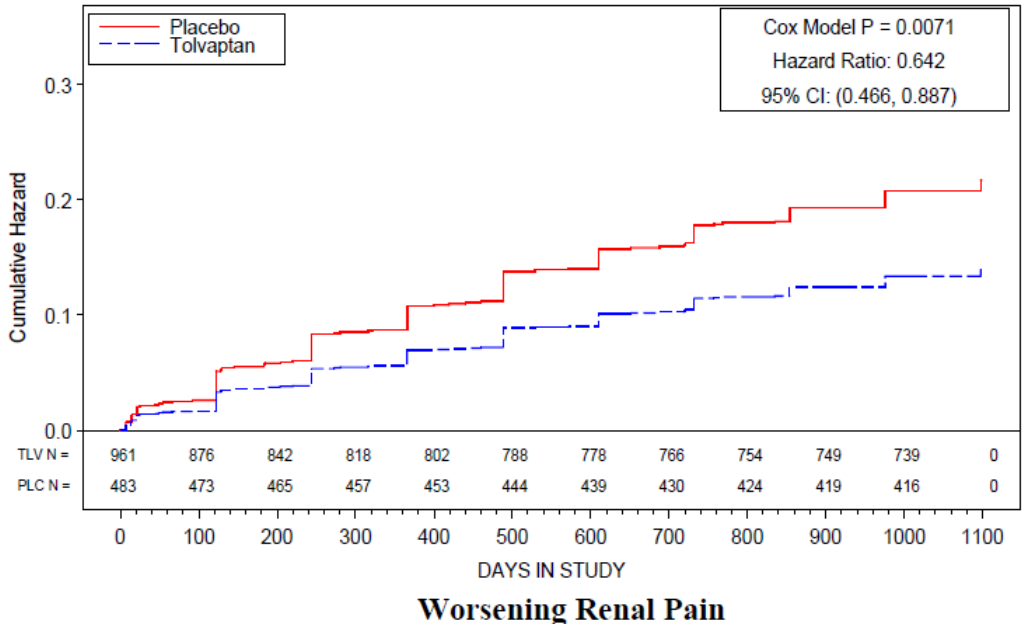


Figure 4. Cumulative hazard function of time to multiple worsening renal pain events

[Source: Clinical Study Report 156-04-251, Figure 9.4.3-1]

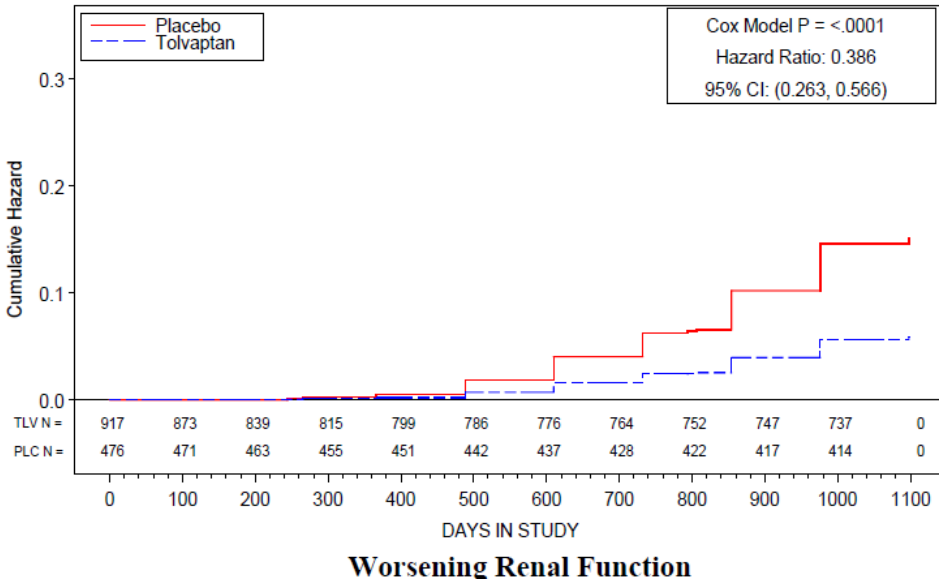


Figure 5. Cumulative hazard function of time to multiple worsening renal function events

[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.[13] 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.

[13] 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

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

[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
1/serum creatinine ([mg/mL]$^{-1}$)		
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	
eGFR by CKD-EPI (mL/min/1.73m^2)		
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-Meir 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^2 by CKD-EPI, $p < 0.0001$). The applicant reported similar results using a Wu-Bailey analysis to account for data missing not at random.

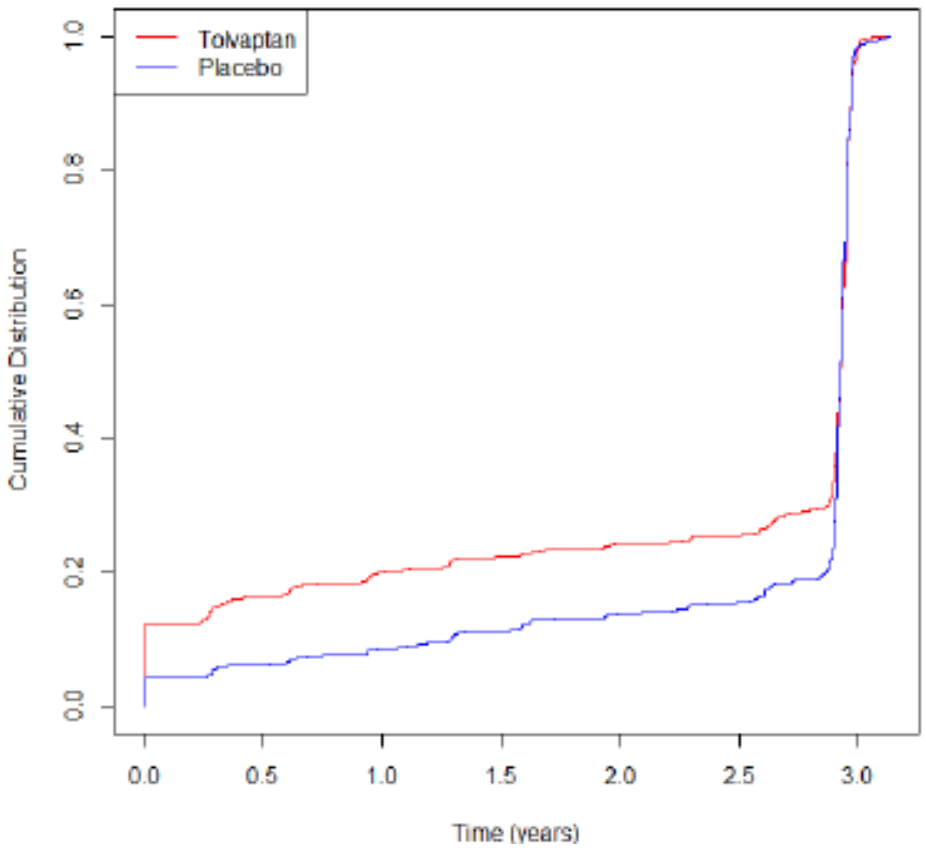


Figure 6. Kaplan-Meier plot of time to last eGFR measurement used in applicant's analysis of rate of GFR change

[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^2 using the CKD-EPI equation.[14] The mean GFR as estimated by the CKD-EPI equation in this subset of subjects was ~51 mL/min/1.73m^2 (both treatment arms). In the study population overall, only 43 subjects (3%) had a GFR less than 45 mL/min/1.73m^2 as estimated using the CKD-EPI equation.

[14] 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.

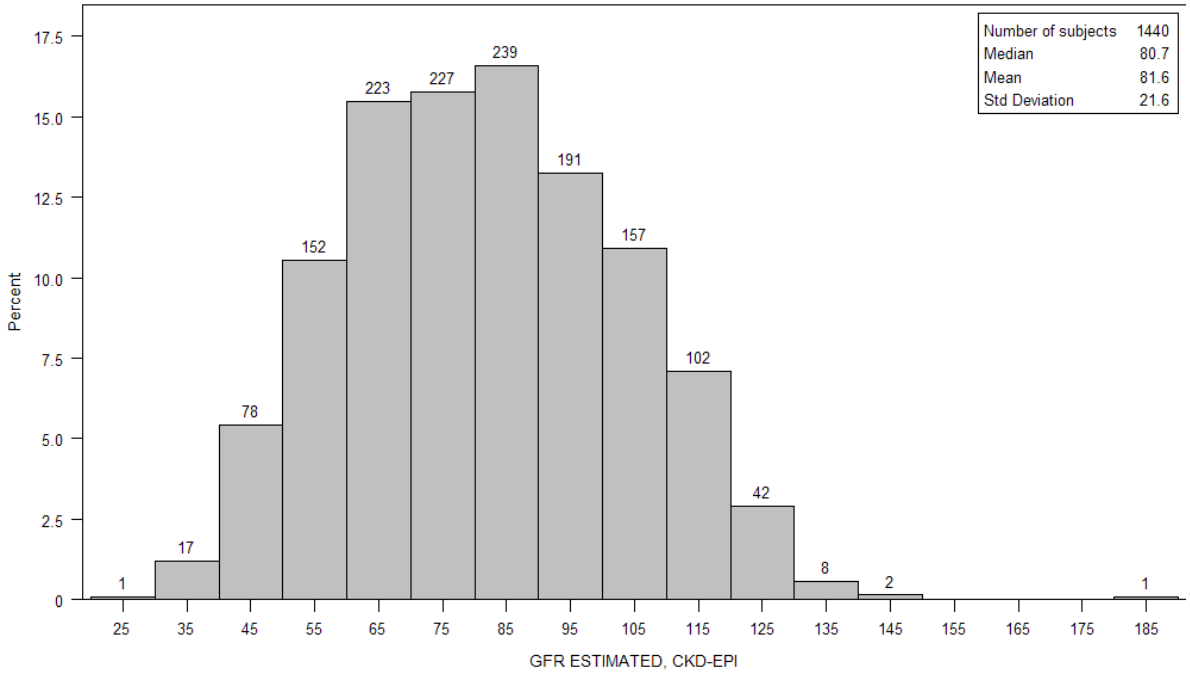


Figure 7. Distribution of baseline GFR by the CKD-EPI equation in the study population

[Source: Reviewer's analysis]

Of subjects with a GFR <60 mL/min/1.73m^2 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.[15] 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^2 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).

[15] The Cockcroft-Gault equation includes a term for weight; the CKD-EPI formula estimates GFR adjusted for body surface area.

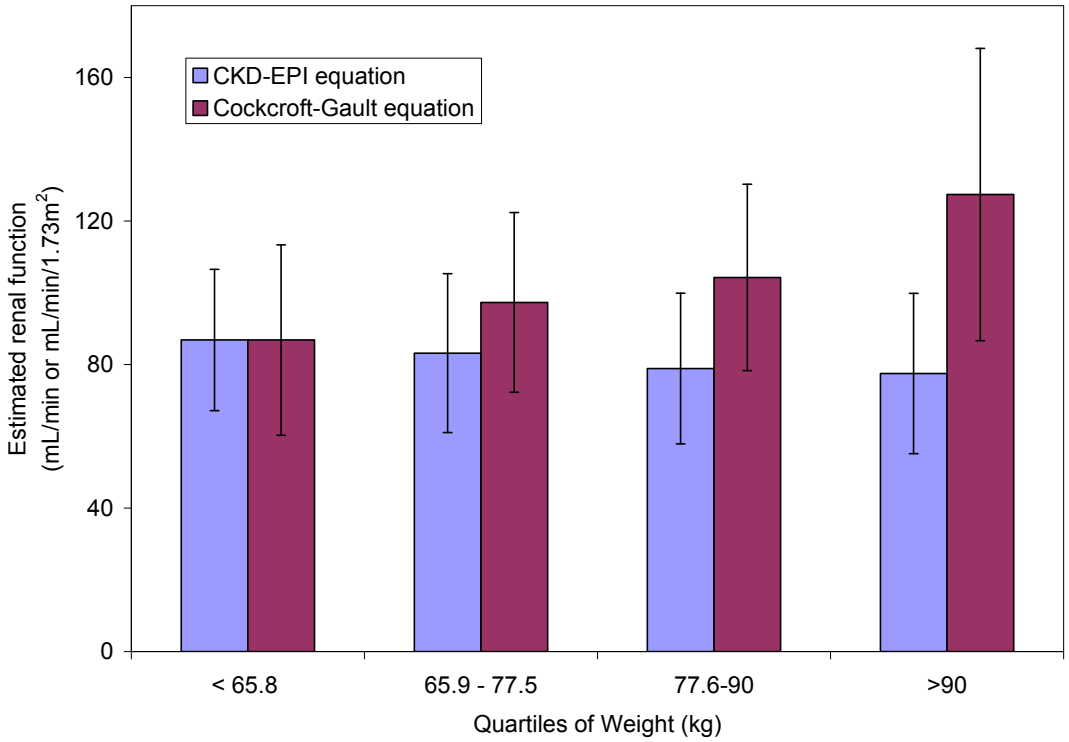


Figure 8. CKD-EPI and Cockcroft-Gault equation estimates of renal function by quartile of weight

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.

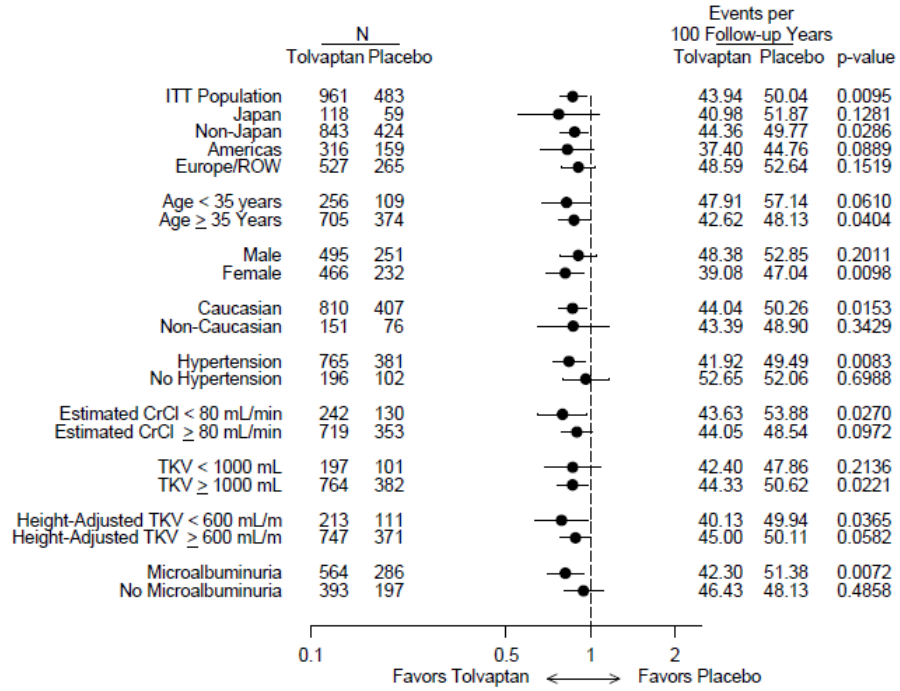


Figure 9. Subgroup analyses of time to multiple events of composite endpoint

[Source: Clinical Study Report 156-04-251, Figure 9.4.2-1]

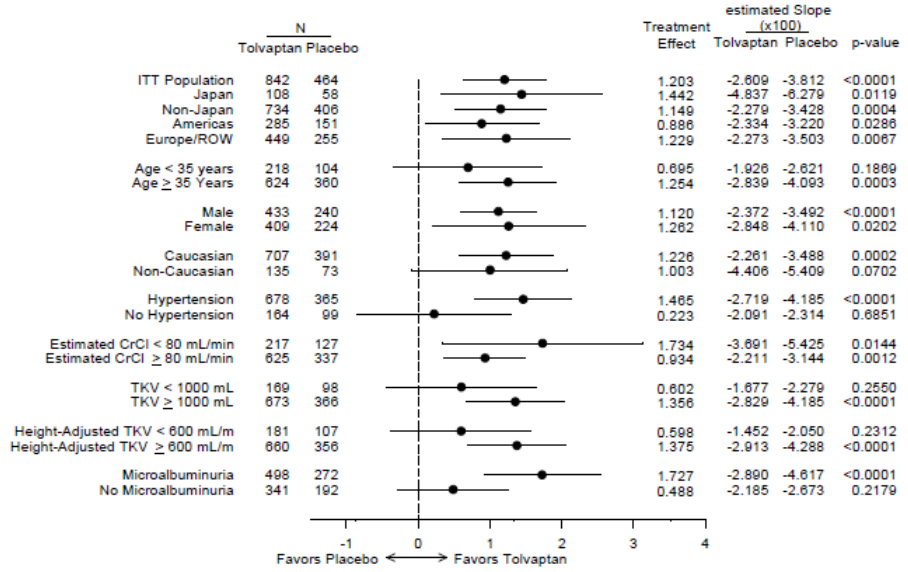


Figure 10. Subgroup analyses of annualized change in renal function (1/serum creatinine [mg/ml])

[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).

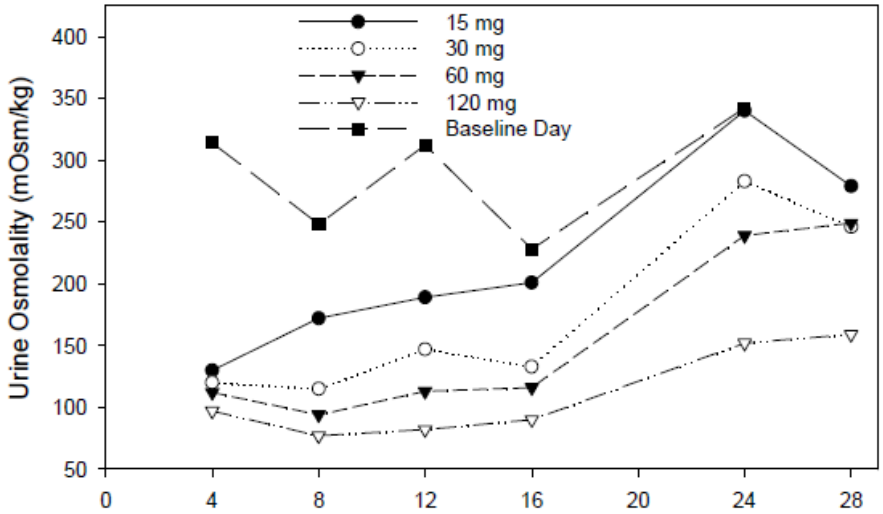


Figure 11. Mean urine osmolality at the end-time of the collection interval at baseline and following ascending single oral doses of tolvaptan

[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.

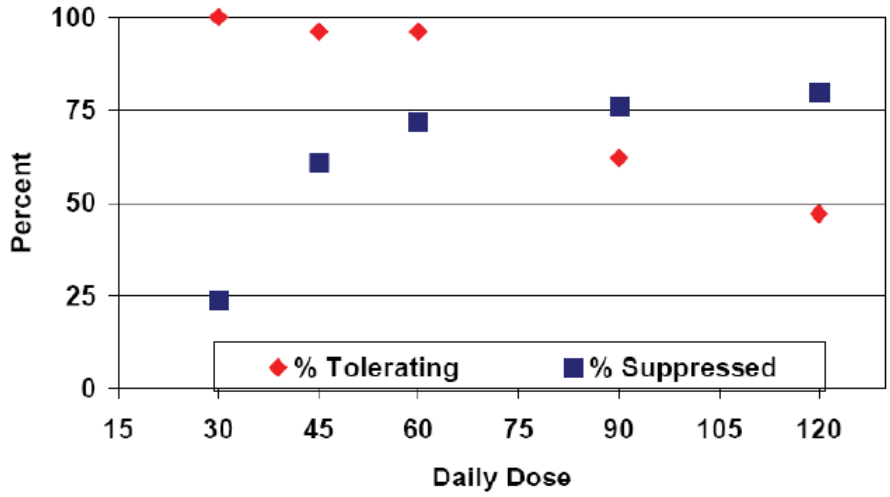


Figure 12. Percentage of subjects who tolerated dose and percentage with trough spot urine osmolality < 300 mOsm/L

[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.[16]

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

[16] 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).

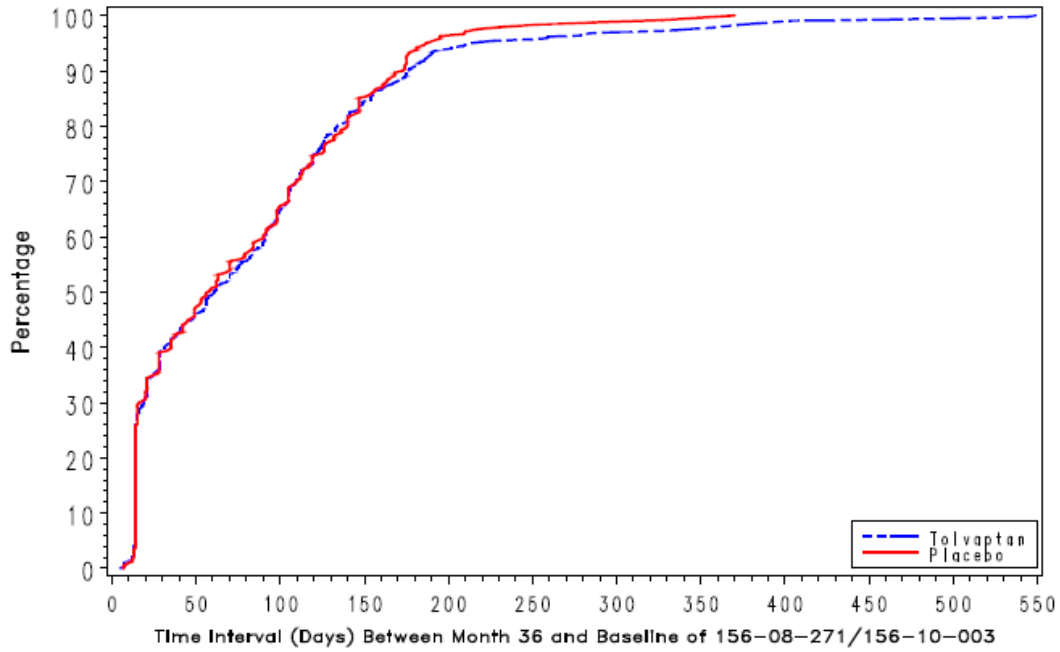


Figure 13. Distribution of the time interval between the month 36 visit in trial 156-04-251 and baseline value obtained for the extension studies (enzymatic assay used for assessments in all trials)

[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.

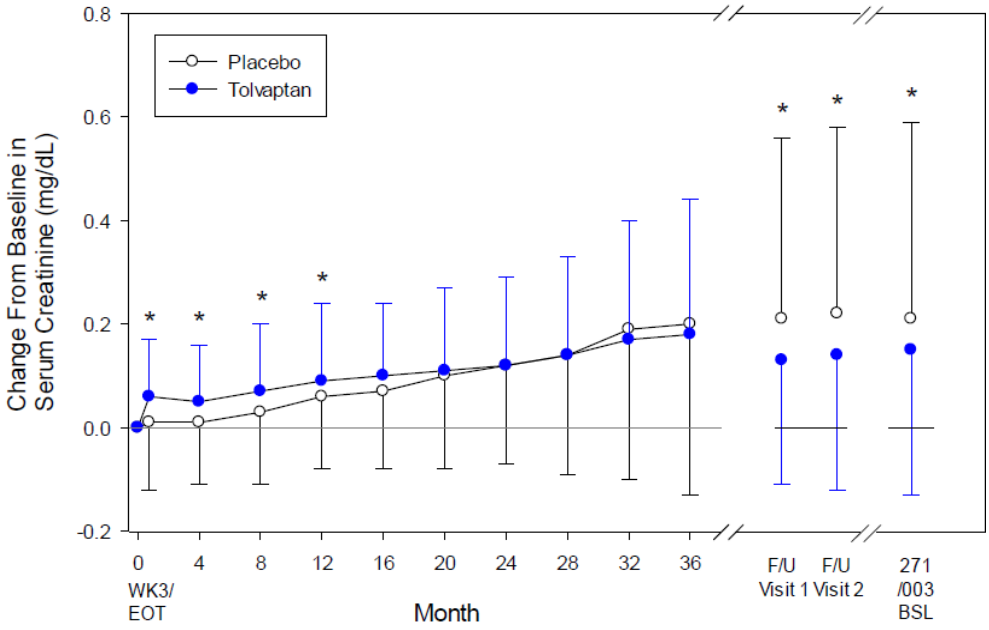


Figure 14. Mean (SD) change from pretitration baseline in serum creatinine in the phase 3 trial and as entering (baseline for) extension studies 156-08-271 and 156-10-003

[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.[17] 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.

[17] 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
Weight						
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)
Hematocrit						
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)
Sodium						
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 ≥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.[18]

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.[19] In addition, the pivotal trial showed a four-fold higher incidence of significant

[18] 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).
[19] 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 x 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 ≤ 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)

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 (≤ 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)[20]
- Dr. John Senior's (FDA, Office of Pharmacovigilance and Epidemiology) consult review on the hepatic safety of tolvaptan dated 28 June 2013

[20] 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.[21]

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.

[21] 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[a] (mg)	n	Average Daily Dose[a] (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.

[a] 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

Modal dose, mg (split dose regimen)	**N (%)**	**Subject-years[1]**	**Median (months)[1]**	**Subject-years[2]**
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

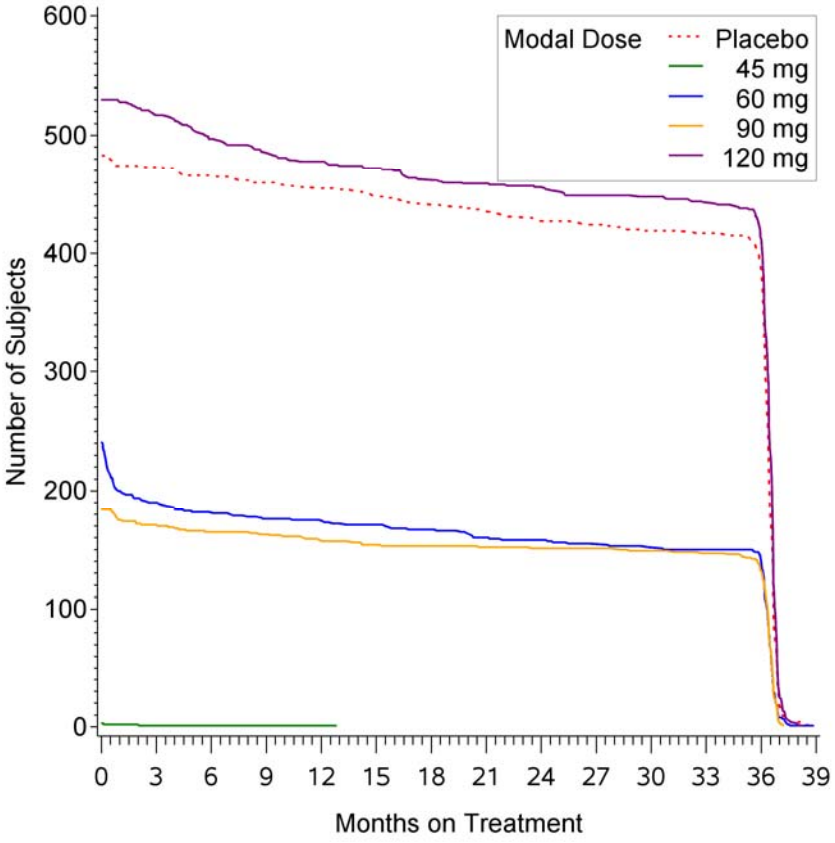


Figure 15. Exposure over time by modal dose in trial 156-04-251

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.

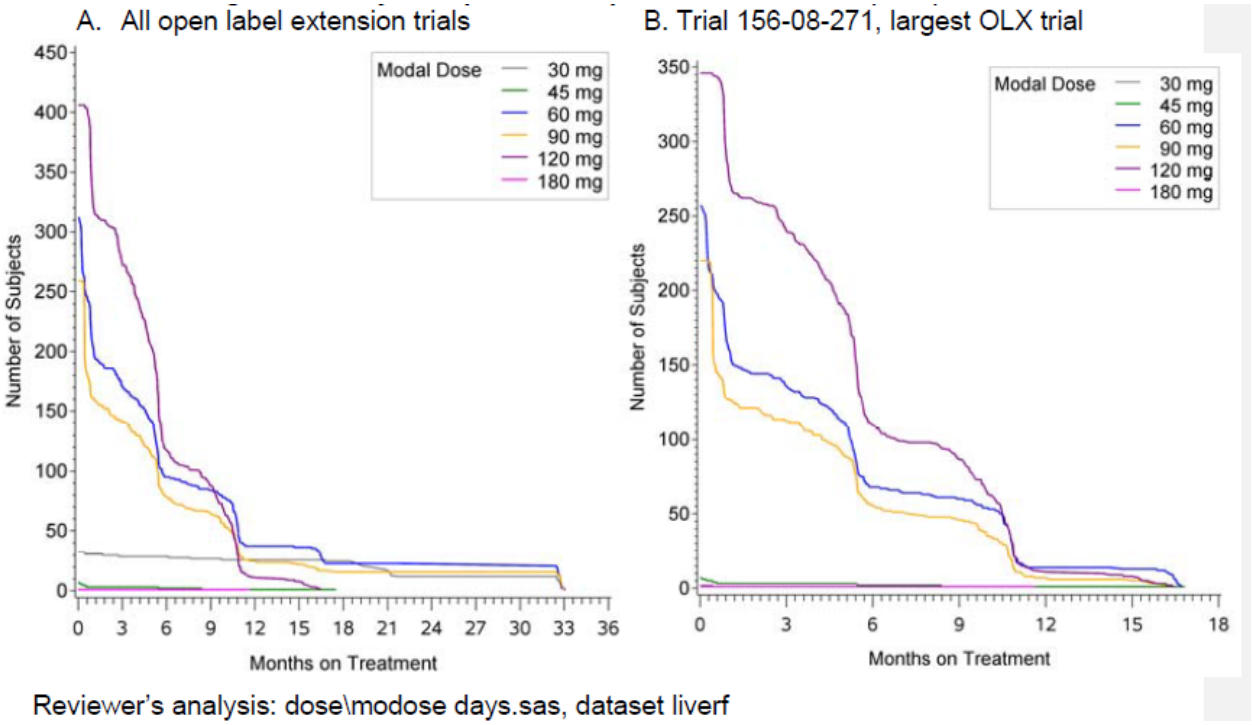


Figure 16. Subject exposure over time by modal dose in open label extension trials

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.[22]

Serious TEAEs that occurred more frequently (a risk difference of ≥ 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 ≥ 3 subjects in the tolvaptan arm in Trial 156-04-251

Preferred term	tolvaptan	%	placebo	%
Total subjects	**177**	**(18.4)**	**95**	**(19.7)**
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, intervetebral 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

[22] 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 ≥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[a]	30 (5.7)	20 (6.8)
Blood and lymphatic system disorders		
Anaemia	2 (0.4)	0
Infections and infestations		
Diverticulitis	2 (0.4)	0
Pyelonephritis	1 (0.2)	1 (0.3)
Urinary Tract Infection	2 (0.4)	0
Injury, poisoning and procedural complications		
Joint Dislocation	1 (0.2)	1 (0.3)
Investigations		
Liver Function Test Abnormal	1 (0.2)	2 (0.7)
Nervous system disorders		
Cerebrovascular Accident	1 (0.2)	2 (0.7)
Renal and urinary disorders		
Renal Cyst Haemorrhage	1 (0.2)	1 (0.3)
Renal Failure Acute	0	2 (0.7)

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	%
Total subjects	**148**	**(15.4)**	**24**	**(5.0)**
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[23]: \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.[24] *However, it is unclear if the treatment emergent AE marked*

[23] 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.

[24] 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.

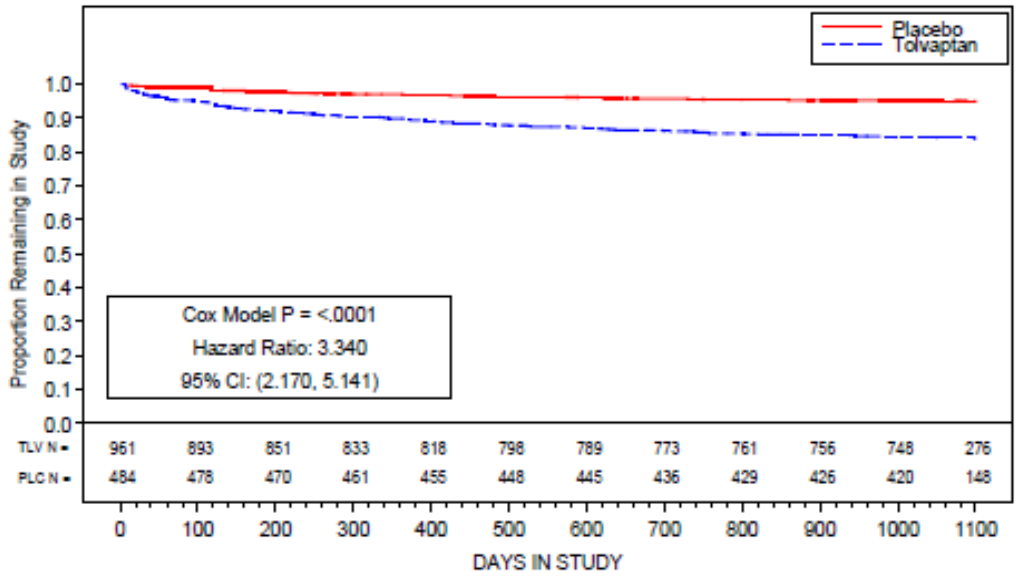


Figure 17. Time to treatment discontinuation due to AE

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)
Total subjects	**56 (5.8)**	**10 (2.1)**
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 ± 17.38 mg/dL in the tolvaptan group and −0.36 ± 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.[25] 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.

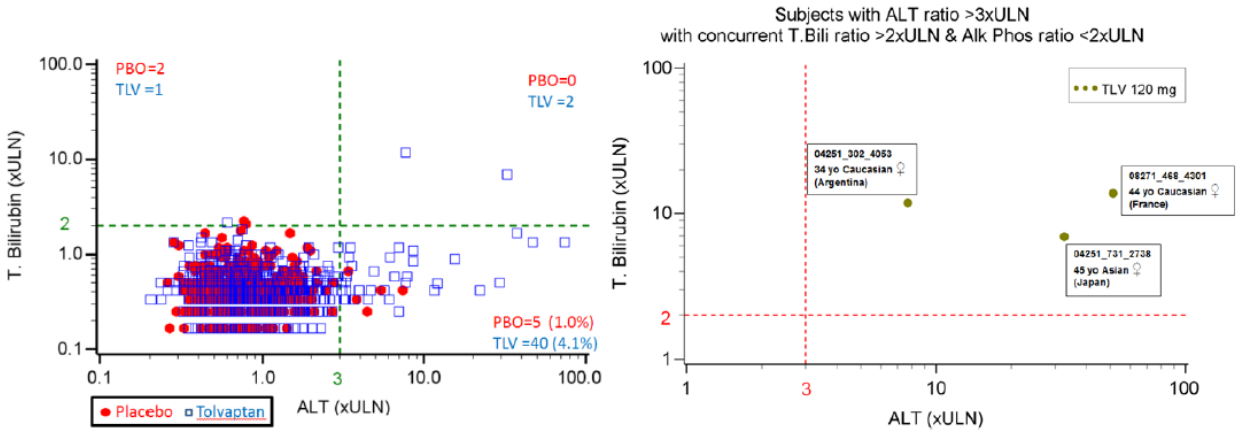
Unlike the data in hyponatremia and HF trials, the liver laboratory data in the ADPKD development program showed two characteristics seen with drugs that are known hepatotoxins, an imbalance of subjects in the potential Hy's Law[26] quadrant and in Temple's Corollary[27] quadrant. Figure A. shows that 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

[25] 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.

[26] 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.

[27] 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.



A. Trial 156-04-251 B. Potential Hy's Law quadrant (all 17 trials)

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 (ID 04251-302-4053 and ID 04251-731-2738) 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 08271-468-4301, 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.[28]

[28] 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 heparslt.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.

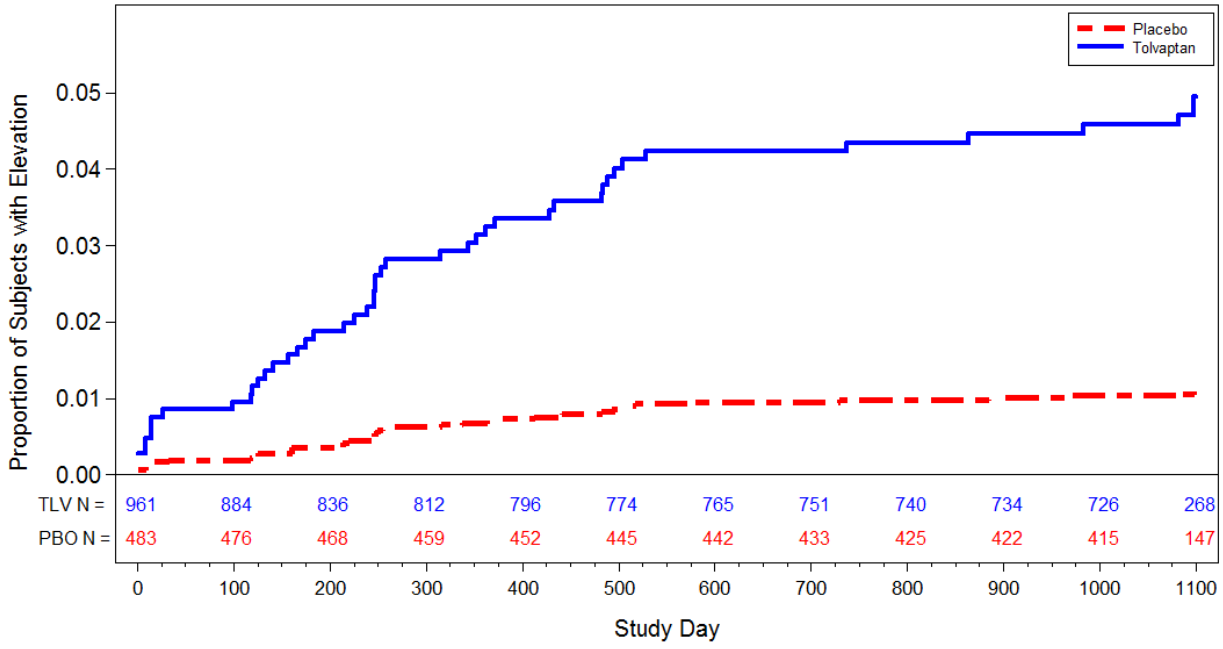
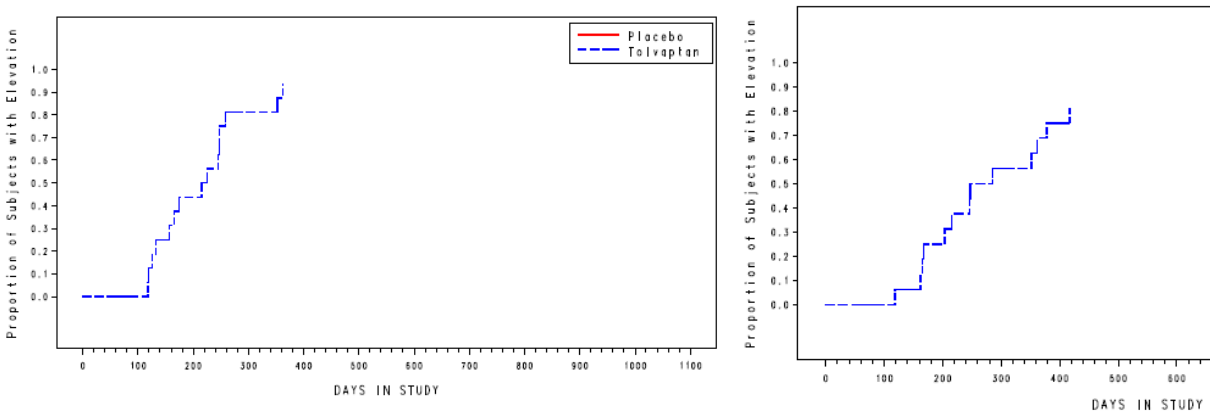


Table 36. Time to first ALT>3xULN, all subjects Trial 156-04-251

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".



A. Time to ALT> 3xULN B. Time to ALT > 5 xULN

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 ≤ 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 ≤ 3xULN 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 ≤ 3xULN 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."

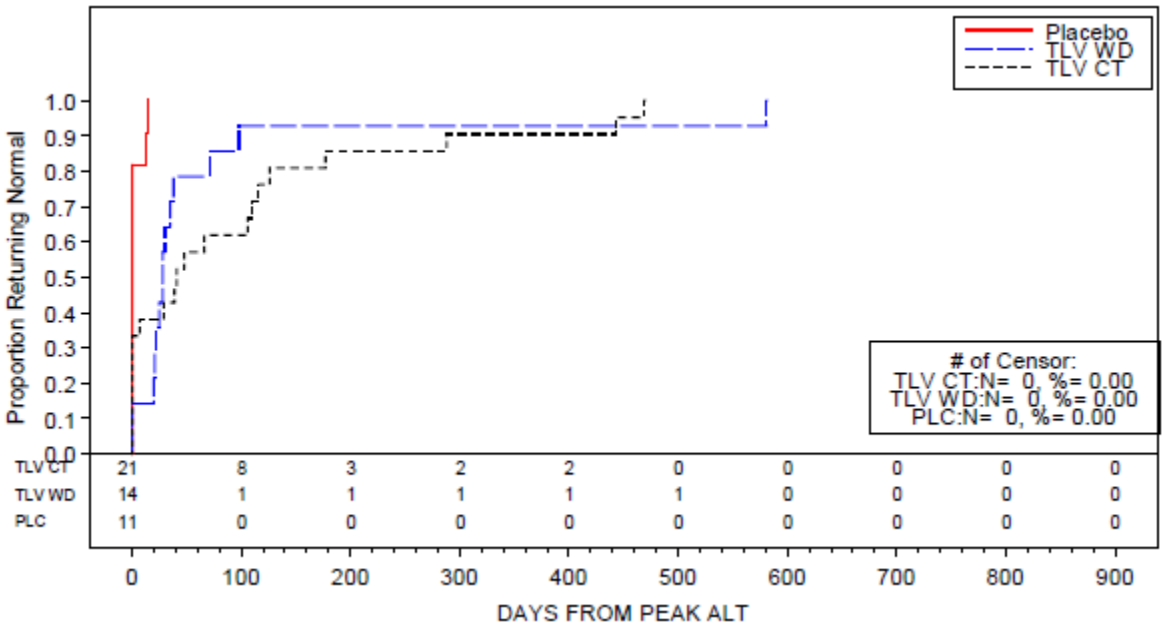


Figure 20. Time from peak ALT to less than 3x ULN, adjudicated subjects, trial 156-04-251

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 identity 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)	Nonadju-dicated (N = 926)	Highly Likely and Probable (N = 1)	Possible and Unlikely (N = 10)	Nonadju-dicated (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
$eGFR_{CKD-EPI}$, $mL/min/1.73m^2$						
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.

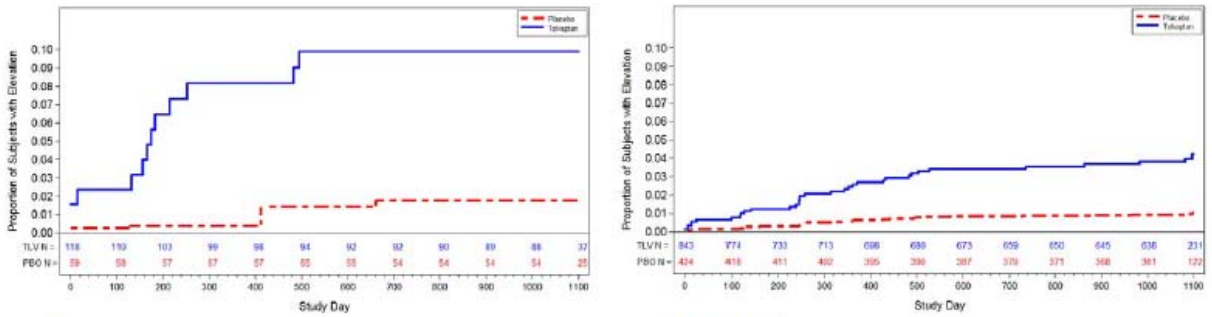


Figure 21. Time to ALT>3xULN in Japan compared to the rest of the world

Source: reviewer's analysis: hep\km\ttt_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[a]	941 (97.9)	469 (97.1)	1410 (97.6)
Blood and lymphatic system disorders			
Anaemia	27 (2.8)	24 (5.0)	51 (3.5)
Cardiac disorders			
Palpitations	**34 (3.5)**	**6 (1.2)**	**40 (2.8)**
Ear and labyrinth disorders			
Vertigo	24 (2.5)	18 (3.7)	42 (2.9)
Gastrointestinal disorders			
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)**
Diarrhoea	128 (13.3)	53 (11.0)	181 (12.5)
Dry Mouth	154 (16.0)	60 (12.4)	214 (14.8)
Dyspepsia	**76 (7.9)**	**16 (3.3)**	**92 (6.4)**
Gastrooesophageal 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)
General disorders and administration site conditions			
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)**
Hepatobiliary disorders			
Hepatic Cyst	13 (1.4)	10 (2.1)	23 (1.6)
Immune system disorders			
Seasonal Allergy	26 (2.7)	10 (2.1)	36 (2.5)
Infections and infestations			
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)
Injury, poisoning and procedural complications			
Ligament Sprain	14 (1.5)	11 (2.3)	25 (1.7)
Investigations			
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	**24 (2.5)**	**6 (1.2)**	**30 (2.1)**
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)
Metabolism and nutrition disorders			
Decreased Appetite	**69 (7.2)**	**5 (1.0)**	**74 (5.1)**
Dehydration	18 (1.9)	11 (2.3)	29 (2.0)
Gout	**28 (2.9)**	**7 (1.4)**	**35 (2.4)**
Hypercholesterolaemia	26 (2.7)	12 (2.5)	38 (2.6)
Hyperglycaemia	6 (0.6)	10 (2.1)	16 (1.1)
Hypernatraemia	**27 (2.8)**	**5 (1.0)**	**32 (2.2)**
Hyperuricaemia	**37 (3.9)**	**9 (1.9)**	**46 (3.2)**
Polydipsia	**100 (10.4)**	**17 (3.5)**	**117 (8.1)**
Musculoskeletal and connective tissue disorders			
Arthralgia	69 (7.2)	28 (5.8)	97 (6.7)
Back Pain	133 (13.8)	88 (18.2)	221 (15.3)
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)
Nervous system disorders			
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)
Psychiatric disorders			
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 (%)
Renal and urinary disorders			
Haematuria	75 (7.8)	68 (14.1)	143 (9.9)
Nephrolithiasis	15 (1.6)	14 (2.9)	29 (2.0)
Nocturia	**280 (29.1)**	**63 (13.0)**	**343 (23.8)**
Pollakiuria	**223 (23.2)**	**26 (5.4)**	**249 (17.2)**
Polyuria	**368 (38.3)**	**83 (17.2)**	**451 (31.2)**
Renal pain	260 (27.1)	171 (35.4)	431 (29.8)
Respiratory, thoracic and mediastinal disorders			
Cough	77 (8.0)	38 (7.9)	115 (8.0)
Dyspnoea	22 (2.3)	6 (1.2)	28 (1.9)
Oropharyngeal Pain	46 (4.8)	18 (3.7)	64 (4.4)
Skin and subcutaneous tissue disorders			
Dry skin	**47 (4.9)**	**8 (1.7)**	**55 (3.8)**
Eczema	**19 (2.0)**	**3 (0.6)**	**22 (1.5)**
Pruritus	33 (3.4)	13 (2.7)	46 (3.2)
Rash	**40 (4.2)**	**9 (1.9)**	**49 (3.4)**
Vascular disorders			
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.

[a] 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 hypernatremia.

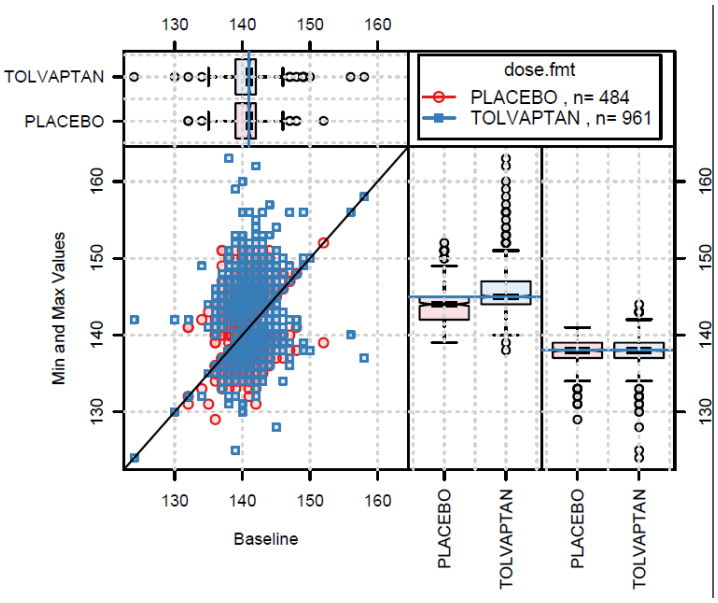


Figure 22. Serum sodium at baseline and minimum and maximum values in trial 156-04-251 (reviewer's analysis)

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.

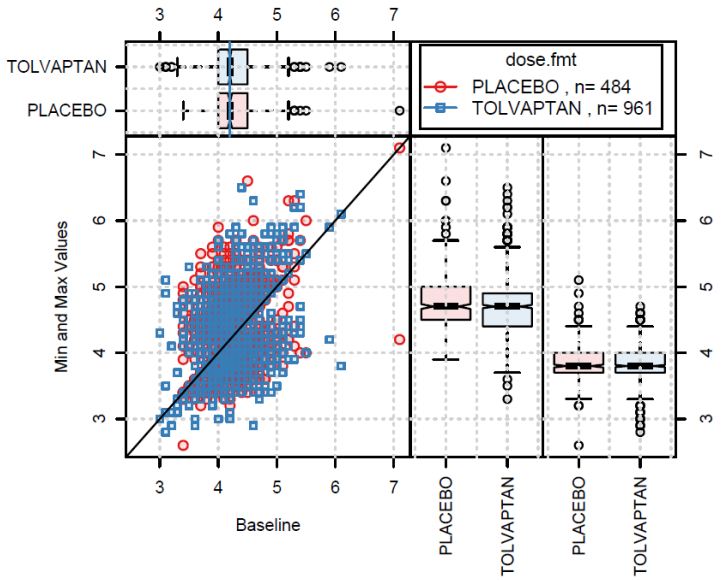


Figure 23. Serum potassium at baseline and minimum and maximum values in trial 156-04-251 (reviewer's analysis)

Glucose

Analysis of laboratory data did not suggest clinically important effects on glucose levels. For discussion see also Section 7.3.4.

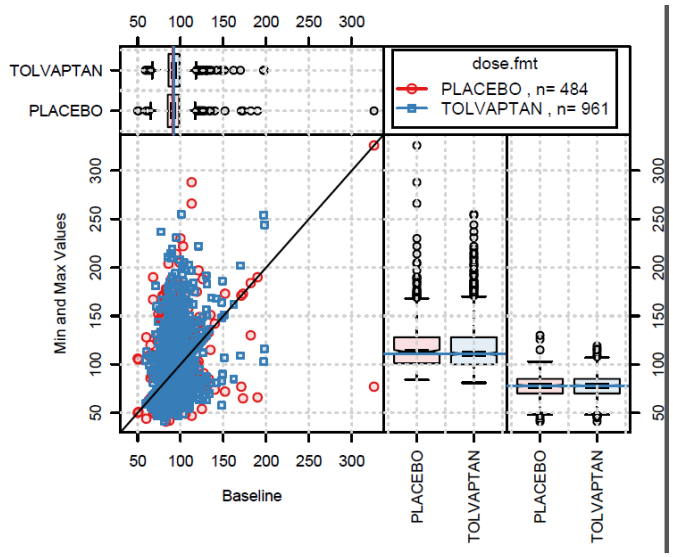


Figure 24. Glucose at baseline and minimum and maximum values in trial 156-04-251 (reviewer's analysis)

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

	Tolvaptan (N=960 treated)	**Placebo (N=483 treated)**
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.

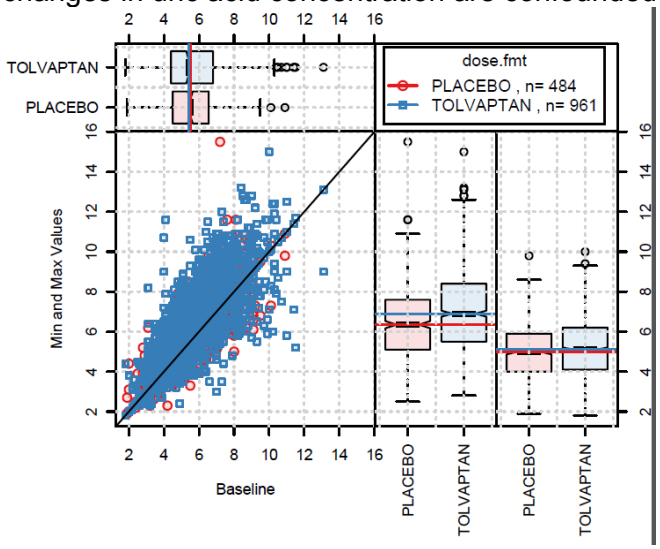


Figure 25. Uric acid at baseline and minimum and maximum values in trial 156-04-251 (reviewer's analysis)

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).

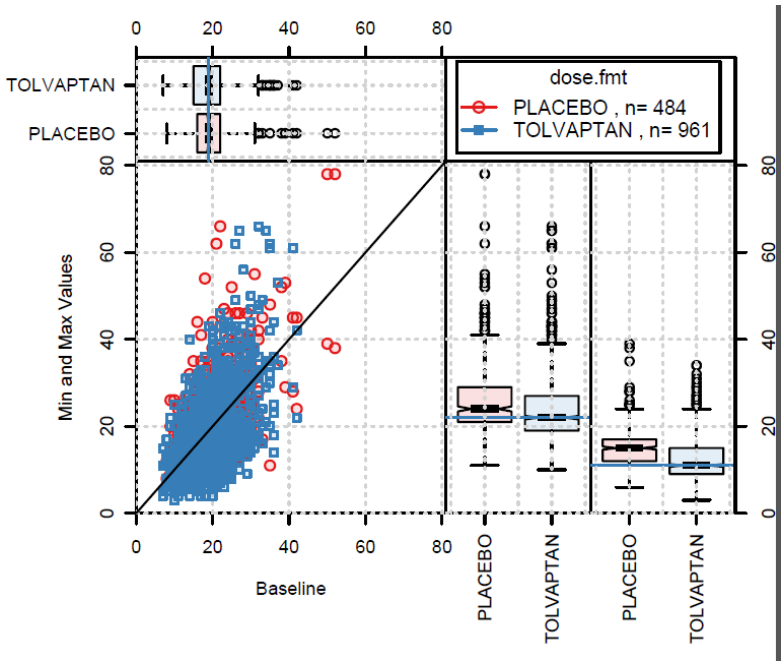


Figure 26. BUN at baseline and minimum and maximum values in trial 156-04-251 (reviewer's analysis)

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[a]	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[a]	0	1 (0.2)	1 (0.1)
Thyroid Neoplasm	0	1 (0.2)	1 (0.1)

Note: Subject 04251-107-0701 reported separate TEAEs of Basal Cell Carcinoma and Squamous Cell Carcinoma. Subject 04251-115-4402 reported separate TEAEs of Malignant Melanoma In Situ and Malignant Melanoma (Table 11.8.1.7.2-2).

[a]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.

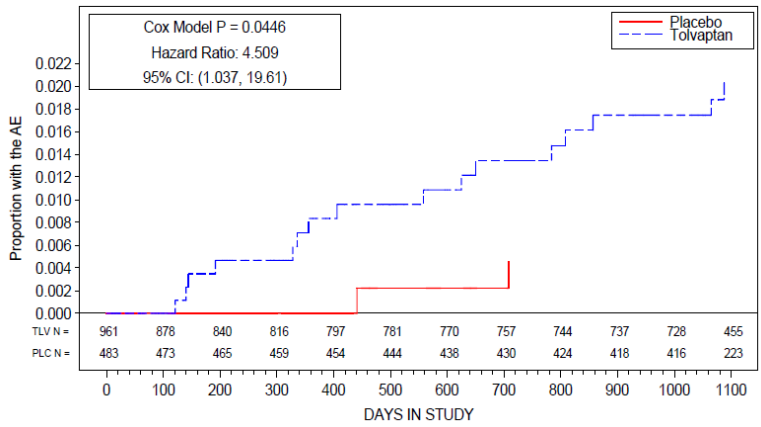
Thyroid Neoplasm
One subject on placebo (0.2%) was diagnosed with a thyroid neoplasm. It was unknown at the time of the report whether the neoplasm was benign or malignant.

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
04251-308-0130	Male	Tolvaptan	Pregnancy of partner	Live birth
04251-181-0330	Female	Placebo	Pregnancy	Spontaneous abortion
04251-159-0722	Female	Placebo	Pregnancy	Elective abortion
04251-662-1857	Male	Tolvaptan	Pregnancy of partner	Live birth
04251-732-2742	Male	Placebo	Pregnancy of partner	Live birth
04251-510-1870	Female	Tolvaptan	Pregnancy	Live birth
04251-467-2224	Female	Tolvaptan	Pregnancy	Elective abortion
04251-515-2231	Female	Tolvaptan	Pregnancy	Elective abortion
04251-711-3001	Female	Tolvaptan	Pregnancy	Elective abortion
04251-530-4225	Female	Tolvaptan	Pregnancy	Spontaneous abortion[a]
04251-673-4537	Female	Tolvaptan	Pregnancy	Elective abortion[a]

[a]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.

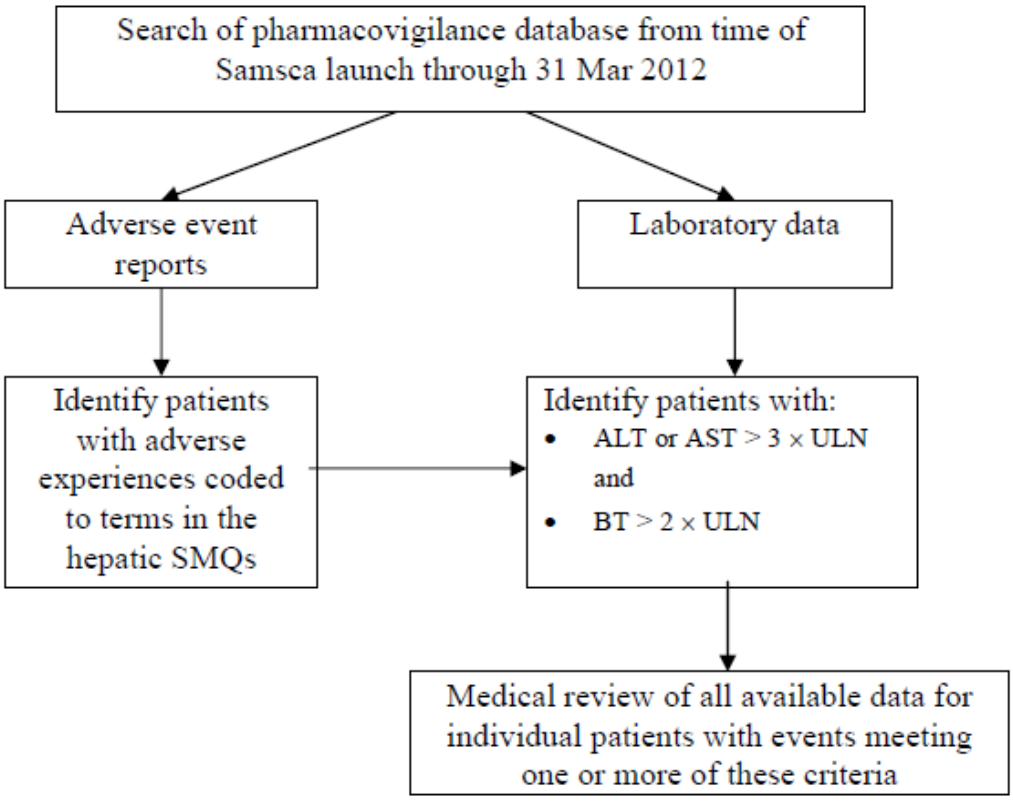


Figure 2.7.4.6.3-1 Process Map for Screening of Postmarketing Surveillance Data

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

Table 11.8.1.6.2-1 Timeline of Events

Date	Observation/Action
01 Mar 2007	First subject randomized.
02 Nov 2007	First IDMC meeting: • Chairman identified and development of charter initiated.
22 Feb 2008	Monthly data transfers to SDAC began.
22 Apr 2008	First hepatic serious TEAE reported to Otsuka (Subject 04251-727-2401; 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).

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: • IDMC reported "no safety concerns". • IDMC recommended continuing the trial according to the protocol.
09 May 2008	First discontinuation of IMP due to a hepatic TEAE (Subject 04251-140-0205 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 04251-727-2401.
03 Jul 2008	Otsuka provided additional information for Subject 04251-727-2401; results of liver biopsy and gastroenterology consultation were pending.
10 Jul 2008	Otsuka submitted liver biopsy and gastroenterology consultation report results for Subject 04251-727-2401 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: • IDMC reported "no safety concerns". • IDMC recommended continuing the trial according to the protocol.
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): • IDMC recommended continuing the trial according to the protocol. • 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.
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	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). • IDMC recommended continuing the trial according to the protocol. • IDMC requested patient history profiles for subjects with clinically significant LFT elevations for future meetings. • IDMC requested that all local laboratory data be collected and made available to SDAC throughout the remainder of the trial.
16 Apr 2009	Response received from the FDA regarding the information provided by Otsuka on 06 Mar 2009. The agency stipulated the following: • 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. • 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. • 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.
23-24 Apr 2009	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.
22 May 2009	IDMC meeting: • IDMC recommended continuing the trial according to the protocol. • 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.
10 Jun 2009	Type C meeting with the FDA regarding SPA.
July 2009	FDA guidance issued: Drug-induced Liver Injury (DILI), Premarketing Clinical Evaluation.
10 Jul 2009	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.
24 Jul 2009	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.
29 Jul 2009	IDMC teleconference: open-session teleconference wherein Otsuka updated the IDMC on the meeting with the FDA and the upcoming protocol amendment addressing efficacy.
30 Jul 2009	IDMC meeting summary recommendations with Hepatic Safety Data updates (initiated in May) submitted to FDA (for 22 May 2009 meeting).
18-19 Sep 2009	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 Table 11.8.1.6.2-2).

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 Table 11.8.1.6.2-2).
28 Oct 2009	IDMC meeting: • IDMC recommended continuing the trial according to the protocol.
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 Table 11.8.1.6.2-2).
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) (Section 17.7.1.1).
01 Jun 2010	Clarification memo sent to the sites regarding Hy's laboratory criteria and requirements for reporting IREs (Section 17.7.1.2).
02 Jun 2010	IDMC meeting: • IDMC recommended continuing the trial according to the protocol. • 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.
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 (Section 17.7.1.3).
26 Aug 2010	IDMC meeting summary recommendations with Hepatic Safety Data update submitted to FDA.
21 Nov 2010	IDMC meeting: • IDMC recommended continuing the trial according to the protocol.
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: • IDMC recommended continuing the trial according to the protocol.
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: • IDMC recommended continuing the trial according to the protocol.
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.

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)[91] 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.[92]
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 × 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: • ALT or AST becomes > 3 × ULN (for subjects with a normal baseline value, elevations < 3 × ULN are common and nonspecific) • ALT or AST becomes > 2 × ULN (for subjects with an elevated baseline value).
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 × ULN may be unnecessary, ie, transient rises and falls of ALT or AST are common): • ALT or AST becomes > 8 × ULN (no rechallenge) • ALT or AST becomes > 5 × ULN for more than 2 weeks (no rechallenge) • ALT or AST becomes > 3 × ULN and BT is > 2 × ULN or INR is > 1.5 • ALT or AST becomes > 3 × 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.

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 04251-731-2738, first Hy's Law case

Subject 04251-731-2738 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, choloplania, 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.

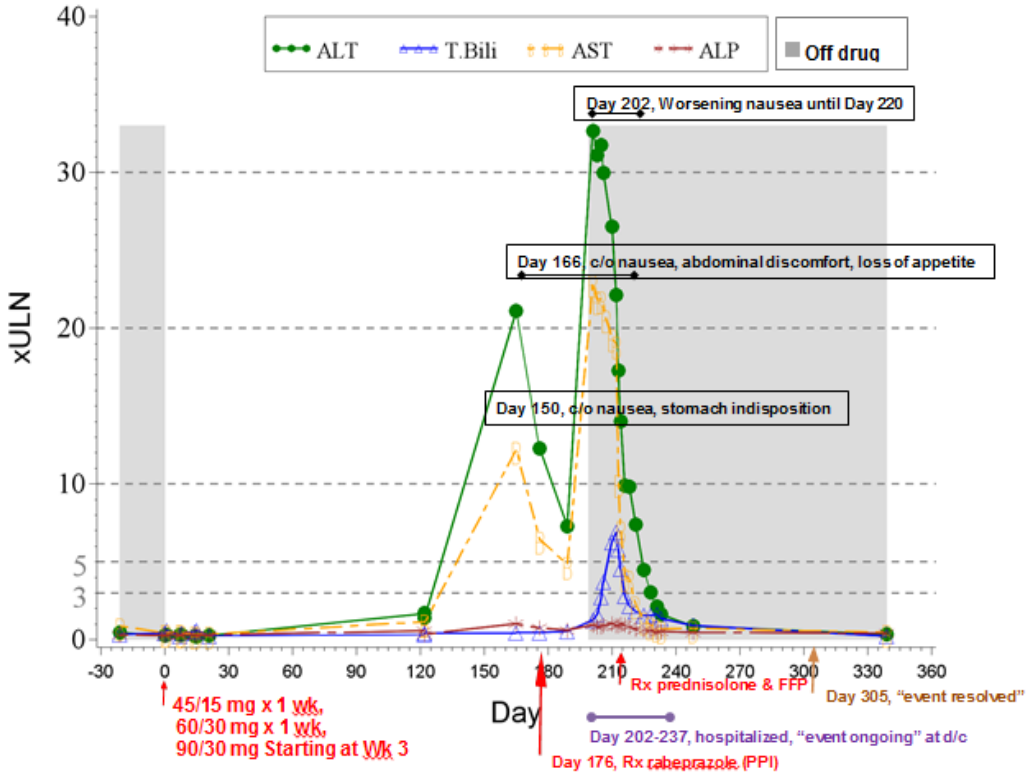
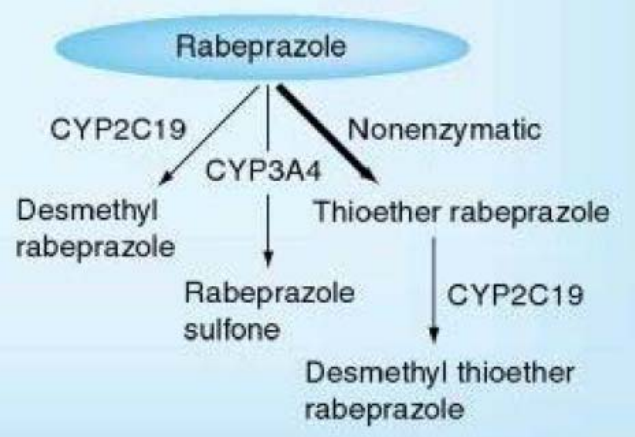


Figure 29. Subject 04251-731-2738: time course of liver tests

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:

a. Rabeprazole increased tolvaptan concentrations via p-gp.
b. Thioether rabeprazole inhibits CYP2C19, 2C9, 2D6, and 3A4. Thioether rabeprazole increased tolvaptan concentrations via CYP3A4.
c. 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.
d. 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 theioether 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 04251-302-4053, second Hy's Law case

Subject 04251-302-4053 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.

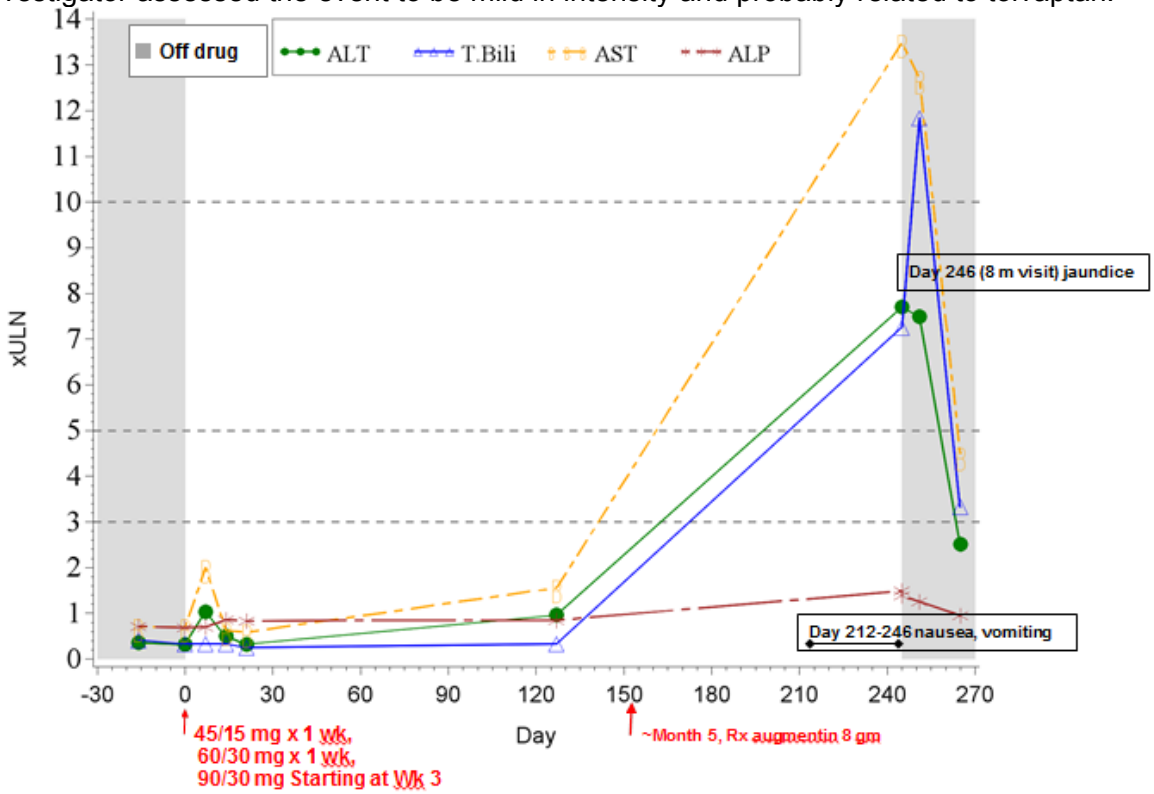


Figure 31. Subject 04251-302-4053: time course of liver tests

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 08271-468-4301, third Hy's Law case

Subject 08271-468-4301 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 the 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.

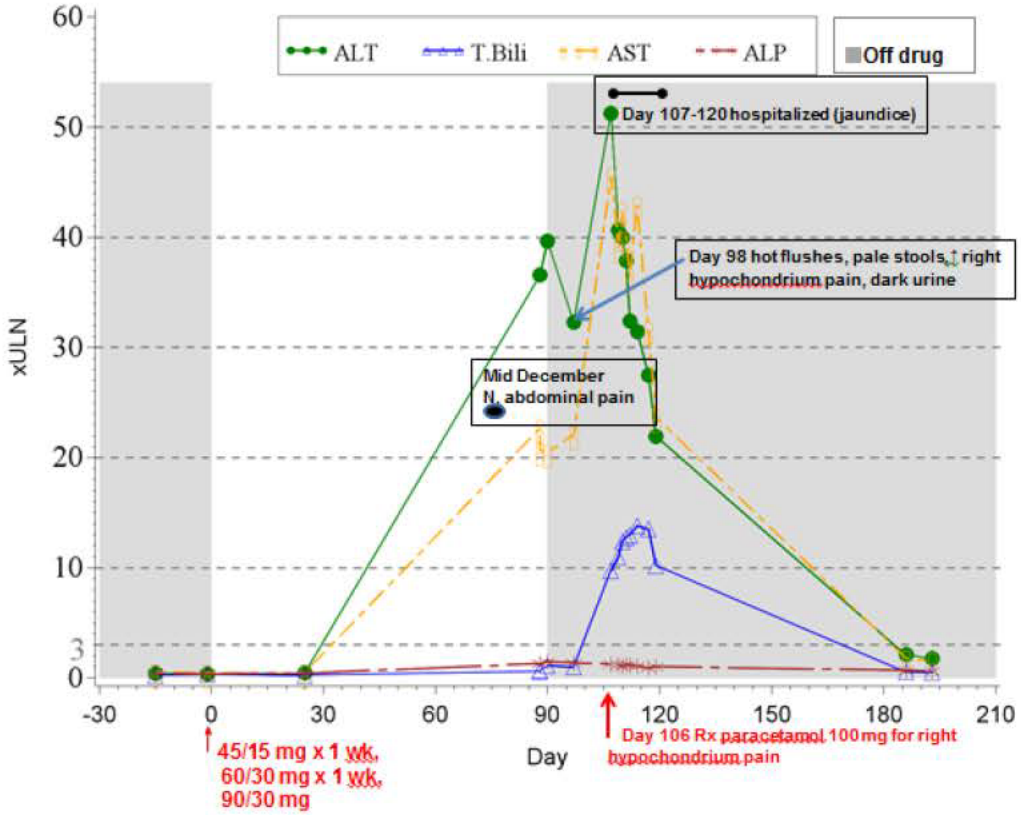


Figure 32. Subject 08271-468-4301: time course of liver tests

9.8.4 Subject 04251-727-2401, rechallenge case

This was the first hepatic serious TEAE (received 22 April 2008). Subject 04251-727-2401 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".

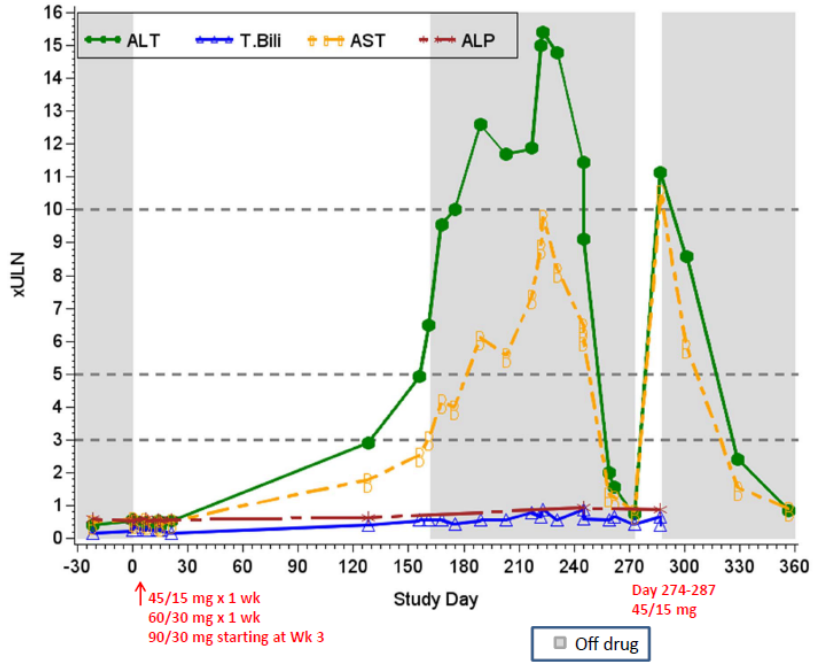


Figure 33. Subject 04251-727-2401: time course of liver tests

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 04251-104-0605, 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 mediation. The HAC states that the rechallenge confirms that the event was due to tolvaptan. Their consensus causality assessment was “probable”.

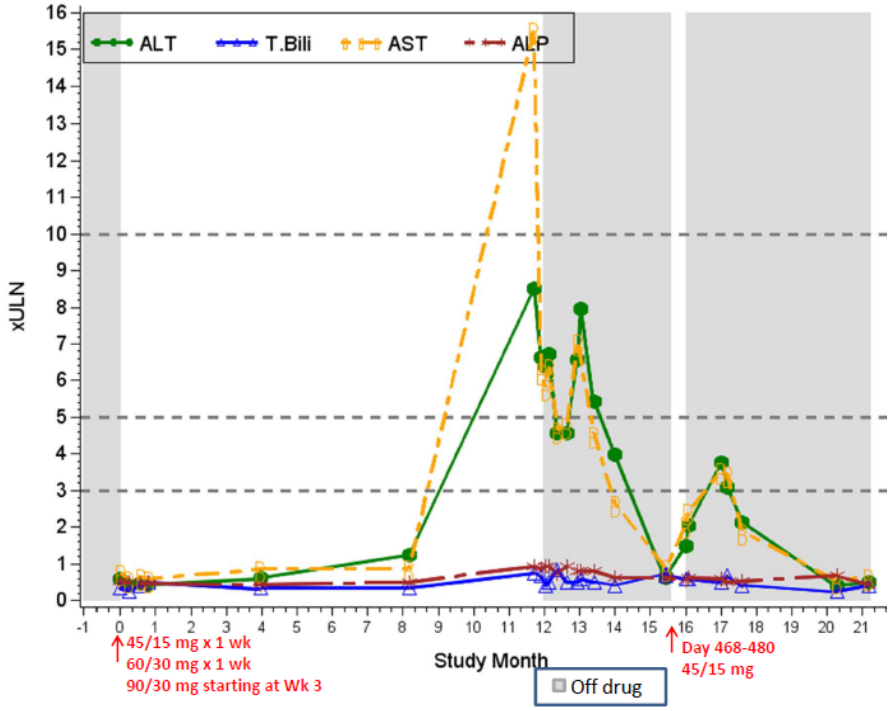


Figure 34. Subject 04251-104-0605: time course of liver tests

Reviewer’s comment: The dose and duration of the paracetamol (another likely cause of DILI) is unclear.

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/s/

ALIZA M THOMPSON
07/07/2013

BACH N BEASLEY
07/07/2013

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 204-441
Supplement #:	
Drug Name:	Tolvaptan
Indication(s):	Slow progressive kidney disease in adults with autosomal dominant polycystic kidney disease
Applicant:	Otsuka
Date(s):	11/15/2012
Review Priority:	Priority
Biometrics Division:	DBI
Statistical Reviewer:	John Lawrence, Ph D
Concurring Reviewers:	Jim Hung
Medical Division:	Cardiorenal.
Clinical Team:	Aliza Thompson MD, Nhi Beasley MD, Steven Grant, MD
Project Manager:	Anna Park

Keywords:
survival analysis, benefit-risk, mixed models, longitudinal data analysis

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EXECUTIVE SUMMARY

This submission contains one Phase 3 study to support the indication. Accordingly, the level of evidence from that trial must be equivalent to two trials with a type I error rate of 0.05 each. According to the medical division, the primary endpoint of total kidney volume is not acceptable for approval. This review focuses on the sponsor's key secondary endpoint, a composite endpoint consisting of events defined by hypertension, renal function, renal pain, and albuminuria. In addition, this review focuses on exploratory analyses of longitudinal changes in estimated kidney function (glomerular filtration rate estimated by the CKD-EPI formula).

There were several statistical issues with the analyses. There was possibly non-ignorable missing data and substantially more missing data in the tolvaptan arm compared to the placebo arm. In some analyses, the ITT population could not be used because there were no valid observations. In addition, assumptions used in the models were clearly violated (assumptions about linear responses over time and assumptions about homogeneous variance of residual errors). Tolvaptan has substantial acute effects on estimated GFR and on total kidney volume that are different than chronic effects. Therefore, simple models do not adequately fit the data.

INTRODUCTION

1.1 Overview

Table: List of all studies included in analysis

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
Study 156-04-251	*Phase 3*	*36 months*	*36 months*	*tolvaptan: 961 placebo:484*	*subjects with ADPKD as defined by a certain number of cysts, estimated creatinine clearance of at least 60 mL/min and TKV>750 mL.*

There was one Phase 3 trial conducted to support this indication. A Special Protocol Assessment was done, but the FDA did not agree with the Protocol. Since there was only one study, a type 1 error rate of 0.01 was to be used for approval decisions. This was communicated to the sponsor. The primary endpoint of TKV was never acceptable to the FDA, but the key secondary endpoint was an acceptable endpoint.

The meeting minutes from a face to face meeting between the FDA and the sponsor on June 10, 2009 state:

"2) We propose that a significance level of 0.0491 (two-sided) will be used to declare statistical significance at the final analysis for the primary endpoint. In addition, we propose that a significance level of 0.05 (two-sided) will be used to declare statistical significance at the final analysis for the key secondary composite endpoint. In a Type A meeting with the Division on 15 Nov 2005 (minutes provided as Attachment 2), Otsuka proposed, "if the primary endpoint and composite key secondary endpoint are both statistically significant, and if the other specified endpoints are supportive, the data from this single phase 3 trial will be sufficient to support a New Drug Application (NDA) approval for the proposed indication." The Division agreed to Otsuka's proposal. **Does the FDA agree that the significance levels specified in the draft SAP are acceptable for approval based on a single pivotal trial?**
Preliminary FDA Response: A p-value < 0.05 from a single trial is acceptable for your primary efficacy endpoint because we do not consider this endpoint a surrogate of benefit. In order to provide convincing evidence of treatment benefit, the composite key secondary endpoint will need a p-value < 0.01.
Additional discussion during the meeting: The sponsor has decided to continue their study as proposed and is aware the Division will likely review the results in a more stringent fashion. Dr. Stockbridge reiterated that the Division was less interested in the primary endpoint as compared to the secondary endpoints. The Division acknowledged the sponsor's decision."

However, the FDA defines a primary endpoint in its guidance document as "Endpoint(s) necessary and/or sufficient to establish efficacy" (not published as of this date, but that definition appears in the slide presentation here: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/03/WC50

0140627.pdf). Since TKV was not necessary or sufficient to establish efficacy, then by the FDA guidance document's definition, it was not a primary endpoint. Even if you don't rely on the definition from the guidance document (which is fair since it is not even published now), it is clear from the minutes above that the FDA told the sponsor that TKV could not be the primary endpoint of the trial. Despite multiple attempts to explain to the sponsor that TKV was not a primary endpoint, the company insisted on calling it the primary endpoint and the FDA was powerless to stop them. In these same meeting minutes, they discuss a plan to stop the trial early at an interim analysis if a benefit was shown on TKV (this adjustment for the interim analysis is the reason for the significance level of 0.0491). This illustrates the difference between how much importance the FDA put on TKV compared to the how much the company put; the company intended to stop the trial early and claim victory if a benefit was shown on TKV while the FDA was telling them they had no interest in TKV.

1.2 Data Sources

Electronic datasets and Study Reports:

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\\cdsesub1\evsprod\NDA204441\0001\m5\datasets\156-04-251\analysis

STATISTICAL EVALUATION

1.3 Data and Analysis Quality

The data quality and analysis quality were both poor.

Many (several thousand) serum creatinine measurements were not included in the sponsor's analysis. There were many subjects that were not included in the sponsor's analysis at all. Other subjects had partial data. Subjects with some missing data is common in clinical trials, but the amount of missing or unreliable data in this trial is uncommon (compared to other trials of cardiovascular or renal disease). In many cases, subjects were not followed at all, or only for a short time if they stopped treatment early. A true intent-to-treat analysis should follow all subjects for all outcomes for the entire planned period (36 months). This was not done here. Baseline for changes in serum creatinine or eGFR was defined as the measurement after titration. This caused many subjects to be excluded from the analysis completely if they could not tolerate the drug during the titration phase. It is very uncommon to define a baseline value so long after randomization (approximately 3 weeks). If all the subjects are still in the trial at that time, there is less of a concern, but that was not the case here.

The sponsor's analysis used assumptions that in some cases can be demonstrated to be false and in other cases could not be verified. The mixed effects models include an assumption that the

residual error variance is homogeneous and that those errors are normally distributed. For the TKV endpoint (after log transformation) and for the eGFR endpoint, both of these assumptions can be shown false using the data. In addition, the sponsor's analyses used simple linear response models. For both endpoints, those models were not adequate and that can be shown with the data. Furthermore, these models use other assumptions about the distribution of random effects and the nature of missing data (missing at random) that cannot be verified. Lastly, the analysis of recurrent events uses assumptions in the estimate of the variance that may exaggerate the significance of the p-value for that analysis (see Section 1.4.4).

1.4 Evaluation of Efficacy

1.4.1 Study Design and Endpoints

Study 156-04-251was a multinational, multicenter trial. 1445 subjects were randomized 2:1 to tolvaptan or placebo. The primary endpoint was change in TKV (total kidney volume) over time. TKV was measured at baseline and every 12 months up to month 36 by MRI. The key secondary endpoint was a composite of clinically relevant outcomes. The composite consisted of four types of events: hypertensive progression (change in category or addition of hypertension medication); renal pain; worsening of albuminuria; worsening of renal function (confirmed rise of 33% in serum creatinine). The composite endpoint was counted with recurrence possible, i.e. not just the first event for each subject, but rather multiple events for each subject were possible and all were counted. Change in renal function (inverse of serum creatinine and other estimates of creatinine clearance or GFR) were also secondary or exploratory endpoints.

1.4.2 Statistical Methodologies

The primary endpoint, TKV, was analyzed using a mixed effects model. First, the TKV was transformed using the base 10 logarithm. Time was measured in years from the time of the first (baseline) TKV (number of days divided by 365.25) and was included as a continuous variable in the model.

The following linear mixed-effect model was fitted to the log-transformed TKV repeated-measures data:

$$Y_{ij} = \beta_1 + \beta_2\, t_{ij} + \beta_3\, Group_i + \beta_4\, t_{ij} \times Group_i + b_{1i} + b_{2i}\, t_{ij} + e_{ij},$$

In this model, Y_{ij} is the $\log_{10}$ (TKV) of subject i at visit j (j = 0, 1, 2, 3), where $Group_i = 0$ for a subject in the placebo group and $Group_i = 1$ for a subject in the tolvaptan group. β_1, β_2, β_3, and β_4 are fixed effects (β_1 is the intercept of placebo, $\beta_1 + \beta_3$ is the intercept of tolvaptan, β_2 is the slope of placebo, and $\beta_2 + \beta_4$ is the slope of tolvaptan), while b_{1i} and b_{2i} are random effects assumed to be normally distributed with mean 0 and unknown

variance covariance structure. The error terms in the model, e_{ij}, are assumed mutually independent and normally distributed as $N(0,\sigma^2)$, and they are also assumed to be independent of the random effects. The primary null hypothesis is H_0: $\beta_4 = 0$ versus the alternative hypothesis H_1: $\beta_4 \neq 0$.

The key secondary endpoint was analyzed using the Anderson-Gill recurrent events model. No covariates were included other than treatment group. Subjects were censored at the last censoring time for all components and were considered to have no events of the type without follow-up at those times where unknown.

1.4.3 Patient Disposition, Demographic and Baseline Characteristics

The patient disposition are shown in Table 1. Significantly more subjects discontinued in the tolvaptan arm. the bottom row shows some of the subjects who discontinued were followed for some PKD outcomes, but that means a phone call in many cases and is not the same as complete follow-up on all outcomes. Figure 1 shows that the proportion of subjects in the tolvaptan arm who discontinued was larger than the proportion in the placebo arm uniformly throughout the trial.

Number of Subjects	**Tolvaptan (N = 961) n (%)**	**Placebo (N = 484) n (%)**	**Total (N = 1445) n (%)**
Screened	-	-	2122
Randomized	961 (100.0)	484 (100.0)	1445 (100.0)
Treated	961 (100.0)	483 (99.8)	1444 (99.9)
Completed	740 (77.0)[a]	417 (86.2)[b]	1157 (80.1)
Discontinued IMP	221 (23.0)	67 (13.8)	288 (19.9)
Lost to follow-up	15 (1.6)	8 (1.7)	23 (1.6)
AE	148 (15.4)	24 (5.0)	172 (11.9)
Subject met withdrawal criteria	4 (0.4)[c]	0 (0.0)	4 (0.3)
Investigator withdrew subject	3 (0.3)	4 (0.8)	7 (0.5)
Subject withdrew consent	50 (5.2)	30 (6.2)	80 (5.5)
Protocol deviation	1 (0.1)[d]	1 (0.2)[d]	2 (0.1)
Discontinued and followed for PKD Outcomes	102 (10.6)	27 (5.6)	129 (8.9)

Table 1 Patient disposition (Table 8.1-1 of Study Report)

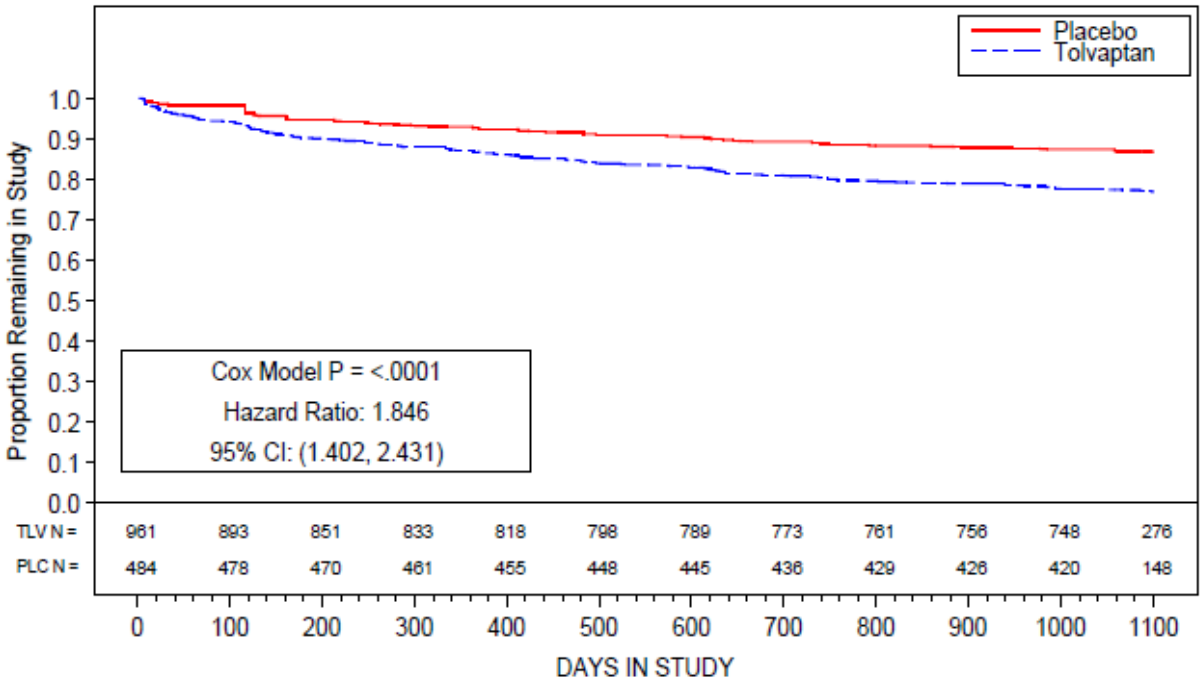

Figure 1 Kaplan-Meier plot of time to discontinuation for all reasons (Figure 8.1-1 of Study Report).

The distribution of the number of reliable eGFR measurements per subject used in the sponsor's analysis by treatment arm is shown in Table 2. In this table, only subjects and measurements used in the sponsor's longitudinal eGFR analysis (Table 9.5.1.1-1 in the Study Report) are included. This includes measurements from end of titration through month 36 for subjects with at least 4 months of follow-up and at least 2 measurements and only counting measurements labeled as reliable. There are only 10 possible visits: End of titration/week 3, Months 4, 8, 12, 16, 20, 24, 28, 32, 36. However, a few subjects had two measurements that fell within a single visit window and both measurements were included. One subject had 11 measurements included in this analysis because they had two measurements in the Month 24 window and one measurement at every other possible visit. Figure 2 shows the cumulative distribution plot of time to last eGFR used in the sponsor's analysis. It can be seen that a relatively high proportion of subjects in the tolvaptan arm were not used in the analysis at all. More than 10% of the subjects in the tolvaptan arm were not included at all and more than 20% had no measurements beyond 1 year from randomization. Table 3 shows the distribution of number of eGFR measurements. The difference between this and the previous table is that it includes measurements labeled unreliable, subjects with less than 4 months follow-up, off-treatment measurements, and measurements from subjects with only one valid measurement. Of note, the sponsor's analysis used 11,785 measurements from 1306 subjects while there were 16,197 measurements from 1445 subjects in the full dataset. If every patient randomized had 13 measurements, there would have been 18,785 measurements.

Number of observations	Tolvaptan n (%)	Placebo n (%)	Total
2	33 (4)	9 (2)	42 (3)
3	23 (3)	7 (2)	30 (2)
4	19 (2)	7 (2)	26 (2)
5	19 (2)	11 (2)	30 (2)
6	15 (2)	12 (3)	27 (2)
7	16 (2)	4 (1)	20 (2)
8	27 (3)	20 (4)	47 (4)
9	105 (12)	57 (12)	162 (12)
10	584 (69)	337 (73)	921 (71)
11	1 (0)	0	1 (0)

Table 2 Distribution of number of eGFR measurements per subject used in sponsor's analysis.

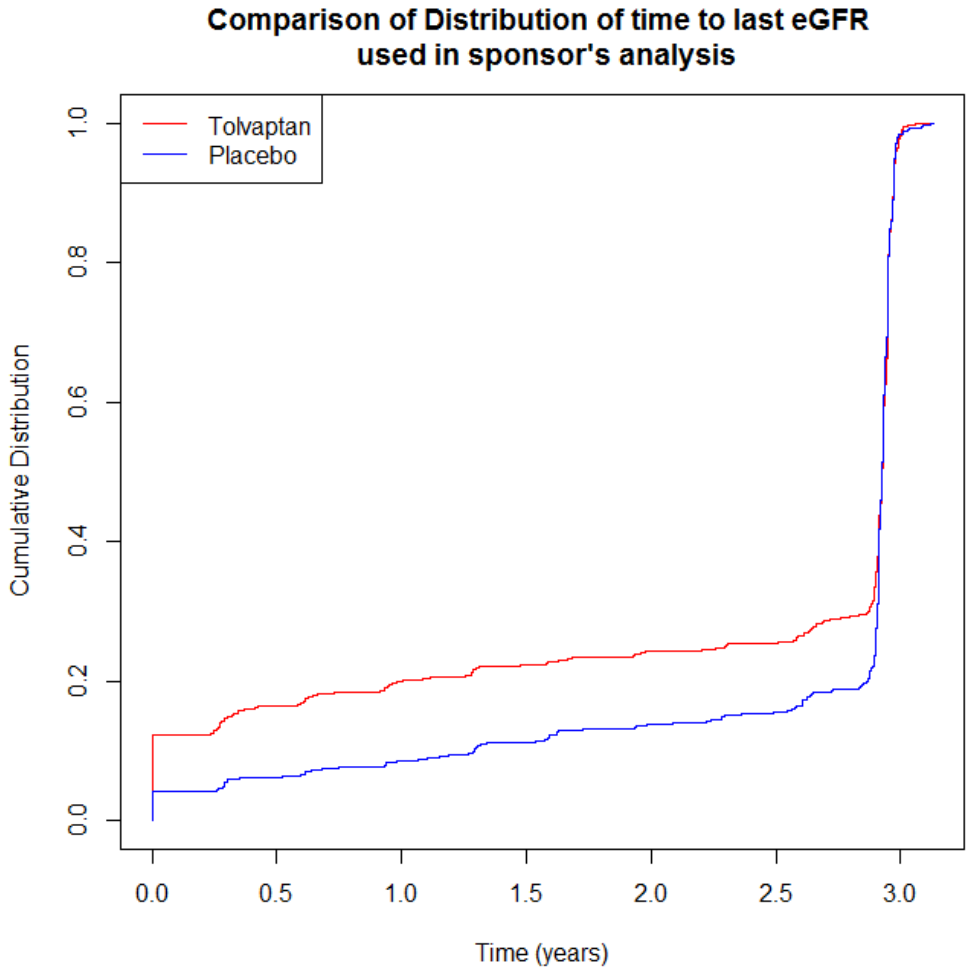

Figure 2 Kaplan-Meier plot of time to last eGFR measurement used in sponsor's analysis (Source: FDA)

Number of observations	Tolvaptan n (%)	Placebo n (%)	Total
1	7 (1)	3 (1)	10 (1)
2	45 (5)	5 (1)	50 (3)
3	56 (6)	5 (1)	61 (4)
4	23 (2)	10 (2)	33 (2)
5	19 (2)	8 (2)	27 (2)
6	22 (2)	9 (2)	31 (2)
7	13 (1)	9 (2)	22 (2)
8	13 (1)	9 (2)	22 (2)
9	7 (1)	4 (1)	11 (1)
10	13 (1)	4 (1)	17 (1)
11	23 (2)	19 (4)	42 (3)
12	110 (11)	49 (10)	159 (11)
13	609 (63)	349 (72)	958 (66)
14	1 (0)	1 (0)	2 (0)

Table 3 Distribution of number of eGFR measurements per subject actually measured.

The patient demographic characteristics are shown in Tables 2 and 3. The demographics were comparable between the two groups.

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

Table 4 Patient demographic characteristics (Table 8.2-1 of Study Report)

Parameter	Tolvaptan (N = 961)	Placebo (N = 484)	Total (N = 1445)
1/serum creatinine ([mg/mL]$^{-1}$)			
Number of subjects	958	482	1440
Mean	102.27	104.30	102.95
SD	27.21	33.87	29.61
Median	100.00	100.00	100.00
Minimum	43.7	35.5	35.5
Maximum	263.2	500.0	500.0
$eGFR_{CKD-EPI}$ (mL/min/1.73 m^2)			
Number of subjects	958	482	1440
Mean	81.35	82.14	81.61
SD	21.02	22.73	21.60
Median	80.76	80.40	80.74
Minimum	32.3	26.4	26.4
Maximum	132.8	186.7	186.7
TKV (mL)			
Number of subjects	961	483	1444
Mean	1704.8	1667.5	1692.3
SD	921.27	873.11	905.31
Median	1456.7	1468.5	1458.8
Minimum	750.0	751.1	750.0
Maximum	7555.4	6751.1	7555.4

Table 5 Patient demographic characteristics (Table and 8.2-3 of Study Report)

1.4.4 Results and Conclusions

The drug had an effect on the primary endpoint, TKV. The effect is not linear over time, but rather there is a large initial drop in TKV in the tolvaptan arm and that difference is maintained for up to 3 years.

The sponsor used the log-transformation in their words, "to reduce heterogeneity in variance and achieve linearity over time" (Study Report). The residual variance was approximately homogeneous (see Figure 3). They were not normally distributed (skewness 2.22, excess kurtosis 6.3). In addition, $\log_{10}$(TKV) was not linear over time. One simple way to see this is to include a second degree term for time in the model (two extra fixed effects, one for each treatment group). When I did that, the log-likelihood improved by about 300 (note that an improvement of 3 in the log-likelihood with two extra parameters would be a significant improvement) and the AIC improved by almost 600.

As in the sponsor's eGFR analysis, their analysis of TKV did not include all the subjects. All 1445 subjects randomized had a baseline TKV measurement, but only 1277 were included in the sponsor's analysis.

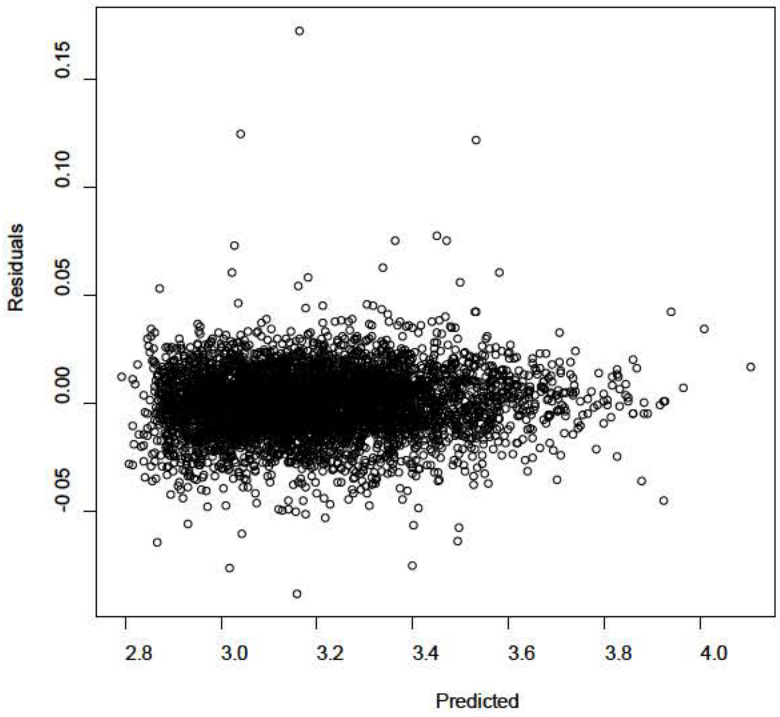

Figure 3 Scatterplot of residuals versus predicted log(TKV) from sponsor's model.

Like I did with the longitudinal change in eGFR, I tried fitting a model with an acute effect and a chronic effect on $\log_{10}$(TKV) and I included a quadratic function of time. I used all TKV measurements in the dataset. My estimated parameters were:

Intercept	3.18
time	0.0158
time^2	0.00258
acute treatment effect	-0.0223
chronic treatment*time interaction	-0.00433

Treatment*time^2 was not included because it did not improve the fit. The estimated standard deviations were: random intercept = 0.194, random slope = 0.0183, residual error = 0.0180. The estimated correlation between the random effects was 0.23.

According to the Study Report, the study was designed based on an assumption of a 7% annual increase in the placebo arm (this model actually estimates 10^(0.0158+0.00258)=1.043, or a 4.3% rate of increase in the placebo group during the first year. The sponsor's analysis estimates a mean increase of 5.6% in the placebo group. Either way, the rate of growth was slower than expected. Also, the study design assumed a standard deviation of 0.017 for the residual error and

a standard deviation of 0.0184 for the random effect of slope (on the $\log_{10}$ scale). Those values turned out to be almost exactly what the estimates are for those parameters in the FDA model.

Figure 4 shows the mean of observed $\log_{10}$(TKV) at each visit, as well as the predictions from the sponsor's model and the FDA model. I transformed everything back to the original scale of TKV by using the exponential function. There is one point for each treatment group at each of four visits. The x-coordinate is at the mean of the times when the observations happened and the y-coordinate is the geometric mean of the observations. The acute effect in the blue curve It looks in the figure like the solid blue curve doesn't fit the points as well as it could, but that's OK because what the mixed effects model is doing is more complicated than just trying to come close to these group means.

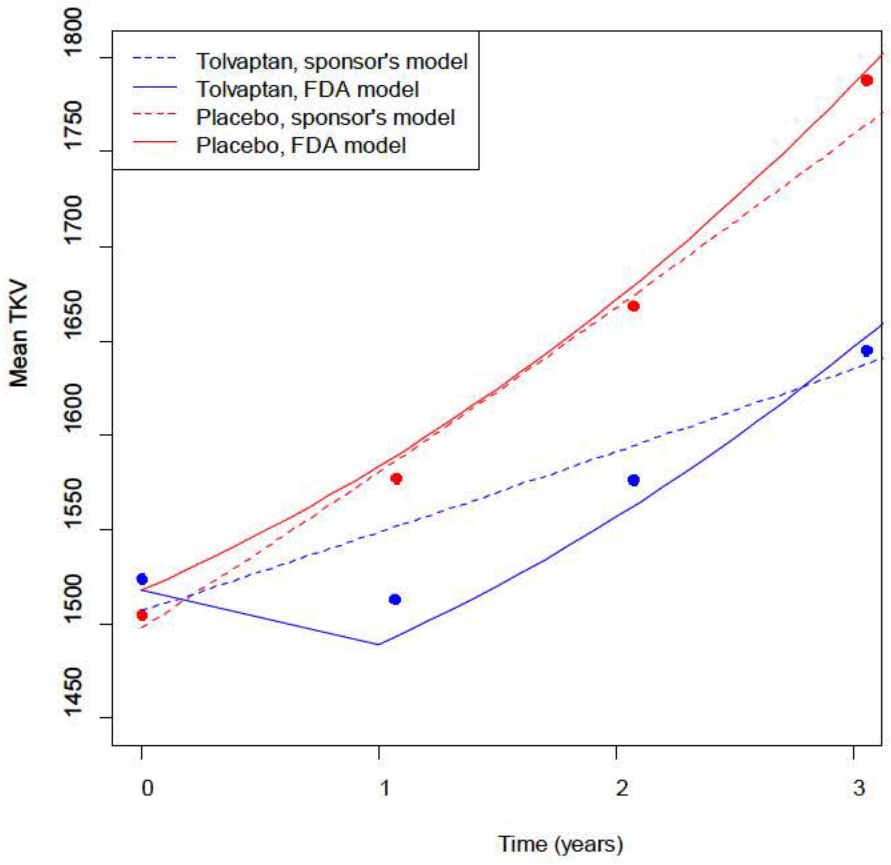

Figure 4 Mean observed and predicted TKV over time.

The trial did not confirm the drug has an effect on the key composite endpoint at a significance level of 0.01. The sponsor's analysis used the Anderson-Gill method for recurrent events. The sponsor's results were a hazard ratio estimate of 0.865 and p-value of 0.0095 using the

investigator reported events. I found the same total number of events (1049 vs. 665) in each group when I tried to repeat the sponsor's analysis and I found the same total number of years of follow-up in both groups (2387 vs. 1329). However, my estimates and p-values were slightly different (hazard ratio of 0.860 and p-value of 0.010).

The statistical issues with this analysis are three-fold. Missing data and ITT analysis, post-randomization baseline used for creatinine component, standard error is estimated under the alternative.

There were more subjects with missing values in the tolvaptan group, as discussed for other endpoints. The way that censoring was done in the sponsor's analysis used the last censoring time for all events, i.e. if there was follow-up on any of the four events, then the subject was not censored for the composite. Handling censoring for a composite endpoint with different censoring times for the components is not straightforward. The sponsor's sensitivity analyses are taken from the Study Report p. 208:

"

In response to a regulatory request to examine the effect of partial missing data on the result of the SAP-defined primary analysis of the key secondary composite endpoint, subjects could only contribute to the treatment group denominator at the last visit where an event occurred or where all 4 components were evaluated. This analysis also favored tolvaptan (HR 0.878, 95% CI 0.787 to 0.979, p = 0.0194) (CT-5.2.16.2).

...

Less restrictive ITT analyses were used to include data collected off treatment up to Month 36. Time to multiple composite ADPKD events analyses used a nonrestricted ITT approach (regardless of treatment period) using either predose baseline (CT-5.2.6.1; HR 0.874, 95% CI 0.784 to 0.974, p = 0.0147) or Week 3/EOT as baseline (CT-5.2.6.2; HR 0.889, 95% CI 0.797 to 0.992, p = 0.0354). Both of these analyses maintained statistical significance.

"

The use of post-randomization baseline for the definition of the creatinine event component and the subjects who dropped out in the first 4 months (and a much higher percentage in the tolvaptan group) complicate the interpretation of this analysis. There is no good way to handle this. It would be better to continue to collect data from subjects after they discontinue study drug. As long as I continue to see studies with a large amount of missing data, I think the best way to handle it is to put some kind of penalty in the analysis whereby subject from the placebo group with missing data are imputed with some kind of neutral or good value, but subjects from the treatment group are given a worse value. Because of the amount of missing data here, that kind of imputation will undoubtedly raise the p-value above 0.05.

Finally, the Anderson-Gill analysis uses a Wald-type estimate of the variance of the treatment effect estimate. That means, the variance is estimated under the alternative hypothesis. For a

clinical trial, when testing the null hypothesis, it is best to calculate the variance using the design-based method. That means, in part, that the variance should be estimated under the null hypothesis. I permuted the treatment assignments 10,000 times and found the variance of those 10,000 estimates. This does not fix the problems with missing data or anything else, it's only an attempt to find the correct variance of the estimate under the null hypothesis. That standard deviation was 0.0617 compared to the estimate in the sponsor's analysis of 0.0558. That may not seem like a big difference, but that is sufficient to change the p-value from $2\Phi(-2.57) \approx 0.010$ to $2\Phi\left(-2.57\frac{0.0558}{0.0617}\right) \approx 0.020$.
The remainder of this section discusses changes in eGFR using the CKD-EPI equation.

The longitudinal analysis of eGFR is complicated because of acute and chronic effects. Many interventions that have effects on creatinine have different acute and chronic effects. This was anticipated and was the reason that the study was designed to have follow-up visits off treatment. The sponsor's analysis attempted to look only at the chronic effect by eliminating the measurements before titration and the measurements off treatment as well as the measurements that were labeled unreliable. However, besides throwing away a large amount of data, the sponsor's analysis had some other drawbacks. Their model assumes that eGFR changes in a linear way over time. Also, their model assumes the residual errors are independent, normally distributed, with a homogeneous variance. The data actually show that all these assumptions are false.

In the tolvaptan arm: the mean change in the 3 week titration phase was -3.9 mL/min/1.73 m^2 and 71% of the subjects had a drop in eGFR. The mean change in the placebo arm was -0.1 mL/min/1.73 m^2 and 47% had a drop in eGFR. These means and percentages are using the observed cases and the data from baseline and end of week 3 only (not based on any model). The estimated densities of the change in eGFR during the titration phase for both groups are shown in Figure 2.

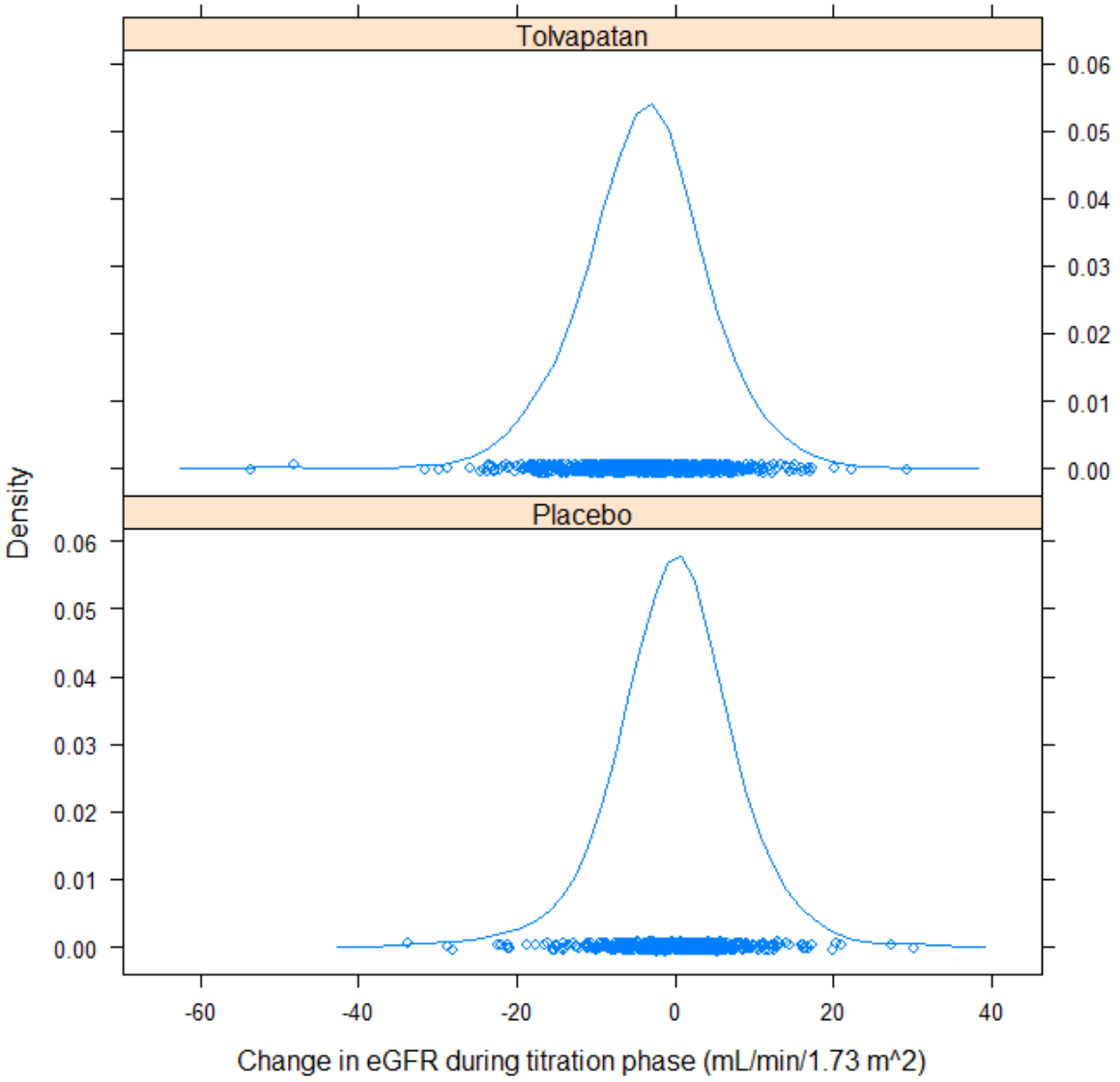

Figure 5 Estimated density of change in eGFR during initial 3 week titration period.

The sponsor's model for longitudinal changes of eGFR over time includes an intercept and terms for baseline, time, treatment group, treatment by time interaction. There are random effects within subject of intercept and time with unstructured covariance matrix. The estimates from the sponsor's model using the sponsor's data are:

Intercept	3.096
treatment	0.749
time	-3.700
baseline	0.954
treatment*time interaction	0.977

The estimated standard deviation of the random intercept is 3.227 and the estimated standard deviation of the random slope is 2.479 and their correlation is 0.663. The residual error standard deviation is 5.560.

The within subject residuals are shown in Figure 4. The red curves show the upper and lower 2.5 percentiles of the distribution as a function of the predicted value. These percentiles are estimated by quantile regression (I used the algorithm from http://www.e-publications.org/ims/submission/index.php/AOAS/user/submissionFile/4295?confirm=37ca4b7) and give some sense of whether the variance is homogeneous. In addition, one can divide the graph into 5 parts from left to right with equal number of points in each part and then calculate the sample variance of the residuals in each of the 5 sections. Doing that, I found variances (from left to right) of 11.5, 19.6, 39.9, 32.8, and 32.3. The three on the right are all significantly larger than the two on the left using the F-test for the ratio of the variances. Therefore, the variance is not homogeneous. Figure 5 shows the normal probability plot for the residuals which confirms they are not normal.

To investigate the linearity assumption, one way is to fit a more complicated model and compare the AIC and/or the likelihood ratio if the models are nested. For example, I tried a slightly more complicated model that includes a quadratic term for time and the interaction with treatment (same random effects as before). This more complicated model (with 2 additional parameters) fits the data better than the linear time model; the AIC improves by 40, minus 2*log-likelihood ratio is 44, which has a p-value of close to 10^{-10}. Also, the model using log(eGFR) as the response and replaces the covariate baseline by log(baseline) fits the data better. It is more complicated to compare these two models and it cannot be done by comparing AIC or likelihood ratios. Instead, to account for the transformation, we have to add the sum of the log(eGFR) to the likelihood in the first model to compare it with the likelihood of the second model. After accounting for the transformation of the response variable, the log-likelihood of the second model is larger by almost 71. The models have the same number of parameters and clearly the second model (using log(eGFR)) fits much better and so is the preferred model between the two.

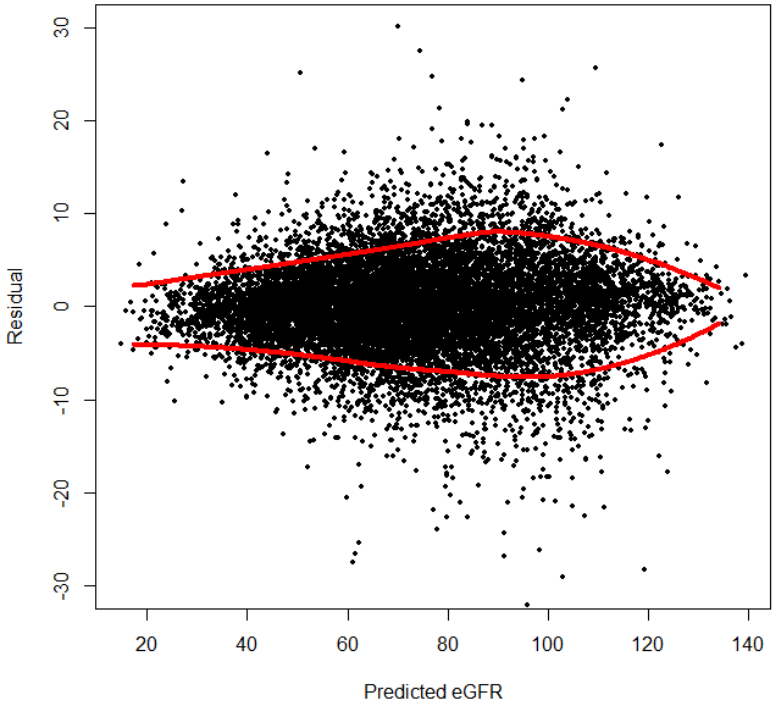

Figure 6 Residuals versus predicted scatterplot from sponsor's eGFR analysis. Red curves are the estimated upper and lower 2.5 percentiles of the distribution. 14 residuals with magnitude larger than 30 not shown.

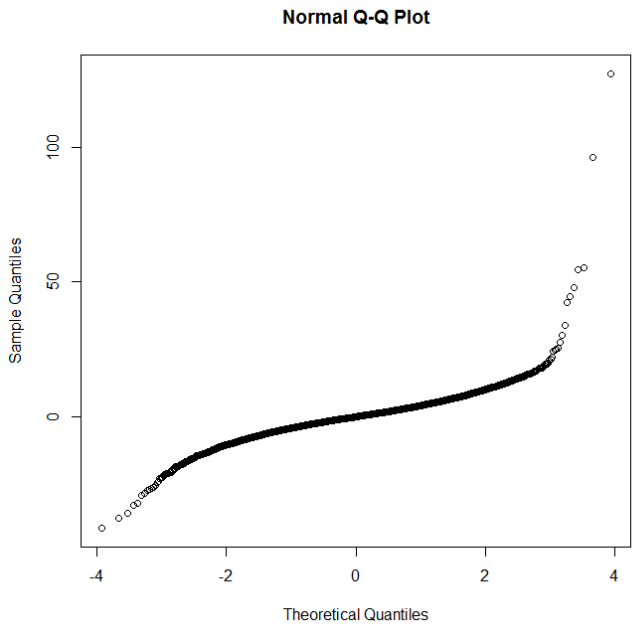

Figure 7 Normal probability plot for residuals from sponsor's eGFR model.

I tried to build a model I thought was reasonable for eGFR that: a) uses all of the measurements and b) accounts for possible acute and chronic effects. Using the log-transformation makes more sense over a long period of time if for no other reason because using a straight line without the transformation will eventually cross into the region where y is negative, but negative values of eGFR are not possible. Since using log(eGFR) fit the data used in the sponsor's analysis better than eGFR confirms this intuition, I used that as a starting point for a model. Next, I included terms for acute drop of eGFR at the start of treatment and for acute rise of eGFR after stopping treatment. Finally, I considered other covariates, but I found that only baseline eGFR (at randomization), baseline log(TKV), and age improved the fit significantly among the covariates I tried. Five people had missing baseline eGFR. Since I used baseline log(eGFR) as a covariate in the model I needed to impute values for those 5 subjects. I tried values that were the same as the subjects' observed data at a nearby timepoint and I also tried other values that were biased against any treatment effect (adding 10 to the reasonable baseline for the two placebo subjects and subtracting 10 to the reasonable baseline from the 3 tolvaptan subjects to make it appear tolvaptan was not effective). However, the estimates in the model were essentially identical in both imputations.

The estimated fixed effects coefficients are:

Intercept	0.0852
log(baseline TKV)	-0.0382
log(baseline eGFR)	0.884
age	-0.00172
time	-0.358
treatment*time interaction	0.0204
log(baseline TKV)*time	-0.0205
log(baseline eGFR)*time	0.102
acute treatment effect at start	-0.0458
acute effect of withdrawal	0.0415

The estimated standard deviation of the random intercept is 0.0882 and the estimated standard deviation of the random slope is 0.0479 and their correlation is -0.052. The residual error standard deviation is 0.0804.

The residuals from this model are shown in Figure 6. The variance looks homogeneous up to the predicted log-eGFR of about 4.5 (eGFR of about 90). The normal probability plot shown in Figure 7 demonstrates that the residuals are not normally distributed. See the appendix for more details about this model including the distribution of the residual errors and the random effects. Also, see the appendix for examples of predictions of GFR for individual subjects based on this model and future predictions for the population based on this model.

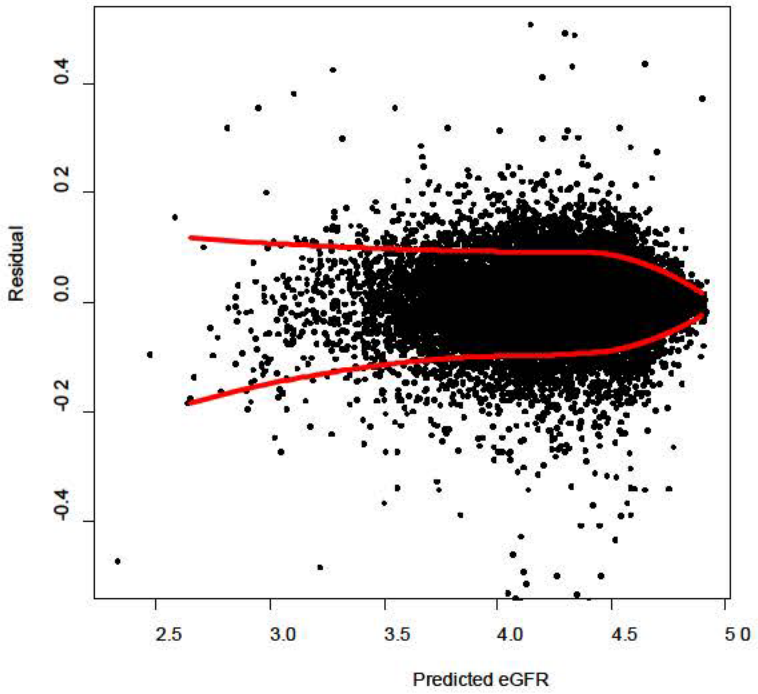

Figure 8 Residuals versus predicted scatterplot from FDA's eGFR analysis. Red curves are the estimated upper and lower 2.5 percentiles of the distribution. 19 residuals with magnitude greater than 0.5 not shown.

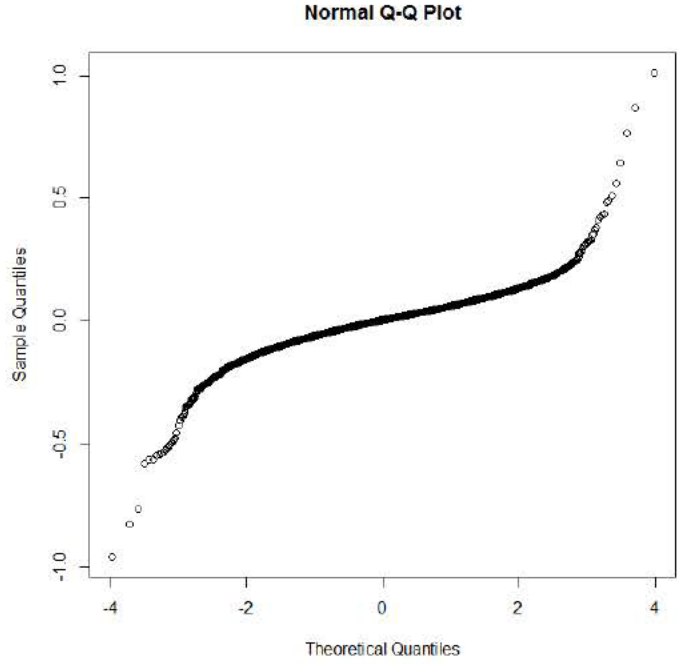

Figure 9 Normal probability plot for residuals from FDA's log-eGFR model.

1.5 Evaluation of Safety

See clinical review.

1.6 Benefit-Risk Assessment (Optional)

See clinical review.

FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

1.7 Gender, Race, Age, and Geographic Region

The sponsor's results for the key secondary endpoint are shown in Figure 8.

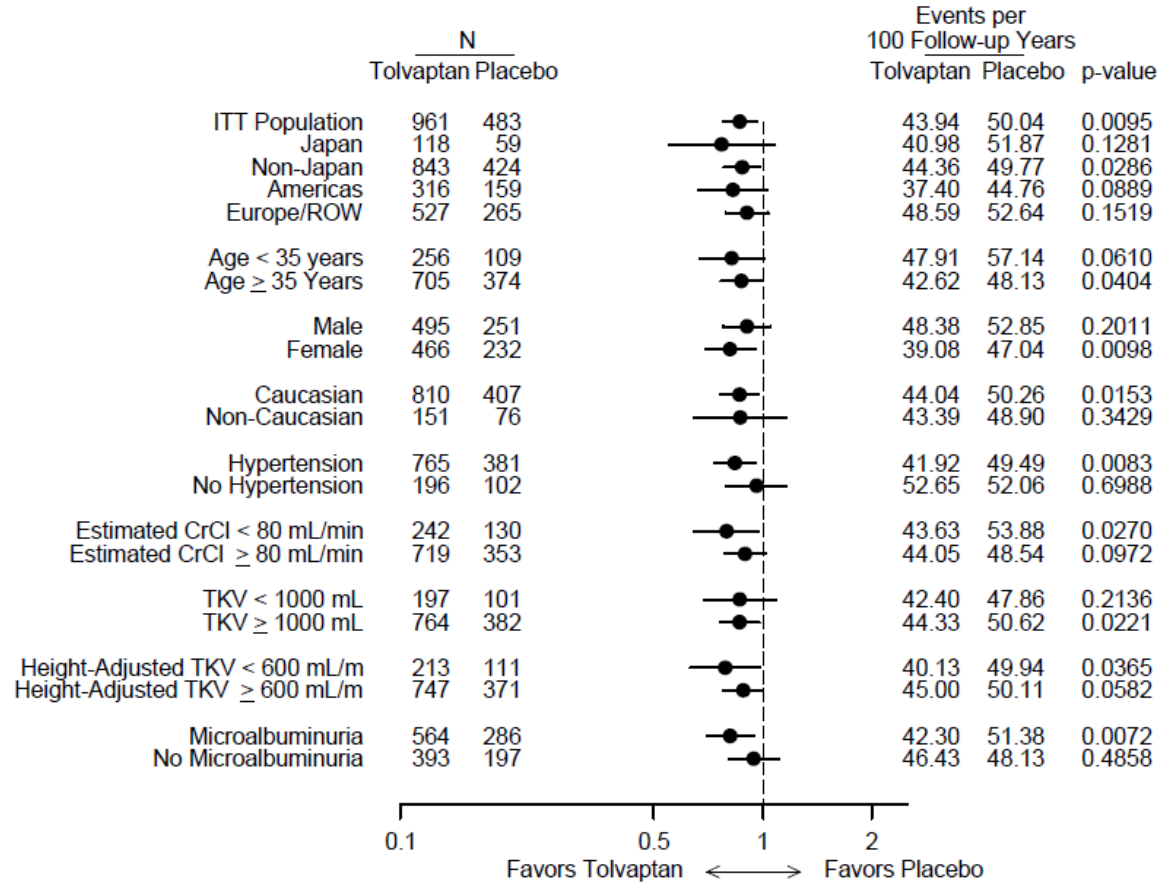

Figure 10 Sponsor's results of key secondary endpoint within subgroups (Study Report Figure 9.4.2-1)

1.8 Other Special/Subgroup Populations

About 4/5 of the subjects were taking an ACE inhibitor or ARB at randomization. The subjects taking those drugs had lower starting eGFR and higher TKV on average (76.4 vs. 89.8 mL/min/1.73 m^2 and 1598 vs. 1200 mL).

In the subgroup not taking ACEi/ARB, the average number of years of follow-up per subject were 2.12 years (tolvaptan) and 2.65 years (placebo). There were 41.0 events per 100 follow-up years (tolvaptan) and 46.6 events/100 follow-up years (placebo). The estimated hazard ratio for the key secondary endpoint was 0.82 in this subgroup.

In the subgroup taking ACEi/ARB, the average number of years of follow-up per subject were 2.57 years (tolvaptan) and 2.77 years (placebo). There were 44.5 events per 100 follow-up years (tolvaptan) and 50.7 events/100 follow-up years (placebo). The estimated hazard ratio for the key secondary endpoint was 0.86 in this subgroup.

SUMMARY AND CONCLUSIONS

1.9 Statistical Issues

The trial should have been planned with a type 1 error rate of 0.01 (two-sided) for a clinically meaningful endpoint, but was not.

Although the trial was technically blinded, the treatment assignment could have been guessed from effects on dehydration and water intake.

There were a high percentage of dropouts, particularly in the tolvaptan arm. Missing values were not imputed, but many subjects were not included at all in the sponsor's analyses. Other subjects were included with missing values but that is always raises problems, even without imputation.

Endpoints that used change in eGFR defined the baseline using a post-randomization value (post-titration) and a high percentage of subjects (particularly from the tolvaptan arm) had no post-titration value.

The analyses used assumptions that in some cases could be shown false with the data.

1.10 Collective Evidence

There was only one phase 3 trial in the submission.

1.11 Conclusions and Recommendations

The results on the clinical composite endpoint from the phase 3 trial, based on the sponsor's analysis, are just below the level they were told would be needed for approval ($p=0.0095$ when they were told they needed $p<0.01$ for approval). There is a large amount of missing data and use of a post-randomization baseline for change in eGFR. The Anderson-Gill method for recurrent events analysis estimates the variance under the alternative hypothesis. If we do nothing about the missing data or the post-randomization baseline, but just replace the variance estimate with an estimate under the null hypothesis, the p-value from the recurrent events analysis is 0.02. Other analyses by the sponsor of the eGFR and TKV endpoints have the same problems related to missing data, but also use unverified model assumptions and in some cases use assumptions that can be demonstrated to be false.

1.12 Labeling Recommendations (as applicable)

NA.

APPENDICES

Distribution of residuals from FDA model of eGFR

The normal probability plot and any test of normality (Anderson-Darling, etc.) show the residuals are not normally distributed. The skewness is 2.88 and the excess kurtosis is 13.9. The empirical cumulative distribution function is shown in Figure A1. Also, the figure shows best fitting normal and Laplace distribution with parameters estimated by maximum likelihood. Neither fits very well, but I believe the Laplace distribution fits a little better. It is not easy to fit mixed effects models outside of the common assumptions of normally distributed errors. However, I think it may still be useful as far as modeling the mean true GFR, at least within the range of the time frame of 3 years from baseline. It may or may not be a reasonable model for extrapolation beyond 3 years.

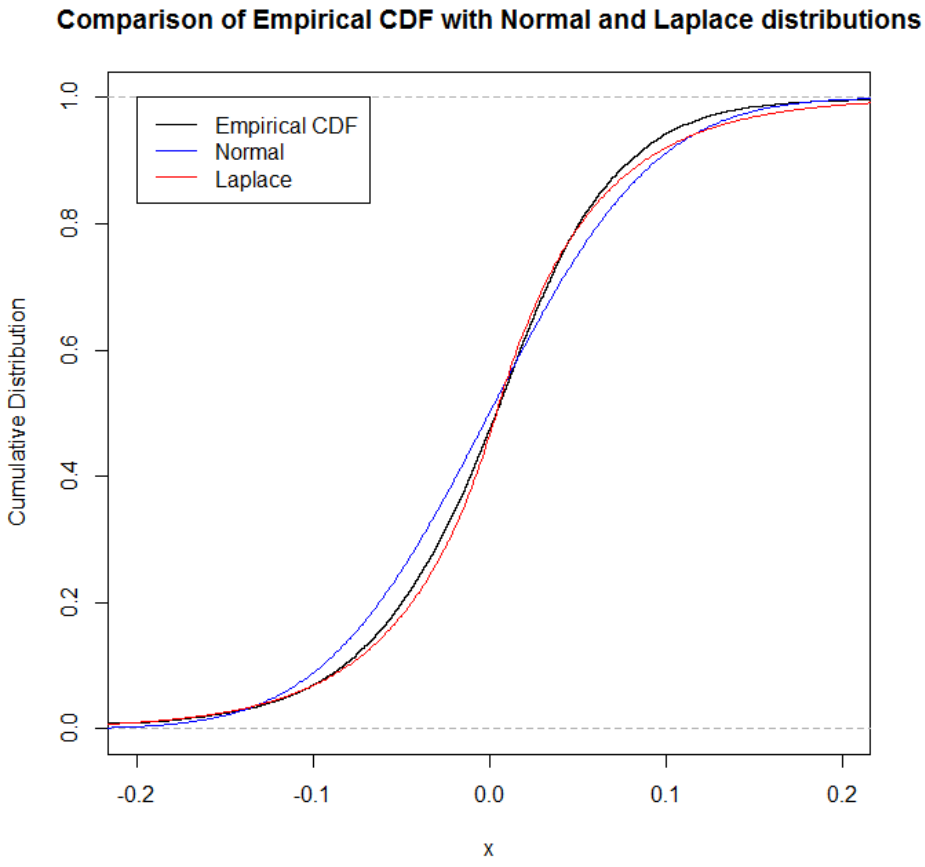

Figure A1 Comparison of Empirical CDF of within subject residuals from model described in the appendix with Normal distribution and Laplace distribution distributions with maximum likelihood estimates of parameters.

Distribution of the random effects

The estimated random effects are also not normally distributed. The scatterplot of the bivariate random effects is shown in Figure A2. Also, some of the estimated slopes are positive. The estimated slopes depend on the random effect for slope, but also on baseline TKV and eGFR. In more than 100 subjects, the estimated slope is still positive after subtracting the estimated chronic effect of treatment on the slope (the estimated slope would be positive for those subjects with no treatment). This doesn't seem to be biologically possible.

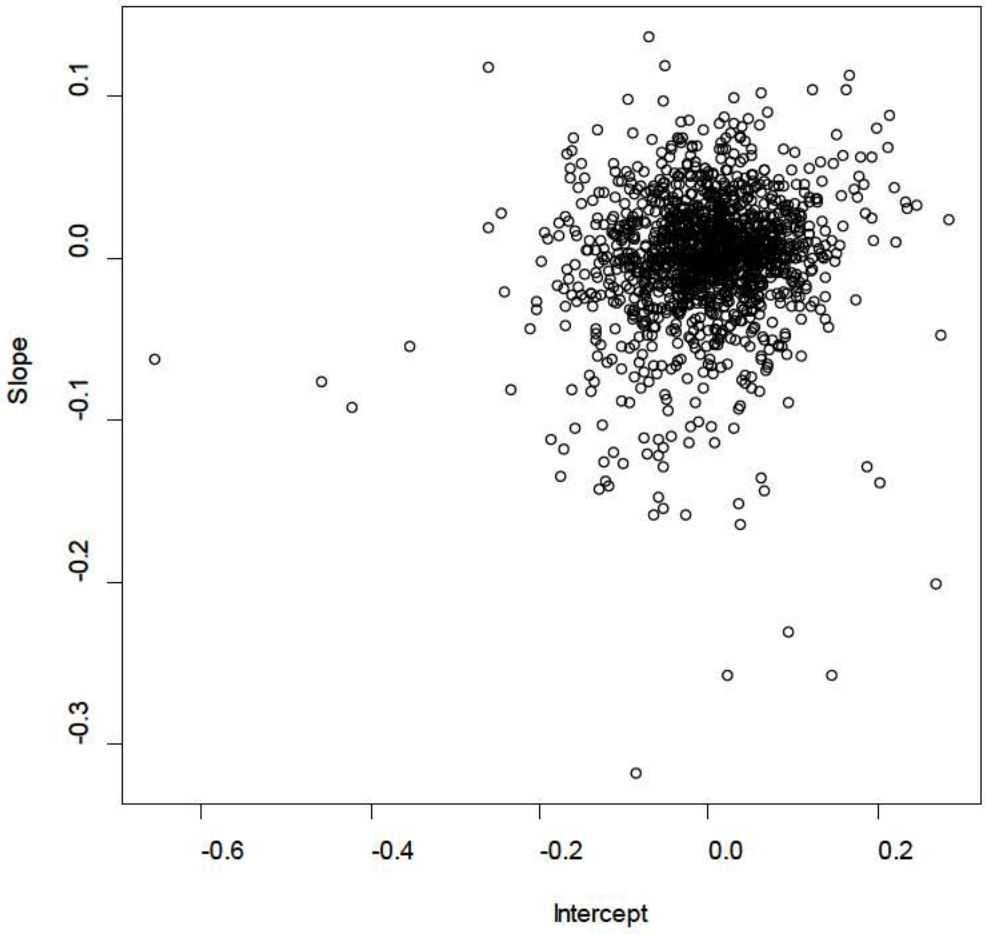

Figure A2 Scatterplot of estimated random intercept and random slope effects.

Model for eGFR between 30 and 45 mL/min/1.73 m^2

The function $f(x)$ is the log-eGFR at time x, $y_1 = \log(45)$, x_1 is the time when the log-eGFR is y_1, d_1 is the slope before reaching a eGFR of 45, $y_1 = \log(30)$, a is the acute effect of the drug withdrawal, d_2 is the slope after reaching the eGFR of 30. We want the acute treatment effect

and the chronic treatment effect to both disappear in a uniform way during the time interval between the eGFR of 30 and 45.

Problem. Suppose that x_1, y_1, d_1, y_2, a, and d_2 are given and that $f(x_1) = y_1$, $f'(x) = d_1$ for x in a neighborhood to the left of x_1. Can we define a continuous extension of f onto the interval $(x_1, x_2]$ for some $x_2 > x_1$ such that the following two conditions hold: i) $f(x_2) = y_2$, and ii) $f'(x) = d_1 + (x - x_1)\frac{d_2 - d_1}{x_2 - x_1} + \frac{a}{x_2 - x_1}$ for all $x \epsilon (x_1, x_2)$?

Solution. By taking the anti-derivative of both sides of the equation in the second condition, we find

$$f(x) = c_0 + \left(\frac{a - d_2 x_1 + d_1 x_2}{x_2 - x_1}\right)x + \left(\frac{d_2 - d_1}{x_2 - x_1}\right)\frac{1}{2}x^2$$

Now, use the conditions $f(x_1) = y_1$ and $f(x_2) = y_2$ and solve those two equations simultaneously for the two unknowns c_0 and x_2 to find

$$x_2 = x_1 - \frac{2(a + y_1 - y_2)}{d_1 + d_2}$$

and

$$c_0 = \frac{(d_1 + d_2)x_1(2a + (d_1 - d_2)x_1)}{4(a + y_1 - y_2)} - d_1 x_1 + y_1$$

Examples

Start with one example from the dataset, the first subject in the dataset. This subject was 46 years old with a baseline TKV of 2343.9, baseline eGFR of 70.0 mL/min/1.73 m^2 and was randomized to tolvaptan. He completed the trial and had 13 total eGFR measured including both follow-up visits. Those two follow-up visits are included in the Figure A3 below using filled circles. There are three scenarios shown, one (in red) assumes he never took the drug, the second (in blue) is where tolvaptan is assumed to always have the same effect. In those first two scenarios, log-eGFR after baseline is a straight line with a constant slope, but the slope is different in the two scenarios. The actual slopes (for log-eGFR) in those two scenarios are estimated from the mixed effects model. The third scenario is shown in brown. This follows the blue curve exactly until GFR hits 45, then uses the solution to the equation shown above for times between GFR of 45 and 30, then has a constant slope identical to the slope of the red curve (on the log scale). It can be seen that during this time period of losing drug effects, the recapture of the acute effect makes the brown curve rise above the blue curve, but later, the blue curve is on top again.

The predicted eGFR shown on the y-axis is a prediction in this sense. For log-eGFR, the prediction is the expected value of an observation at that time point assuming the model with the estimated parameters and the empirical Bayes estimate of the random effects for this subject. It is the mean and median of an observation at that time with those assumptions. I transformed this prediction to the original scale of eGFR by evaluating the exponential function at that prediction. This is no longer the expected value of an observation on the original scale, but it is the median of the distribution of those values. Other ways of handling the transformation in the prediction

may be better. As already noted, the residuals on the log-scale are not normally distributed or even symmetric, so methods based on that assumption might not be adequate.

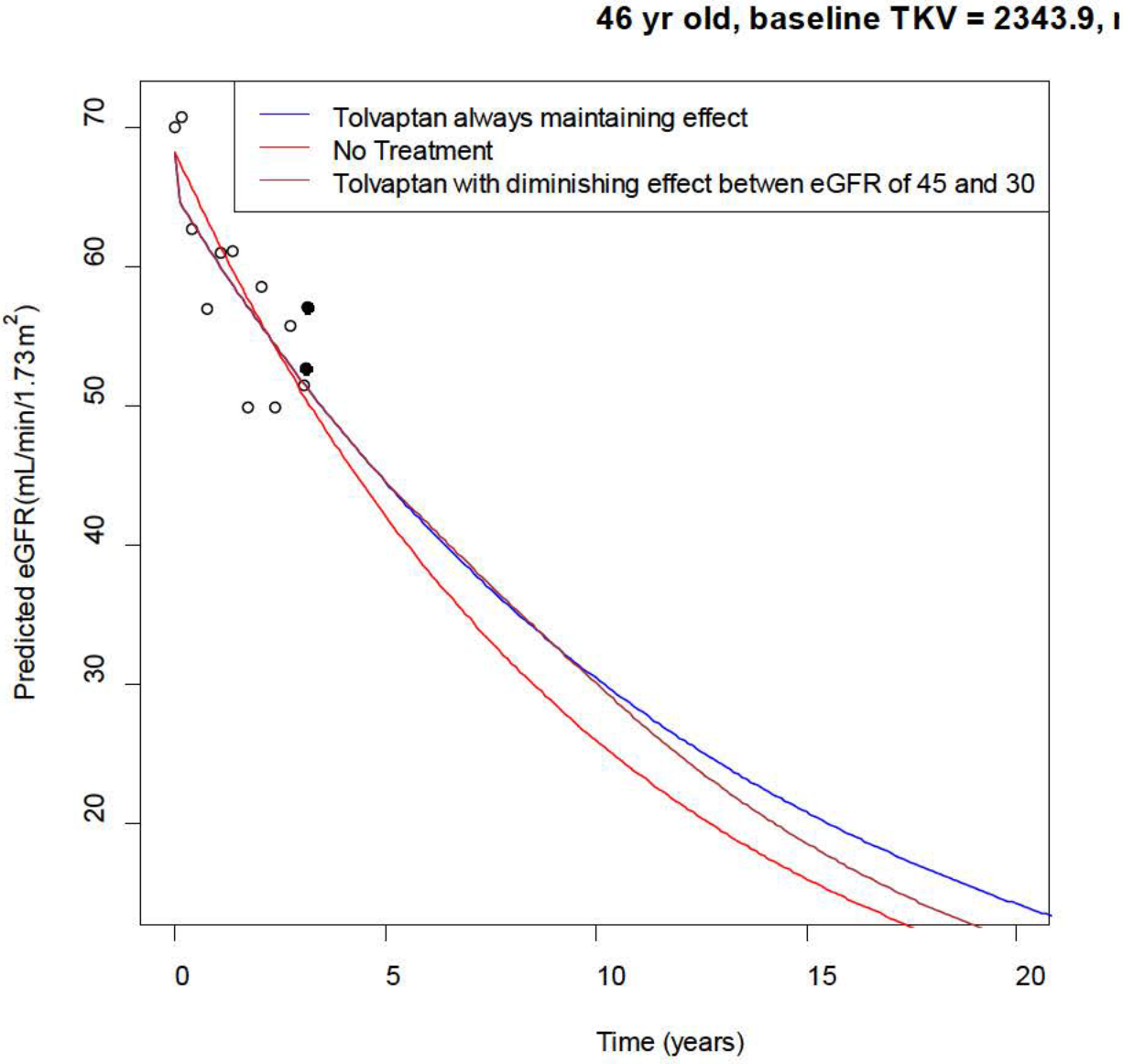

Figure A3 Predicted eGFR for one subject.

A second example from the dataset, a 20 year old subject with baseline eGFR of 88.3 and TKV of 5546.1 is shown in Figure A4. For almost the entire time shown in the figure, the brown curve is on top of the blue curve (the blue curve is there, but hidden under the brown curve). This figure shows that the model predicts an enormous benefit in terms of delaying ESRD. In fact, even reaching a GFR of 60 (CKD stage 3) is delayed by the treatment for a good 15 years in this figure. However, the figure also shows that we only have data for a short period of time. It is left

to the reader to decide how much faith to put into extrapolations of treatment effects 40 years into the future even if they are totally convinced that there is a beneficial effect on eGFR over 3 years.

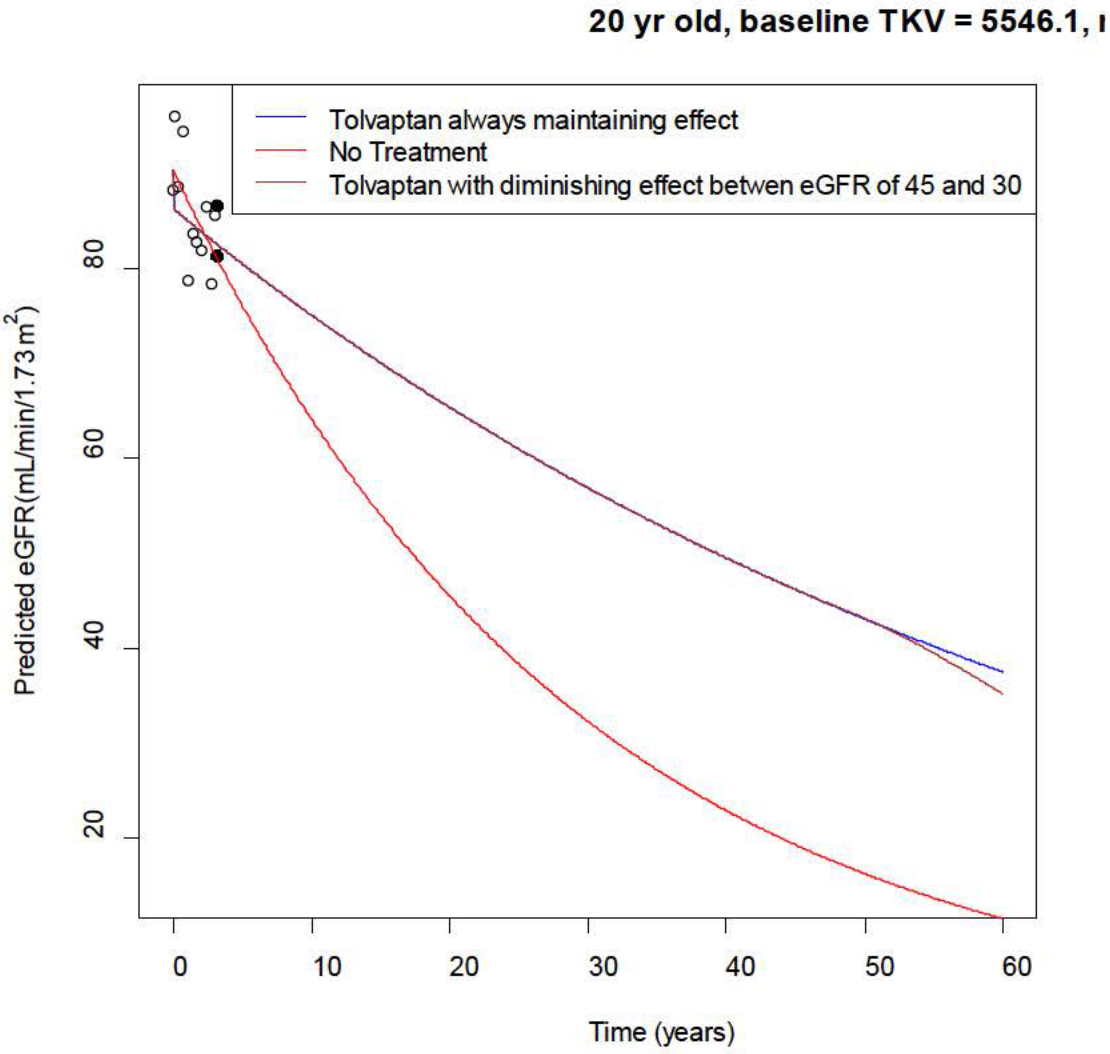

Figure A4 Predicted eGFR for one subject.

Using the model to predict into the future

Taking the subjects in the trial and using their age, baseline TKV, baseline eGFR and estimated random effects, the model allows us to extrapolate into the future and also allows us to estimate what would happen for each subject if they took tolvaptan or did not. We can then estimate for each time point in the future what proportion of subjects would have GFR<15 mL/min/1.73 m^2 and compare those proportions assuming all the subjects took tolvaptan and had that estimated

treatment effect versus not taking tolvaptan. These are big assumptions about what will happen in the future. Figure A5 shows that the treatment effect could be somewhere around a 4 year delay in the time to GFR<15 mL/min/1.73 m^2.

To be more specific, start with the estimated coefficients in the model:

Intercept	0.0852
log(baseline TKV)	-0.0382
log(baseline eGFR)	0.884
age	-0.00172
time	-0.358
treatment*time interaction	0.0204
log(baseline TKV)*time	-0.0205
log(baseline eGFR)*time	0.102
acute treatment effect at start	-0.0458
acute effect of withdrawal	0.0415

For subject *i*, let α_i and β_i be their estimated random effects. If they took no drug, the predicted log-GFR at time *t* years from randomization is:

$$\log(GFR(t)) = 0.0852+\alpha_i-0.0382 \log(\text{baseline TKV}_i) + 0.884 \log(\text{baseline eGFR}_i)-0.00172\ \text{age}_i + \{-0.358+\beta_i -0.0204 \log(\text{baseline TKV}_i) + 0.102 \log(\text{baseline eGFR}_i) \} * t$$

and their estimated time when their GFR is 15 is:

$$\tau_i = \{\log(15) - (0.0852+\alpha_i-0.0382 \log(\text{baseline TKV}_i) + 0.884 \log(\text{baseline eGFR}_i)-0.00172\ \text{age}_i)\}/\{-0.358+\beta_i -0.0204 \log(\text{baseline TKV}_i) + 0.102 \log(\text{baseline eGFR}_i)\}$$

The estimated proportion of subjects with GFR<15 at time *t* is then

$$\frac{1}{n}\sum_{i=1}^{n} I(\tau_i < t)$$

The red curve in the figure is a graph of this for *t* between 0 and 40.

The blue curve is more complicated because there is no fixed τ_i for each subject assuming they take the drug. The time to reach GFR<15 depends now on how long they take the drug, which is a random variable. I assumed the time to withdrawal had a constant hazard in the first 4 months and another different constant hazard beyond 4 months. The hazards were defined to make it so they had a 10% chance of withdrawal during the first 4 months and, if they passed that point, a 5% chance of withdrawal each year thereafter.

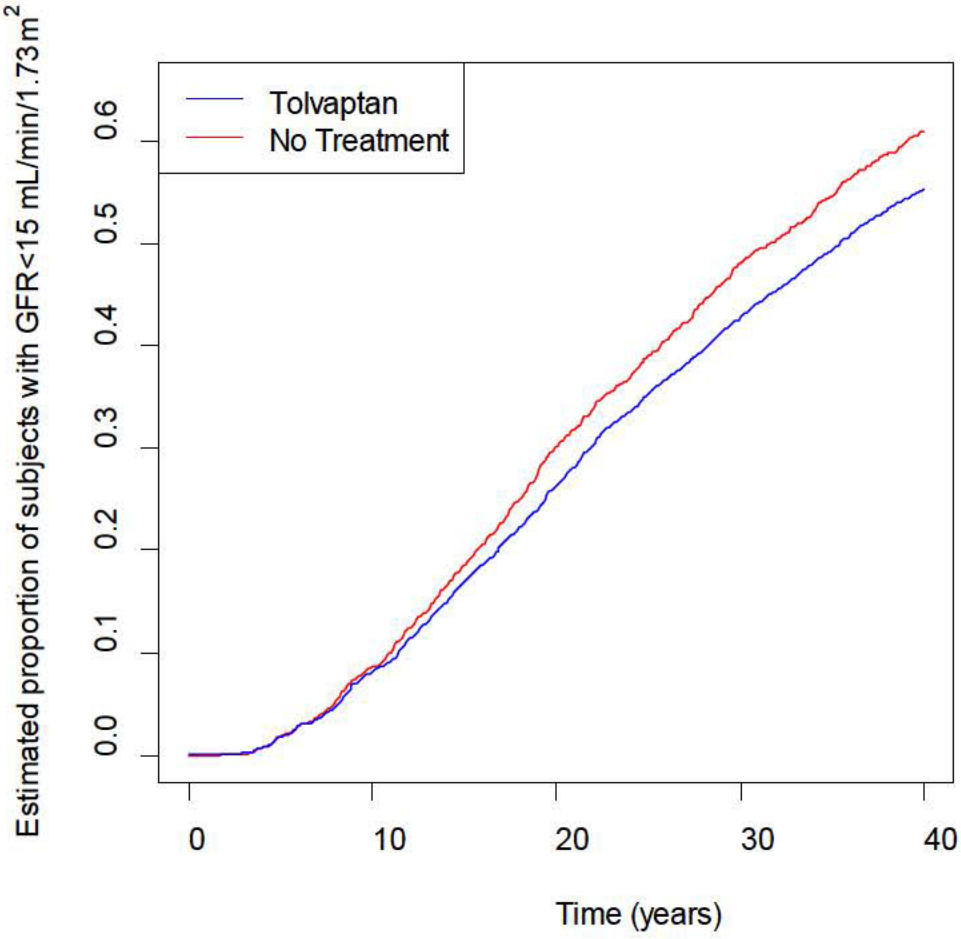

Figure A5 Estimated proportion of subjects with GFR<15 mL/min/1.73 m^2 using FDA's model and extrapolating from 3 years of data into 40 years into the future.

The next figure is based on a similar model, but assumes that after 3 years there is no treatment effect.

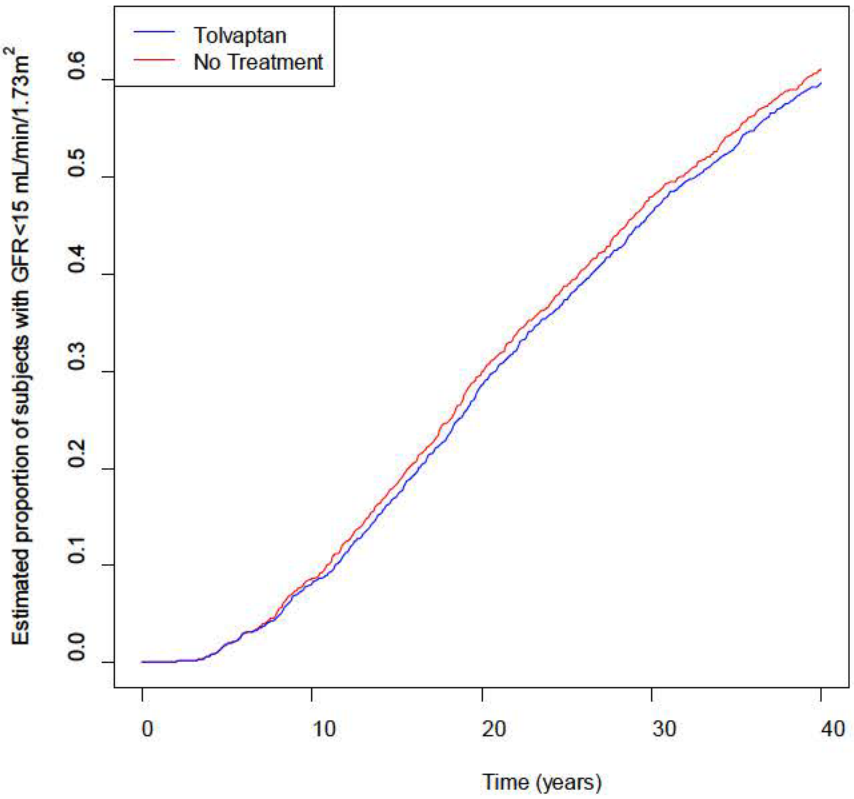

Figure A6 Estimated proportion of subjects with GFR<15 mL/min/1.73 m^2 using FDA's model, assuming no treatment effect beyond 3 years.

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/s/

JOHN P LAWRENCE
06/25/2013

HSIEN MING J HUNG
06/25/2013

GENERAL CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Brand Name	TBD
INN Name	Tolvaptan
NDA Number and Type	204,441
Applicant Name	Otsuka
Submission Date	March 1, 2013
EDR Link	\\cdsesub1\evsprod\nda204441
Indication	Treatment of ADPKD
Dosage Form & Strengths	15, 30, 60, 90 mg immediate release tablets
OCP Division	OCPI, Cardiovascular and renal products team
OND Division	ODEI, Division of cardiovascular and renal products
Reviewer	Martina Sahre, PhD
Pharmacometrics Reviewer	Fang Li, PhD
Team Leader	Rajanikanth Madabushi, PhD
Pharmacometrics Team Leader	Yaning Wang, PhD

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1 Executive Summary

Otsuka Pharmaceutical Company, Ltd., is seeking approval of tolvaptan (NDA 204441) to slow progressive kidney disease in adults with autosomal dominant polycystic kidney disease (ADPKD). There are no approved treatments for this indication. Tolvaptan is currently approved for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (NDA 022275) with the proprietary name SAMSCA®.

In support of this indication, the submission consists of 10 clinical pharmacology study reports, a single pivotal, placebo controlled efficacy (Study 156-04-251 also referred to as TEMPO) and an uncontrolled clinical efficacy trial enrolling ADPKD patients from PK/PD studies.

The pivotal efficacy trial followed a 3-week dose titration of a split dose regimen starting from 45 mg AM/15 mg PM (45/15 mg) to 90 /30 mg dose based on tolerability. Following the titration phase, the maintenance phase began at the dose level tolerated at the end of titration. The applicant states that the rate of total kidney volume (TKV) over 3 years was significantly less for tolvaptan subjects than for placebo and the occurrence of renal pain and albuminuria was significantly reduced in the tolvaptan arm. With regard to safety, there were 3 cases of Hy's Law identified in trial 156-04-251 (Study 251), two during the main trial phase and one in a patient who switched from placebo to tolvaptan active treatment in the extension phase. Increases in ALT also seem to be more common in patients treated with tolvaptan.

The clinical pharmacology program was aimed at elucidating the pharmacokinetics, pharmacodynamics and efficacy in patients with ADPKD. The applicant is seeking approval of a 90 mg strength, which is to-be-marketed based on the results of a bioequivalence study.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the clinical pharmacology and biopharmaceutics (CPB) information submitted to NDA 204441. From a clinical pharmacology perspective, the NDA is acceptable.

1.2 Identify recommended Phase 4 study commitments if the NDA is judged approvable

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

- Tolvaptan exhibits dose proportional pharmacokinetics following single dose (15 to 120 mg).

- The multiple dose study at doses of 15 mg BID, 30 mg BID, 30+15 mg split dose BID and a single 30 mg QD dose given for 5 days, likewise showed proportional increases in exposure and little accumulation at steady state.
- The to-be-marketed 90 mg formulation was demonstrated to be bioequivalent to 3x30 mg tablets in a healthy volunteer study. With a high fat meal, Cmax increased about 2-fold compared to administration in fasted state. Administration of food did not alter the AUC. This finding is consistent with that previously reported for SAMSCA®. In the phase 3 study tolvaptan was administered without regard to food intake. While the impact of food (varying fat content) may not be significant with respect to maintaining effect, the possibility that a higher Cmax may manifest tolerability issues such as dizziness, increased polyuria, or thirst cannot be ruled out.
- A renal impairment study (not done in ADPKD patients) showed that in subjects with moderate renal impairment, AUC of total tolvaptan increased by 100%, whereas the unbound AUC was increased negligibly by 5%. In subjects with severe impairment of renal function (10 – 28 mL/min/1.73 m^2) the, total AUC and unbound AUC were increased by 114% and 92% respectively.
- A trend for dose-dependent decrease in urine osmolality over the range of 15 – 120 mg was observed following single dose of tolvaptan in ADPKD patients. Near maximum effects were observed within the first urine collection interval from 0 to 4 h post dose. A trend for dose dependent increase in the duration of the effect was also observed. The effect on urine osmolality with 15 mg dose reached baseline levels by 24 hrs.
- Multiple dose study in ADPKD patients indicates that there was no difference between once daily dosing or twice daily dosing with respect to lowering of urine osmolality (after correcting for baseline). Further, there was no trend for dose dependent effects.
- In ADPKD patients, glomerular filtration rate (GFR) decreased acutely (at week 3) after initiation of tolvaptan treatment (duration: 3 weeks) and returned to baseline 3 weeks after discontinuation. This decrease is larger in the patients with normal renal function or mildly impaired renal function compared to patients with moderate and severe impairment of renal function.

1.4 Summary of Pharmacometric Findings

- In the pivotal Phase III trial of study 251, all tested tolvaptan doses showed significantly lower kidney growth than the placebo after three years of treatment. The slope in total kidney growth of tolvaptan treatment was about half of the placebo, indicating favorable treatment effect. However, based on the modal

doses, the effect was not dose-dependent under the tolerability based titration design. Lower slope values were not observed in patients with higher modal tolvaptan doses. However, the lack of dose-response relationship could be due to the trial design if the patients' tolerability to tolvaptan was associated with the patients' sensitivity for the desired effect, e.g. less tolerable patients were more sensitive to the drug's desired effect.

- In study 251, tolvaptan treatments showed significantly slower rate in the worsening of renal function than the placebo over three years of therapy. Tolvaptan treatment effect was evident but not dose-dependent based on the modal doses. Higher tolvaptan doses were not associated with lower pace of renal worsening. The lack of dose-response relationship could be due to the trial design if the patients' tolerability to tolvaptan was associated with the patients' sensitivity for the desired effect.
- There existed significant association between total kidney volume (TKV) and worsening of renal function measured as GFR using CKD-EPI equation. Higher volume of total kidney was associated with lower renal function. Correlation between percent changes of last visit TKV and last visit renal function was significant (p value <.0001)
- There was a clear dose-response relationship for time to first severe renal pain based on the modal doses. Higher modal doses were associated with longer time to first severe renal pain. This observed relationship was also subjective to the confounding issue due to the titration trial design.
- There was no dose-response relationship for time to first severe worsening of renal function based on the modal doses. The lack of dose-response relationship could be due to the trial design if the patients' tolerability to tolvaptan was associated with the patients' sensitivity for the desired effect.
- There was an imbalance in subjects experiencing abnormally elevated serum ALT between tolvaptan and the placebo. Tolvaptan are more likely to have peak ALT > 3 x ULN and carries higher risk of hepatocellular injury. However, the risk is not dose-related based on the modal doses. The lack of dose-response relationship could be due to the titration trial design based on the tolerability.

2 Question-Based Review (QBR)

This is an abbreviated review of the drug tolvaptan. Tolvaptan was approved by the FDA under the brand name Samsca® in May 2009. The approved doses for Samsca are 15 to 60 mg of tolvaptan daily. The clinical pharmacology of this drug has been extensively reviewed for NDA 22,275 (Peter Hinderling, 6/9/2008). This review will focus on studies that have been submitted for the ADPKD indication.

The IND for the ADPKD indication has been active since 2005 and the drug was given Fast Track designation in 2006. Subsequently, the drug was given orphan drug status in 2012 and rolling review was granted. The final submission for this indication was received on March 1, 2013.

2.1 General attributes of the drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Tolvaptan belongs to a class of drugs that are developed as antagonists at the vasopressin receptors. The structure of tolvaptan is shown in Figure 1; the molecular weight is 448.94 g/mol and it appears as a white crystalline powder. The tolvaptan molecule has one stereoisomeric center and thus two enantiomers. The drug substance is a racemic mixture of both enantiomers. The solubility was measured in various solvents at 25°C and showed higher solubility in lipophilic solvents as compared to water, where it was practically insoluble (0.00005% w/v). In Britton-Robinson buffer (phosphoric acid, acetic acid, boric acid and sodium hydroxide) at pH levels ranging from 2 to 12 no change in solubility was observed (0.00004% w/v) and partition coefficients between buffer and octanol showed an overwhelming preference for the lipophilic phase ($P_{O/W}$ >5000).

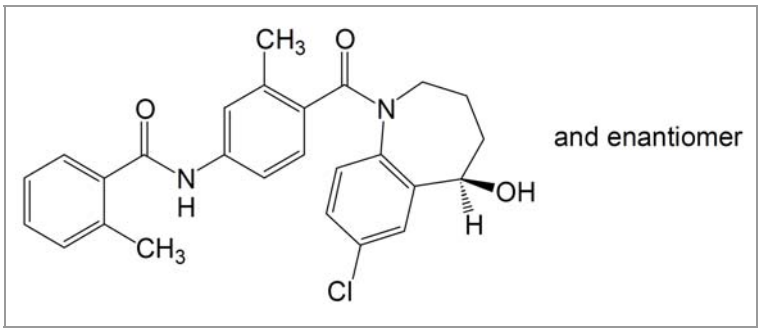

Figure 1. Tolvaptan structure

2.1.2 What is the proposed mechanism of action and therapeutic indication?

ADPKD is a hereditary genetic disease that is characterized by mutations in the genes encoding for polycystin-1 and polycystin-2. These two proteins are found expressed on cilia that protrude into the lumen of the collecting duct and they are thought to be working together on flow-induced calcium signaling. It is hypothesized that in ADPKD, due to the mutations, intracellular calcium level homeostasis might be impaired and as a result, cyclic adenosine monophosphate (cAMP) levels are not suppressed as they ordinarily would be. The second messenger cAMP is involved in promoting an environment for cyst growth.

Vasopressin binding to the V2-receptor uses the second messenger cAMP to elicit the downstream effect of incorporation of water channels (aquaporins) in the luminal membranes of collecting duct cells. Therefore, binding of vasopressin would increase intracellular cAMP and therefore promote a proliferative environment for cyst growth.

Tolvaptan is a selective antagonist at the vasopressin 2 receptor (V2R) located in cells in the collecting duct and distal convoluted tubules of the kidney. The antagonism at the receptor leads to decreased influence of vasopressin (aka arginine vasopressin (AVP) or antidiuretic hormone (ADH)) on the kidney and, by virtue of counteracting vasopressin's antidiuretic activity, leads to increased free water clearance and retention of sodium, which in turn increases sodium concentrations in plasma. Tolvaptan is also hypothesized to limit the increase in second messenger cyclic adenosine mono phosphate (cAMP) after the binding of vasopressin to the receptor and thus provide its effect in ADPKD.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

For treatment of ADPKD, tolvaptan is to be taken orally. Daily doses are to be split unevenly between a morning dose and an afternoon dose taken approximately 8 hours after the morning dose. Tolvaptan is titrated to the highest tolerated dose, with initial dose (morning/afternoon) being 45/15 mg, followed by a first titration step to 60/30 mg to the target dose of 90/30 mg. The label recommends weekly intervals between titration steps, which is consistent with the titration implemented in the pivotal clinical trial. To facilitate this dosing regimen, the applicant is seeking approval of two new strengths of 45 mg and 90 mg tablets in addition to the previously approved strengths of 15 mg, 30 mg and 60 mg tablets.

2.2 General clinical pharmacology

This section provides information about the PK and PD properties of tolvaptan that are pertinent to the current indication, population and the dose ranges studied.

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

As a part of their clinical pharmacology package in support of the current indication, the applicant provides 10 clinical pharmacology study reports. These included: PK/PD studies in healthy volunteers, ADPKD patients following single and multiple doses, studies exploring the impact or tolvaptan on renal function and the impact of renal function impairment on the pharmacokinetics of tolvaptan, and lastly a bioequivalence study that provides the information to bridge the new 90 mg to-be-marketed strength with the 30 mg strength that was studied in the Phase 3 trial. This study also evaluated the impact of high fat meal on the pharmacokinetics of tolvaptan for this new strength of 90 mg tablets.

The applicant performed one randomized, double-blind, placebo controlled trial in subjects with ADPKD who had a total kidney volume of >750 mL, as this was thought to define a population at for progression of the disease. The trial lasted 36 months. The titration scheme used in the trial is the same that is proposed for the label.

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

The biomarker measured to ascertain effect of study drug in clinical pharmacology studies was urine osmolality. Vasopressin increases urine osmolality by increasing reabsorption of water from the collecting duct. Inhibition of vasopressin action should therefore lead to lower urine osmolality as was observed in clinical pharmacology studies.

Urine osmolality is measured in two ways in clinical and clinical pharmacology studies in this submission. One way was to collect urine in defined intervals over a 24-hour period and then determine osmolality for each pooled interval. Another way was to take a spot urine sample and determine urine osmolality in the spot sample. Healthy, normal values of urine osmolality range from 300 to 800 mOsm/kg in spot urine samples. Normal daily variation of urine osmolality exists; it is usually larger in the morning sample. Water consumption will usually decrease urine osmolality, as the release of vasopressin precursor from the anterior pituitary is prevented.

Total kidney volume (TKV) is the primary efficacy response in Phase 3 (156-04-251). It is measured using magnetic resonance imaging (MRI) at 12, 24, and 36 months. The Agency indicated to the applicant that TKV is not an acceptable surrogate. The Agency suggested that the applicant study the proposed secondary endpoints in the TEMPO trial, such as pain, hematuria, infection, nephrolithiasis and considered rate of GFR change to be important. The applicant's final secondary endpoint consisted of renal pain, albuminuria, hypertension, and worsening renal function.

One of the expected impacts of the treatment of ADPKD would be a decreased progression of renal function decline and the slope of renal function was another secondary endpoint in trial 156-04-251. The main marker to measure renal function was

reciprocal serum creatinine. Other metrics of renal function considered in the study were estimated creatinine clearance as measured by either the Cockcroft-Gault equation, or the Modification of Diet in Renal Disease method (MDRD), or using the Chronic Kidney Disease Epidemiology Collaboration method (CKD-EPI). Of note, the applicant chose to assess the baseline at the end of titration, with the intention of excluding the acute decrease in GFR due to hemodynamic changes.

2.2.3 Exposure-response

2.2.3.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

Urine Osmolality

After single doses of 15, 30, 60, or 120 mg tolvaptan, urine osmolality decreased quickly, within the first urine collection interval from 0 to 4 h post dose. The effect of tolvaptan on urine osmolality was numerically ordered in a dose dependent fashion as shown in the Figure 2 below. However, by 24 hrs, there was loss of the treatment effect with the 15 mg dose returning to baseline levels.

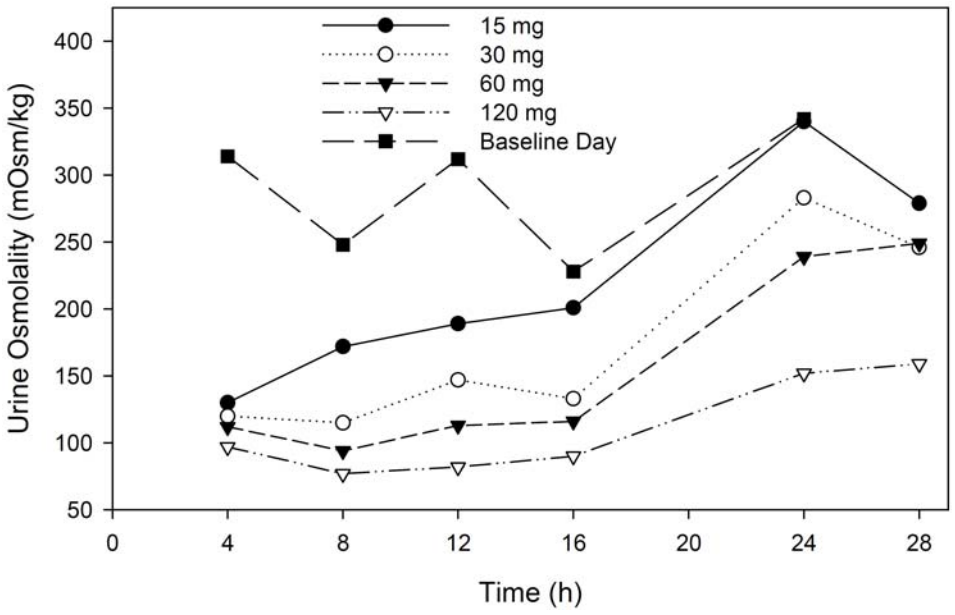

Figure 2. Mean urine osmolality [mOsm/kg] after single oral doses of tolvaptan
Source: CSR 156-04-248 Figure 9.3.3-1, page 78

Similar effects were observed following repeat administration as shown in Figure 3. The urine osmolality remained below 300 mOsm/kg for the entire dosing interval after twice daily dosing, while the 30 mg QD arm showed that urine osmolality gradually increased following the last dose reaching 300 mOsm/kg.

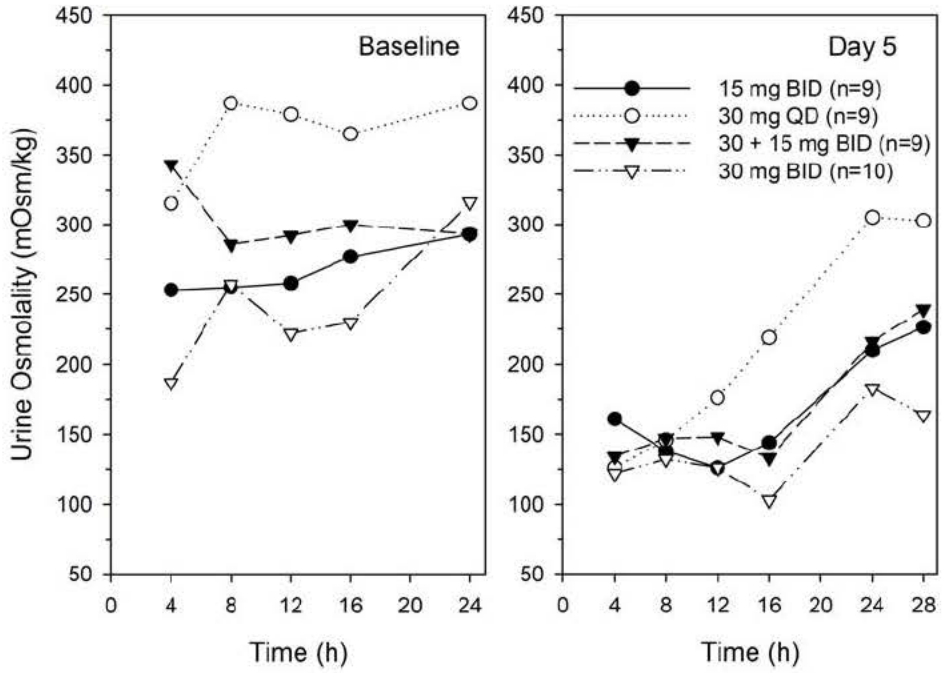

Figure 3. Mean urine osmolality [mOsm/kg] at baseline and after 5 days of dosing with tolvaptan
Source: CSR 156-04-249 Figure 9.3.3-1, page 86

The baseline values were not similar between dose groups. When corrected for baseline, there did not seem to be any dose or dosing regimen related difference in the effect of tolvaptan on urine osmolality as shown in Figure 4.

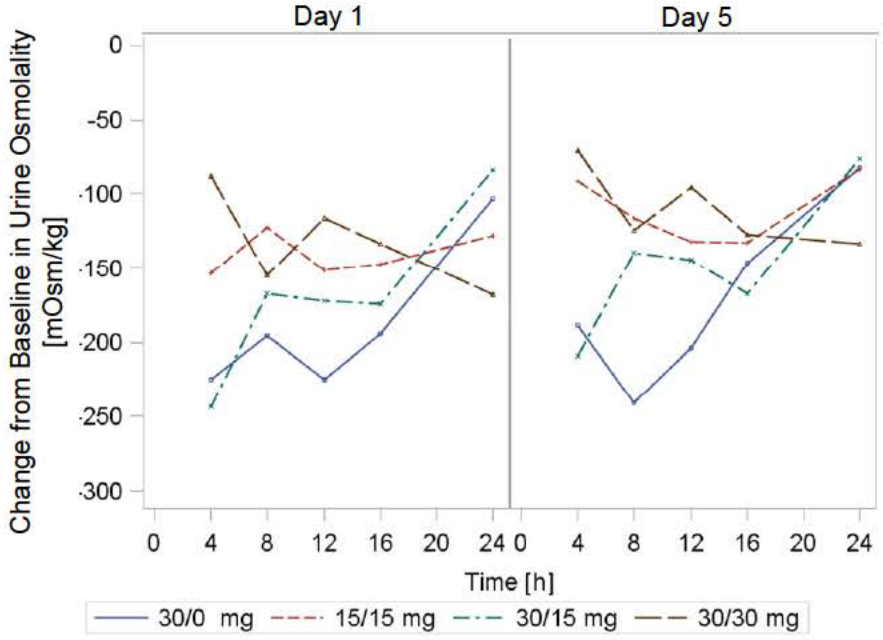

Figure 4. Change from baseline in urine osmolality in study 156-04-249
Source: CSR 156-04-294, urin0.xpt

Change in Total Kidney Volume

In study 251(Phase 3 study 156-04-251) all tested tolvaptan doses showed significantly lower kidney growth than the placebo after three years of treatment, but no clear dose-response relationship was observed for TKV slope based on the modal doses. Tolvaptan treatment demonstrated a TKV slope that was about half of the placebo, indicating a favorable effect for tolvaptan. However, the effect was not dose-dependent under the tolerability based titration design. Lower slope values were not associated with higher modal tolvaptan doses. However, the lack of dose-response relationship could be due to the trial design if the patients' tolerability to tolvaptan was associated with the patients' sensitivity for the desired effect, e.g. less tolerable patients were more sensitive to the drug's desired effect. The numerical trend among the three modal dose groups suggested that those patients who could only tolerate the lower dose seemed to be more sensitive to tolvaptan's effect in reducing the TKV slope.

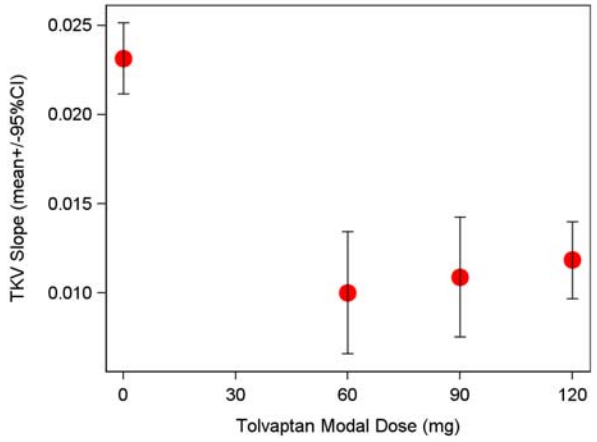

Figure 5: Relationship between total kidney volume (TKV) slope and varying tolvaptan modal doses. The dose of 0 mg is the placebo treatment.

Change in Renal Function

In study 251, after three years of treatment, the tolvaptan arm showed significantly slower slope in worsening of renal function than the placebo. Tolvaptan treatment effect was evident but there was no clear modal dose-response relationship for the decrease in GFR values using CKD-EPI equation. Higher modal tolvaptan doses were not associated with lower slope of renal worsening. However, the lack of dose-response relationship could be due to the trial design if the patients' tolerability to tolvaptan was associated with the patients' sensitivity for the desired effect.

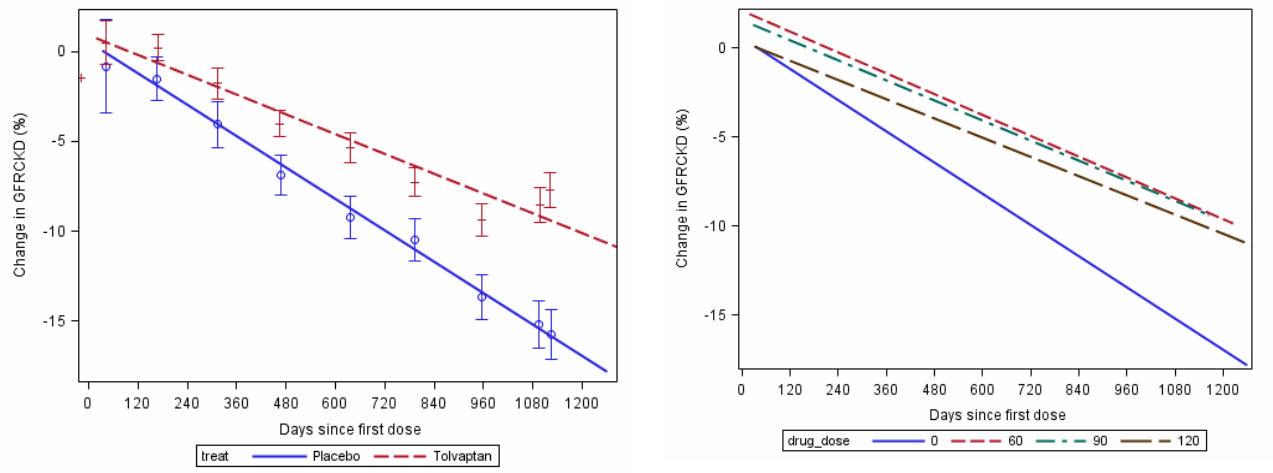

Figure 6: Percent change in renal function measured as GFR (mean with 95% CI) using CKD-EPI equation over time since first dose stratified by treatment (tolvaptan vs. placebo; left) and varying tolvaptan modal doses (right); the lines were regression lines.

Correlation between Change in Total Kidney Volume and Worsening of Renal Function

There existed significant association between TKV and worsening of renal function measured as GFR using CKD-EPI equation. Higher volume of total kidney was associated with lower renal function. Correlation between percent changes of last visit TKV and last visit renal function was significant (p value <.0001)

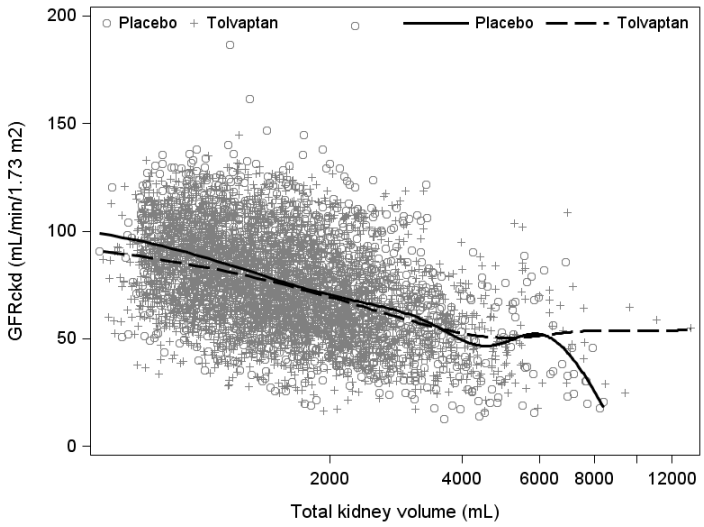

Figure 7: Relationship between GFR using CKD-EPI equation and total kidney volume

Time to First Severe Renal Pain

First severe renal pain was defined as the first occurring event being severe renal pain requiring a prescribed intervention from Day 1 onwards. As indicated in the figure below, tolvaptan showed a clear treatment effect in delaying the occurrence of renal pain. There was a dose-response relationship for renal pain even though the dose was not a randomized dose but a modal dose. Higher doses, especially the 120 mg daily doses (90 mg+30 mg), appeared to have a better effect, while the lowest daily doses (60 mg) showed an effect being no different from the placebo. This observed relationship was also subjective to the confounding issue due to the titration trial design.

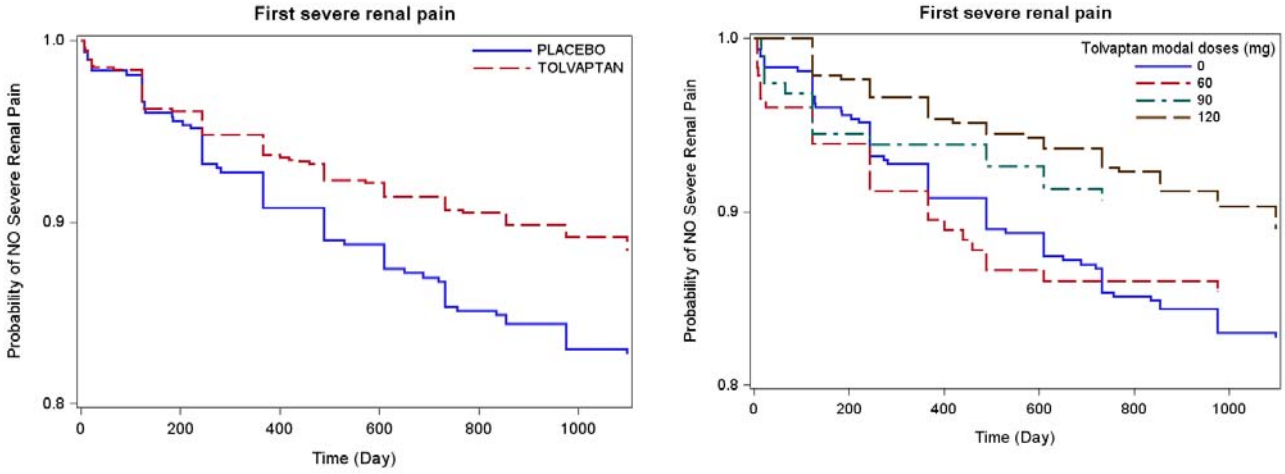

Figure 8: Kaplan-Meier plot of time to first severe renal pain stratified by treatment (Tolvaptan vs. Placebo, left) or varying tolvaptan modal doses (right)

Time to First Severe Worsening of Renal Function

First severe worsening of renal function was defined as a reproducible 25% decrease in reciprocal serum creatinine from Week 3/EOT onwards. As demonstrated in figure below, tolvaptan showed a clear treatment effect in delaying the occurrence of severe worsening of renal function. However, there was no apparent modal dose-response relationship for worsening of renal function. Higher doses were not associated with longer time to the first severe worsening of renal function. However, the lack of dose-response relationship could be due to the trial design if the patients' tolerability to tolvaptan was associated with the patients' sensitivity for the desired effect.

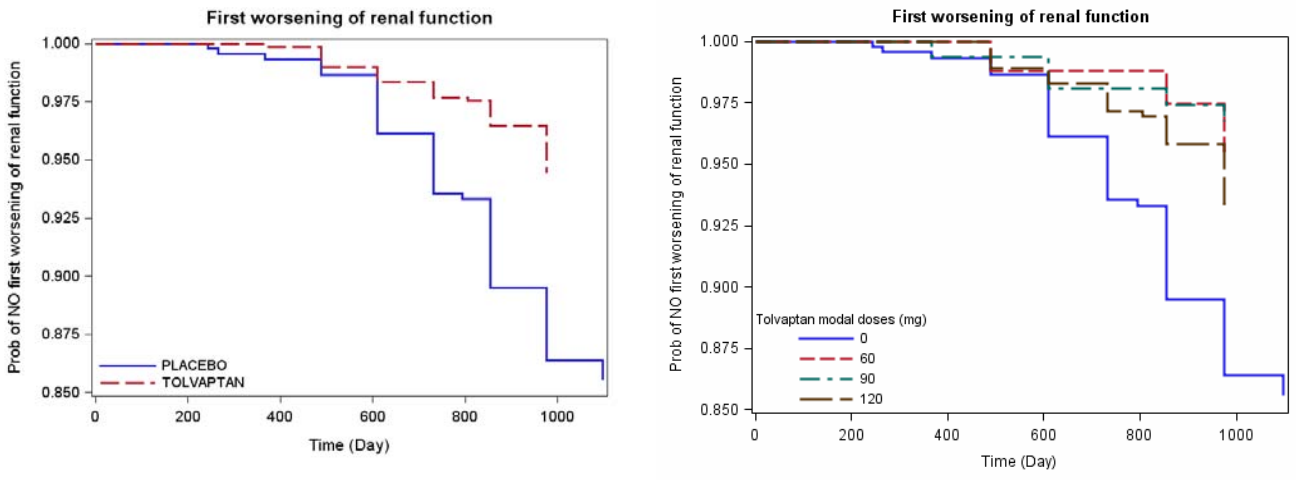

Figure 9: Kaplan-Meier plot of time to first severe worsening of renal function stratified by treatment (Tolvaptan vs. Placebo, left) or varying tolvaptan doses (right)

2.2.3.2 What is the time-course of treatment effects?

The time-course of effects on urine osmolality is already described under Section 2.2.3.1

Glomerular Filtration Rate (GFR)

Acute effect on GFR after tolvaptan dosing was assessed in a clinical study in patients with varying degrees of renal function. A pooled analysis adjusted for baseline GFR showed that at the end of treatment period, i.e., 3 weeks of forced titration from 45/15 mg to 90/30 mg, there was a statistically significant reduction in GFR (Figure 10). Three weeks after discontinuation of tolvaptan treatment, the GFR returned to baseline levels (Figure 10). The acute decrease in renal function was largest in patients with GFR >60 mL/min/1.73 m^2, compared to the moderate and severe renal impairment groups.

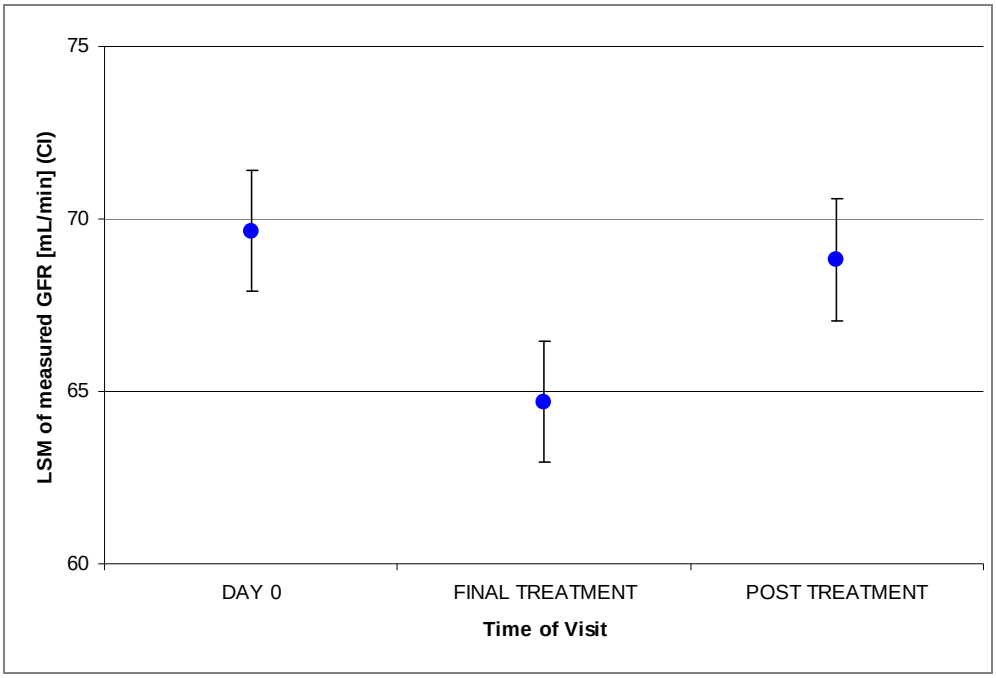

Figure 10. Least square mean measured GFR pooled across groups, adjusted by baseline GFR
Source: 156-09-284, pdparm0.xpt

Total Kidney Volume (TKV)

Change in total kidney volume at two dose levels was assessed in study 156-04-250, which enrolled patients who had been previously enrolled in the single and multiple dose PK/PD studies. Patients had an MRI measurement at screening (baseline) and at 2 months, 12, 24, and 36 months after treatment initiation. The results are shown in Figure 11 below. It is difficult to interpret the impact of treatment on progression, as there is no placebo group for comparison; however, after an initial drop in TKV by month 2, it increases with approximately the same rate between the dose groups.

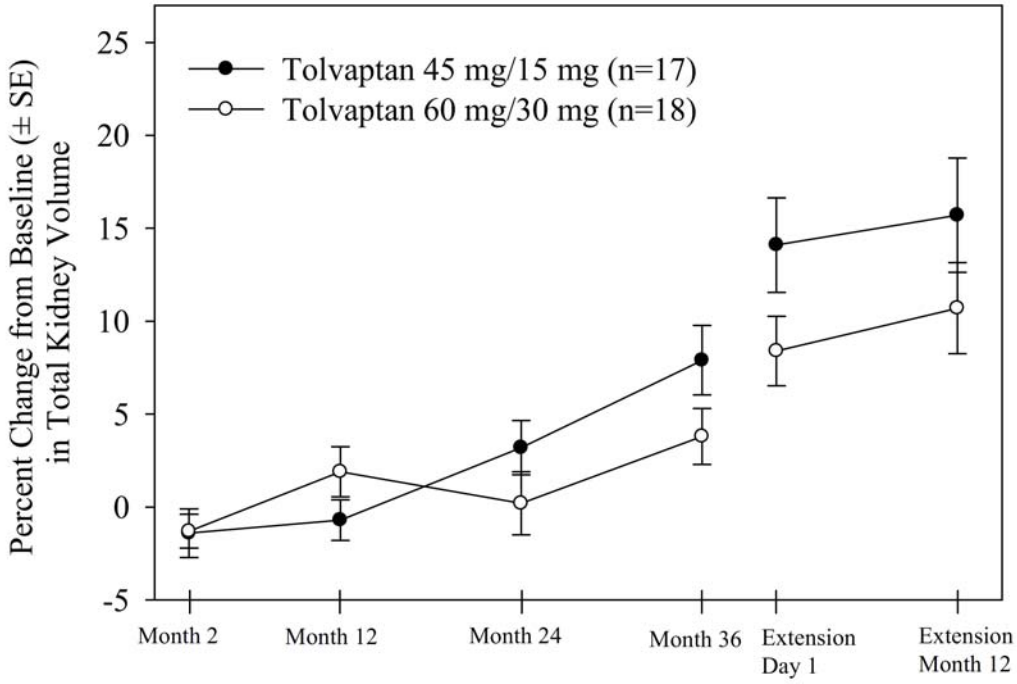

Figure 11. Percent change from baseline in TKV by dose regimen assigned at month 2
Source: CSR 156-04-251 Figure 9.4.2.1-3, page 82

A similar time-course of effect on total kidney volume was observed in a shorter duration study after 3 weeks on tolvaptan treatment and subsequently after 3 weeks off treatment in patients with varying renal function. Changes in TKV were highest in patients with normal renal function or those with mild-moderate impairment of renal function. The reduction in TKV from baseline was ~4.5%. In contrast, the severe renal impairment group had a reduction in TKV of ~2%. Three weeks after the end of tolvaptan treatment, TKV increased. The TKV at the end of treatment was not found to be different compared to baseline (see Table 1 below).

Table 1. Mean TKV [mL] after 3 weeks on treatment and 3 weeks after the end of treatment with tolvaptan

Parameter	$eGFR_{MDRD}$ > 60 mL/min/1.73 m^2 (N = 9)	$eGFR_{MDRD}$ 30 to 60 mL/min/1.73 m^2 (N = 9)	$eGFR_{MDRD}$ < 30 mL/min/1.73 m^2 (N = 9)
Baseline	1376.7 (723.6)	1812.8 (1126.3)	4360.7 (3252.5)
Final Treatment	1315.1 (703.5)	1735.3 (1093.8)	4276.2 (3187.0)
Percent Change from Baseline	−4.5 (3.7)[a]	−4.6 (2.7)[a,b]	−1.9 (1.9)[a]
Post Treatment	1359.3 (729.3)	1759.3 (1101.3)	4558.2 (3415.1)
Percent Change from Baseline	−1.5 (2.3)	−2.4 (3.8)	−0.7 (2.5)

[a] P-value for assessment of significance for the change from baseline < 0.05.

[b] P-value for comparison of change in $eGFR_{MDRD}$ 30 to 60 group to change in $eGFR_{MDRD}$ < 30 group < 0.05.

Source: CSR 156-09-284 Table 9.3.3.4-1, page 86

2.2.3.3 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

One major concern for tolvaptan in ADPKD patients is liver safety. After the completion of trial 156-04-251, an abnormal elevation of serum alanine aminotransferase (ALT) was revealed with incidence in the tolvaptan arm much higher than in the placebo. The potential of tolvaptan for development of drug-induced liver injury (DILI) was then evaluated. As mentioned early, three cases (two during treatment) were found matching Hy's law, with serum ALT >3 x ULN and total bilirubin > 2 xULN. The eDISH plot for study 251 was followed below. It can be observed that there is a clear imbalance between tolvaptan and placebo subjects experiencing serum ALT elevation exceeding 3 x ULN. In the right-upper (Hy's Law) quadrant, there are two tolvaptan treated subjects and no placebo treated subjects.

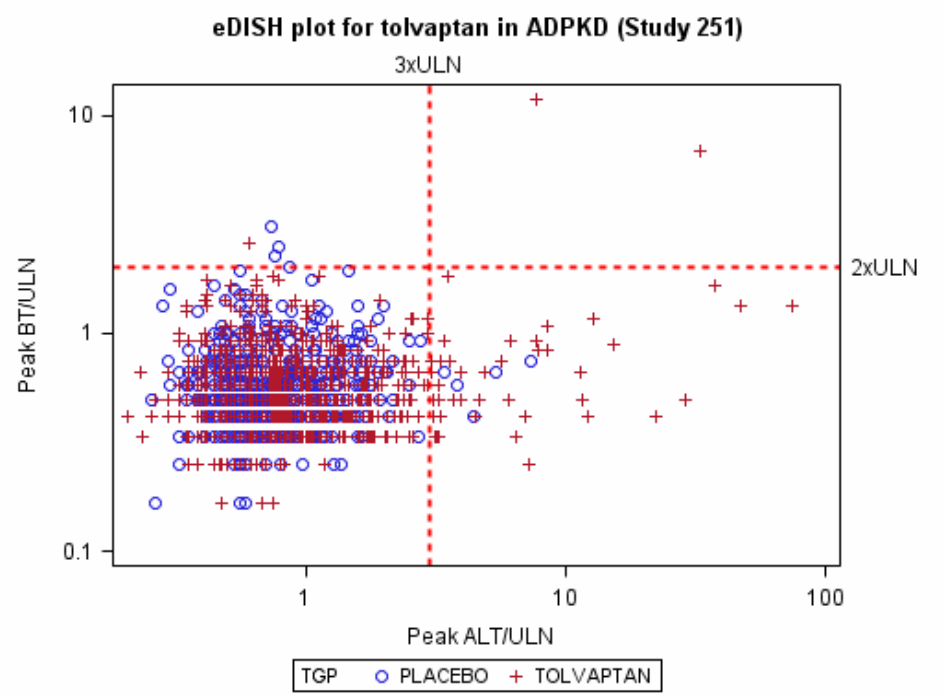

Figure 12: eDISH plot for peak total bilirubin vs. peak ALT in patients receiving placebo or tolvaptan in study 156-04-251

The Kaplan-Meier plot for time to peak ALT >3 x ULN was followed. Tolvaptan showed a much higher probability than the placebo to have peak ALT >3 x ULN. However, the risk was not dose-related based on the modal doses. There was no dose-response relationship for the risk of elevated ALT levels. The lack of dose-response relationship could be due to the titration trial design based on the tolerability.

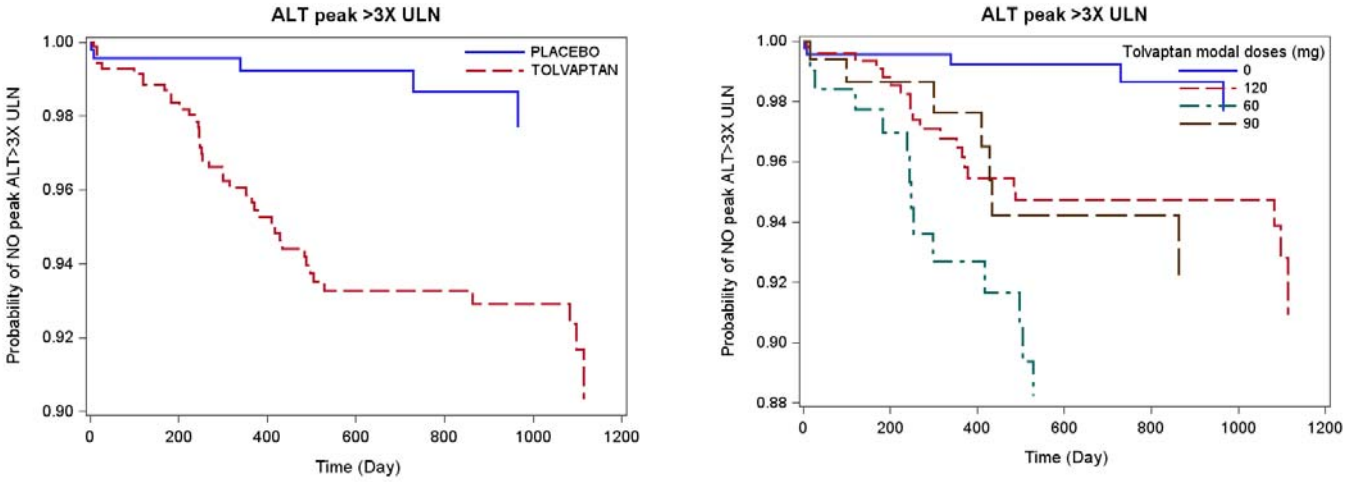

Figure 13: Kaplan-Meier plot for time to peak ALT > 3 x ULN stratified by treatment (tolvaptan vs. placebo, left) and various tolvaptan modal doses (right)

2.2.3.4 Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The applicant's goal for dose selection during the development of tolvaptan for the treatment of ADPKD was to lower urine osmolality to below 300 mOsm/kg and to maximally decrease the marker throughout the dosing interval.

A single dose study (see results in Figure 2) showed that a 15 mg dose was too low, as urine osmolality returned to baseline at the end of the dosing interval. Likewise, higher doses of 30 and 60 mg kept urine osmolality below the threshold of 300 mOsm/kg, but increased towards the end of the dosing interval. Only the 120 mg single dose depleted urine osmolality until the end of the dosing interval. Based on the single-dose study, a multiple dose approach with split doses was chosen to potentially decrease occurrences of nocturia in patients. In the multiple dose Phase 2 study, the following doses were studied: 30 mg QD, 15 mg BID, 30 /15 mg, and 30 mg BID. The first dose was given at around 8-9 am and the second dose approximately 8 h later. The time course of change from baseline in urine osmolality in the multiple dose study can be seen in Figure 4. There does not seem to be a dose response associated with urine osmolality, i.e. all doses achieved a reduction in urine osmolality to approximately the same degree and it is not clear that a case for a BID dosing, split or otherwise, provides a clear advantage over a once daily dose of tolvaptan.

In another study (Study 250), ADPKD patients who were enrolled in the single and multiple dose trials (and thus not eligible to enroll in the pivotal trial) were able to receive study drug for a three year duration. It is not clear how much time was required to elapse between the end of the single or multiple dose studies and enrollment in study 156-04-

250. Both studies 1(Study 56-04-248 and 249) had follow-up periods of 5 days, which would allow enough washout time for tolvaptan from a PK perspective. In study 250, patients were started on a dose of 30/15 mg tolvaptan and were up-titrated weekly to 45/15, 60/30, and finally 90/30 mg. At 2 months, patients were randomized to either 45/15 mg or 60/30 mg doses for the remaining 34 months on trial. Spot urine osmolality was measured throughout and the results of the marker during the titration period are shown in Table 2 below.

Table 2. Mean (SD) urine osmolality[mOsm/kg] after one week of treatment at each dose

Time of Day	Week of Treatment and Dose					
	Day 0	Week1	Week 2	Week 3	Week 4[a]	
	Baseline n=45[b]	30+15 mg n=45	45+15 mg n=43	60+30 mg n=43	45+15 mg n=14	90+30 mg n=27
Prior to First Dose	467 (227)	276 (143)	264 (104)	239 (122)	300 (99)	174 (98)
Prior to Second Dose	455 (237)	191 (108)	154 (66)	140 (70)	175 (85)	136 (58)
Prior to Bedtime	438 (207)	170 (106)	163 (75)	136 (110)	206 (109)	108 (28)

Source: CSR 156-04-250 Table 9.4.1.1-1 (page 76)

At the end of titration, the 90/30 mg dose achieved a mean urine osmolality of 108 mOsm/kg prior to bedtime and 174 mOsm/kg prior to the morning dose. Prior to the morning dose, 15% of patients were below a 300 mOsm/kg threshold, which is the lowest achieved percentage of patients below this threshold compared to the other titration doses. Presumably as a result, the applicant chose 90+30 mg as the target dose.

2.2.4 What are the PK characteristics of the drug and its major metabolite?

This part of the review will focus on the pharmacokinetics in ADPKD patients. For a review of the PK in healthy volunteers and hyponatremic as well as heart failure patients please refer to the clinical pharmacology review for NDA 22,275 (Peter Hinderling, 6/9/2008).

Briefly, in healthy subjects, peak exposure of tolvaptan is reached with 2-4 hours post dose and about 56% of administered drug is absorbed from the intestines. The drug is >99% protein bound and is a substrate of CYP3A4 and MDR1 (P-gp). It is also an inhibitor of P-gp. Two metabolites are of interest, metabolite DM-4103 because of its long half-life of ~180 h, and DM-4107 because is the major circulating metabolite. The drug is mostly eliminated hepatically and its terminal half-life is around 8-10 h.

2.2.4.1 What are the single dose and multiple dose PK parameters?

Pharmacokinetics of tolvaptan following single and multiple doses were similar to that previously observed in healthy volunteers. After, oral administration in ADPKD patients, peak plasma concentrations are observed around 1 – 3 hrs. Tolvaptan generally follows a monoexponential decline with an elimination half-life of 4 – 6hrs as shown in Figure 14 below. Tolvaptan exhibits dose proportional pharmacokinetics following single dose (15 to 120 mg).

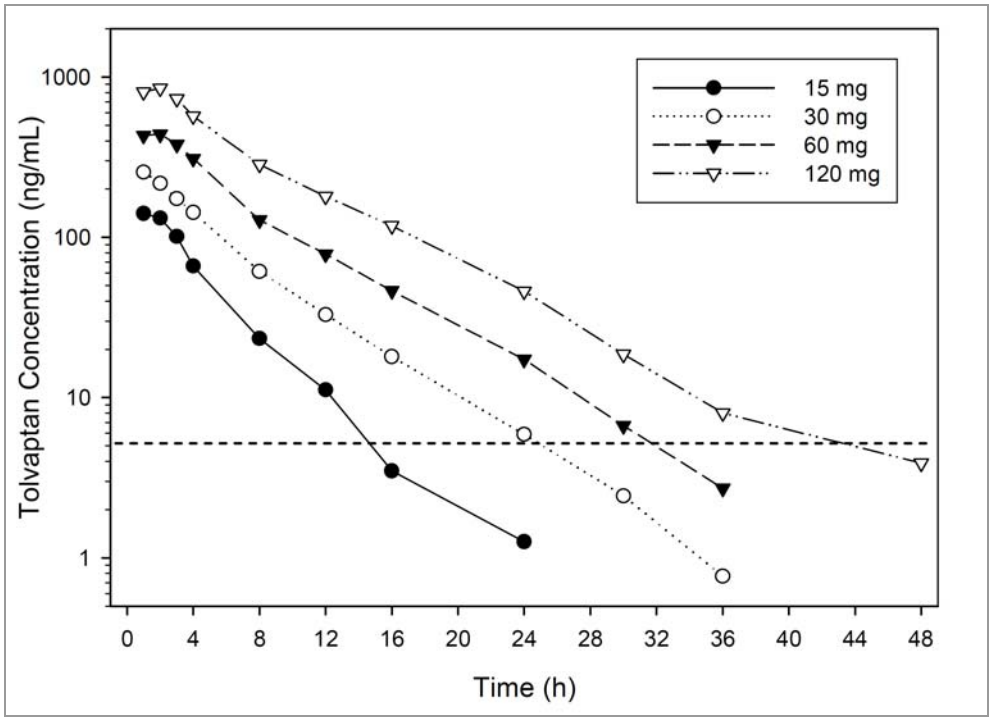

Figure 14. Semi-log plot of mean plasma concentrations of tolvaptan after ascending single oral doses

Source: CSR 156-04-248 Figure 9.2.3-1, page 74

The multiple dose study at doses of 15 mg BID, 30 mg BID, 30+15 mg split dose BID and a single 30 mg QD dose given for 5 days, showed slightly less than proportional increases in exposure and little accumulation at steady state as shown in Figure 15 below.

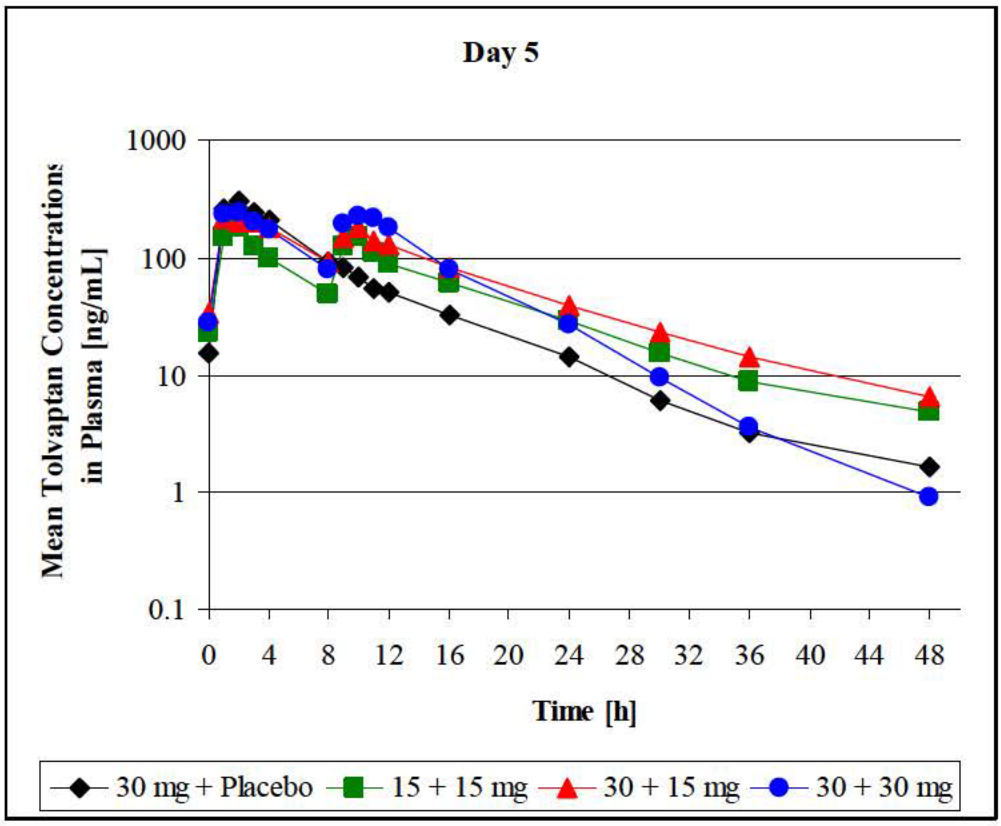

Figure 15. Mean tolvaptan concentrations in plasma after 5 days of dosing
Source: 156-04-249 pk0.xpt

2.2.4.2 Renal Impairment

A study on the effect of renal impairment on tolvaptan PK (not ADPKD patients) had been previously reviewed (Dr. Peter Hinderling, 12/15/2011, IND 54,200). The study showed that in subjects with moderate renal impairment, AUC of total tolvaptan increased by 100%, whereas the unbound AUC was increased negligibly by 5%. In subjects with severe impairment of renal function (10 – 28 mL/min/1.73 m^2) the, total AUC and unbound AUC were increased by 114% and 92% respectively.

No dose adjustment is required for patients with mild or moderately impaired renal function, as this population was studied in the TEMPO trial. One entry criterion for the TEMPO trial was a baseline GFR of at least 60 mL/min/1.73 m^2. Based on the results observed in Study 284, tolvaptan may not be the treatment of choice for patients with severe renal impairment.

2.3 Extrinsic Factors

2.3.1 CYP3A4 Inhibition

The interactions of tolvaptan with other drugs have previously been reviewed. Tolvaptan is a substrate for CYP3A4 and is thus subject to drug-drug interactions with CYP3A4 inhibitors and inducers.

A 200 mg once daily dose of ketoconazole caused a 3.5-fold and 5-fold increase in tolvaptan Cmax and AUC, respectively. A 50% increase in the terminal half-life is also observed. Concomitant administration with the CYP3A4 inducer rifampin reduced Cmax and AUC of tolvaptan to 10 and 20%, respectively as compared to tolvaptan administered alone.

The US package insert for SAMSCA® recommends not using tolvaptan with strong CYP3A4 inhibitors and avoiding use with moderate CYP3A4 inhibitors while considering a dose adjustment with CYP3A4 inducers.

In the pivotal clinical trial (156-04-251, TEMPO) in ADPKD patients, the applicant cautioned against the use of potent CYP3A4 inhibitors. A total of 287 out of 1444 patients in the study received CYP3A4 inhibitors (163/961 on tolvaptan and 124/483 placebo). Co-medication that inhibited CYP3A4 included ketoconazole (topical application) and itraconazole, other azole antimycotics, diltiazem, alprazolam, atorvastatin, fluoxetine and ranitidine, among others. Side effects such as fatigue were observed more commonly in patients on a CYP3A4 inhibitor for both placebo and tolvaptan groups, however, the occurrence was higher in the tolvaptan group. Numerically, there did not appear to be a difference in the occurrence of ALT or AST elevations in either the tolvaptan or the placebo arm when coadministered with a CYP3A4 inhibitor (CSR 156-04-251 Table ST-1.9.1, page 4754); however, numbers were small overall. For bilirubin, a clear trend was not observed, again because of a limited number of observations. Dizziness, polyuria, nocturia did not occur more often in the CYP3A4 inhibitor treated groups, however, renal pain and hematuria did (Table ST-1.9.1, page 4771 f.).

A population pharmacokinetic study (156-11-296) assessed the impact of CYP3A4 inhibitors and found that on average CL/F was reduced by 27% when tolvaptan was coadministered with an inhibitor. In a total of 1067 subjects, there were only 50 subjects with at least one instance of strong, moderate or weak CYP3A4 inhibitor co-administration. Of 6437 observations, less than 3% observations were associated with CYP3A4 inhibitor co-administration. However, the model only included a logical value (Yes/No) for coadministration at any time during trial participation. In addition, information about the duration of the concomitant administration or verification of sample collection for PK during concomitant administration was not collected. Hence

the impact of strong or moderate CYP3A4 inhibitors may not be fully elucidated from this analysis.

The applicant proposes dose adjustment only for patients on potent CYP3A4 inhibitors as shown in Table 3 below.

Table 3. Proposed dose adjustment when tolvaptan is coadministered with strong CYP3A4 inhibitors

Standard Split Dose	Adjusted Daily Dose
90/30 mg	30 mg upon waking
45/15 mg	15 mg upon waking

Source: Annotated label, (b) (4) ®

While the proposal to decrease the daily dose by a factor of ¼ seems reasonable, it should be noted that the reported increase with ketoconazole in AUC to tolvaptan was 5-fold. This was observed at a ketoconazole dose of 200 mg dose QD, which is a sub-maximal dose. Hence the proposed dose adjustment may not fully alleviate the interaction. Further, there is no proposed recommendation for patients who might be stabilized on a tolvaptan dose of 60/30 mg. Based on the above proposal, such patients may need a dose of ~20 mg, however the applicant does not have a dose strength of 20 mg available.

Hence, it may be prudent to avoid concomitant administration of systemically (i.e. not topically) administered strong CYP3A4 inhibitors.

2.4 General Biopharmaceutics

2.4.1 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The to-be-marketed 90 mg formulation was demonstrated to be bioequivalent to 3x30 mg tablets in a healthy volunteer study as shown in Figure 16.

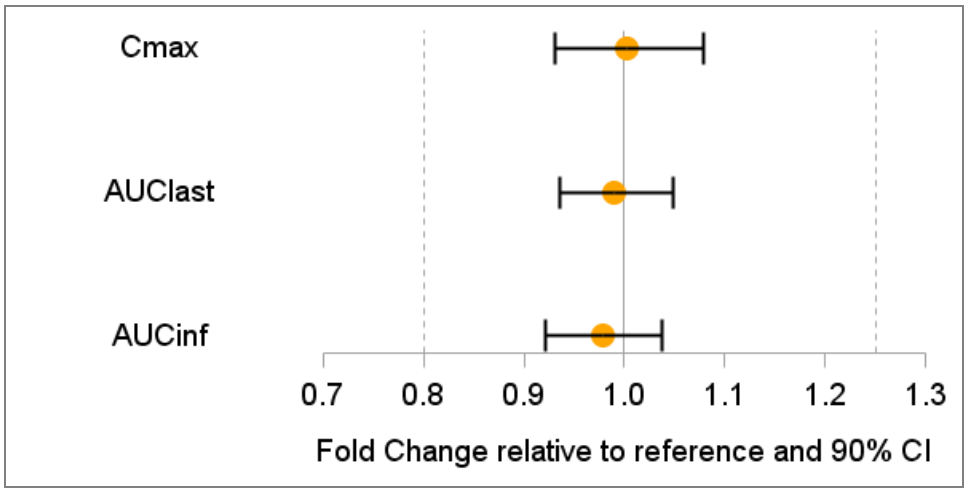

Figure 16. Forest plot of geometric mean ratios for bioequivalence study
Source 156-11-295 pk0.xpt

2.4.2 What is the effect of food on the bioavailability (BA) of the drug from the dosage form?

With a high fat meal, Cmax increased about 2-fold compared to administration in fasted state as shown in Figure 17. Administration of food did not alter the AUC.

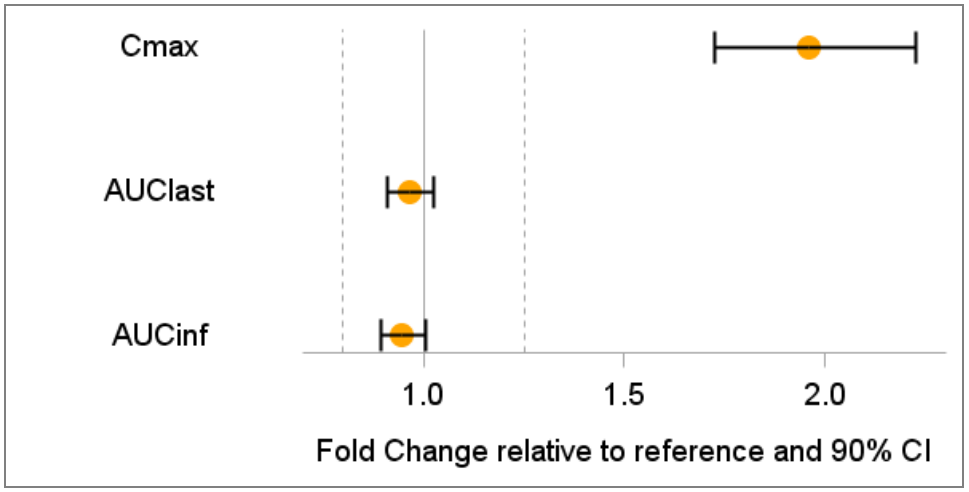

Figure 17. Forest plot of geometric mean ratios for food effect study
Source 156-11-295 pk0.xpt

This increase in Cmax was also observed in a previously reviewed food effect study for tolvaptan and was deemed not clinically relevant. The pivotal phase 3 study for ADPKD (156-04-251) was conducted without regard to food intake. While the impact of food (varying fat content) may not be significant with respect to maintenance of effect, the

possibility that a higher Cmax may manifest tolerability issues such as dizziness, increased polyuria, or thirst cannot be ruled out.

The plot of the concentration-time course shows that half-life is longer in the fasted compared to the fed dose group (Figure 18).

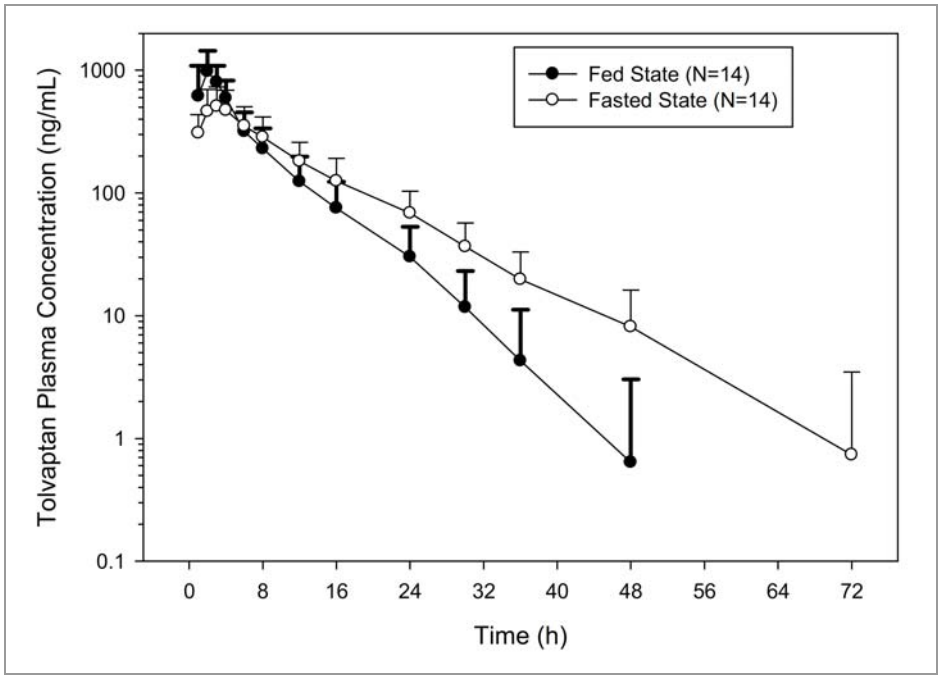

Figure 18. Mean tolvaptan concentrations over time, fed vs fasted
Source: CSR 156-11-295 Figure PKF-2, page 294

This is an unusual finding for a food effect study. One potential explanation can be provided based on physicochemical properties (refer to Section 2.1.1): Tolvaptan is a very lipophilic drug with a logP value of approximately 5. The drug is practically insoluble in water. Therefore it could be hypothesized that a high fat meal could increase the solubility of tolvaptan and provide more drug to be absorbed faster, whereas in the fasted situation, a slow but continuous release from the dosage form occurs, which resembles flip-flop kinetics. Tolvaptan oral tablets demonstrated flip-flop kinetics in an absolute BA study (study 156-05-254).

2.5 Analytical section

2.5.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Tolvaptan, the only clinically active moiety, is quantified using liquid chromatography separation with tandem mass spectrometry quantification (LC/MS/MS).

2.5.2 Which metabolites have been selected for analysis and why?

Selected metabolites are DM-4103, chosen for its long half-life of ~180 h, and DM-4107, of interest because it is the major circulating metabolite.

2.5.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

For all trials done for the ADPKD indication, total concentrations were assessed.

2.5.4 What bioanalytical methods are used to assess concentrations?

For ADPKD studies, the method used was LC/MS/MS for all three molecules (tolvaptan, DM-4103, and DM-4107).

Properties of the methods used to characterize concentrations are shown in Table 4 below.

Table 4. Characteristics of methods used to quantify tolvaptan and its metabolites

Parameters	Method 1		Method 2			Method 3		
Study	156-04-248, 156-04-249, 156-11-295		156-09-284			156-06-260		
Method Report	157209 (Lot: 001)		176574 (Lot: 001)			167151 (Lot: 001)		
Matrix	Plasma		Plasma			Plasma		
Analytes	Tolvaptan	DM-4103	Tolvaptan	DM-4103	DM-4107	Tolvaptan	DM-4103	DM-4107
Calibration Range [ng/mL]	5.0-1000.0	12.5-2500.0	5.0-1000.0	12.5-2500.0	12.5-2500.0	5.0-1000.0	12.5-2500.0	12.5-2500.0
Calibration Curve Fit*	0.998	0.998	0.998	0.997	0.998			
QC Concentrations [ng/mL]	15.0, 80.0, 800.0	37.5, 200.0, 2000.0	15.0, 80.0, 800.0	37.5, 200.0, 2000.0	37.5, 200.0, 2000.0	15.0, 80.0, 800.0	37.5, 200.0, 2000.0	37.5, 200.0, 2000.0
Accuracy	91.26-98.00%	92.85-105.60%	-5.4188	-9.973	-10.725	<4%	<7%	<5.5%
Precision	2.37-8.30%	3.10-9.11%	<5%	<12%	<5%	<7.7%	<7.5%	<7.9%
Stability	Yes		Yes			Yes		
Internal Standard	OPC-41100		OPC-41100			OPC-41100		

* Weight = $1/concentration^2$

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/s/

MARTINA D SAHRE
07/02/2013

RAJANIKANTH MADABUSHI
07/02/2013
concur with clin pharm reviewer findings

FANG LI
07/02/2013
Pharmacometrics

YANING WANG
07/02/2013

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
OFFICE OF PHARMACOVIGILANCE AND EPIDEMIOLOGY

DATE: 30 June 2013

FROM: John R. Senior, M.D., Associate Director for Science, Office of Pharmacovigilance and Epidemiology (OPE)

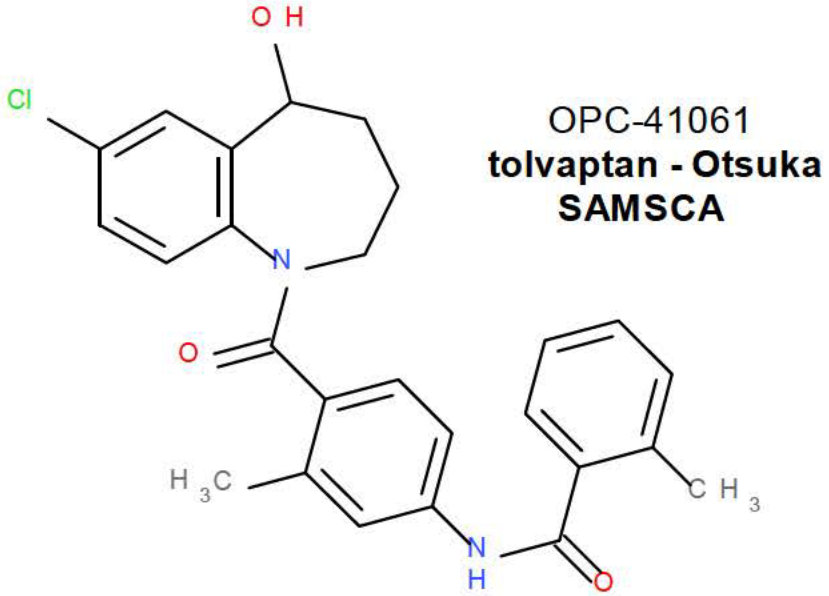
TO: Norman Stockbridge, M.D., Director, Division of CardioRenal Products (DCRP), Office of New Drugs (OND)
Stephen Grant, M.D., Deputy Director, DRCP
Mary Ross Southworth, Pharm.D., Deputy Director for Safety, DCRP
Aliza Thompson, M.D., Medical Reviewer, DRCP
Nhi Bach Beasley, Pharm.D., Safety Reviewer, DRCP

VIA: Gerald Dal Pan, M.D., Director, Office of Surveillance and Epidemiology
Solomon Iyasu, M.D., Director, OPE

SUBJECT: Hepatic safety of **tolvaptan** (NDA 204441), proposed for slowing progression of autosomal dominant polycystic kidney disease (ADPKD). Tolvaptan, as (SAMSCA® Otsuka), was approved 19 May 2009 for treatment of retention of fluid in patients with heart failure, cirrhotic ascites, and the syndrome of inappropriate antidiuretic hormone (SIADH) in patients with symptomatic hyponatremia, or were resistant to fluid intake restriction, or for clinically significant hyper- or eu-volemic hyponatremia (serum sodium <125 mEq/L).

Documents reviewed:
1) Consultation request 2 April 2013 from Dr. Aliza Thompson via Ms. Lori Wachter (DCRP) and Ms. Cherye Milburn (OSE), requesting response by I July 2013, OSE tracking #2013-1420;
2) Otsuka proposal for Risk Mitigation Plan dated 13 November 2012, including report from consulting hepatologist Paul B. Watkins dated 28 October 2012 ("A review of the liver safety database for tolvaptan in the treatment of Autosomal Dominant Polycystic Kidney Disease");
3) Previous consultation request 29 November 2012, alerting us that the sponsor (Otsuka) had identified a potentially serious signal for liver injury in ADPKD studies, with possible impact on labels for approved indications, prior to our receipt of data for the new PKD work, with partial consultation responses dated 3 and 13 February 2013;
4) Memorandum on Tolvaptan (Samsca) and hepatotoxicity, TSI # 1332, NDA 22275, dated 13 December 2012 from D. Mary Ross Southworth to file;
5) Otsuka letter to Healthcare Providers, 22 January 2013, **IMPORTANT DRUG WARNING** of significant liver injury associated with the use of SAMSCA (tolvaptan);
6) Approved labeling for tolvaptan (SAMSCA, Otsuka) for treating euvolemic or hypervolemic hyponatremia, last updated 3 May 2013.

Tolvaptan, initially designated OPC-41061 by the Otsuka development team (Yamamura et al., 1998), was designed as a new orally effective non-peptide agent for blocking renal collecting ductular arginine-vasopressin (AVP) V2-receptors to inhibit reabsorption of free water from glomerular filtrate, for treatment of water-retaining states such as hepatic cirrhosis, congestive heart failure, nephrotic syndrome, and inappropriate anti-diuretic hormone secretion. Earlier potent peptide vasopressin antagonists had not been found to be clinically useful because of low oral bioavailability and anti-diuretic effect in humans. Otsuka chemists had reported in 1991-2 the synthesis of OPC-21268 and OPC-31260 as non-peptide AVP antagonists of interest, active at cyclic adenosine monophsphate-dependent V1 and 2 receptors. Stable expression of cloned human AVP receptors in HeLa cells allowed development of a more potent non-peptide human AVP-V2-receptor antagonist leading to OPC-41061. Testing in male Sprague-Dawley rats using oral doses of 1 or 10 mg/kg showed very significant aquaretic effects after single and multiple doses for up to 28 days. The encouraging results of effectiveness and apparent safety had already led to initiation of human studies (IND 050533, 17 May 1996) for investigation of effects of OPC-41061 on states of hyponatremia, and for treatment of hyponatremia (IND 054200, 23 September 1997). Using generic name tolvaptan under IND 072975 submitted 28 July 2005 it was studied in patients with hyponatremia in liver cirrhosis, congestive heart failure, and syndrome of inappropriate antidiuretic hormone (SIADH).



OPC-41061
tolvaptan - Otsuka
SAMSCA

New Drug Application 022275 for tolvaptan (SAMSCA®, Otsuka) was approved 19 May 2009 for treating clinically significant hyper- and eu-volemic hyponatremia. Since that approval for marketing and clinical use, only one report of liver test abnormalities associated with tolvaptan has been published (Cabello Ortiz, et al. 2011), occurring in a 75-year-old man with SIADH who showed sharp rises in serum ALT, AST, and GGT activities 24 days after starting at 15 mg/day and increasing to 30 mg/day. Stopping the drug led to reversal of the abnormalities after 11 and 23 days, thought to be possibly drug-related, although liver metastases confirmed by biopsy were found later. No symptoms or functional abnormality of bilirubin or prothrombin were reported, but details make the findings likely to have been superimposed tolvaptan-induced mild injury.

Study of tolvaptan for slowing the rate of progression of autosomal dominant polycystic kidney disease (ADPKD) was started under IND 072975, and clinical trials since then have resulted in pre-submission of NDA 204441 on 15 November 2012. This genetically transmitted disease is said to affect about 600,000 persons in the United States, and is the 4th most common cause of end-stage renal disease, after diabetes, hypertension, and glomerulonephritis (Helal et al., 2012). The development program for use of tolvaptan for slowing progression of ADPKD was granted fast-track designation 20 January 2006, and orphan drug designation 6 April 2012, according to a review submitted by Otsuka on 13 November 2012 (despite having prevalence of greater than that usually specified for orphan drug status as the upper limit [200,000 in USA].

It is somewhat unclear exactly when the sponsoring company became aware of the problems of possible tolvaptan-induced liver injury, but the issue was discussed with FDA in July 2012 when the accumulated long-term data from pivotal clinical trial 156-04-251 in 1444 adult subjects with ADPKD were being evaluated in preparation for submission of NDA 204441. The concerns were enough that Otsuka convened a special consulting committee of four academic hepatologists (Drs. Paul Watkins, James Lewis, Neil Kaplowitz, and David Alpers) to review the clinical data and render an opinion as to whether they believed tolvaptan to be the probable cause of several cases of serious (but not fatal) liver injury and dysfunction. Results of those studies showed a notable increase in the frequency of moderate to severe elevations of serum ALT and AST activities in patients treated with tolvaptan, compared to those receiving placebo. The report of the expert hepatology consultants, submitted by Paul Watkins on 28 October 2012, indicated that the consultants had carefully reviewed the data, and they concluded that long-term treatment with tolvaptan carried a risk of liver failure in about 1 per 3000 treated patients. They opined that the risk of liver injury would probably be lowered with more frequent monitoring of serum liver tests but would not likely be eliminated. Further, they agreed that a hepatotoxicity risk from the approved SAMSCA tolvaptan product could not be discerned among patients treated for serum hyponatremia due to hepatic cirrhosis, congestive heart failure, or SIADH, perhaps because of the lower doses used in those patients, but also suggesting a mechanistic link between ADPKD and susceptibility to tolvaptan-induced liver injury.

Following receipt of the consultants' report, Otsuka submitted updated labeling for SAMSCA on 16 November 2012, not even mentioning hepatotoxity, but almost simultaneously submitting a proposal (13 November) for negotiating with DCRP a risk mitigation plan, and followed that by an urgent letter to all healthcare providers sent 22 January 2013 as an **IMPORTANT DRUG WARNING** of the potential risk of liver injury with use of SAMSCA® (tolvaptan) that it has the potential to cause irreversible and even fatal liver injury, as derived from the data in the ADPKD trials. They also noted that SAMSCA is not approved for treatment of ADPKD**.** This led to a proposed new brand name (b) (4) for the same drug, but at higher dose for much longer time in the proposed indication for slowing the rates of renal cyst enlargement and of renal function loss. It also led to labeling revision in April 2012, promulgated 2 May 2013, for the approved product SAMSCA that limits its use to 30 days at up to 60 mg/day, removes the indication for use in patients with cirrhosis, and mentions tolvaptan-induced liver toxicity. This confusing and apparently internally inconsistent behavior of the sponsor had led DCRP to request a review of the old data, dating back to 1996-2004 on clinical trials of its use for treatment of hyponatremia due to various disorders. DCRP refused to accept the proposed new trade name pending further review of the clinical data.

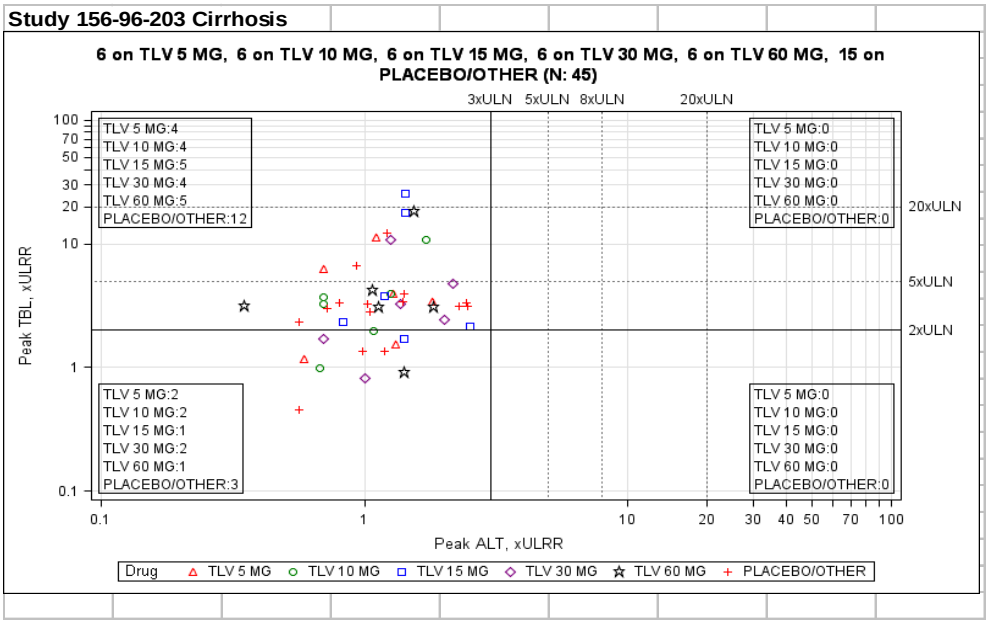
Results of Past Studies for Treatment of Hyponatremia

The earliest trials were those for cirrhosis (156-96-203), where 156- refers to tolvaptan, 96- to the year when the study was started, and 203 to the protocol number. In referring to individual study subjects randomized to treatment with tolvaptan or other, they are identified within each study by numbers such as 03236-304-0905, in which the first two digits are the year of the study, and the next three of the five the protocol number (03 236), the next set of three the site where the study was done (304, in Argentina), and the last four the individual subject number.

Cirrhosis	Heart Failure	Hyponatremia
156-96-203	156-00-220	156-02-235
	156-01-232	156-03-238
	156-03-236	156-04-246

These studies included about 45 patients with cirrhosis, 4685 with heart failure, and 610 with huponatremia (5340 in all). After attempting to get those data into format suitable for eDISH analyses for over two months, the data were forwarded to Dr. Guo on Wednesday 30 Jan 2013. Dr. Guo very promptly prepared a first-cut, preliminary version of those data, sorted by dose of tolvaptan or alternative drug given, and I began looking at the more serious cases that showed elevations of both serum alanine aminotransferase (ALT) activity and serum total bilirubin (BLT) concentration (at the same time or with BLT following ALT).

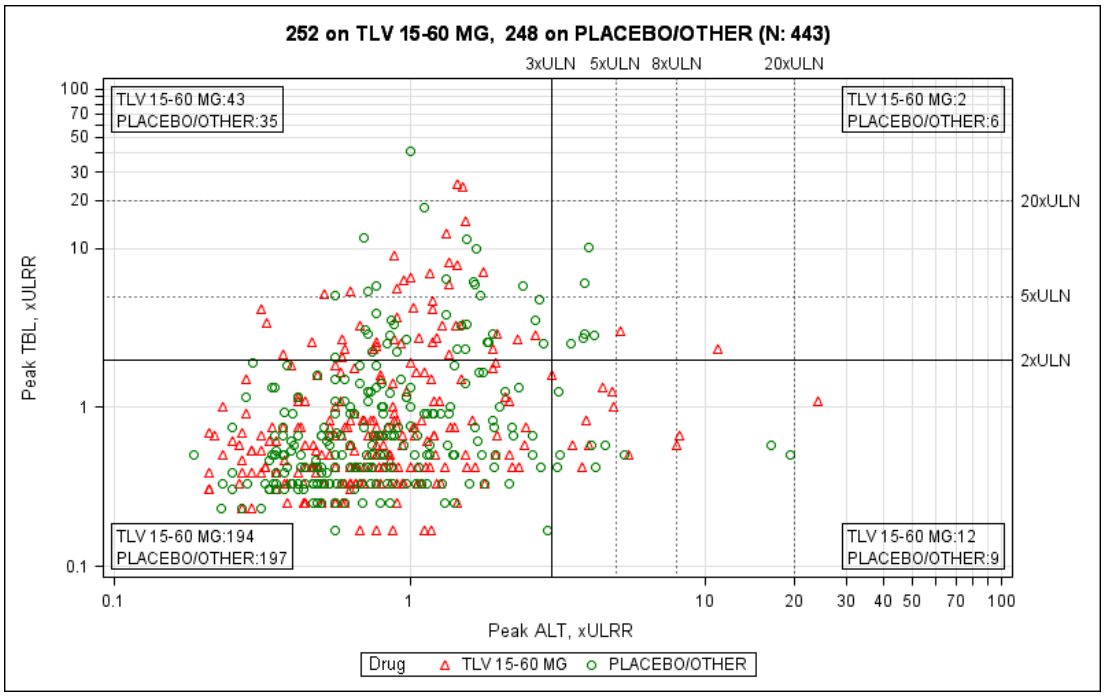
For the 45 patients with cirrhosis, no narratives were provided for any of them, nor were any needed, because none of them showed any increased serum activity of ALT during the course of treatment with tolvaptan (see graph, attached). Elevated bilirubin levels observed appeared to be consequences of damage from what had caused the cirrhosis, not acute tolvatptan-induced injury.



Inspection of the data on January 31 using eDISH showed that there had been *NO* serious cases among the 45 cirrhotic patients in the very old (1996) and cautious dose-ranging studies, but an incidence of about 1.4% of serious liver dysfunction in both the other groups (heart failure and hyponatremia) that did not appear to be related, either to whether or not the patient had received placebo or tolvaptan, or to the dose of tolvaptan given, but were more likely related to the very severe underlying cardiac or other diseases in these very sick patients (see below)

For the hyponatremia studies we chose to focus attention on the subjects who had shown peak levels of ALT and BLT at some time, but not necessarily at the same time, in their courses of observation on or off drug.

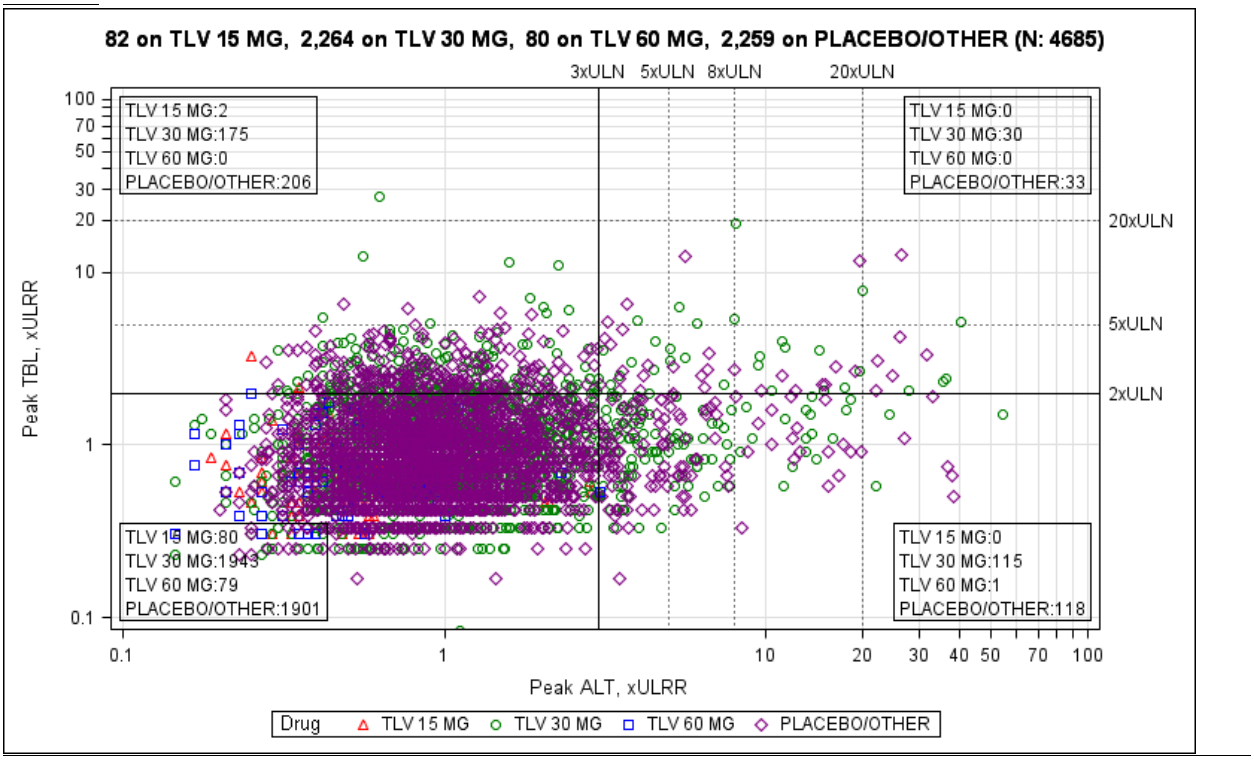
TOLVAPTAN Hyponatremia Studies 156-02-235, 156-03-238, 156-03-244: 500 patients



In the hyponatremia studies there were data provided for 443 patients in Studies 02-235 and 03-238, in which there were 8 patients showing both ALT and BLT elevations, 2 on tolvaptan and 6 on placebo. In the follow-up Study 03-244 of 110 patients, another 3 on tolvaptan showed both ALT and BLT elevations during the course of their observations, bringing to 11 the total of patients of special interest, 5 on tolvaptan and 6 on placebo. For them, 10 narratives were submitted (none for patient 03328-137-3021, an 80-year-old man studied in the USA who showed peak ALT of 383 U/L,10.9 times the upper limit of the normal range (xULN) with no rise in his ALP activity and only modest peak BLT of 2.8 mg/dL, 2.33 xULN. Further, his ALT and BLT were elevated even before tolvaptan was given for only 2 days, so it was very unlikely the cause of the abnormalities. In the other 10 cases an alternative clinical cause could be found in the clinical narrative in all but one (02235-031-3010, an almost obese Hispanic man of 49 with only modest elevation of ALT that occurred over a week after he was off placebo In summary, no cases of probable tolvaptan-induced serious liver injury were found among the studies of the 610 patients in the hyponatremia studies.

By far the largest clinical experience submitted was for treatment of fluid retention in patients with congestive heart failure, with data from one study (156-03-236) including 4685 patients, many of them quite sick with various manifestations of circulatory problems that often impacted adversely of hepatic function.

TOLVAPTAN Heart Failure Studies 156-01-232, 156-03-236. (4685 patients)

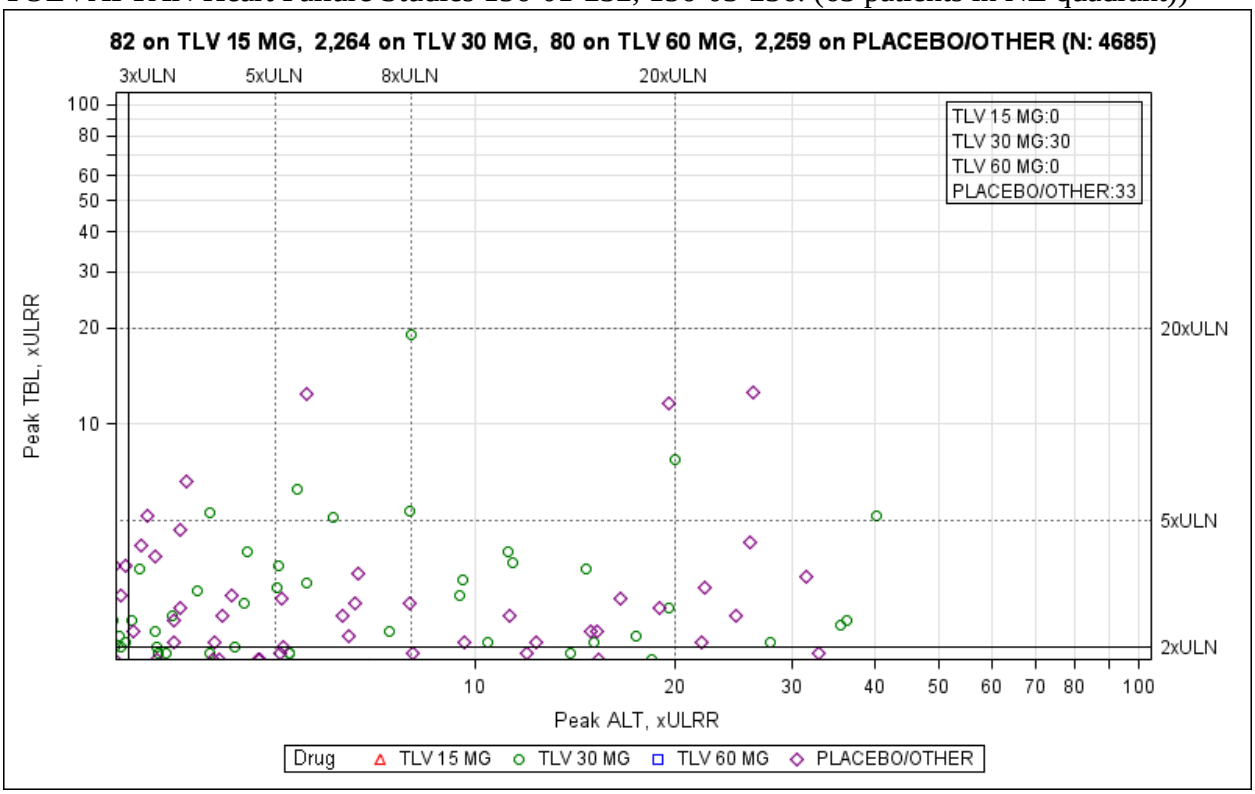


In this study (03-236) there were many very sick patients, with some dying of their cardiac insufficiency, which caused secondary back–up of blood into the liver or reduced flow of blood from the liver. The consequences were depletion of oxygen in the hepatic sinusoidal blood, most marked in the centrilobular zones, where metabolically active hepatocytes had used most of the oxygen and had become so depleted that their necrosis led to leakage of enzymes from the cytoplasm into the plasma, to elevations of serum ALT and especially AST, as well as increased bilirubin concentrations. Even more striking rises in serum AST and ALT occurred in those patients who also had cardiogenic shock or at least severe hypotension, with decreased hepatic arterial flow of oxygenated blood into the liver, sometimes leading to enormous and rapid rises in serum aminotransferase enzyme activities. These were often rapidly reversible if treatment of the cardiac problems improved the circulation and supply of oxygen to the hepatocytes.

It is evident from a glance that there was no imbalance in the incidence of marked abnormal liver tests, and from Tables II and III in the attached Excel listing. However, confident assessment of causality could not be made for more than two-thirds because of insufficient diagnostic information or no narratives at all. The eDISH displays show no imbalance in the incidence of either ALT increases only or both ALT and TBL, in the studies on patients with heart failure.

Because of the very large number of patients in study 156-03-326, we chose to focus on those who showed the more serious evidence of secondary liver test abnormalities, those in the right upper (or "NE") quadrant of the eDISH display. They included 1 patient (01232-252-1061) and 29 more from study 156-03-236 who had been treated with tolvaptan, and 33 patients from the latter study who had been randomized to placebo. Those 63 patients, plus the 11 (5 tolvaptan, 6 placebo) from the hyponatremia studies mentioned above, have their data tabulated in Tables I, II, and III, attached after references. Let us focus on the 63 (30 tolvaptan, 33 placebo) from the heart failure studies who were more severely affected, as displayed below:

TOLVAPTAN Heart Failure Studies 156-01-232, 156-03-236. (63 patients in NE quadrant))



A major deficiency of this submission of old data was the lack of narrative information from so many of the 63 cases (see attached EXCEL table submitted as a supplement to this review). Only 12 of 30 of the heart failure cases randomized to tolvaptan and 6 of 33 who were randomized to placebo had narratives, and many of them were of such poor quality that they provided little sound information that could be used in differential diagnosis of what might have caused the abnormalities in liver tests found. Although the eDISH program did provide time-course graphics for all of the 63 patients who showed both ALT and BLT elevations, much uncertainty remained and the retrospective attempt to determine probable causes for the liver test abnormalities was not convincingly effective. It is likely that the long time passage for cases treated all over the world made the sponsor's narrative writers left with nothing but case reports to use in attempting to write the stories of the cases. It seems unlikely that the sponsor will be able to do much better in this retrospective attempt at re-diagnosis, even with greater efforts and expenditures. We are left with much uncertainty as to the real causes of the abnormalities found in most of these cases.

In the EXCEL tables there were no cases listed from the 1996 cirrhosis Study 203 because none showed ALT elevations. Table I, shows the 11 cases of hyponatremia subjects, all studied in the United States in 2002-2003; Table II, the 30 cases with heart failure who had been treated with tolvaptan 30 mg daily for sometimes long periods of time, over a year in four, over two years in one, and more than 6 months in another 11 cases; and Table III, the 33 cases who were assigned to placebo or other control regimens for over a year in 6, more than 6 months in another'10 patients, of the 33. In total, of the 74 such cases, 35 on tolvaptan, and 39 on placebo, approximately equal numbers of patients on each, there was no imbalance in the incidence, but no adequate assessment of likely causality could not be done using the data provided. For many but not all of those patients, narrative summaries of the clinical course and other information were provided by the sponsor, and time-course graphs of ALT, AST, ALP, and BLT for all submitted data for those patients were available via eDISH.

The sponsor prepared graphic displays, using their own versions of our eDISH program (see the Watkins' report [28 October 2012] in the sponsor's Risk Mitigation Proposal of 13 November 2012.), but only for the initial ALT-BLT x-y plots (both with log10-transformations to keep values in somewhat more comparable ranges, since ALT tends to vary far more than BLT), with a point showing one pair of values for each subject. Although Watkins did show selected time courses of ALT, AST, and BLT, the sponsors did not submit any graphic displays of the time-courses of all the data (ALT, AST, ALP, and BLT) for a given subject over the entire period of observation in the study.

*Comment: The sponsor showed only the group ALT-BLT plots, and no time- courses for individuals, perhaps because they mistakenly considered points in the right upper quadrant (or "NE" in the parlance of Ted Guo and the eDISH program) as diagnostic of "Hy's Law." That is a totally incorrect interpretation. Hy Zimmerman's adage was "**drug-induced** hepatocellular jaundice is a serious lesion, with substantial likelihood of mortality," and not just a pair of abnormal serum chemistry values. The observation has been repeatedly confirmed in decades since, both at FDA and in academic reports. However, the clinical adjudication of probable causality is a medical process of careful differential diagnosis to establish the most likely cause of the abnormal findings, a process of reasoning and information gathering and weighting familiar to and practiced by clinicians, but not by statisticians, pharmacologist, toxicologists, or other preclinical scientists., A time course of changes is a clue to possible causal relationships, for if jaundice results (follows or is coincident with) from loss of liver cell functional capacity to remove bilirubin from blood plasma as it circulates through the liver, then causal relationship becomes more likely. Bilirubin elevations that precede the ALT rise are far more likely to have another cause such as inherited Gilbert syndrome (reduced ability to conjugate bilirubin with glucuronide), biliary tract disease, or some cholestatic problem. Because there is no accurate or dependable pathognomonic biomarker for diagnosing drug-induced liver injury, it is necessary to consider all of the many possible causes for the observed abnormal findings, many of which do have truly accurate diagnostic biomarkers, and eliminate them to show that DILI cannot be excluded confidently, or find some other very likely cause that eliminates or makes DILI very unlikely. Diagnosis of the probable cause requires much more information than just a pair of abnormal liver tests. Most valuable is a well written medical narrative, discharge summary, or death summary composed by a physician, but not by a research assistant.*

Issues on which DCRP wanted feedback in the initial consultation of 29 November 2012 were:

- **Based on the time-course of serum transaminase elevations observed, is it likely that periodic monitoring of liver enzymes would minimize the risk of developing significant liver injury?**

Monitoring of serum enzyme activities in labeling assumes that it will be done and the results both interpreted and acted upon appropriately. Reality has shown repeatedly that this is not done consistently or for long. If it isn't done, it won't minimize risk of detecting more serious liver injury and subsequent dysfunction. Therefore, experience has shown it isn't likely to work.

- **What do we know about dose-response as it relates to DILI in general? Duration of therapy? Because of the low exposure to tolvaptan for hyponatremia (both in the clinical trials and postmarketing) it is not surprising that we have not seen cases, but the sponsor asserts that this may be because the dose and duration of therapy for hyponatremia is lower and shorter, and therefore this risk may not apply to this population. Is this consistent with our experience with other drugs?**

After drugs have been evaluated during development to detect and eliminate compounds likely to cause predictable dose-related hepatotoxicity, the form of idiosyncratic DILI seen in humans both before and after marketing tends to be rare, dependent more on individual characteristics of the people being treated (therefore "idiosyncratic"), and less clearly on the dose. This is due to the increased susceptibility of a few people to show liver injury at doses well tolerated by most people, for reasons not yet known, This susceptibility is actually dose-related but often at a far lower range of dosing. We cannot at present identify those individuals likely to show initial susceptibility to liver injury or who cannot adapt to repeated exposure; only observation will tell us. Genetic biomarkers of susceptibility are only in their infancy, and are still far too general for individual prediction.

There have been at least two rather clear situations in which duration of dosing showed very definite effects: fialuridine and bromfenac. Both drugs seemed to be tolerated for short times but then showed very severe, even irreversible and fatal liver failure on prolonged exposure.

- **Is there any reason to think that patients with ADPKD would be at increased risk for hepatotoxicity with tolvaptan?**

Not from the polycystic renal disease itself, but from the need for very long or life-time drug treatment administered in hope of slowing the inexorable progression of this genetic disorder. Treatment could conceivably to be started in childhood when the diagnosis might be made by finding hypertension or hematuria in a child, confirmed by testing for genetic markers PKD1 or PKD2. There could possibly be a duration-related factor of importance, in addition to perhaps a requirement for higher doses. This is something that will need to be considered and explored, in comparing the data for the short-term use of SAMSCA for correction of hyponatremia, and the very long-term need for " (b) (4) *in hope of slowing progression of ADPKD to renal failure.*

Now to consider the cases in ADPKD studies that caused concern at Otsuka and resulted in their raising questions to DCRP at the pre-NDA meeting on 19 July 2012, and to deciding on the basis of full risk assessment of the ADPKD data if they would submit with the NDA a Risk Evaluation and Mitigation Strategy (REMS). After reviewing the data, Otsuka decided that a REMS would be appropriate for tolvaptan in treating ADPKD, to focus education about the risk of possible hepatotoxicity and strategies to reduce the risk of liver injuryy. A Risk Mitigation Plan Proposal was submitted 13 November 2012, involving measures beyond labeling, to include:

1) A Medication Guide to be provided to patients before starting tolvaptan, educating them on the need for liver function testing prior to starting therapy, regular monthly testing for the first 18 months, and the need to self-monitor for signs or symptoms, prompt reporting, and interruption of treatment followed by immediate retesting.
2) A Communication Plan for healthcare providers likely to prescribe tolvaptan for ADPKD treatment, conveying to them the risk of potential hepatotoxicity especially within the first 18 months, and periodically thereafter, and to re-educate patients on the same points listed above, plus a Dear Healthcare Provider Letterwithin 60 days of approval and every 3 years. Copies of the letters were to be sent to appropriate professional and patients organization, and posted at a Tolvaptan ADPKD REMS website, with full prescribing information and the Medication Guide.
3) Additional voluntary safety measures to be developed by Otsuka, as necessary (but not specified).to ensure effective education of both patients and prescribers.
4) Otsuka proposed to submit REMS assessments to FDA at 18 months, 3 and 7 years after initial approval.

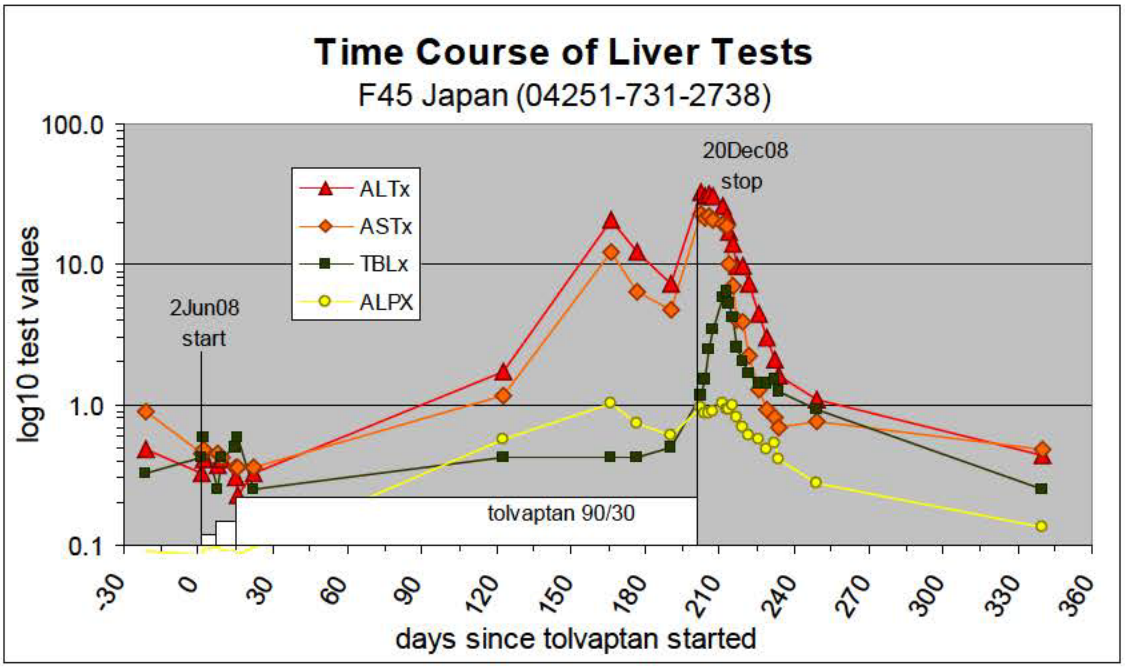
In reaching this conclusion to accept a REMS, the sponsor reviewed the findings in 1444 adult patients studied in the placebo-controlled pivotal trial 156-04-251, with an open-label follow-up study 156-08-271, plus an additional ten clinical pharmacology studies in Japan, Korea and USA in both patients and healthy subjects, and another placebo-controlled trial 156-09-290 and five open-label studies in patients. Patients treated with tolvaptan showed statistically significantly slower increase in kidney volume of 2.80%.year, compared to 5.51%/year in patients on placebo.

Reduced incidence rates of a combined (declining renal function (serum creatinine concentration, renal pain, progressive hypertension, and albuminuria) biomarker showed 0.439/year in patients on tolvaptan, compared to 0.500/year on placebo, driven mainly by renal function and renal pain. Renal function, calculated by Cockcroft-Gault or Modification of Diet in Renal Disease formulae also favored tolvaptan – 2.61 vs -3.80 for placebo, as 100/serum creatinine, mg/dL.

Of 961 patients treated with tolvaptan for an average of 2.4 years, and 483 treated on placebo for an average of 2.7 years, the tolvaptan-treated patients showed considerably higher incidence of thirst, polyuria, nocturia, and pollakiuria (frequency) than those on placebo, and slightly more dry mouth, fatigue, diarrhea, dizziness, and glaucoma. Incidence was higher also for elevations in serum ALT and AST, uric acid, sodium, and cholesterol. Elevations of ALT or AST above 10 times upper limit of normal (xULN) were seen only in tolvaptan-treated patients, and there were two who also showed total bilirubin elevations. A set of 46 patients treated with tolvaptan who showed elevation liver tests was selected for individual case review and adjudication for the most likely cause by the panel of four hepatologists (Watkins' report 28 October 2012).

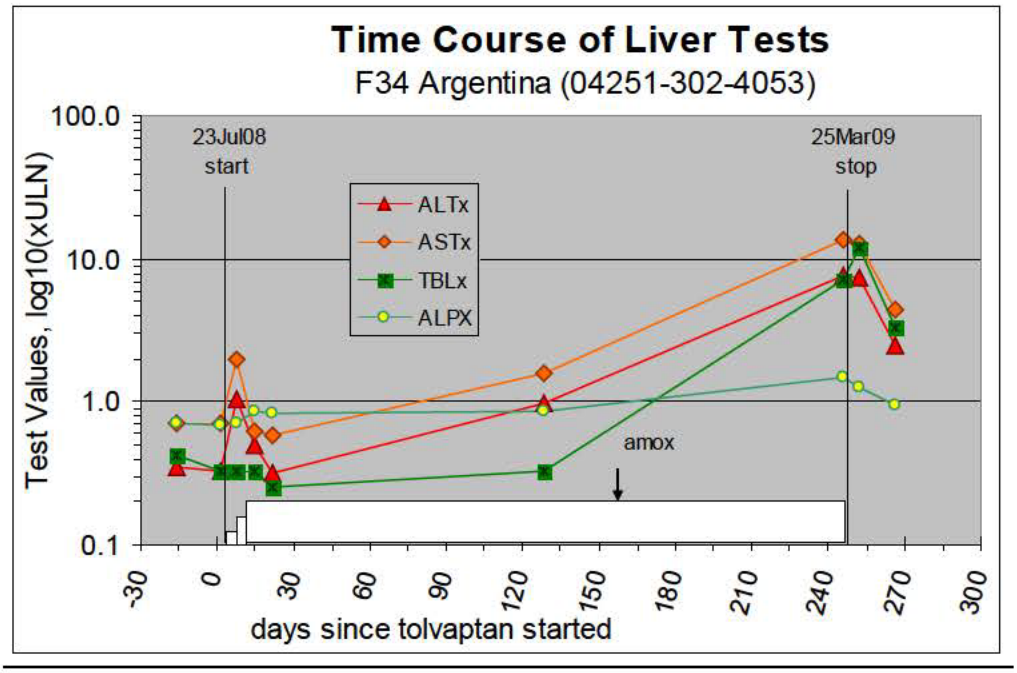
The Otsuka report of 13 November 2012, "Risk Mitigation Plan Proposal," reviewed briefly the history of developing tolvaptan for a new indication of slowing progression of ADPKD in adult patients. Before submitting the new NDA 204441 for the ADPKD indication, the sponsor proposed a full risk assessment of the data obtained in study of adults with that disorder since submission of IND 072975 in 2005. Let us review in a little more detail the index cases of apparently serious liver injury occurring in patients under treatment with tolvaptan.

The first of the cases (04251-731-2738) appeared in November 2008, in Japan (at site 731 (b) (6)) in a 45-year-old woman (date of birth (b) (6)), after she had been on tolvaptan since 2 June, starting at 45/15, increasing to 60/30, and to 90/30 mg/day at weekly intervals. She complained of nausea and stomach discomfort on (b) (6) (Day 166), and marked elevations of ALT and AST were found, repeat testing of serum enzyme activities on 25 November and 8 December showed them to have declined somewhat but her nausea persisted and became worse on (b) (6) (Day 202) at which time her serum bilirubin began to rise (without visible jaundice) and the ALT and AST were even higher. She was hospitalized for imaging studies and investigation, but no other cause was found, the tolvaptan was stopped. Her bilrubin continued to rise, with jaundice, despite declining serum enzyme activities, and IV prednisolone was initiated on (b) (6) (Day 213). Symptoms subsided, test values declined, oral prednisolone was substituted on 7 January, and she was discharged 17 days later (Day 237).



Comment: This episode of liver injury, with nausea and jaundice, prolonged hospitalization, treatment with steroids, was thought by the investigator to be caused by tolvaptan. The experts also agreed that the findings were probably (>50-75% likely) due to tolvaptan. The slight ALT and AST rises in early October (Day 123) were not rechecked for almost six weeks. The rate of enzyme release began to slow immediately upon stopping the drug, but the bilirubin continued to rise for 11 more days, and she was clinically ill. The injury was almost entirely hepatocellular, with almost no increase in alkaline phosphatase.

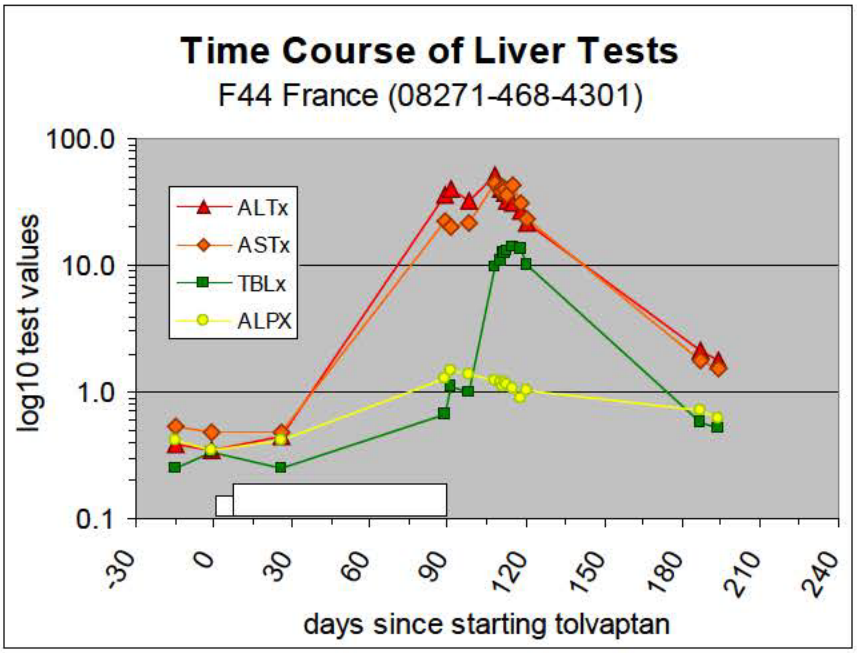
The second case appeared in Argentina a few months later, in March 2009, in a 34-year old woman (04251-302-4053; date of birth (b) (6), site 302, (b) (6)). treated since (b) (6) with tolvaptan starting at 45/15 and increasing to 60/30 and to 90/30 mg/day at weekly intervals. She had a history of urinary tract infections, nephrolithiasis, and hypertension. She was not closely followed, appeared (b) (6) (Day 246) with obvious jaundice, nausea and vomiting, and was found to have marked elevations of AST and ALT. The tolvaptan was stopped that day. She gave a history of a toothache at the end of December (Day 158), for which she was given a single dose of 8 g amoxicillin-clavulanate. She was seen again on 31 March and 14 April, after which she refused to return, said she felt better, and her liver test abnormalities were declining. The investigator spoke with her by telephone on 24 September, but she did not return and was removed from the study.



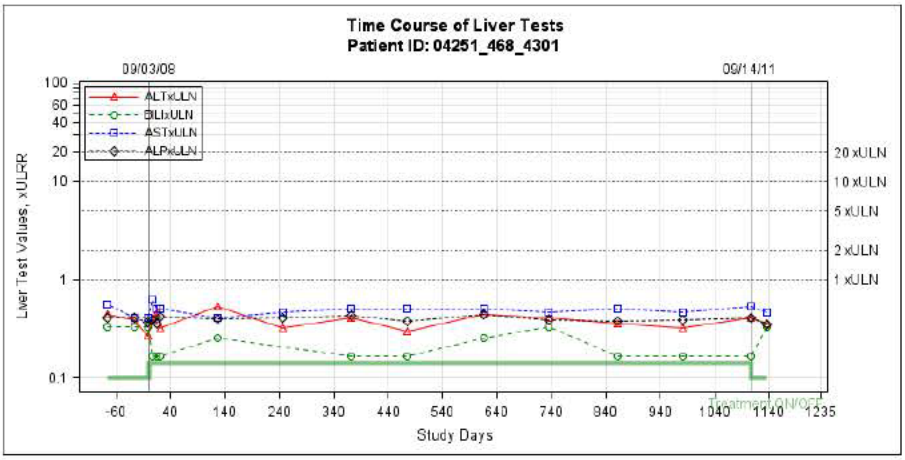
Comment: The investigator judged that the liver injury was relatively mild but tolvaptan-related, and the sponsor was said to have agreed. The expert hepatology panel also decided that the liver injury was probably tolvaptan-induced. In retrospect, there was a very slight bump upward of the AST activity after the first dose increase, but the second dose increase was tolerated with no recurrent rise. It is unclear why the AST was somewhat higher at peak than ALT, but both enzyme elevations subsided quickly after stopping tolvaptan.

The third case occurred in France in January 2012 in a 44-year-old woman ((b) (6), 08271-268-4301, date of birth (b) (6) site 268 (b) (6)) who had participated for three years (2005-8) in study 04-251 but had been randomized to placebo. She had reported no problems except for a bout of tonsillitis and a knee sprain not attributable to study drug. She entered open-label study 08-271 on 28 September 2011, started tolvaptan 45/15 on (b) (6), increasing to 60/30 and 90/30 on (b) (6). Her history included hematuria, proteinuria, kidney pain urinary infections, hypertension, smoking, and ectopic pregnancy. On (b) (6) (Day 89) she showed elevated serum ALT and AST, with no symptoms or notable bilirubin

elevation, but tolvaptan was stopped the next day. Despite this, she developed hot flushes, pain in the right upper quadrant, dark urine on (b) (6) (Day 98), and 10 days later was obviously jaundiced. Liver test abnormalities then subsided slowly over months. Tests in hospital for viral hepatitis A, B, C, and E showed no acute infection, liver biopsy only cytolytic inflammation, and no alternative explanation was found, leaving only tolvaptan induced. The investigator assessed the liver injury as moderately severe, probably related to tolvaptan; the sponsor as "possibly" so.



This patient's earlier three-year participation in study 04-251 on placebo, during which she showed no liver test abnormalities, as may be noted in the eDISH time-course plot shown below:



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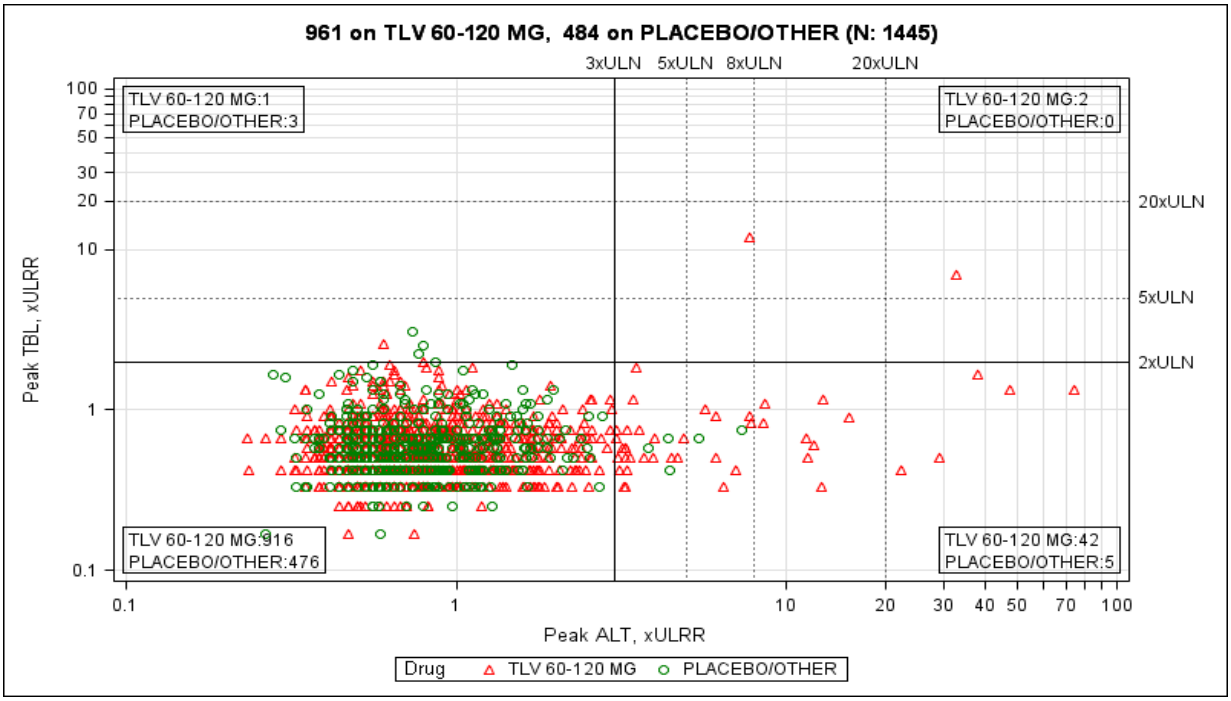
Comment: The expert hepatology panel consensus was that the findings were highly likely (>75-95% likely) tolvaptan-induced. We are all looking at the same information, and we concur in this third case. They also reviewed several of the other cases chosen for them to review, cases in which there were very notable increases in serum ALT and AST activities, but without jaundice or significant rise in serum bilirubin concentration, of which several appeared to be

tolvaptan-induced, with no alternative causal explanation. They found significant preponderance of cases attributable to tolvaptan versus placebo in those patients with ADPKD.

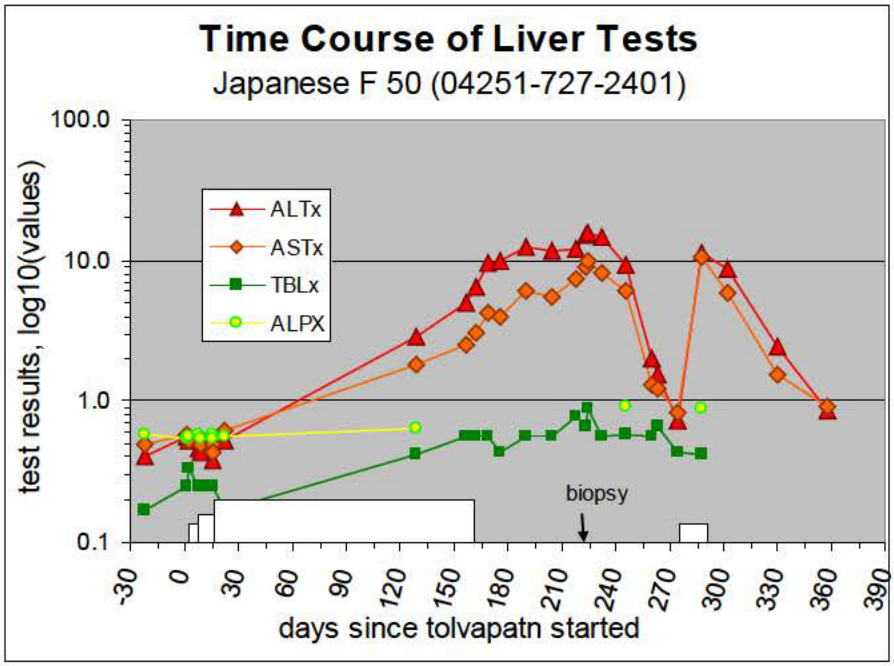
However, in their review of the earlier experience in non-ADPKD patients with heart failure, hyponatremia, and cirrhosis they selected 28 cases of serum ALT increases >5xULN ***AND*** *BLT>3xULN they found none clearly attributable to tolvaptan. They concluded, as have we, that patients with ADPKD may have greater susceptibility to tolvaptan-induced liver injury than patients with heart failure, cirrhosis, and hyponatremia, with no clear explanation as yet, and that the problem is idiosyncratic rather than simply dose-related. Extrapolation of the results based on extensive previous experience with DILI in general suggests that roughly 10% of patients who show drug-induced hepatocellular jaundice may progress to liver failure and risk of death or need for transplantation.*

The point that patients with ADPKD may be different in their risk of liver injury from tolvaptan than were previously treated patients with water retention from cirrhosis or heart failure or with hyponatremia from other causes may be seen by glancing at the current pivotal trial data for the controlled study 156-04-251 in which almost a thousand patients with ADPKD were treated with tolvaptan, compared to about half that number on placebo.



At a glance it may be seen that there was a marked preponderance of tolvaptan-treated patients (red triangles) who showed significant serum ALT elevations of >8 and >20xULN (seen in the right lower quadrant of the plot) compared to none on placebo, and two more who also showed serum total bilirubin elevations (right upper quadrant), described above as 04251-731-2738 and 04251-302-4053, both patients meeting criteria for “Hy’s Law” cases because of probable cause by tolvaptan. Of the 961 patients randomized to tolvaptan there were two Hy’s Law cases, plus another 42 with ALT elevations >3xULN without bilirubin increase, an incidence of of 4.6% (unadjudicated), compared to 5 of 484 (1.0%) among those on placebo. In addition to the two

Hy's Law cases, it may be noted fron the eDISH plot that there were 5 patients who showed ALT peak values >20xULN, and 8 more > 8xULN, compared to none among placebo patients. Of particular interest are two patients who showed serum aminotransferase elevations of considerable magnitude but little or no rise in bilirubin concentration before the tolvaptan was stopped, after which the enzyme elevations subsided, only to recur when tolvapatan was restarted (a positive rechallenge).



Comment: A Japanese woman 50, diagnosed with ADPKD at age 44, was started on 45/15 daily of tolvaptan on 11 September 2007, increased a week later to 60/30, and a week later to 90/30 (120 mg daily). Modest elevations of aminotransferases were noted 18 January 2008 (Day 129) but greater increases on Days 257 and 162 led to interruption of treatment on 20 February 2008 and closer follow-up. Aminotransferase elevations, even somewhat greater, persisted for about 12 weeks until May (Day 246) with only slight rise in total bilirubin within the normal range, before finally subsiding and normalizing over 4 weeks in June (Day 274). Liver biopsy on 21 April (Day 223) showed centrilobular inflammation and focal necrosis, portal-central bridging and slight portal fibrosis, diagnosed as drug-induced liver injury. After subsidence of the liver test abnormalities, restart of tolvaptan at the low dose of 45/15 daily on 11 June (Day 274) led to almost immediate recurrence of aminotransferase elevations and drug was permanently stopped on 25 June 2008 (Day 288). Follow-up of the patient showed no development of jaundice or symptoms over the next 10 weeks and her elevated aminotransferases subsided to normal. There was no increase in serum alkaline phosphatase activity to indicate cholestasis or biliary disease, and the reaction appeared almost purely hepatocellular.

Another case followed shortly thereafter, at site 104 in Chicago IL:

Comment: This patient, a 49-year-old woman in Chicago, was diagnosed with ADPKD at age 16, and was started on tolvaptan in Study 251on 9 November 2007, at 45/15 for a week, then 60.30 for another week, and then on 90/30 (120 mg daily, the larger dose in the morning and lower dose in the evening). A very slight rise in ALT was recorded after 8 months (Day 246) but when a much greater rise occurred four months later (Day 352, 25 October 2008), tolvaptan administration was interrupted. Both ALT and AST activities subsided and normalized over the next 15 weeks and tolvaptan was restarted 18 February 2009 (Day 464) at the lower daily dose of 45/15. The prompt rise in aminotransferases led to permanent discontinuation of tolvaptan in less than two weeks on 2 March 2009.

It cannot be known whether continued administration of tolvaptan might have caused rise in serum bilirubin concentration or other evidence of whole liver dysfunction in either case, if the drug had been continued longer, but cases such as these pose substantial concerns about the possibility. Nothing in these patients' histories suggested any reason for special susceptibility to tolvaptan-induced liver injury, which must be considered idiosyncratic.

It has been noted that there appears to be a marked contrast between the review findings for patients with water retention from heart failure, cirrhosis, or hyponatremiua from various causes, with respect to their lack of susceptibility to tolvaptan-induced liver injury, compared to that seen in patients with ADPKD. The sponsor was not quick to realize this, and it took from the first real Hy's Law case in Japan in November-December 2008, the second in Argentina in March 2009, and then the third in France in January 2012 for the problem to be recognized, or at least acted upon by convening the panel of four expert hepatologists who reviewed cases last summer and early fall 2012 and issued the Watkins' report 28 October. It also slowed submission of the recently received NDA 204441, discussed back in July 2012, until 1 March 2013.
The new consultation request was sent 2 April 2013 as a supplementary set of questions following those posed in November (see above, page 9). Those questions, for which DCRP would like comments, were:

1. Otsuka has provided an eDISH plot and narratives of 60 subjects for the pivotal trial 156-04-251. Do you agree that they have provided narratives for all subjects who may have had tolvaptan-induced liver injury? Are all narratives adequate? Please provide feedback about adequacy of the information provided as quickly as possible, as reviews for this NDA must be completed by the end of June.

Comment: It is not possible to be certain that Otsuka has submitted narratives and clinical data for <u>all</u> subjects who may have had tolvaptan-induced liver injury, because we are dependent on their detection systems and reporting. What they have submitted is of fairly good quality and allows reasonable assessment of the problem. Although not every case submitted has been reviewed again in detail here, we have examined the more serious cases, plotted, reviewed, and discussed findings in the consultation response above, sufficient to appreciate the seriousness of the problem. In order to allow time for thoughtful discussion of the problems and consideration of issues raised in this response, we aim to submit it by the end of May (31st). In view of the high visibility of the liver injury issue, it seems unlikely that Otsuka would be negligent in reporting

cases, especially serious ones. Whether or not their systems for detecting cases of liver injury or dysfunction were fully adequate is another matter, but it was not the aim of any of the studies to detect meticulously and investigate cases of possibly tolvaptan-induced serious hepatotoxicity. In view of the time elapsed, and the worldwide scope of the studies, we shall probably have to take the information we have received as nearly all we can expect.

2. If the information is adequate please provide an estimate with 95% confidence intervals for the expected incidence of tolvaptan-induced liver injury in patients with ADPKD if tolvaptan is approved for treatment of ADPKD.

Comment: Although such an estimate and exact confidence intervals would be nice to have, it is not so easy to provide. The important consideration is that the severity of liver injury is not a simple binary problem, but a range of severity progressing from just serum enzyme elevations that may be transient and reversible, to more severe cases with enough hepatocellular injury to cause some dysfunction of the whole liver, with reduced ability to clear the plasma of bilirubin, conjugate it and excrete it into bile, or to synthesize proteins such as albumin (not very sensitive) or prothrombin so that the international normalized ratio (INR) is raised. Beyond that level of injury even more severe hepatocellular dysfunction causes clinical illness, jaundice, diasability, hospitalization; even more severe injury results in acute liver failure, with life-threatening risks of secondary renal failure (hepatorenal syndrome), encephalopathy, bleeding, and consideration of need to transplant the liver to avoid death. The less severe levels of drug-induced injury are far more frequenly seen, but are often reversible because of the great capacity of opst people's livers to adapt and change themselves so that the drug is tolerated and can be continued. We are caught between the two horns of stopping the drug too soon and unnecessarily, and continuing it too long to the point of progressive irreversibility. This cannot be reduced to a single number with confidence intervals.

3. Please identify all other drugs with similar or higher rates of drug-induced liver injury (DILI) that are marketed in the USA. Please describe previous FDA regulatory action (e.g., approval, non-approval, withdrawal) on other drugs with similar rates (or lower) rates of DILI.

Comment: To answer this request would require a book, or at least a chapter. We have learned that DILI comes in many guises, is not just one narrowly defined disorder, and varioes both in its severity and in the types of responses that individual patients show. Fortunately it is usually quite rare, at least in its more serious degrees of severity. It cannot be treated as ace simple binary diagnosis: present or not. The incidence of the less serious forms, just elevations of serum aminotransferase activity without symptoms of evidence of whole organ dysfunction (such as jaundice or prolonged prothrombin time (elevated INR), is far greater than that for the more serious degrees of liver injury that are extensive enough to reduce the ability of the whole liver to carry out its true functions such as clearing plasma of bilirubin and synthesizing critical proteins need for controlling bbleeding. Once again: serum enzyme tests are not measues of liver function, should not be termed thoughtlessly as "LFTs", and their degree of elevation is NOT a valid measure of the severity of the injury. The severity of the injury is measurable only by how much impaired are the true functions of the liver. That is why we use the combined peak values of both ALT and BLT as a screening test to identify patients who deserve more detailed study and investigation to determine the time course and probable cause of the abnormal findings. Use of

eDISH has been badly misinterpreted by statisticians and toxicologists in the pharmaceutical industry to diagnose "Hy's Law," because they make no attempt to determine the probable or likely cause of the findings, the very first point emphasized by Dr.Hyman Zimmerman when he stated that ***"drug-induced hepatocellular jaundice is a serious lesion"*** *with substantial (10 to 50%) mortality.*

FDA (CDER) has not approved a drug since 1997 that subsequently had to be taken off the market because of induced hepoatotoxicity, following the disastrous approvals in January 1997 of troglitazone, and in July 1997 of bromfenac, both of which drugs promptly began to kill patients with acute liver failure. Bromfenac was withdrawn in June 1998, but it took until March 2000 to overcome the political and financial arguments of the troglitazone sponsor, until less dangerous –glitazones (rosi- and pio-) were available. In the summer of 1998 we began to plan a program of educating FDA reviewers (mostly CDER, some CBER, a few CDRH) about hazards of drug-induced liver injury, extended in 2001 to include industry and academia, and continuing annually (DILI Conference XIII was just held 20-21 March 2013; the entire meeting, the slides shown, comments made about them, and full texts of discussions that followed were available on the internet last week (go to www.aasld.org , point to heading Training/Education, drop down and select Drug-Induced Liver Injury 2013 Program), or via the FDA public web site, but not Inside FDA, (enter "drug liver toxicity"into the search box). Programs back to April 1999 are posted there, along with detailed slides and texts from recent years since 2009 (text only at FDA website because of 508 rules).

*Because of this increased awareness of the problem of dangerous hepatoxicity of drugs, we developed the eDISH (**e**valuation of **d**rug-**i**nduced **s**erious **h**epatotoxicity) to identify cases of special interest for further diagnostic investigation for selected patients in large clinical trials, using the time courses for all liver test results available for a given poatient, and clinical narratives preferably prepared by the treating or investigating physician). The first major use of the system resulted in the rejection in 2004 for approval of ximelagatran (EXANTA, AstraZeneca) despite its approval in Europe and vigorous protests by the sponsor, who finally conceded in 2007 to study patients who had shown liver injury versus those who had not, and discovered that patients with a genetic marker in the HLA system, DRB1*0701, had increased susceptibility to sustain hepatotoxicity from the drug, as reported by Kindmark et al. in 2008 and Andersson et al. in 2009.. The FDA also refused* (b) (4) *following publication of work by Singer et al. showing that patients with HLA haplotype DRB1*1501 were particularly susceptible to luniracoxib-induced liver injury.*

On the other hand, isoniazid, useful for preventing tuberculosis, has been known for many years, since the work of Mitchell et al. in 1975 revealed the high incidence of elevations of serum aminotransferase activities in patients on prophylactic treatment against tuberculosis. Some 15-20% of patients starting isoniazid (only) may show significant elevations in activities of aminotransferases, often asymptomatic, but nearly all of them (>99%) show adaptation by the liver to the drug, and therefore become tolerant to its continuation or resumption. It was then shown that it is not necessary to stop the drug permanently in all those who show only initial serum enzyme increases, although those rare cases, 1 or 2 per 1000, who failed to adapt are at serious risk for progressive injury and fatal liver failure if the drug is not stopped. The classic observation by Nolan et al. in 1999 was that routine laboratory monitoring over-diagnosed the problem, and that clinical monitoring and vigilant follow-up based on education of both patients

and physicians was far more effective in preventing serious hepatotoxicity from isoniazid while still allowing its beneficial effects in those who could adapt to it.

It is overly simplistic just to list drugs that are still on the market with similar or higher rates of at least some liver injury. Tacrine and heparins induce very high rates of minor serum transaminase elevations, but not progressive, severe liver dysfunction leading liver failure and death or need for transplantation. The ratio of severe injury and life-threatening dysfunction to minor "transaminitis" from various drugs is not constant, and a single figure is not valid for each drug. This discussion certainly does not cover all drugs, but is illustrative of the problem faced. As far as experience to date with use of tolvaptan is concerned, we have not yet found any case of explosively rapid progression to irreversible liver damage and fatality as seen with troglitazone ---- BUT experience with tolvaptan is very limited. It did not appear to cause serious liver injury in patients treated with SAMSCA under the previously approved indications, but even that was rather limited exposure in terms of numbers, shorter exposure times, at a lower dose, si it is not statistically proved that patients with ADPKD are different. More information will be needed, and caution is advised.

4. A single dosing regimen was tested in the pivotal trial 156-04-251. In your experience, are small changes (<0.5 log) in dosing likely to have significant effect of the incidence of DILI?

Comment: The choice of a single dose of 90/30 (120 mg daily) for all patients did not appear to be well established by the pharmacologic data prior to that, and appears to have been driven by marketing considerations that "one dose fits all." It is far more likely that the hepatotoxicity seen in some patients with ADPKD is idiosyncratic, depending on particular sensitivity of some individuals, than simply a dose effect. Change of <0.5 $\log_{10}$ (about three-fold) are less likely to be important than individual susceptibility, although the evidence for that is so far flimsy. It was of interest that the very prompt rise in serum enzyme activities upon rechallenge in the two cases discussed above (both from Study 04-251: the Japanese woman 50, 727-2401, and the woman 49 from Chicago, 104-0605) occurred at half the dose that had caused the more delayed initial rise in serum enzyme activities.

5. Otsuka asserts, in the Watkins Tolvaptan Safety Report, that there were 3 cases of DILI among 860 ADPKD subjects exposed long term, and no cases in the 589 non-ADPKD subjects. If the true incidence is 3/860, then no cases will be observed in 589 subjects about 13% of the time. Please comment on the apparent difference in rate of incidence in the two clinical programs. In your experience, is DILI likely to vary among patients based on indication, or is it more likely that the rate of DILI is independent of indication?

Comment: This statistical comparison is not at all compelling, as is pointed out. However, the whole clinical trial program for ten years from 1999 until approval, and the several thousands of patients treated since approval, did not disclose a problem with liver injury from the SAMSCA version of tolvaptan. This suggests, but certainly does not prove, that patients with ADPKD may be different in some way. We know that they differ in a least one respect, a genetic inheritance of PKD1 or PKD2 genes that lead to renal tubular cyst development and slow growth. It is not known whether this might also confer some increased risk of hepatocellular injury (apart from the also associated development of liver cysts). The liver injury observed was not that of a slow

cyst-growth obstructive type, but of rapid, although delayed and seldom immediate, injury to the hepatocytes in affected individuals. The sponsor should be tasked to investigate whether PKD1 or PKD2 are associated with an increased chance of hepatocellular injury in patients with the disease being treated ADPKD.

All this states the problem, but does not address what should be done about it. The sponsor has submitted a Risk Mitigation Plan (proposal of 13 November 2012), even before submission of the NDA 204441 itself. A Medication Guide to supplement appropriate labeling is proposed, to educate patients on the risk of liver injury, the importance of monthly blood testing foe evidence of early liver injury for at least 18 months, the need to self-monitor daily for early symptoms of liver dysfunction, and to report them promptly to their physicians so that investigation can be done to determine the probable cause, interrupting drug use until the questions are resolved. These are reasonable provisions to implement. Review of the sponsor's proposal by the Risk Evaluation Mitigation Strategy team of OSE, has emphasized the educational aspects of the proposal, but considers monthly blood testing unnecessary, based on the long history of failed laboratory monitoring plans.

Comment: Both the sponsor and the OSE Division of Risk Management (DRISK) are right, but neither goes far enough. We have learned that sensitive serum enzyme tests, such as high alanine aminotransferase activities, may occur before symptoms, but are not specific or diagnostic. Conversely, in some patients symptoms may develop within the 28- or 30-day"monthly" monitoring intervals, demanding immediate recheck of the serum tests within a few days. Use of routine laboratory monitoring often has not worked because it simply is not done well, results are not known or used, and both physicians and their patients and physicians grow weary of normal test results, especially if they do not understand why the monitoring is being done. Even with the drug troglitazone, despite reported deaths from its use, monitoring was not done well by many physicians (Graham et al., 2001, 2003).

It is recognized that there is no other known treatment for ADPKD, but the studies done to date have been inadequate to answer many questions. No experience has been sought for use in children, in whom the genetic defect might be recognized, especially if some treatment was to become available. The optimal dose, for what time, in which patients, needs to be determined better. Whether some patients may have different susceptibility to liver injury is a critical point that still needs to be established. Because there is no biomarker to predict or diagnose DILI, only careful clinical observation can serve to protect patients from potentially severe harm from liver failure. That hasn't been seen so far, but the exposure has not yet been adequate in number or time to be reassuring. How to make the treatment safely available to those who need it, without being overly cautious and excluding those with trivial, transient, reversible serum enzyme rises, but not missing the few who may progress to severe injury, dysfunction, and liver failure, is the difficult path to find.

Recommendations:

1. Accept the sponsor's proposal for monthly monitoring of serum ALT, with vigorous attempts to educate both patients, or their parents, and physicians as to the reasons and need for it, to have the patients also informed of the results, and insist that their doctors know them.

2. Accept also the plans for education emphasized by the REMS group of OSE, but not their proposal to eliminate monthly laboratory testing.

3. Carry out pre-treatment baseline evaluation of liver tests (ALT, AST, ALP, BLT and BLD) at least twice before starting tolvaptan, and repeat the whole set immediately in case of elevated serum enzyme activities or suspicious symptoms, interrupting tolvatan administration until the probable cause of the problem is found.

4. .Establish a registry to keep careful track of a cohort of the first 5000 patients who are treated, to be supported by the sponsor but maintained by an independent agency such as the National Institutes of Health, with annual reporting for five years.

5. Carry out studies to investigate the role of PKD1 and PKD2 on both the rate of respoinse to tolvaptan, as measured by imaging measurements of renal volumes, with parallel testing of renal functions. Additional genome-wide testing, as done earlier for ximelagatran and lumiracoxib, should also be undertaken by the sponsor.

John R. Senior, M.D.,

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31 May 2013

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Attach Excel Table I, II, III (Tables_SAMSCA_NEs.xcl)

Tolvaptan (SAMSCA, Otsuka drug 176): studies of cirrhosis, heart failure, hyponatremia –
(selected cases with {peak ALT>3xULN & peak total bilrubin>2xULN } (eDISH RU or NE quadrant)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Date: July 8, 2013

To: Members of Cardiovascular and Renal and Risk Management Advisory Committees

From: Division of Risk Management
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology (OSE)

Subject: Risk Management Considerations

Product: Tolvaptan (NDA 204441)

1 INTRODUCTION

This memorandum summarizes Otsuka Inc.'s proposed risk evaluation and mitigation strategy (REMS) and provides an analysis of the minimally required risk mitigation tools necessary to address the risk of drug induced liver injury (DILI) associated with tolvaptan.

2 BACKGROUND

2.1 PRODUCT INFORMATION

Proposed Indication

Tolvaptan is an aquaretic that competitively blocks the binding of arginine vasopressin to V2 receptors. Otsuka is currently seeking approval to market tolvaptan (NDA 204441) to slow kidney disease in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).

Product Dosage and Administration

Tolvaptan for ADPKD will be available as 15 mg, 30 mg, 45 mg, 60 mg, and 90 mg immediate release tablets. The proposed initial dosage 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) to be titrated upward to a split-dose regimen of 90 mg (60 mg/30 mg) per day then to a target split-dose regimen of 120 mg (90 mg/30 mg) per day as tolerated. Patients should be maintained on the highest tolerable dose.

2.2 RISK EVALUATION AND MITIGATION STRATEGIES[1]

Section 505-1 of the Food, Drug, and Cosmetic Act (FDCA) authorizes the FDA to require pharmaceutical sponsors to develop and comply with a Risk Evaluation and Mitigation Strategy (REMS) for a drug if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. A REMS is a required risk management plan that uses risk minimization strategies beyond the professional labeling. The elements of a REMS can include: a Medication Guide or patient package insert (PPI), a communication plan to healthcare providers, elements to assure safe use, and an implementation system. FDAAA also requires that all REMS approved for drugs or biologics under New Drug Applications (NDA) and Biologics License Applications (BLA) have a timetable for submission of assessments of the REMS. These assessments are prepared by the sponsor and reviewed by FDA.

Elements to assure safe use (ETASU) can include one or more of the following requirements:

- Healthcare providers who prescribe the drug have particular training or experience or special certifications
- Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified
- The drug may be dispensed only in certain healthcare settings
- The drug may be dispensed to patients with evidence of safe-use conditions
- Each patient must be subject to monitoring
- Patients must be enrolled in a registry

Because ETASU can impose significant burdens on the healthcare system and reduce patient access to treatment, ETASU are required only if FDA determines that the product could be approved only if, or would be withdrawn unless, ETASU are required to mitigate a specific serious risk listed in the labeling. Accordingly, the statute [FDCA 505-1(f)(2)] specifies that ETASU:

- Must be commensurate with specific serious risk(s) listed in the labeling.
- Cannot be unduly burdensome on patient access to the drug.
- To minimize the burden on the healthcare delivery system, must, to the extent practicable, conform with REMS elements for other drugs with similar serious risks and be designed for compatibility with established distribution, procurement, and dispensing systems for drugs.

[1] FDA Draft Guidance for Industry – *Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications*, dated September 2009. Available at: http://www.fda.gov/downloads/Drugs/Guidances/UCM184128.pdf.

3 BENEFIT/RISK CHARACTERIZATION

3.1 INTENDED POPULATION: AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD)

According to a 2008 article (NEJM 359:1477), 300,000 to 600,000 Americans have ADPKD. Hypertension frequently develops during early adulthood (and even during childhood). Pyelonephritis and renal-cyst infections are serious problems requiring aggressive antimicrobial therapy. Kidney failure requiring renal-replacement therapy occurs in approximately 50% of patients and typically develops in the fourth to sixth decade of life. Patients with advanced ADPKD undergo dialysis and transplant to manage their disease. There is no other pharmacologic therapy FDA approved to slow kidney disease in adults with ADPKD.

3.2 EXPECTED BENEFIT

One trial was conducted to support the proposed ADPKD indication. The study included 1445 adult patients with rapidly-progressing ADPKD (as indicated by kidney volume ≥ 750 ml), who were randomized 2:1 to treatment with tolvaptan or placebo for 36 months. Otsuka states in the proposed PI that the relative rate of "ADPKD-related events" was decreased by 13.5% in tolvaptan-treated patients, 44 vs. 50 events per 100 subject-years of follow-up; hazard ratio, 0.87 (95% CI, 0.78 to 0.97); p=0.01. ADPKD-related events were a composite of 1) worsening kidney function (25% reduction in reciprocal serum creatinine during treatment), 2) kidney pain, 3) worsening hypertension, and 4) worsening albuminuria. The result was driven by differences in worsening kidney function and kidney pain with little effect on hypertension and albuminuria. A complete assessment of the clinical benefit is covered under a separate review by the Division of Cardiovascular and Renal Products.

3.3 RISK OF CONCERN: DRUG-INDUCED LIVER INJURY (DILI)

DILI attributable to tolvaptan has been observed in a controlled trial in patients with ADPKD. Otsuka convened a panel of experts on DILI to review the liver safety database for tolvaptan in the treatment of ADPKD. 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 x 10, or about 1:3000 patients (who) receive long term treatment with tolvaptan".

Of note, no cases of drug-induced liver injury have been reported in studies of other indications (i.e., hyponatremia and heart failure). However, one case of a patient developing probable mild tolvaptan-induced liver toxicity (transaminase elevations only) that abated following discontinuation of tolvaptan was reported in the medical literature.

In interpreting this information, the following should be considered:

- Relatively few subjects in clinical studies for hyponatremia and heart failure were exposed long term (approximately 1300 subjects exposed to tolvaptan for > 6 months and about 817 exposed for > 1 year)

- Clinical studies for hyponatremia and heart failure utilized doses of 30 mg once daily, which is lower than the dose of 60 – 120mg daily studied in ADPKD studies.
- Postmarketing utilization of tolvaptan from approval in May 2009 through February 2013 approximately 4,500 patients who received a prescription for tolvaptan from U.S. outpatient retail pharmacies.[2]
- Patients with heart failure, cirrhosis and SIADH can have transaminase elevations related to the underlying disease so determining causation of transaminase elevations is problematic.

Therefore, there is inadequate information available to conclude that DILI associated with tolvaptan is specific to the ADPKD population.

The incidence of DILI in the post-market setting is not expected to differ much from that observed in the clinical trial. However, patients are likely to have more serious outcomes in the post-marketing setting if patients are not followed closely as DILI may progress to severe liver injury. In addition, DILI associated with tolvaptan has not been fully characterized and there is the potential that some cases could rapidly progress to more serious liver injury (i.e. liver failure, liver transplant or death) despite close monitoring and prompt discontinuation of tolvaptan. No treatment for idiosyncratic DILI has been demonstrated to be effective.

4 RISK MANAGEMENT OPTIONS

If approved for ADPKD, a risk mitigation strategy (beyond professional labeling) is required to address the risk of DILI associated with the administration of tolvaptan. The Sponsor's proposed REMS and the Division of Risk Management's (DRISK) proposed REMS are summarized below.

4.1 OTSUKA'S PROPOSED REMS

The Sponsor's proposed REMS includes a Medication Guide (MG) and elements to assure safe use (ETASU), which include prescriber certification, documentation of safe use, pharmacy certification, and a registry.

The following summarizes the Sponsor's proposal based on the submissions received on March 1, 2013 and updated on June 17, 2013.

1. Goals

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:

[2] IMS, Vector One®: National (VONA) and Total Patient Tracker (TPT) Databases. May 2009- February 2013. Extracted February 2013.

- 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

2. Medication Guide

A Medication Guide will be dispensed with each prescription.

3. Healthcare Provider Certification for Prescribers

The Sponsor proposed that only outpatient prescribers will be required to be certified.

In order to become certified, healthcare provider (HCPs) who prescribe tolvaptan for outpatient use will complete a *Tolvaptan Healthcare Provider Training and Certification Program* which includes education about:

- The risk of hepatotoxicity associated with the use of tolvaptan
- Strategies to enhance early detection and intervention for the risk of hepatotoxicity including the need to:
  - Monitor plasma hepatic transaminases and total bilirubin prior to initiation of tolvaptan, continuing monthly for 18 months and at regular intervals (e.g., 3-6 month) thereafter
  - 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

After completing the *Tolvaptan Healthcare Provider Training and Certification Program*, prescribers will complete and submit a *Prescriber Enrollment Form* to the tolvaptan REMS program. The Prescriber will agree or attest to the following REMS requirements:

- Completion of the *Tolvaptan Healthcare Provider Training and Certification Program* (including the post-training knowledge assessment).
- Understanding of the requirements of the Tolvaptan REMS Program and that they must comply with the REMS Program in order to prescribe Tolvaptan for out-patients.
- Understanding of the risk of hepatotoxicity associated with Tolvaptan
- To enroll each outpatient in the Tolvaptan REMS Program by completing and submitting the *Patient Enrollment Form* to the Tolvaptan REMS.
- Agree to the following, prior to prescribing Tolvaptan for an outpatient:
  - Order liver function tests (hepatic transaminases and total bilirubin) as directed in the PI and review the results.
  - Review the Medication Guide and discuss the risks of Tolvaptan with the patient.

- Educate the patient on the REMS requirements and the importance of liver function testing during treatment with Tolvaptan.
- Confirm at least every two months using the *Liver Function Test Confirmation Form* that the liver function laboratory tests have been completed per the PI recommendations and that the patient is an appropriate candidate to continue Tolvaptan.
- Agree to provide information regarding the reason for patient discontinuation of tolvaptan, specifically as to whether or not it was related to liver injury (elevated hepatic transaminases and/or bilirubin).
- Re-enroll in the Tolvaptan REMS Program every 2 years by completing the *Tolvaptan Healthcare Provider Training and Certification Program* (including a post-training knowledge assessment) and submitting a new *Prescriber Enrollment Form* to the Tolvaptan REMS Program.

4. Documentation of safe use conditions

The Sponsor proposes the following documentation of safe use conditions:

- Prescribers will document that baseline liver tests were performed on the *Patient Enrollment Form*.
- Prescribers will complete the *Liver Function Test Confirmation Form* (LCF) every two months to ensure that liver testing has been ordered and reviewed in order for the patient to be REMS-eligible to continue tolvaptan.

5. Pharmacy Certification

The Sponsor will ensure that tolvaptan is acquired and dispensed only through pharmacies that are specially certified. There are different requirements for inpatient and outpatient pharmacies.

- Inpatient Pharmacies
  - An authorized designee (e.g., hospital pharmacy director or attending physician) shall be specially trained and certified in lieu of individual prescribers (e.g., house staff).
  - Must have policies and procedures in place to assure no outpatient prescriptions will be dispensed

- Outpatient Pharmacies
  - Otsuka proposed to contract with a small number of certified specialty pharmacies (SPP) to dispense tolvaptan only under conditions of safe use.
  - To become certified, an authorized specialty pharmacy representative must contractually agree to the following on behalf of the pharmacy:
    - All pharmacists and staff involved with the dispensing of tolvaptan will be educated about the risk of hepatotoxicity associated with tolvaptan and about the requirements of the REMS.
    - The pharmacy will acquire tolvaptan only through an Otsuka certified agent.

        - The pharmacy will only dispense to healthcare providers who are certified in the REMS Program.
        - The pharmacy will only dispense to patients that are enrolled in the registry.
        - The pharmacy will verify that the tolvaptan REMS has a record of liver testing confirmation within the prior two months for the patient.
        - At the time of each shipment, the SPP will confirm with the patient whether he/she is still on treatment or has discontinued.
        - The SPPs send shipping and discontinuation data to the REMS.
        - Tolvaptan will only be dispensed with a 28 day supply.
    - Must re-certify bi-annually

6. Patient Registry

All outpatients will be required to enroll into the Tolvaptan REMS registry in order to receive tolvaptan in the outpatient setting.

- The prescriber and patient will complete the *Patient Enrollment Form* (PEF) in order to enroll in the registry. The PEF will include agreements by the patient that they:
    - have reviewed the MG with their prescriber
    - understand the risk of hepatotoxicity
    - understand the need for baseline and monthly bloods tests during treatment
    - understand they will be enrolled in the Tolvaptan REMS program
- The registry will capture the frequency of Liver Function Test confirmations and can be used to estimate compliance with required monitoring, which will provide data to evaluate if the risk mitigation plan is working effectively.
- The registry will capture the reason for discontinuation as solicited from prescribers by the specialty pharmacies and recorded in the REMS registry. All severe liver injury will be evaluated fully by Otsuka pharmacovigilance and the registry will capture the frequency and timing of severe liver injury.

4.2 SUMMARY OF DRISK'S PROPOSED REMS

1. DRISK proposes the following revised 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 (HCPs) 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.

Rationale:

The key components necessary to mitigate the risk of DILI associated with the administration of tolvaptan include (1) adequate education for healthcare providers and patients; (2) assurance that adequate monitoring is completed and assessed; and (3) data are available to further characterize the risk of DILI. The first 3 goals outlined above are included to ensure the following: Prescribers need to be adequately informed about the potential risk of DILI associated with the use of tolvaptan and how it can be appropriately mitigated (i.e. early detection, prompt discontinuation when DILI is detected). Additionally, patients must be informed about how to recognize signs and symptoms of liver injury and the importance of seeking medical attention if the signs and symptoms do occur. Goal 4 focuses on the need for documentation of safe use conditions. In order to mitigate the risk of progression from liver toxicity to liver failure, FDA recommends prescribers document laboratory monitoring and prescribers verify this safe use condition is met prior to dispensing every prescription. Finally, the last goal is specified since a registry is recommended in order to further characterize this serious risk in the post marketing setting.

2. The REMS should include a DILI specific *Patient Education Tool* (i.e. Patient Information Sheet, patient brochure). The tolvaptan MG should not be a component of the REMS. However, a MG will be available as a component of approved labeling.

   The *Patient Education Tool* will focus on the risk of DILI associated with the administration of tolvaptan. The tool should describe 1) the signs and symptoms associated with liver toxicity and 2) the appropriate actions to take should they occur (i.e. contact the prescriber, discontinue tolvaptan). Prescribers should review the tool with every patient receiving outpatient tolvaptan therapy and provide it to patients as a reference at initiation and periodically while the patient is on outpatient tolvaptan.

   Rationale:

   A patient's early recognition and reporting of signs and symptoms of hepatotoxicity is essential to mitigate the risk of DILI because signs and symptoms can present in the interim period between laboratory testing requirements. The Sponsor's proposed REMS relies on the MG as the primary tool to educate patients about the risks of hepatotoxicity. However, the important safety information about the risk of DILI, which is the focus of the REMS, will be diluted by other important safety messages in the MG. Therefore, the MG is not the recommended strategy to ensure that patients are educated adequately on how

to recognize signs and symptoms of DILI and the recommended actions to take if signs and symptoms are observed.

3. Prescribers should document that monthly laboratory monitoring has been reviewed and is acceptable to continue tolvaptan treatment every month, instead of bimonthly as the Sponsor proposed. Pharmacies will verify this documentation prior to dispensing any prescriptions for tolvaptan in the outpatient setting.

   Rationale:

   The Sponsor's proposed REMS contains prescriber education about the recommended monthly monitoring to detect DILI early in order to prevent further progression to liver failure. However, the documentation of safe use conditions the Sponsor proposes require documentation every 2 months. Therefore, the Sponsor's proposed program does not include adequate assurance that testing for DILI has occurred during the interval months.

   The goal of monthly laboratory monitoring enables prescribers to detect abnormal liver laboratory results early which will result in prompt discontinuation of tolvaptan and thereby prevent progression to liver failure. However, monthly monitoring is not of value if prescribers and patients do not comply with the recommendations. Historically, HCPs' and patients' adherence to routine monitoring decreases over time. Therefore, requiring documentation of routine monitoring through the Tolvaptan REMS program will provide additional assurance that monitoring occurs throughout a patient's tolvaptan treatment.

4. All prescribers of tolvaptan need to be certified regardless of healthcare setting. FDA agrees that certification of prescribers is an essential component of the Tolvaptan REMS. However, the Sponsor does not recommend certification for inpatient prescribers.

   Rationale:

   The REMS should include a requirement that all prescribers become trained and certified in the REMS program, regardless of practice setting. The Sponsor's proposed REMS program only requires that HCPs who prescribe tolvaptan for outpatient use be specially trained and certified. Based on currently available data, there is insufficient evidence to suggest that the risk of DILI is only associated with the ADPKD population; therefore, all prescribers, regardless of practice setting, must be educated and certified in order to ensure patients are adequately monitored and educated regarding the risk of DILI.

5. DRISK agrees with the Sponsor's recommendation to require the development and maintenance of a tolvaptan patient registry. As proposed, the patient registry would enroll all outpatients at initiation of therapy and outpatient specialty pharmacies would follow up with prescribers about patient discontinuations. However, in addition, FDA recommends pharmacies and prescribers must agree 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 (AE) reporting form would be utilized to collect data on AEs 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 (i.e. actions taken, how the patient was managed, patient outcomes, etc.)

Rationale:
The risk of DILI is an identified risk based on the ADPKD clinical development program; however, the risk has not been fully characterized due to the small number of patients exposed in the premarketing clinical trials. Therefore, in addition to the Sponsor proposed registry and follow-up by the certified pharmacy on any patient who discontinues tolvaptan, prescribers should be required to report any suspected case of severe liver injury and information about the case (i.e. actions taken, how the patient was managed, patient outcomes, etc.) to the tolvaptan registry.

5 FACTORS CONSIDERED IN DETERMINING THE RISK MANAGEMENT APPROACH

When considering the need for a REMS for tolvaptan the following factors were taken into consideration:

- Based upon the clinical development program for ADPKD, the Sponsor's expert panel estimates an incidence of 1/3000 patients who will develop liver failure or death associated with the administration of tolvaptan.
- The limited size of the clinical development program does not permit a full characterization of DILI associated with the administration of tolvaptan.
- The demonstrated risk of liver injury associated with the administration of tolvaptan was observed with less than 18 months of use. For patients with ADPKD, the expected benefit (delay in progression to end stage renal disease) may not be realized for many years or even decades on treatment.

Based on the aforementioned considerations, a REMS is required for tolvaptan to ensure the benefits outweigh the risk of DILI.

A successful REMS for tolvaptan will ensure adequate education of patients and HCPs about the risk of hepatotoxicity and will ensure adequate monitoring of patients for drug-induced liver injury. Adequate monitoring for DILI includes patient self-monitoring and monthly hepatic laboratory monitoring. Furthermore, the requirement for prescribers to document monthly monitoring, the evaluation of the results and medication discontinuation are essential to help ensure that DILI is detected early (possibly prior to patients experiencing symptoms), is evaluated promptly and medication is stopped in order to mitigate the risk of progression to severe liver injury. If hepatic injury occurs, reporting of the event and relevant patient specific data to a patient registry is important in order to further characterize this risk.

Finally, prescriber and pharmacy enrollment in the REMS program are required to ensure that the drug is dispensed only when prescribed by certified healthcare providers who understand the risks and appropriate use of tolvaptan.

6 LIMITATIONS OF A REMS FOR TOLVAPTAN

While the FDA proposed REMS with ETASU contains the minimally necessary requirements to provide some assurance that the benefit of treatment with tolvaptan outweighs the serious risk of hepatotoxicity, the REMS will not prevent all instances of serious liver injury (i.e., liver failure or death) associated with the administration of tolvaptan. Currently available data provides limited information regarding the characterization of DILI associated with the administration of tolvaptan; therefore, such characteristics as patient risk factors, time to onset, etc. have not been adequately identified at this time. Due to these limitations, it is unknown whether the recommended monitoring will be adequate to detect liver injury at a point when it can be mitigated. In addition, no specific intervention, including monthly monitoring, has been shown to decrease the risk of hepatotoxicity associated with tolvaptan. Monthly monitoring was not utilized in phase 3 clinical trials for tolvaptan, since hepatotoxicity was not recognized as a risk during early clinical development. Furthermore, there is no known, effective treatment for DILI.

7 IMPACT OF THE REMS ON BURDEN TO THE HEALTHCARE SYSTEM AND PATIENT ACCESS

The proposed Tolvaptan REMS program will increase healthcare system burden and permit patient access to tolvaptan for the treatment of ADPKD.

The REMS will add administrative burdens to prescribers and pharmacies. It requires prescribers and pharmacies to enroll and become certified before they can prescribe and dispense tolvaptan. It also requires prescribers to enroll their outpatients in the patient registry. Furthermore, the required documentation of laboratory monitoring will add administrative burden to prescribers who would otherwise be ordering and reviewing laboratory results at their discretion without this additional required step. Verification of REMS requirement by certified pharmacies will increase healthcare burden, as well.

The increased burden to prescribers and pharmacies will potentially impact patient access. The requirement for prescriber certification will likely limit the number of healthcare providers willing to obtain certification since it requires mandatory education and enrollment. Furthermore, many prescribers who have not treated patients with ADPKD in the past may not enroll in the program initially. It is unclear to what extent this will result in a limitation of access to patients who are appropriate candidates for therapy. However, this burden may be offset by eliminating prescribers who are not willing to commit to the necessary monitoring requirements to mitigate the risk of hepatotoxicity.

Furthermore, the required documentation of safe use may result in treatment interruptions because patients may be denied tolvaptan from the pharmacy because of noncompliance with the program requirements.

In order to decrease the impact on burden and access, the proposed REMS includes distinctions based on inpatient and outpatient care settings. Additionally, the REMS utilizes a limited number of tools, each serving multiple purposes (e.g., PPAF that enrolls the patient in the REMS registry and documents patients have received adequate education regarding the risk of DILI).

The burdens of a restricting distribution in some manner must be carefully considered in light of the risk of DILI and the drug's benefits. Implementing the proposed components imposes substantial burden for the prescriber, pharmacists, and patients.

8 SUMMARY

FDA has the authority to require a REMS if additional measures beyond labeling are necessary to ensure the benefits of a drug outweigh the risks. In considering a REMS for tolvaptan, the following should be taken into consideration:

- Based upon the clinical development program for ADPKD, the Sponsor's expert panel estimates an incidence of 1/3000 patients who will develop liver failure or death associated with the administration of tolvaptan.
- The demonstrated risk of liver injury associated with the administration of tolvaptan was observed with use of less than 18 months. For patients with ADPKD, the expected benefit (delay in progression to end stage renal disease) may not be realized for many years, or possibly decades, on treatment.
- While the revised proposed REMS contains the minimally necessary requirements to provide some assurance that the benefit of treatment with tolvaptan outweighs the serious risk of hepatotoxicity, the REMS will not prevent all instances of serious liver injury (i.e., liver failure or death) associated with the administration of tolvaptan.
- Implementing the proposed REMS requirements imposes substantial burden for the healthcare system, prescriber, pharmacists, and patients.