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FDA Cardio-Renal Drugs Advisory Committee meeting to evaluate tolvaptan for use in polycystic kidney disease: August 5, 2013

We have no conflicts of interest

Concerns of Cardio-renal advisory committee about tolvaptan for hyponatremia during 6/08 FDA meeting

- Inadequate safety data base: “limited long-term follow-up data in a drug that will likely be used over a much longer term than was studied in most of these [patients]” (Dr. Lincoff)

- Missing efficacy data

Safety Concerns in patients with post-marketing exposure for hyponatremia indication

From May 2009 to February 2012, 4500 patients received a prescription from US retail pharmacies

AERS reports of six patients with osmotic demyelination syndrome, including one death

AERS reports of 50 patients with hypernatremia, including eight deaths

Prescriptions from briefing documents PDF page 212; FDA AERS data from 2010 through first half of 2012

Essential Elements of Efficacy Needed for Drug Approval

- Drug must show a significant advantage over placebo at achieving relevant clinical outcomes.
  - Data analysis of relevant clinical outcome(s) must be done in a systematic fashion, including all reasonable factors that may effect final results.

- The study must accurately account for patients lost to attrition.

Determining Relevant Clinical Outcome

- "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. (emphasis added)"*

- The relevant clinical outcome: a composite endpoint including time to multiple event analysis for hypertension, severe renal pain, worsening albuminuria, and worsening renal function.

Table 1: Summary of key regulatory milestones, agreements and advice. June 6, 2009 Pre-IND meeting. "FDA Briefing Document." Cardiovascular and Renal Drug Advisory Committee Meeting. 8/5/2013. p.16-17

Evaluating Relevant Clinical Outcome

- While Otsuka reported a significant ($p<0.01$) improvement in the composite endpoint, "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."(1)

- With regard to other endpoints, Dr. Lawrence shows that the modeling of eGFR and total kidney volume ("a supportive endpoint") , "use unverified model assumptions and in some cases use assumptions that can be demonstrated as false." (2)

1. "FDA Briefing Document." Cardiovascular and Renal Drug Advisory Committee Meeting. 8/5/2013. p45.
2. Lawrence, J. "Tolvaptan" Statistical Review and Evaluation. FDA. 11/15/2012. p25 of review.

Determining Relevant Clinical Outcome

- "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." (emphasis added)*

Table 1: Summary of key regulatory milestones, agreements and advice. July 19, 2012 Pre-IND meeting. "FDA Briefing Document." Cardiovascular and Renal Drug Advisory Committee Meeting. 8/5/2013. p.17

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- “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.”

Lawrence, J. “Tolvaptan” Statistical Review and Evaluation. FDA. 11/15/2012. p7.

Dr. Lawrence's further critique of study

Although technically blinded, the treatment could have been guessed from effects on dehydration and water intake. [64.5% of subjects on tolvaptan versus 33.3% of subjects on placebo with potentially drug-related events suggestive of dehydration]

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.

The study must accurately account for patients lost to attrition.

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%)

"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."

"FDA Briefing Document." Cardiovascular and Renal Drug Advisory Committee Meeting. 8/5/2013. p42.

The study must accurately account for patients lost to attrition.

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%)

- Subjects lost due to adverse events were 3x more likely to be in tolvaptan group,

"less than half of the subjects who discontinued study medication prematurely were followed for these outcomes after discontinuation of study medication."

Table 11: Subject disposition "FDA Briefing Document." Cardiovascular and Renal Drug Advisory Committee Meeting. 8/5/2013. p.38

RCTs should involve significantly increased H_2O consumption for both groups to determine whether tolvaptan or any drug confers any benefit, beyond water, in vasopressin-suppression/helping patients

A 2009 article by Dr. Vicente Torres, principle investigator for TEMPO, was entitled “A Case for Water in the Treatment of Polycystic Kidney Disease”

In it, he advocate a solute-free, daily water intake of 2.5 to 4 liters, drunk evenly in ADPKD patients with GFR’s > 60,. He stated the risk is minimal and the benefit: “Likely reduction in the rate of cyst growth by suppressing the secretion of AVP and its effect on tubular cell proliferation and fluid secretion.”

Clin J Am Soc Nephrol 4: 1140–1150, 2009.

Torres cites a study of water therapy: PCK rat model

"The central observations are that increased water intake (*1*) decreased urine osmolality; (*2*) reduced renal expression of AVPV2 receptors, B-Raf, P-ERK, and PCNA positive renal cells; (*3*) decreased the size of renal cysts and total kidneys; and (*4*) **improved renal function**. Therefore, physiologic inhibition of AVP by simply increasing fluid intake was sufficient to suppress cAMP-dependent B-Raf/MEK/ERK activity and proliferation of the cyst-lining cells to slow renal enlargement in the PCK rat."

J Am Soc Nephrol 17: 2220–2227, 2006

Response of Dr. Torres to NEJM letter from a nephrologist after TEMPO 3:4 publication

NEJM letter question: "it is hard to understand why the investigators did not instruct both groups to ingest large amounts of water, as two of the authors had previously recommended. Had they done so, we would have known whether tolvaptan is superior to a high fluid intake alone."

Torres answer: "In the TEMPO 3:4 study, all patients were encouraged to drink enough water to avoid dehydration…. **A specifically designed clinical trial would be necessary to determine whether high water intake and tolvaptan are equally effective treatments."**

Question and answer citation: n engl j med 2013: 368;13

Torres, et al's stated barrier to such a human study, the research question of which is to see if any drug beats increased water consumption

"Financial support for a trial of increased hydration in ADPKD seems unlikely, because present regulations make a trial mandatory for a drug such as tolvaptan, but not for water, a natural product consumed in variable amounts."

(NIDDK: are you listening?)

bromfenac, troglitazone and tolvaptan

Drug	bromfenac	troglitazone	tolvaptan
Drug vs placebo: % with ALT> 3X ULN	2.8 vs 0	1.9 vs 3	4.4 vs 1
Hy's Law cases	2	2	3
Risk severe liver injury	1/5000 to 1/10,000	1/3000 to 1/10,000	1/3000

January 2007 FDA: **Premarketing Evaluation of Drug-Induced Liver Injury :** by Hepatotoxicity Working Group. Tolvaptan data from briefing documents for this meeting.

"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." (Briefing Document PDF page 66)

FDA 16-year record of not approving hepatotoxic drugs

Following the disastrous FDA approvals of two hepatotoxic drugs in 1997, troglitazone and bromfenac, both of which “promptly began to kill patients with acute liver failure”, FDA convened a hepatotoxicity working group to educate FDA reviewers on evaluating drugs for hepatotoxicity. It is now 16 years without any FDA approval of a drug that later had to be withdrawn because of hepatotoxicity. This excellent record needs to be sustained. FDA’s recommendation against approval is correct.