CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204441Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	April 23, 2018
From	Aliza Thompson
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	204441
Applicant	Otsuka Pharmaceutical Company, Ltd.
Date of Submission	October 24, 2017
PDUFA Goal Date	April 24, 2018
Proprietary Name / Non-Proprietary Name	Jynarque/Tolvaptan
Dosage form(s) / Strength(s)	Tablets / 15 mg, 30 mg, 45 mg, 60 mg, and 90 mg
Applicant Proposed Indication(s)/Population(s)	"TRADENAME is indicated to slow kidney function decline (b) (4) in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD)."
Recommendation on Regulatory Action	*Approval*
Recommended Indication(s)/Population(s) (if applicable)	"JYNARQUE is indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD)."

Material Reviewed/Consulted	
Quality Assessment (3/23/18)	Thomas Wong, Steve Hertz, Zhihao Peter Qiu, Zhuojun Zhao, Jing Li, Grafton Adams, Wendy Wilson-Lee (Application Technical Lead)
Pharmacology Toxicology Review (2/27/18)	G. Jagadeesh and Thomas Papoian
Clinical Pharmacology Review (4/16/18)	Martina Sahre, Sudharshan Hariharan
Clinical Review (4/19/18)	Melanie Blank (Efficacy) and Nhi Beasley (Safety)
Statistical Review (2/27/18)	John Lawrence and Hsien Ming Hung
Office of Surveillance and Epidemiology (3/6 and 3/13/18)	Paolo Fanti (Pharmacovigilance Memo) John Senior (Review of case of suspected tolvaptan-induced liver failure requiring liver transplantation)
Division of Medication Error Prevention and Analysis Review (2/16 and 3/8/18)	Sarah Thomas and Chi-Ming (Alice) Tu
Office of Prescription Drug Promotion Review (4/6/18)	Puja Shah
Pediatric Labeling Review (3/6/2018)	Elizabeth Durmowicz, Mona Khurana, John Alexander
Division of Pediatric and Maternal Health Memorandum-Pregnancy and Lactation labeling (2/21/18)	Kristie Baisden, Tamara Johnson, Lynne Yao
Patient Labeling Review (4/10/18)	Morgan Walker, Puja Shah, LaShawn Griffiths
Division of Risk Management Review (4/13/18)	Mona Patel, Joan Blair, Leah Hart, Jamie Wilkins
Risk Evaluation and Mitigation Strategy (REMS) Memorandum (4/20/18)	Mary Ross Southworth
Sentinel ARIA Sufficiency Memo (4/20/18)	Marie Bradley, Efe Eworuke, Lockwood Taylor

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

On October 24, 2017, Otsuka submitted an application to market Jynarque (tolvaptan) to slow kidney function decline [redacted] (b) (4) in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).[1] ADPKD is a genetic disease 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, including kidney failure, as well as other complications. Although the disease has a variable clinical course, factors, such as kidney volume (in the context of a patient's age and level of renal function), the age of onset of high blood pressure, and the causative mutation, can be used to identify patients at high risk of rapidly progressive disease.

Benefit: Two pivotal efficacy and safety trials were conducted in patients with ADPKD. One of these trials was conducted in patients at an earlier stage of disease (TEMPO 3:4) and one was conducted in patients at a later stage of disease (REPRISE). These trials indicate that Jynarque (tolvaptan) is effective in slowing the loss of kidney function in patients with ADPKD. When taken together, the efficacy findings from these trials provide evidence that the treatment effect on the loss of kidney function will continue to accrue over time and across the various stages of disease, assuming a patient remains on therapy. In patients who take Jynarque (tolvaptan) chronically, this effect on the loss of kidney function is expected to translate into a meaningful effect on the time to and risk of progression to kidney failure.

Risks: Use of Jynarque (tolvaptan) carries significant risk. Jynarque (tolvaptan) can cause severe and potentially fatal liver injury. In addition to providing data to support efficacy, the REPRISE trial tested a strategy intended to reduce the risk of severe drug induced liver injury in patients with ADPKD. This strategy included frequent liver tests, the exclusion of patients with underlying abnormalities in liver function, and rules for follow-up testing and stopping tolvaptan in patients who developed certain findings. Data from this trial indicate that the strategy used in REPRISE will likely reduce the risk of liver failure requiring liver transplantation or resulting in death. Although no case of acute liver failure requiring liver transplantation or resulting in death has been reported in clinical trials, one case of irreversible tolvaptan-induced liver injury (acute liver failure requiring liver transplantation) has been reported in the postmarketing setting (the drug is approved for the treatment of ADPKD outside the United States). In sum, available data indicate Jynarque (tolvaptan) can cause serious and potentially fatal liver injury in patients with ADPKD. Based on the experience in clinical trials, such cases would be expected to be rare, assuming appropriate patient selection, monitoring and suspension of drug.

[1] Otsuka first submitted an application to market tolvaptan to slow kidney disease in adults at risk of rapidly progressing ADPKD in 2013. In support of the application, Otsuka submitted the results of a clinical trial conducted in patients with early, rapidly progressing ADPKD. The Agency did not approve the application, citing insufficient evidence of efficacy. The Agency stated that for the application to be approved, Otsuka needed to conduct an additional efficacy trial that tests the hypothesis that tolvaptan slows the loss of renal function. The letter further stated that "Because the effect of tolvaptan appears to be small and long-term studies are clearly infeasible, we think that the confirmatory study should be conducted in patients at a later stage of their disease." In response, Otsuka conducted a second trial in patients at a later stage of disease.

To mitigate the risk of severe drug induced liver injury, Jynarque (tolvaptan) will be approved with a risk evaluation and mitigation strategy (REMS). The Agency believes that a REMS is need to ensure that the benefit of treatment with tolvaptan in patients with ADPKD outweigh its risk of serious and potentially fatal liver injury. Goals of the REMS include ensuring that healthcare providers are educated on the risk of serious and potentially fatal liver injury associated with the use of Jynarque (tolvaptan), the requirement for monitoring at baseline and periodic monitoring, and the need to counsel patients about the risk of serious and potentially fatal liver injury and the need for monitoring at baseline and periodic monitoring; ensuring that healthcare providers adhere to the requirement for monitoring at baseline and periodic monitoring; and ensure that patients are informed about: the risk of serious and potentially fatal liver injury and the requirement for monitoring at baseline and periodic monitoring. Patients will also be enrolled in a registry to further support long term safety and safe use of Jynarque (tolvaptan). Information obtained from this registry will be used to determine the incidence rate of severe (fatal and potentially fatal) drug induced liver injury in patients who take Jynarque (tolvaptan) following drug approval.

In addition to this serious risk, some patients who chose to take Jynarque (tolvaptan) may find it difficult to remain on long-term treatment because of side effects such as excessive urination and thirst.

Conclusions on Benefit-Risk: In their clinical review, Drs. Beasley and Blank state that: "It is the reviewers' opinion that the uncommon risk of liver failure resulting in transplantation or death despite an intensive liver monitoring program is outweighed by the reduction in risk for ESRD, dialysis and transplantation in patients with rapidly progressing ADPKD who take tolvaptan on a chronic basis." Considering the serious nature of the disease; the lack of approved therapies; the evidence that Jynarque (tolvaptan) slows the loss of renal over time and across the stages of disease; the ability to identify patients at higher risk of progression to kidney failure (and thus the ability to identify patients in whom the benefit could reasonably be concluded to exceed the rare risk of liver failure); and the available tools to help manage and mitigate this risk, I, too, recommend approval. Ultimately, it will be for patients to decide if Jynarque (tolvaptan) is the right treatment for them.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Autosomal dominant polycystic kidney disease (ADPKD) is a genetic disease 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, including kidney failure, as well as other complications. • The disease has been reported to affect 300,000 to 600,000 patients in the United States; however the clinical course of disease is variable and the prevalence of symptomatic disease is not well understood. • The disease is caused by two known genetic mutations. PKD1 mutations are	ADPKD is a serious disease. Although the clinical course of disease is variable, patient characteristics can be used to identify patients at high risk of rapidly progressive disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	more common than PKD2 and are associated with a worse prognosis. In those with PKD1 mutations who progress to kidney failure, organ failure typically occurs in the early 50's. Progression to kidney failure is less common in patients with PKD2 mutations and those who progress to kidney failure typically do so in their early 70's. • Other complications of disease include hypertension, acute and chronic pain, urinary tract infections, visible hematuria (blood in the urine), cyst hemorrhage and rupture, kidney stones, liver cysts, and intracranial aneurysms. • Factors, such as kidney volume (in the context of a patient's age and level of renal function), the age of onset of high blood pressure, and the causative mutation, can be used to identify patients at high risk of rapidly progressive disease.	
Current Treatment Options	• No drug is approved in the United States to slow progression of kidney disease in patients with ADPKD.	There is unmet need for drugs that can slow, and ideally prevent, progression to kidney failure in patients with ADPKD. There is also unmet need for drugs that can treat and/or prevent the development of other complications of disease.
Benefit	• Tolvaptan was effective in slowing the loss of kidney function in a clinical trial conducted in patients with early stage ADPKD at high risk of rapidly progressive disease (TEMPO 3:4). Tolvaptan was also effective in slowing the loss of kidney function in a clinical trial conducted in patients at a later stage of the disease (REPRISE). Although neither trial provides direct evidence of an effect on progression to kidney failure, the trials do provide evidence that tolvaptan slows disease progression in earlier and later stages of disease and that the benefit accrues over time (1- 3 years). In the two trials, tolvaptan slowed the loss of kidney function by ~ 1 mL/min/1.73m^2/year. Hence, it seems reasonable to infer that tolvaptan, if used chronically, will have a meaningful impact on the risk of progression to kidney failure. For example, if a hypothetical patient with an eGFR of 100 ml/min/1.73m^2 at age 20 and with high risk characteristics	Taken together, the findings from these two trials indicate that that tolvaptan is effective in slowing the loss of kidney function in patients with ADPKD at high risk of rapidly progressive disease. In patients who take tolvaptan chronically, this effect on the loss of kidney function is expected to compound and ultimately translate into a meaningful effect on the time to and risk of progression to kidney failure. Because tolvaptan slows, but does not prevent disease progression, patients who initiate tolvaptan at an earlier stage of their disease and remain on tolvaptan are expected to realize a

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	similar to those of patients in TEMPO 3:4 initiated chronic therapy with tolvaptan at age 25, initiation of dialysis could be delayed by about 3 years. (See Dr Lawrence's statistical review for further discussion of the assumptions underlying this example/prediction). • Data from TEMPO 3:4 and its extension trial indicate that tolvaptan has an acute/early effect on kidney size. In TEMPO 3:4, the difference in total kidney volume between treatment groups was observed within the first year (the earliest assessment), with little further difference in the second and third year of the trial. In an extension trial in which all patients were treated with tolvaptan, the difference between the groups was not maintained. These data indicate that tolvaptan has little effect on kidney size beyond what accrues during the first year of treatment. • See the discussion on "Benefit" in the clinical review for a more detailed discussion of the efficacy findings.	greater benefit (with regard to delaying progression to kidney failure) than those who initiate treatment at a later stage of disease. (b) (4) [redacted]
Risk	• Data from clinical trials in patients with ADPKD indicate that tolvaptan can cause severe drug-induced liver injury. Although no case of acute liver failure requiring liver transplantation or resulting in death has been reported in clinical trials, one case of irreversible tolvaptan-induced liver injury (acute liver failure requiring liver transplantation) has been reported in the postmarketing setting (the drug is approved for the treatment of ADPKD outside the United States). It is difficult to obtain a precise estimate of the risk of drug-induced liver injury. According to the Clinical Review, the applicant's Hepatic Adjudication Committee estimates a risk of acute liver failure in 1 out of 6200 ADPKD patients receiving chronic tolvaptan. • Tolvaptan promotes the excretion of water and causes excessive urination and thirst. In clinical trials of tolvaptan, excessive urination and thirst were common side effects and led some patients to discontinue treatment. • See the discussion on "Risk" in the clinical review for additional information.	Tolvaptan can cause serious and potentially fatal liver injury in patients with ADPKD. Based on the experience in clinical trial, such cases would be expected to be rare, assuming appropriate patient selection, monitoring and suspension of drug. The Jynarque (tolvaptan) REMS (see discussion under Risk Management) is expected to help manage and mitigate this risk. In addition, information obtained from a required registry will be used to determine the incidence rate of severe (requiring liver transplant and fatal) drug-induced liver injury in patients who take Jynarque (tolvaptan) following drug approval. These data will enable a more precise estimate of this risk in patients taking Jynarque (tolvaptan) and provide information that will be important for assessing

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		the risk-benefit of the marketed product and the ability of the REMS, in its current form, to adequately manage and mitigate this risk. Because of side effects such as excessive urination and thirst, some patients who decide to take Jynarque (tolvaptan) may find it difficult to remain on long-term treatment.
Risk Management	• A trial conducted in patient with later-stage ADPKD tested a strategy intended to risk the severe drug induced liver injury. This strategy included frequent liver tests, the exclusion of patients with underlying abnormalities in liver function, and rules for follow-up testing and stopping tolvaptan in patients who developed certain findings. Data from this trial indicate that the strategy used in the trial will likely reduce the risk of liver failure requiring liver transplantation or resulting in death.	Jynarque (tolvaptan) is being approved with a risk evaluation and mitigation strategy (REMS). The Agency believes that a REMS is need to ensure that the benefit of treatment with tolvaptan in patients with ADPKD outweigh its risk of serious and potentially fatal liver injury. The goals of the REMS are to 1. Ensure that healthcare providers are educated on the following: • the risk of serious and potentially fatal liver injury associated with the use of Jynarque • the requirement for monitoring at baseline and periodic monitoring as described in the Prescribing Information • the need to counsel patients about the risk of serious and potentially fatal liver injury and the need for monitoring at baseline and periodic monitoring as described in the Prescribing Information 2. Ensure that healthcare providers adhere to: • the requirement for monitoring at baseline and periodic monitoring as described in the Prescribing Information 3. Ensure that patients are informed about: • the risk of serious and potentially fatal liver injury associated with the use of Jynarque • the requirement for monitoring at baseline

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		and periodic monitoring as described in the Prescribing Information The REMS will also require the enrollment of all patients in a registry to further support long term safety and safe use of Jynarque (tolvaptan).

2. Background

Tolvaptan is a vasopressin V2 receptor antagonist approved for the treatment of clinically significant hypervolemic and euvolemic hyponatremia. On March 1, 2013, Otsuka submitted NDA 204441 seeking approval to market tolvaptan to slow kidney disease in adults at risk of rapidly progressing ADPKD. The principal support for safety and efficacy was provided by TEMPO 3:4, in which the long-term safety and efficacy of tolvaptan oral split-dose regimens (titrated between 60 mg/day and 120 mg/day) were compared to placebo in patients with early, rapidly progressing ADPKD.

The Agency issued a Complete Response Letter for NDA 204441 on August 26, 2013 indicating that the design, conduct, and results of study 156-04-251 provided insufficient evidence of efficacy to support approval. The Agency concluded that "for this application to be approved, (Otsuka needs) to conduct an additional efficacy trial that tests the hypothesis that tolvaptan slows the loss of renal function and is successful at a p-value < 0.05." The letter further stated that "Because the effect of tolvaptan appears to be small and long-term studies are clearly infeasible, we think that the confirmatory study should be conducted in patients at a later stage of their disease."

In response, Otsuka conducted the REPRISE trial-- a phase 3, double-blind, placebo-controlled trial in patients with later-stage ADPKD. This trial was completed in early 2017 and, on October 24, 2017, Otsuka resubmitted their application to market tolvaptan for the treatment APDKD. The clinical and statistical reviewers agree that the two phase 3 trials- one conducted in patients at an earlier stage of disease and one conducted at a later stage of disease, provide substantial evidence that tolvaptan is effective in slowing the loss of kidney function in patients with ADPKD. From a safety perspective, tolvaptan can cause serious and potentially fatal liver injury. This risk and the design of the REMS (i.e., strategy that would be used to ensure the benefits of tolvaptan in patients with ADPKD outweigh the risk of serious and potentially fatal liver injury) received considerable attention during the review.

3. Regulatory background and marketing history

The REPRISE trial was conducted under a Special Protocol Assessment (SPA). Prior to submission of a request for SPA, Otsuka and the Agency engaged in extensive discussions about the design of the trial. These discussions focused on aspects of trial design, conduct and/or analysis that had raised concern and/or caused the Agency to question the reliability of the efficacy findings in TEMPO 3:4. Hence, the discussions centered around the endpoint that would be used in the trial to establish benefit, and specifically whether treatment effects on renal function should be assessed using on-treatment or off-treatment measurements. The discussion also focused on measures that would be implemented to limit the amount of missing data and increase the likelihood that subjects who were randomized would remain on treatment. From a safety perspective, the trial was intended to serve as a test of Otsuka's strategy to mitigate the risk of severe drug-induced liver injury. As discussed in the clinical review and later in this review, hepatotoxicity, an unanticipated risk, was observed in TEMPO 3:4 and its extension trial. While there was no case of severe liver injury (i.e., cases requiring liver transplantation or resulting in death) in these trials, three Hy's Law cases were reported in tolvaptan- treated subjects, indicating tolvaptan's potential to cause severe liver injury in patients with ADPKD.

For further discussion of these issues, see the Clinical Review dated April 19, 2018, and also the Clinical Review of TEMPO 3:4, dated July 7, 2013.

4. Product Quality

OPQ recommends approval of the application from a quality perspective. As discussed in the OPQ review, three of the proposed tablet strengths (15 mg, 30 mg, and 60 mg tablets) are currently marketed in the U.S. for the treatment of clinically significant hypervolemic and euvolemic hyponatremia. Two additional tablet strengths (45 mg and 90 mg tablets) are proposed for the treatment of ADPKD. The CMC information supporting these strengths were reviewed and approved by OPQ during the prior review cycle of the NDA. There are no unresolved issues at this time and no phase 4 commitments are needed.

Drug Product: Tolvaptan is supplied in 15 mg, 30 mg, 45 mg, 60 mg and 90 mg immediate release tablets. All tablets are non-scored, blue, shallow-convex, and debossed with "OTSUKA" and the strength on one side. The different tablet strengths have different shapes: triangular (15 mg); round (30 mg); square (45 mg); modified rectangular (60 mg); and pentagonal (90 mg).

The tablets are supplied in the three different weekly packs containing a 7-day dosage regimen child-resistant blister card of 14 tablets: a weekly pack with seven 15 mg tablets and seven 45 mg tablets; one with contains seven 30 mg tablets and seven 60 mg tablets ; and one with seven 30 mg tablets and seven 90 mg tablets. Monthly Cartons contain 4 weekly packs. Inactive ingredients include: corn starch, hydroxypropyl cellulose, lactose monohydrate, low-substituted hydroxypropyl cellulose, magnesium stearate and microcrystalline cellulose and FD&C Blue No. 2 Aluminum Lake as colorant.

Expiration Date and Storage Conditions: According to the Quality Assessment, the available stability data support the proposed expiry dating of 30 months for the drug product. Tolvaptan should be stored at Store at 20 to 25°C (68 to 77°F), with excursions permitted between 15°C and 30°C (59°F to 86°F).

Other notable issues: Since the prior review, new FDA guidelines on elemental impurities in brand and generic drug products have gone into effect. As required, the applicant has provided an elemental impurities risk assessment in accordance with ICH Q3D Elemental Impurities. The risk assessment and test results indicate little or no risk of the presence of Class 1 and 2A elemental impurities in tolvaptan tablets. Based on this information, both the applicant and OPQ agree that controls for elemental impurities in the final drug product are not needed.

Facilities review/inspection: According to OPQ, the planned manufacturing facilities are acceptable for the listed responsibilities.

5. Nonclinical Pharmacology/Toxicology

The application may be approved from a pharmacology-toxicology perspective. The pharmacology-toxicology review includes a brief summary of key findings in preclinical studies that were previously reviewed by the Agency. It also includes a discussion of nonclinical studies investigating possible mechanisms for tolvaptan-induced hepatotoxicity seen in patients with ADPKD. These investigations included in vitro studies of transporters involved in bile acid transport, in silico modeling using DILIsym®, use of a panel of inbred mouse strains to study the effect of genetic heterogeneity on tolvaptan-induced hepatotoxicity, and in vitro studies using primary human hepatocytes. These studies indicate that tolvaptan and its metabolites inhibit multiple bile acid transporters, and suggest that multiple mechanisms may contribute to tolvaptan induced hepatotoxicity, including bile acid accumulation, mitochondrial dysfunction/inhibition of the mitochondrial electron transport chain, and oxidative stress. According to the pharmacology-toxicology review, the studies also provide early, preliminary data on non-invasive biomarkers that could be explored for their ability to identify patients who may be at increased risk for tolvaptan-induced liver injury.

6. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) recommends approval of the application from a clinical pharmacology perspective. The resubmission includes additional investigations of tolvaptan's drug interaction liability including the results of *in vitro* drug transporter inhibition studies and a clinical drug interaction study with fluconazole.

Transporter-mediated drug interactions: The in vitro drug transporter inhibition studies indicate that tolvaptan has the potential to inhibit BCRP and P-gp, and that DM-4103 (the major circulating moiety in plasma, with a half-life of around 180 hours) has the potential to inhibit OAT3 and OATP1B1/3. The applicant has conducted a clinical drug interaction study to evaluate for an interaction with P-gp[2], but has not conducted clinical drug interaction studies for BCRP, OAT3 or OATP1B1/3. As discussed in Section 12, OCP is recommending that the applicant be given postmarketing requirements to conduct clinical drug interaction studies for BCRP, OAT 3 and OATP1B1/3. I agree with their recommendation and the proposed approach to labeling pending the results of these studies (i.e., the recommendation to avoid concomitant use of tolvaptan with BCRP, OATP1B1/B3 and OAT3 substrates).

CYP3A enzyme mediated interactions: Tolvaptan is metabolized almost exclusively by CYP3A. In a previously conducted clinical drug interaction study with ketoconazole, tolvaptan's AUC was ~5 times as large after co-administration with a submaximal dose of ketoconazole (200 mg). According to the OCP review, coadministration of fluconazole and tolvaptan produced a 200% and 80% increase in tolvaptan AUC and Cmax, respectively. Based on these findings, OCP is recommending a contraindication against use with strong CYP3A inhibitors and dose reductions in patients taking moderate CYP 3A inhibitors. I agree with their recommendations.

[2] In a clinical drug interaction study with digoxin, co-administration of tolvaptan 60 mg and digoxin did not result in a clinically relevant impact on digoxin exposure.

7. Clinical/Statistical

The clinical and statistical reviews contain an excellent, comprehensive discussion of the efficacy and safety data supporting approval. I refer the reader to their reviews for additional information.

Efficacy

As previously noted, the Agency's Complete Response letter indicated that for the application to be approved, Otsuka would need to conduct an additional efficacy trial testing the hypothesis that tolvaptan slows the loss of renal function and that the trial should be conducted in patients at a later stage of their disease. In response, Otsuka conducted a phase 3b, multicenter, randomized-withdrawal, placebo-controlled, double-blind, parallel-group trial to compare the efficacy and safety of tolvaptan (45 to 120 mg/day, split-dose) in subjects with CKD (late Stage 2 to early Stage 4) due to ADPKD.

The trial included sequential single-blind run-in periods during which subjects received placebo for 1 week, followed by tolvaptan titration for 2 weeks, and then treatment with tolvaptan at the highest tolerated dose achieved during titration for 3 weeks. Only subjects who could tolerate the two highest doses of tolvaptan (60 mg/30 mg or 90 mg/30 mg) during the 3-week titration period were randomized 1:1 to double-blind treatment with tolvaptan or placebo for 12 months; after completion of the 12-month treatment period, subjects entered a 3-week post-treatment period to assess renal function off treatment.

The primary endpoint was the treatment difference in the change of eGFR, as calculated using the Chronic Kidney Disease-Epidemiology (CKD-EPI) formula, using multiple assessments of eGFR from pretreatment baseline to post-treatment follow-up, annualized (divided) by each subject's treatment duration.

The key secondary endpoint was the treatment difference in annualized slope of eGFR calculated for individual subjects using observations from placebo run-in, tolvaptan run-in (not including tolvaptan titration), double-blind treatment, and post-treatment follow-up (not including data collected in the first week after the last IMP dose) time points.

> *Reviewer's comment: As noted in the clinical review, the sequential run-in periods were used to limit the amount of missing data and increase the likelihood that subjects who were enrolled in the double-blind treatment would remain on treatment for the duration of the 12-month double-blind treatment period. By including a placebo run-in period, in addition to the tolvaptan run-in and titration periods, the sponsor was able to obtain an appropriate baseline value for their key secondary endpoint analysis, which used eGFR values obtained on treatment to assess for a treatment effect.*

A total of 1519 adult patients entered the 8-week single-blind pre-randomization phase (screening, placebo run-in, tolvaptan titration and tolvaptan run-in). Of these, 1370 subjects completed the pre-randomization phase and were randomized and treated during the 12-month double-blind period. Because 57 subjects did not complete the off-treatment follow-up period, 1313 subjects were included in the primary efficacy analysis; 57 subjects were excluded because they did not complete the off-treatment follow-up period.

As discussed in the statistical and clinical reviews, the measures taken to limit the amount of missing efficacy data were effective. Approximately 96% of subjects completed the month 12 visit. In his statistical review, Dr. Lawrence notes that both the data and analysis quality "were excellent" in REPRISE and goes so far as to describe the trial as "an exemplar" for not only future trials in ADPKD, but for all clinical trials.

The trial met its primary endpoint. The change of eGFR from pretreatment baseline to post-treatment follow-up was −2.3 mL/min/1.73 m^2/year with tolvaptan vs −3.6 mL/min/1.73 m^2/year with placebo, corresponding to a treatment difference of 1.3 mL/min/1.73 m^2/year ($p < 0.0001$) and a 35% slower decline in renal function in the tolvaptan arm relative to placebo.

The trial also met its key secondary endpoint, which assessed effects on eGFR using "an appropriate" baseline (a value obtained in the placebo-run in period for subjects randomized to placebo and a value obtained in the tolvaptan titration period for subjects randomized to tolvaptan) and available, post-randomization, on-treatment assessments. Using this method, the slope of eGFR change was −3.2 mL/min/1.73m^2/year and −4.2 mL/min/1.73 m^2/year in subjects on tolvaptan and placebo, respectively, corresponding to a treatment effect of 1.0 mL/min/1.73 m^2/year ($p < 0.0001$) and a 24% slower rate of decline in the tolvaptan arm relative to placebo.

Safety

As discussed in the clinical review, drug induced liver toxicity was identified as an important safety issue in the prior clinical trial. Dr. Beasley's analyses focused on the risk of drug-induced liver injury and tolerability issues related to tolvaptan's aquaretic effect.

Drug-Induced Liver toxicity

In the initial application, there were three Hy's law cases in tolvaptan-treated subjects. Two of these cases were adjudicated as probable and one as highly likely related to tolvaptan. Based on the data collected in the initial trial and its extension, it was estimated that tolvaptan carried a risk of severe liver injury (i.e., requiring transplantation or resulting in death) of 1:3000. REPRISE included several measures intended to mitigate this risk. These measured included frequent liver tests, the exclusion of patients with underlying abnormalities in liver function, and rules for follow-up testing and suspension of study drug in patients who developed abnormalities (see the Clinical Review for further discussion).

This strategy appeared to be effective in mitigating the risk of severe liver injury in the trial population. As in the first trial, ALT elevations > 3 time the ULN occurred at a greater incidence in the tolvaptan arm than in the placebo arm. However, in contrast to the first trial, there were no Hy's Law cases in REPRISE. Following submission of the NDA, a case of liver injury requiring liver transplantation was reported in a patient in Japan who was taking tolvaptan for the treatment of ADPKD. Dr. John Senior was asked to review the case and provide his assessment of the causal relationship between tolvaptan and liver failure. In his consult memo, Dr. Senior states "…I agree with the two external reviewers … that the information provided is incomplete and unsatisfactory, but still think that the liver failure in this patient was probably and very likely caused by tolvaptan."

> *Reviewer's Comment: Dr. Senior's memo also discusses his perspective on the approval of tolvaptan for the treatment of ADPKD. In brief, Dr. Senior recommends that the product not be approved for the treatment of ADPKD, citing, among other things, his belief that the applicant has not established a benefit that outweighs the product's risk.*

Aquaretic effects

Tolvaptan's aquaretic effects were the most common reason for discontinuation of tolvaptan in the TEMPO 3:4 trial. Increased urination (i.e., polyuria, pollakiuria, nocturia, and micturition urgency), thirst and dry mouth were also the most common adverse reactions reported in tolvaptan as compared to placebo-treated subjects in TEMPO 3-4.

As discussed in the Clinical Review, during the tolvaptan titration and run-in period, 52 (3.5%) of subjects discontinued from the study because of the aquaretic effect. Adverse reactions related to increased urination and thirst and drug mouth were also commonly reported in subjects receiving tolvaptan in REPRISE, as shown in the tables below.

Table 1: REPRISE Titration Period: Aquaresis, polydipsia and thirst

Custom MedDRA Query/Preferred Term	*Number of subjects*	*Proportion (%)*
Aquaresis CMQ	652	43.6
Polyuria	475	31.8
Nocturia	308	20.6
Pollakiuria	70	4.7
Micturition urgency	6	0.4
Urine output increased	5	0.3
Enuresis	2	0.1
Polydipsia or thirst CMQ	575	38.4

Source: Table 22, FDA Clinical Review

Table 2: REPRISE Randomized Period: Aquaresis, polydipsia and thirst

	Tolvaptan (N=681)		**Placebo (N=685)**	
Custom MedDRA Query/Preferred Term	Number of subjects	Proportion (%)	Number of subjects	Proportion (%)
Aquaretic CMQ	76	11.2	25	3.7
Polyuria	36	5.3	11	1.6
Nocturia	32	4.7	12	1.8
Pollakiuria	12	1.8	2	0.3
Micturition urgency	5	0.7	2	0.3
Polydipsia or thirst CMQ	39	5.7	16	2.3

Source: Table 23, FDA Clinical Review

Other

As discussed in Dr. Beasley's review, other adverse effects/risks of tolvaptan include hypernatremia and increases in uric acid, hypovolemia and dehydration. These events were uncommon and/or generally mild in nature. Of note, subjects in REPRISE were instructed to ingest fluids in anticipation of, or at the first sign of thirst to avoid excessive thirst or dehydration,

encouraged to drink at least 2-3 liters of fluid per day, ingest water before bedtime regardless of perceived thirst, and replenish fluids overnight with each episode of nocturia. Labeling will indicate that patients should be instructed to drink water when thirsty, and throughout the day and night if awake and to monitor for weight loss, tachycardia and hypotension because they may signal dehydration.

8. Advisory Committee Meeting

The initial application was discussed at an advisory committee meeting on August 5, 2013. The meeting discussion focused on concerns with the efficacy data and the risk of severe drug-induced liver injury. When asked whether tolvaptan should be approved to slow kidney disease in adults at risk of rapidly progressing ADPKD, six members voted "yes" and nine voted "no."

There are no additional issues that require advisory committee input; hence a second advisory committee meeting was not held.

9. Pediatrics

Tolvaptan has orphan designation for the treatment of ADPKD; hence PREA requirements do not apply. The Division of Pediatric and Maternal Health was consulted regarding appropriate language in Section 8.4 of the label (pediatric use) given the risk of severe liver injury. According to Dr. Durmowicz's memo "DPMH has not identified concerns that tolvaptan would be ineffective in pediatric patients or that pediatric patients would be at greater risk for increased frequency or severity of tolvaptan associated liver toxicity compared to adult patients. If DCaRP agrees with this assessment, the applicant's proposed language for the Pediatric Use subsection of labeling, "Safety and effectiveness of TRADENAME in pediatric patients have not been established." is acceptable and appropriate." I agree with this assessment. The REMS for Jynarque and proposed changes to the Samsca label (discussed later in this review) are likely to limit off-label use of tolvaptan in children. Should such use occur, the REMS would capture any cases of severe liver injury that occur in children.

10. Other Relevant Regulatory Issues

Financial disclosures and Good Clinical Practice: According to the clinical review, the applicant has adequately disclosed financial arrangements with clinical investigators. The submitted information does not raise concern about the integrity of the data. As also noted in the clinical review, the applicant has provided attestation that REPRISE was conducted in compliance with U.S. regulations pertaining to Good Clinical Practice.

Office of Scientific Investigations (OSI) audits: Foreign and domestic site were inspected during the prior review cycle (i.e., for TEMPO 3:4) and supported the conclusion that the data generated by these sites should be considered reliable. No clinical sites in REPRISE drove study results and review of financial disclosure information did not raise significant concerns. Hence clinical site inspections were not conducted for REPRISE.

11. Labeling

Labeling has been reviewed by the clinical, statistical, clinical pharmacology, pharmacology-toxicology and product quality reviewers and also by reviewers from the Division of Medication Error Prevention of Analysis, Office of Prescription Drug Promotion, Division of Pediatric and Maternal Health and Patient labeling. Extensive edits were made based on their input, as well as the input of Mike Monteleone, the Associate Director for Labeling, and Dr. Mary Ross Southworth, the Deputy Director for Safety. I thank Mike Monteleone and Anna Park, Senior Regulatory Project Manager, for their leadership and management of this process.

Prescribing Information

Agreement has been reached on labeling.

- Efficacy: The applicant will be granted an indication "to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD)." The applicant will not be granted the proposed indication (b) (4) [redacted] The primary endpoint in TEMPO 3:4 was the intergroup difference for rate of change of total kidney (TKV) normalized as a percentage. There has been significant back and forth with the applicant on how best to describe the primary endpoint findings in labeling. The review team and applicant agree that it is important to include information on the treatment effect on TKV in Section 14; however, it was a challenge to craft language that provides an appropriate description of tolvaptan's effect on total kidney volume (i.e., one that does not mislead or confuse the prescriber).

- Safety: The label will include a Boxed Warning for serious liver injury and Warnings and Precautions containing (1) instruction on appropriate monitoring and discontinuation of study medication and (2) information about the Jynarque REMS. In addition, the label will contain a contradiction against use in patients with a history, signs or symptoms of significant liver impairment or injury. The contraindication will also state that it does not apply to patients with uncomplicated polycystic liver disease. The label will also include contradictions against use with strong CYP3A inhibitors and in patients with uncorrected abnormal blood sodium concentrations, inability to sense or respond to thirst, hypovolemia, hypersensitivity to tolvaptan or one of its components, uncorrected urinary outflow obstruction or anuria.

Other Labeling

- Proprietary name: The proposed proprietary name, JYNARQUE, has been deemed acceptable by the Office of Medication Error Prevention and Risk Management

12. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

The applicant, the Division of Risk Management (DRISK), the clinical review team, and Dr. Southworth agree that a risk evaluation and mitigation strategy (REMS) with elements to assure safe use (ETASU) is needed to ensure the benefits of Jynarque outweigh its risk of serious and potentially fatal liver injury. The REMS will ensure that prescribers and pharmacies are certified,

patients will have appropriate baseline and periodic monitoring, and that Jynarque will only be dispensed with documentation of safe use conditions. The REMS Program will also include a REMS Registry that will be used to collect data on serious and potentially fatal liver injury events.

I thank the reviewers from DRISK and in particular Mona Patel as well as Dr. Southworth for their work on the REMS.

To address the potential for use of Samsca (tolvaptan) and future Samsca (tolvaptan) generics outside of the REMS, the label for Samsca (tolvaptan) will also be updated to include a boxed warning indicating that Samsca (tolvaptan) should not be used for ADPKD outside of the FDA approved REMS because of the risk of hepatotoxicity, as well as a contraindication against use in patients with ADPKD outside of the FDA approved REMS; the text in the Warning and Precaution on liver toxicity has also been updated to reflect the more recent data on the risk of liver toxicity and to echo statements in the boxed warning regarding use of Samsca (tolvaptan) to treatment patients with ADPKD outside of the FDA approved REMS. Use of Samsca (tolvaptan) to treat ADPKD will be monitored in the post-marketing setting (to see if changes in use occur over time) and additional measures will be implemented as needed.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

The applicant will be given a PMR to conduct a prospective cohort study of patients enrolled in the Jynarque (tolvaptan) REMS registry, with the primary objective of determining the incidence rate of severe (fatal and potentially fatal) drug induced liver injury A study is needed because an analysis of spontaneous postmarketing adverse events will not be sufficient to assess this risk and, for the reasons discussed in Dr. Bradley's memo, FDA's new pharmacovigilance system (i.e., Sentinel's Active Risk Identification and Analysis System) will not be sufficient to adequately assess the incidence rate of such events.

The Office of Clinical Pharmacology is recommending PMRs for clinical drug interaction studies to evaluate the potential interaction between (1) tolvaptan and a relevant BCRP substrate; (2) DM-4103 and a relevant OATP1B1/3 substrate; and (3) DM-4103 and a relevant OAT3 substrate. I agree with this recommendation. In vitro studies indicate that tolvaptan or the oxobutyric acid metabolite of tolvaptan (i.e., DM-4103) may have the potential to increase exposure of drugs that are substrates of these transporters, and hence labeling recommends avoiding concomitant use with BCRP, OATP1B1/B3 and OAT3 substrates. Given the likely concomitant use of drugs that are substrates of these transporters in the proposed population, clinical drug interaction studies are needed to provide more definitive information on the interaction potential in patients.

As previously noted, tolvaptan has orphan designation for the treatment of ADPKD; hence PREA requirements do not apply.

13. Recommended Comments to the Applicant

None.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALIZA M THOMPSON
04/23/2018

NORMAN L STOCKBRIDGE
04/23/2018
With my full concurrence.