

August 5, 2013
Meeting of the Cardiovascular and Renal Drugs Advisory Committee

**Summary Minutes of the Drug Safety and Risk Management Advisory Committee
Meeting**

August 5, 2013

**Location: FDA White Oak Campus, Building 31, the Great Room, White Oak
Conference Center
(Rm. 1503), Silver Spring, MD**

**All external requests for the meeting transcripts should be submitted to the
CDER, Freedom of Information office.**

**These summary minutes for the August 5, 2013 Meeting of the Cardiovascular
and Renal Drugs Advisory Committee of the Food and Drug Administration were
approved on 10/17/13.**

**I certify that I attended the August 5, 2013 Meeting of the Cardiovascular and
Renal Drugs Advisory Committee and that these minutes accurately reflect what
transpired.**

_____/s/_____
**Kristina A. Toliver, PharmD
Designated Federal Officer
Cardiovascular and Renal Drugs
Advisory Committee**

_____/s/_____
**A. Michael Lincoff, MD
Chairperson**

The Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research, met on August 5, 2013 at the FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Room 1503), Silver Spring, MD. Prior to the meeting, members and temporary voting members were provided copies of the background material from the FDA and Otsuka Pharmaceutical Company, Ltd. The meeting was called to order by A. Michael Lincoff, MD (Cardiovascular and Renal Drugs Advisory Committee Chairperson); the conflict of interest statement was read into the record by Kristina A. Toliver, PharmD (Designated Federal Officer). There were approximately 100 persons in attendance. There were 10 Open Public Hearing speakers.

Issue: The committee met and discussed New Drug Application 204441, tolvaptan tablets, submitted by Otsuka Pharmaceutical Company, Ltd for the proposed indication of slowing kidney disease in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (autosomal dominant polycystic kidney disease is a genetic disease that affects the kidney and can lead to kidney failure).

Attendance:

Cardiovascular and Renal Drugs Advisory Committee Members Present (Voting):

Scott Emerson, MD, PhD; Linda F. Fried, MD, MPH; A. Michael Lincoff, MD (Chairperson); Vasilios Papademetriou, MD; Stuart Rich, MD; Philip Sager, MD

Cardiovascular and Renal Drugs Advisory Committee Member (Non-Voting):

Rob Scott, MD (Industry Representative)

Temporary Members (Voting):

Susan Broyles, RN (Patient Representative); Naga P. Chalasani, MD; William Cooper, MD, MPH; Michael Flessner, MD; Jay Hoofnagle, MD; Alan S. Kliger, MD; Elaine Morrato, DrPH; Michele Orza, ScD (Acting Consumer Representative); Michael Proschan, PhD, MS

Cardiovascular and Renal Drugs Advisory Committee Members Not Present (Voting):

James deLemos, MD; Julia Lewis, MD; Jennifer Li, MD, MHS

FDA Participants (Non-Voting):

Norman Stockbridge, MD, PhD, Robert Temple, MD, Ellis Unger, MD

Designated Federal Officer:

Kristina A. Toliver, PharmD

Open Public Hearing Speakers:

Sidney Wolfe, MD (Public Citizen's Health Research Group); Diane E. Dorman (National Organization for Rare Disorders); Harold A. Saul (National Kidney Foundation, PKD Foundation); Cheryl Bost; Bill Brazell; Michelle Davis (CEO, PKD Foundation); Sarah Franklin (statement read by Michelle Davis); Katherine Michiels; Cathy Perkins; Ashley Phelps (statement read by Lorrie Rome)

The agenda was as follows:

Call to Order Introduction of Committee	A. Michael Lincoff, MD Chairperson, Cardiovascular and Renal Drugs Advisory Committee (CRDAC)
Conflict of Interest Statement	Kristina A. Toliver, PharmD Designated Federal Officer, CRDAC
Opening Remarks	Norman Stockbridge, MD, PhD Director, Division of Cardiovascular and Renal Products (DCaRP), Office of Drug Evaluation I (ODEI), Office of New Drugs (OND), CDER, FDA
<u>Sponsor Presentations</u> Introduction	<u>Otsuka Pharmaceutical Company, Ltd</u> Robert McQuade, PhD Executive VP & Chief Strategic Officer Otsuka Pharmaceutical Development and Commercialization Inc. (Otsuka)
Autosomal Dominant Polycystic Kidney Disease (ADPKD) Pathophysiology ADPKD Disease Progression	Vicente Torres, MD, PhD Professor of Medicine, Mayo Clinic Arlene Chapman, MD Professor of Medicine, Emory University
Efficacy of Tolvaptan in ADPKD	Frank Czerwiec, MD, PhD Sr. Director, Global Clinical Development, Otsuka
Sponsor Response to FDA Comments	Robert McQuade, PhD
Safety of Tolvaptan in ADPKD	Christopher Zimmer, MD Sr. Director, Global Clinical Development, Otsuka
Risk Evaluation/Mitigation & Net Benefit Clarifying Questions to the Presenters	Robert McQuade, PhD
BREAK	
<u>FDA Presentations</u> Clinical and Statistical Findings	John Lawrence, PhD Biometrics Reviewer Office of Biostatistics/CDER Aliza Thompson, MD Clinical Team Leader

Risk Management

Kimberly Lehrfeld, PharmD
Drug Risk Management Analyst
Division of Risk Management/ Office of Medication
Error Prevention and Risk Management/Office of
Surveillance and Epidemiology (OSE)/CDER

Clarifying Questions to the Presenters

LUNCH

Open Public Hearing

Questions to the Committee and Committee Discussion

BREAK

Questions to the Committee and Committee Discussion (cont.)

ADJOURNMENT

Questions to the Advisory Committee:

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 (≥ 60 mL/min as determined by the Cockcroft-Gault equation), but 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 (hypertension, renal pain, albuminuria, and renal function).

1. **(DISCUSSION)** Please comment on the *design* of the trial including:
 - a. inclusion criteria
 - b. use of a post-randomization measurement to assess tolvaptan's effect on renal function
 - c. planned follow-up of subjects who discontinued study medication prematurely

Committee Discussion: *Questions 1-a through 1-c were discussed together. The committee stated that the inclusion criteria were appropriate, although some felt it might have been beneficial to also include patients who were sicker. Most members of the committee agreed that the post-randomization measurement was not ideal. Additionally, the committee was very concerned that there was incomplete follow-up on patients who discontinued the study drug, making it challenging to interpret the results of the study. It was stated that the general approach to the sensitivity analysis taken by the sponsor was in the right direction, although the emphasis on the post-randomization variable made the results difficult to interpret.*

Please see the transcript for details of the committee discussion.

2. **(DISCUSSION)** Please comment on the *analysis* of the trial's findings.
- Do the prespecified analyses of the ADPKD clinical progression endpoint adequately address the effects of missing data? If not, how should tolvaptan's effects be assessed, given the missing data?
 - Do the prespecified analyses of the first non-composite secondary endpoint, the rate of change in renal function, adequately address the effects of missing data? If not, how should tolvaptan's effects be assessed, given the missing data?

Committee Discussion: *Questions 2-a and 2-b were discussed together. The committee stated that it is difficult to compare the patients who dropped out to those who did not. It was difficult to assess if they had similar outcomes. The committee also stated that because of the missing data, it is unknown whether patients who tolerate the drug are different from those who do not tolerate the drug in terms of some other risk factor or whether or not they had similar outcomes. They stated that the sensitivity analysis showed what appeared to be a treatment effect, but that there was still concern because of the missing data.*

Please see the transcript for details of the committee discussion.

3. **(DISCUSSION)** Please comment on *effectiveness*. Did the phase 3 trial demonstrate an effect of tolvaptan on...
- ...reducing ADPKD clinical progression events?
 - ...slowing the loss of renal function?
 - ...reducing 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.

Committee Discussion: *Questions 3-a through 3-c, along with the follow-up question were discussed together. The committee stated that there was a lot of confusing data, which made the results difficult to analyze. They stated that the only clinical event that was examined was renal pain events and that was not a pre-specified primary or secondary endpoint. Some members felt the trial did show a clear effect of the intervention. Some committee members stated that there was also a clear effect on renal events and pain events, but that slowing of loss of renal function was more difficult to determine with confidence. Additionally, members were concerned that the change in creatinine considered for a renal event in this trial is less than what has been used in any other trials. Although it was not part of the question, it was felt that kidney size was a meaningful outcome and that the drug seemed to show benefit for reducing kidney size. However, there was concern from some members that there was not a large effect and that the drug was not universally effective, but patients would be treated with this drug for life. Others members felt the data were not sufficient to support the use of kidney size as a surrogate.*

Please see the transcript for details of the committee discussion.

4. **(DISCUSSION)** Please comment on tolvaptan's risk of drug-induced liver injury and whether you think the proposed risk mitigation strategy is...
- ... sufficient to mitigate the risk of severe liver injury.
 - ...overly burdensome.

Committee Discussion: *Questions 4-a and 4-b were discussed together. The committee stated that the risk evaluation and mitigation strategy (REMS) was not overly burdensome, unless one questions whether or not the benefit of the drug is worth the risk of liver injury. The closed-loop system of the REMS is*

critical, while the centralization of the lab is less important. They stated that educating patients about signs and symptoms of liver failure is inadequate since seeking treatment at the point that symptoms develop is too late. Therefore target thresholds [hepatic laboratory values] should be developed as well as dosing and monitoring guidance for providers. There should also be explicit recommendations regarding whether therapy can be restarted as well as information on when to stop treatment because treatment is futile. The committee expressed concern regarding poor, uneducated patients and patients with language barriers. These patients may not understand the education or the need for follow up; and even if they do understand they may lack access to follow up. The lack of understanding of education and/or the lack of access to follow up can result in patients going into liver failure. The committee suggested that draft materials must be pre-tested before launch to help make sure the educational materials are effective. Concerns were also raised about the lack of an evaluation plan and that there should be measurement of burden in addition to measurement of knowledge and comprehension about the risks associated with the drug.

5. **(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?

Yes: 6 No: 9 Abstain: 0 No Voting: 0

The committee members that voted yes stated that tolvaptan met an unmet medical need. They stated that the REMS program was difficult, but it should work, especially since the drug is used in a motivated patient population. It was stated that there are other drugs on the market that also result in liver injury. It was also stated that slowly progressive diseases that lead to death such as ADPKD are hard to study.

Some committee members who voted no stated that there was not enough evidence that the benefit of the drug outweighed the risk of liver injury. Other committee members felt efficacy had not been established. They stated that there were compelling data regarding kidney volume; however there were not enough data for the other FDA required endpoints. Committee members also stated that the follow-up was not long enough for a drug that has to be taken for a lifetime.

Please see the transcript for details of the committee discussion.

6. **(DISCUSSION)** 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?

Committee Discussion: *The committee stated the need for study in patients with both less severe kidney disease and more severe kidney disease than what was studied. For younger patients with less severe kidney disease, they stated that it may help determine if the drug will help prevent progression of disease. In patients with more severe kidney disease, at least stage 3 chronic kidney disease, the committee wanted progression studied as well and to determine if there is any benefit to starting patients on tolvaptan at that point. The committee wanted to see more safety data as well as a long-term follow-up of the current studies. They also stated they'd like to see an active run-in phase for any future trial so that randomization could be confined to those who tolerate the drug. Additionally they suggested a time-varying model to include kidney volume as a predictor in both arms. Furthermore, the committee stated more minorities need to be included in the trials.*

Please see the transcript for details of the committee discussion.

Meeting adjourned at approximately 5:15 p.m.