NDA 204441 Tolvaptan
Clinical and Statistical Findings

Cardiovascular and Renal Drugs
Advisory Committee Meeting

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Outline

- Trial design and regulatory history
- Efficacy findings and statistical issues
- Tolvaptan-induced liver injury
- Risk-Benefit

Trial design and regulatory history

- Who was enrolled and why
- Efficacy endpoints and baseline definition
- Subject follow up
- Blinding

Who was enrolled and why

- Inclusion criteria for the phase 3 trial: an "estimated GFR≥ 60 mL/min" as determined by the Cockcroft-Gault equation
- Stated rationale:

  "Subjects will have a GFR ≥60 mL/min … 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."

Source: Protocol 156-04-251

Renal volume as a surrogate endpoint

"If the hypothesis that early treatment is necessary to affect outcome is correct, we recognize the difficulty of demonstrating effects on renal function, a late consequence. On the other hand, there is no intervention to alter renal volume that is known to affect renal function, so it is hard to accept renal volume as a surrogate…"

Division's feedback on renal volume as an efficacy endpoint, September 2005

Efficacy endpoints

- The trial's *primary endpoint*: rate of change in renal volume
- The trial's *first secondary endpoint*: the time to multiple ADPKD clinical progression events*
- We told Otsuka that the *first secondary endpoint would be considered the key efficacy endpoint* and that a p-value < 0.01 would be needed to support approval based on the findings of a single trial.

*Also referred to as the "composite secondary endpoint"

Composite secondary endpoint: Baseline measurement for analysis

Component of Secondary Endpoint	Time "baseline" measured
Hypertension (worsening in category or need for treatment)	Day 1
Renal pain (requiring medical intervention)	Day 1
Albuminuria (worsening in category)	Day 1
Renal Function (25% decrease in reciprocal of serum creatinine)	Week 3/End of titration

Other issues

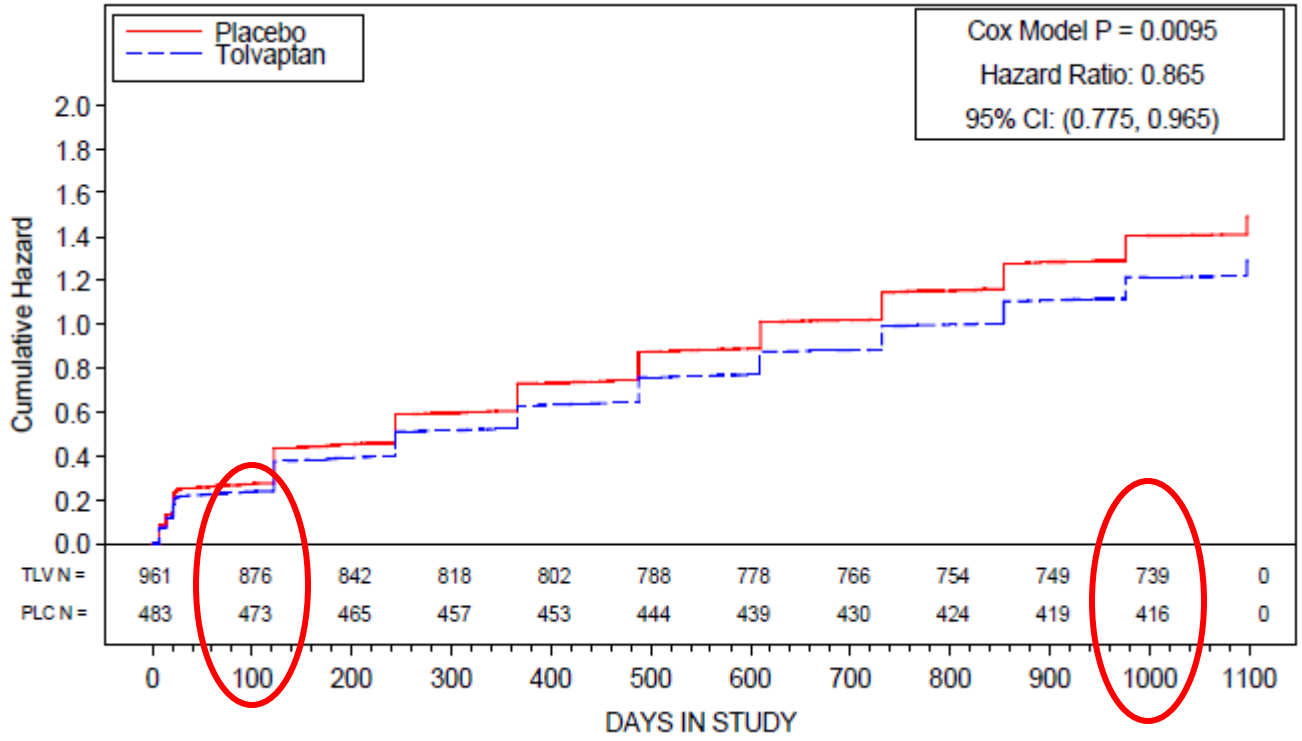
- Subject follow up: Data for key efficacy endpoints (e.g., creatinine values) were not collected after discontinuation of study medication. The protocol stipulated that these subjects were followed by telephone contact.
- Blinding: Tolvaptan increases urinary volume and frequency likely unblinding investigators and/or subjects to treatment assignment.

Efficacy findings

Secondary composite endpoint

(Applicant's analysis)

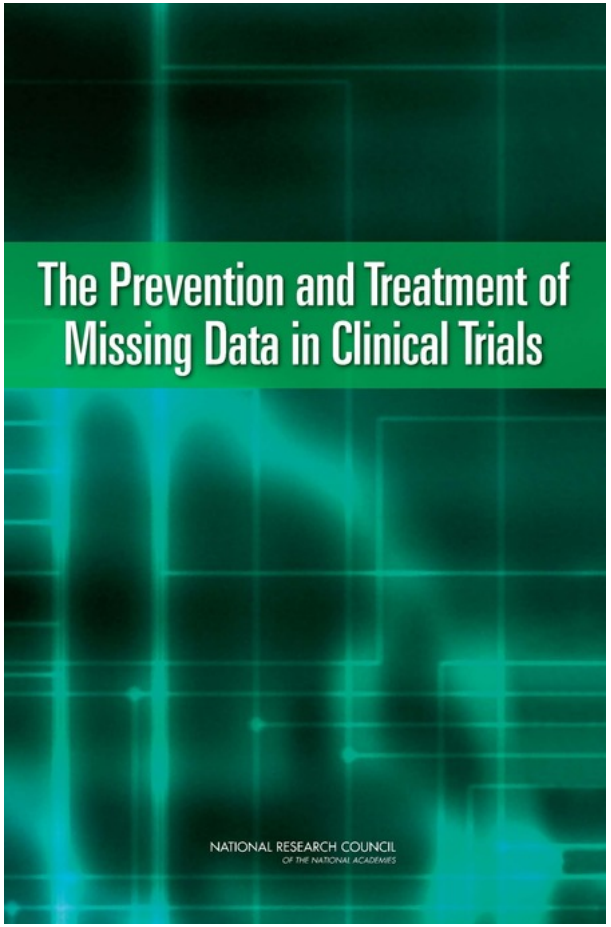
Time to multiple ADPKD clinical progression events



Tolvaptan: ~91% of subjects
Placebo: ~98% of subjects

Tolvaptan: ~77% of subjects
Placebo: ~86% of subjects

The National Research Council's Panel on Handling Missing Data



"There is no 'foolproof' way to analyze data subject to substantial amounts of missing data; that is, no method recovers the robustness and unbiasedness of estimates derived from randomized allocation of treatments."

Secondary composite endpoint: Statistical issues

1. **When baseline is defined**
2. **Missing data and how it is handled**
3. How tied event times are handled
4. How the variance of the treatment effect is estimated

Secondary composite endpoint: When baseline is defined

Component of Secondary Endpoint	As specified in primary analysis	Baseline week 3 for all components
time to multiple events	p = 0.01	p = 0.020
time to the first event	p = 0.005	p = 0.078

Source: Study Report, CT-5.2.1.2.1, CT-5.2.1.1.2, and CT-5.2.1.2.2

Secondary composite endpoint: Missing data

Sensitivity Analysis: Multiple Imputation on Analysis of Time to Multiple Event of Key Secondary Endpoint

ITT, Regardless of Treatment Period

Percentage of Risk Used in Imputation for Tolvaptan Compared to Placebo	HR	95% CI Lower Limit	95% CI Upper Limit	P-value
100%	0.888	0.794	0.993	0.0372
105%	0.894	0.799	1.000	0.0495
110%	0.901	0.806	1.007	0.0663

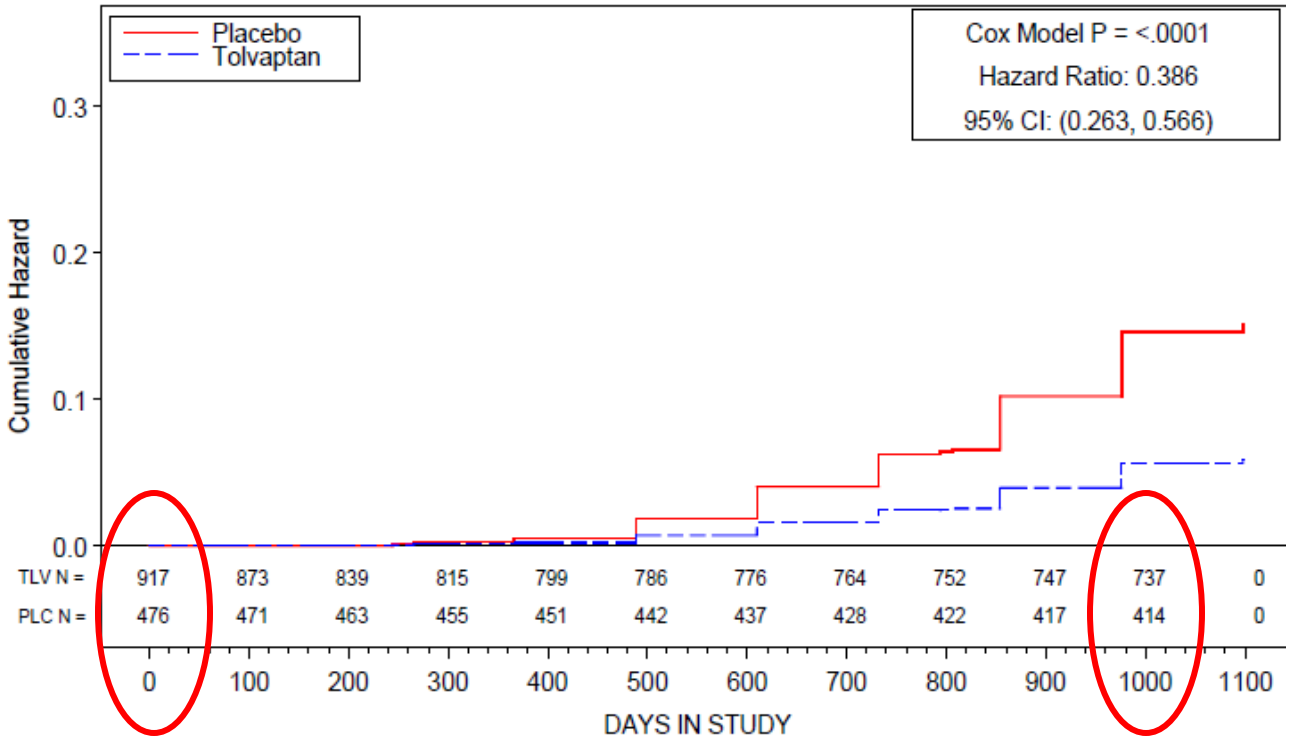
Source: Study Report, ST-2.7.3.1

Secondary composite endpoint: Summary

- The p-value of 0.01 was not robust.
- Baseline at randomization for all components?

Secondary composite endpoint: Renal function component

(Applicant's analysis)



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Renal function component of the secondary composite endpoint

- Analysis of baseline factors (renal function, hypertension and kidney volume) did not suggest more severe underlying kidney disease in tolvaptan subjects with missing data.
- Sensitivity analyses meant to address data missing not at random suggested a treatment effect on renal function.

Effect of tolvaptan on rate of decline in renal function

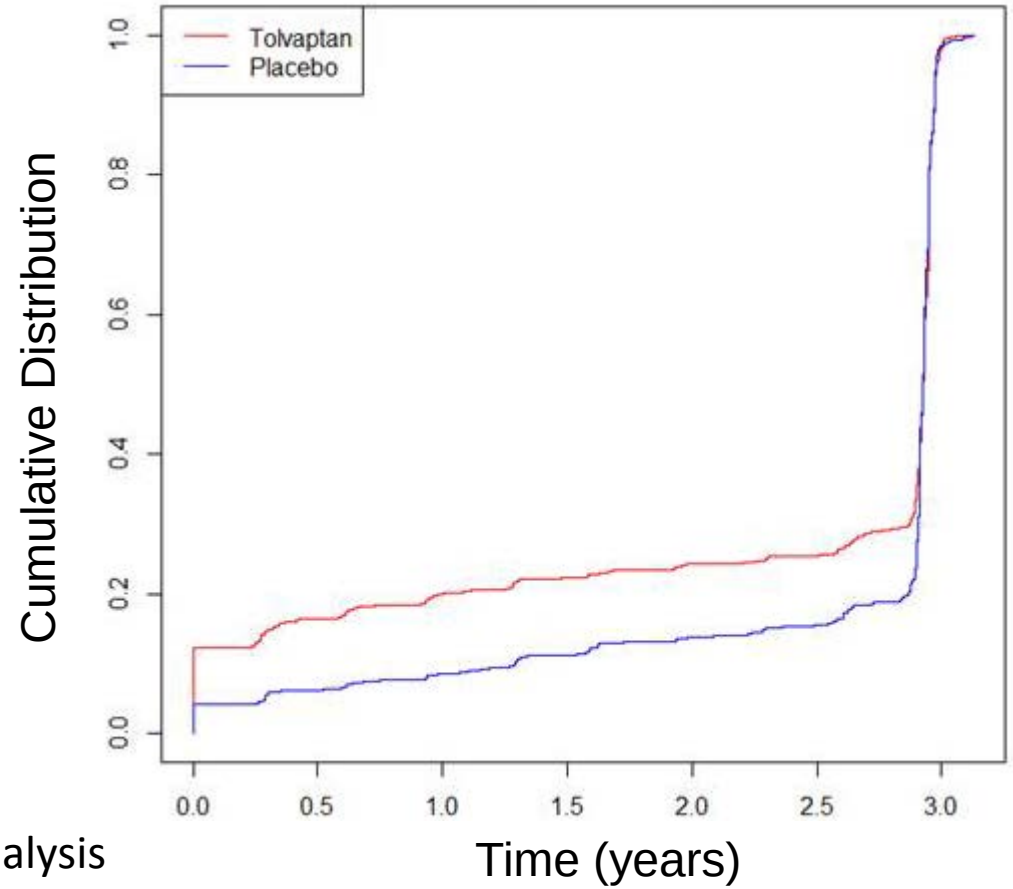
(Applicant's analysis)

Estimated GFR (CKD-EPI)	Tolvaptan N=842	Placebo N=464
Mean rate of change per year in estimated GFR (mL/min/1.73m^2)	-2.7	-3.6
Treatment effect (95% CI): difference between slopes in the tolvaptan and placebo arms	1.0 mL/min/1.73m^2 per year (0.6, 1.4)	

Source: Study Report for 156-04-251

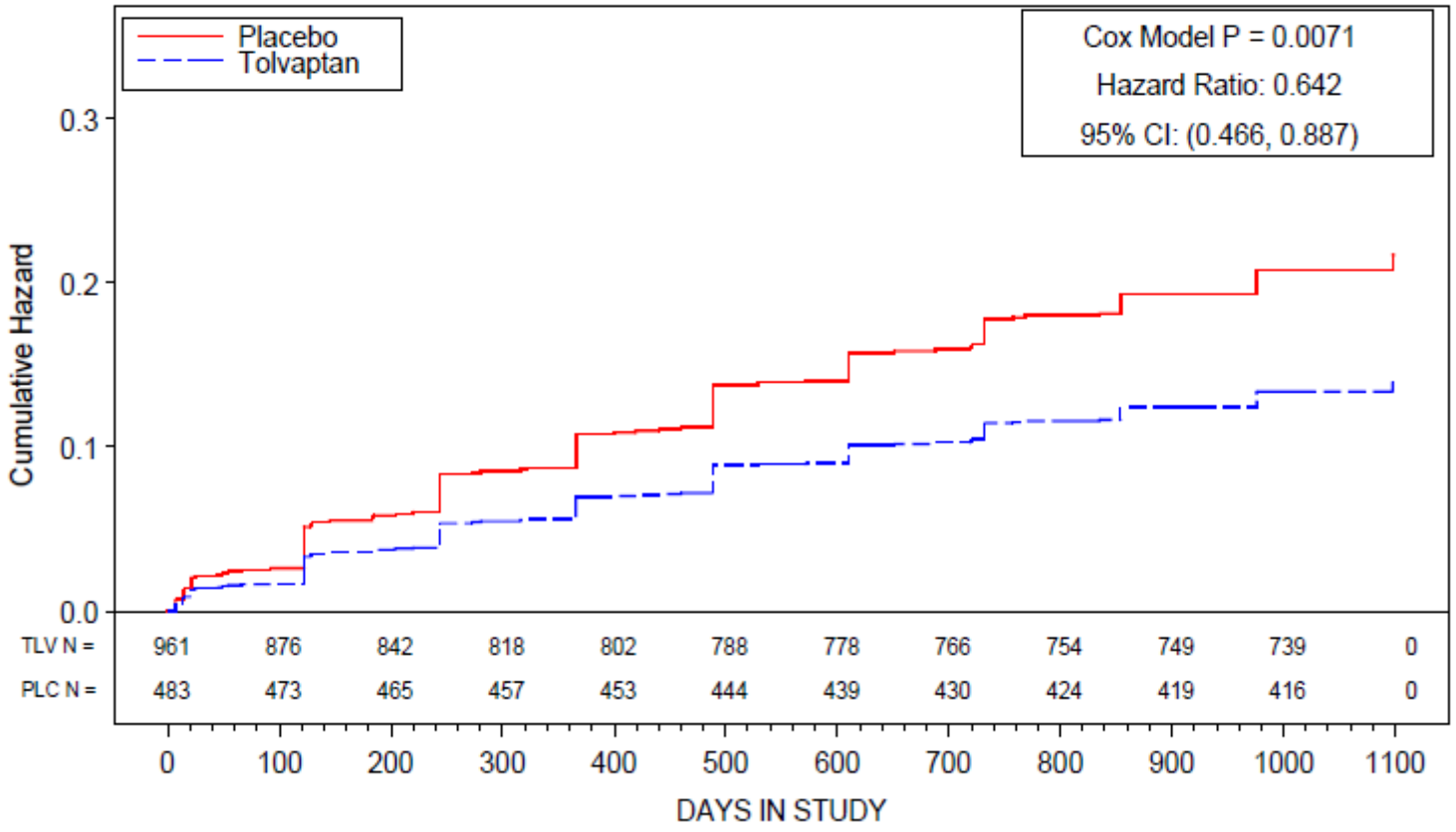
Rate of change in renal function: Missing data

Distribution of time to last eGFR



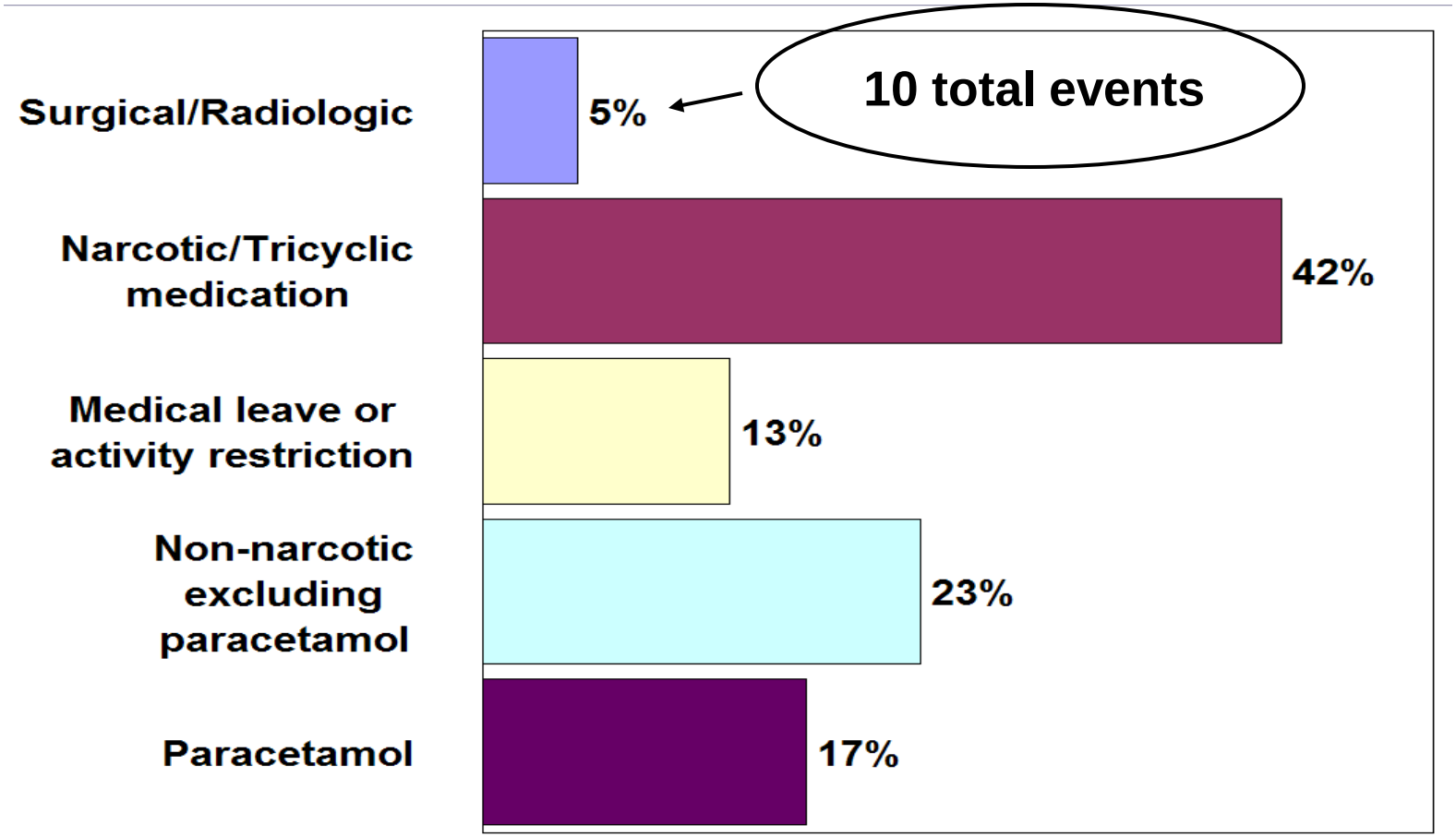
Source: FDA analysis

Secondary composite endpoint: Renal pain component



Source: Study Report for 156-04-251

Interventions for relief of renal pain as a percentage of renal pain events



Secondary composite endpoint: Renal pain component

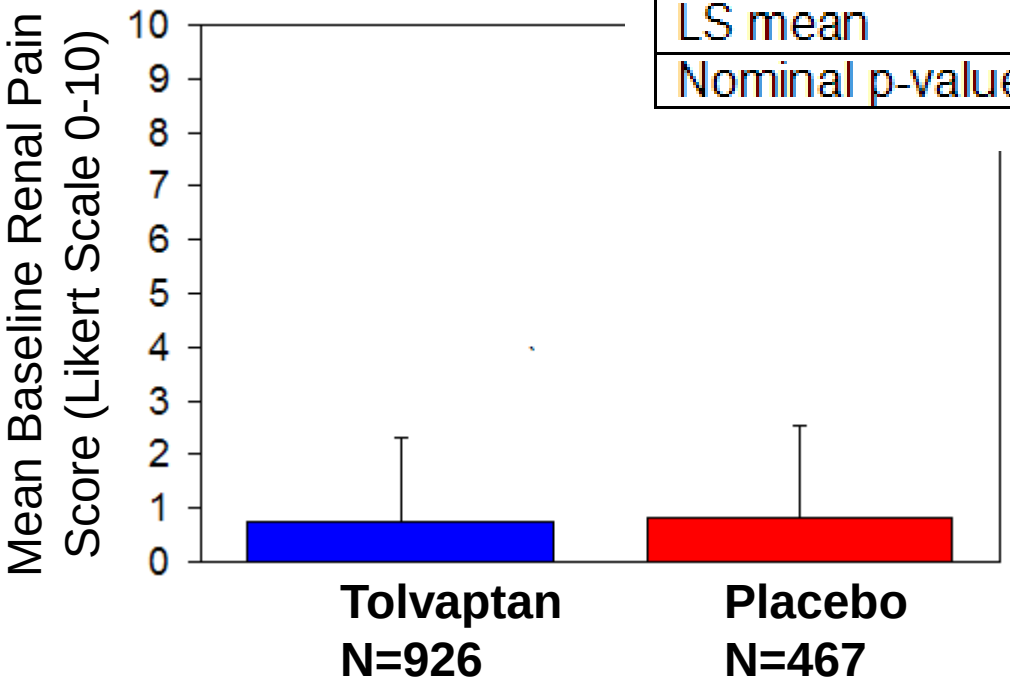
- The endpoint is subjective and because of tolvaptan's aquaretic effect, it was likely difficult to maintain blinding.
- Subjects with missing data appeared to be more likely to have a history of renal pain (though this finding was more pronounced in the placebo group).
- The cause of renal pain events was not captured in the case report form and hence our understanding of these events is limited.

Renal pain scores

Subjects not taking renal pain medication at baseline

Time averaged AUC of change from baseline

	Tolvaptan N=926	Placebo N=467
LS mean	0.0	0.08
Nominal p-value	0.16	



- No treatment effect
- Findings suggest that pain did not significantly impact daily function in most subjects

Source: Study Report for 156-04-251 and FDA analysis
Pain scores censored once a subject starts pain medication

Efficacy conclusions

- The p-value of 0.01 for the composite secondary endpoint was not robust.
- Tolvaptan slowed the loss of renal function (~1 ml/min/1.73m^2 per year).
- Because of loss of subject follow-up, especially in the tolvaptan arm, the estimate of the size of the treatment effect may not be accurate.

Clinical significance

Chronic Kidney Disease: GFR categories (ml/min/1.73m^2)

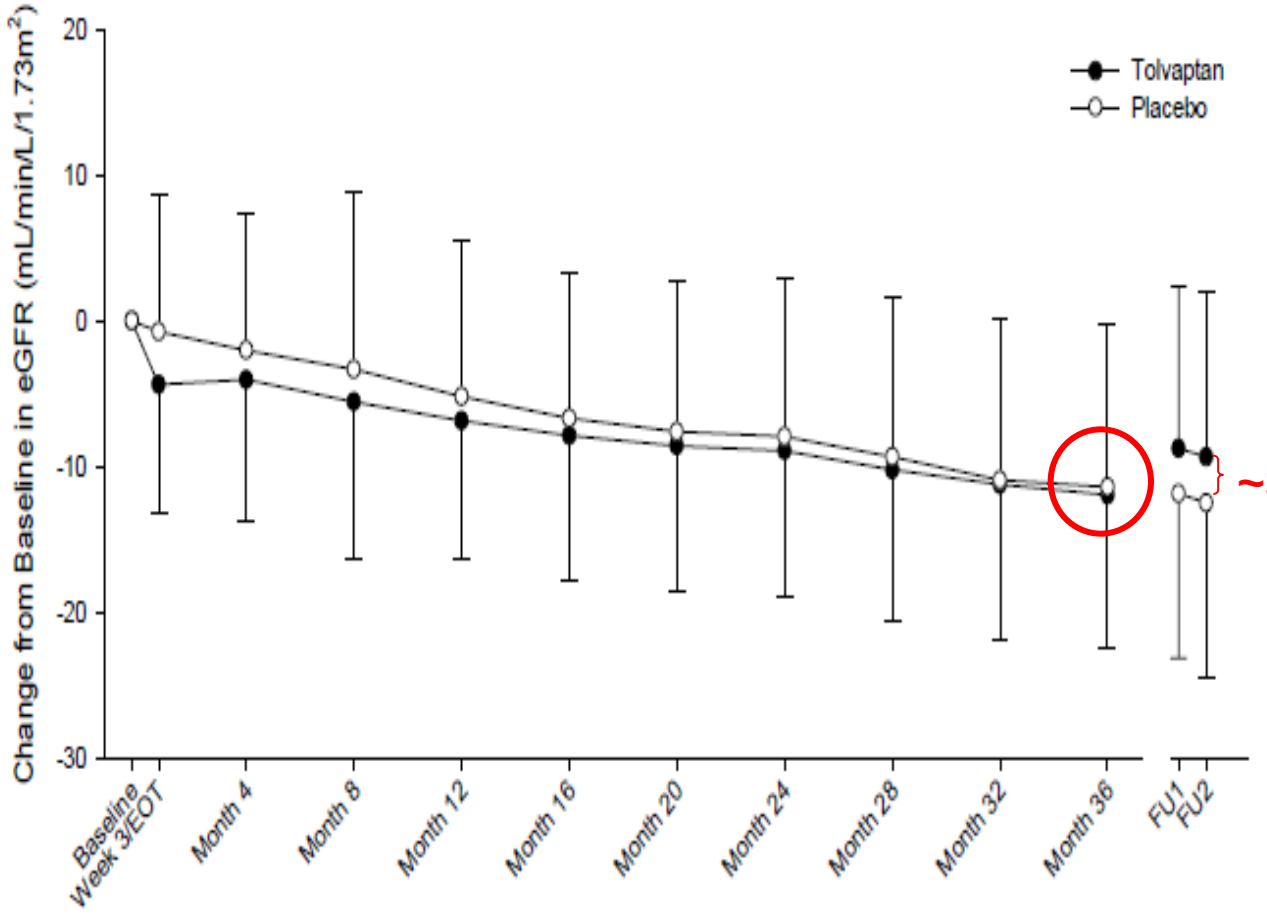
G1	Normal or high	≥ 90
G2	Mildly decreased	60-89
G3a	Mildly to moderately decreased	45-59
G3b	Moderately to severely decreased	30-44
G4	Severely decreased	15-29
G5	Kidney Failure	< 15

KDIGO 2012 Clinical Practice Guideline

Baseline estimated GFR in the study population (CKD-EPI equation):
~82 ml/min/1.73m^2

Observed difference between treatment arms in the rate of loss of renal function: ~ 1 ml/min/1.73m^2 per year

Change from baseline in renal function



~3 mL/min/1.73m²

Source: Applicant's Summary of Clinical Efficacy
*Estimated GFR calculated by CKD-EPI

The projected benefit

- Study subjects were for the most part remote from end-stage kidney disease and treatment effects on this outcome were not directly observed.
- A treatment effect on end-stage kidney disease would be expected, if over time, tolvaptan continues to slow the rate of loss of renal function.
- 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 kidney disease.

Tolvaptan-induced liver injury

Tolvaptan-induced liver injury

- Three subjects developed significant hepatocellular liver injury judged to be at least probably due to tolvaptan by an expert panel of hepatologists.
- These subjects did not progress to liver failure but these cases indicate that tolvaptan has the potential to cause severe liver injury.
- A rough estimate of the risk of liver failure requiring transplantation or death if marketed: 1:3000 patients.

Context

"Only the most overt hepatotoxins can be expected to show cases of severe DILI [drug-induced liver injury] in the 1,000 to 3,000 subjects typically studied and described in a new drug application…"

"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…"

Source: FDA's Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation (2009)

Window of potential risk

- Available data are compatible with a “signature period of risk” (between 3 to 14 months)
- 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)
- Experts have noted, “drugs with characteristic signatures may produce injuries without all of the characteristics of that signature”

→ It is unknown if the risk of severe drug-induced liver injury is limited to a finite period

Benefit, Risk and…Uncertainty

- **Benefit:** delay in the onset of end-stage kidney disease
  - Not directly observed in clinical trial.
  - Missing data and lack of data in patients with more advanced stages of disease make it difficult to describe tolvaptan's benefit.
- **Risk:** liver injury resulting in liver transplant or death
  - Not directly observed in clinical trial but estimated incidence of 1:3000.
  - Period of risk unknown.
  - The extent to which this risk will be mitigated by close patient follow-up and careful patient selection is unknown.

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Medication Error Prevention	Kimberly De Fronzo
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Risk Management Considerations

Tolvaptan for autosomal dominant polycystic kidney disease (ADPKD)

Meeting of the Cardiovascular and Renal Drugs Advisory Committee

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Can the risk of severe liver injury caused by tolvaptan be mitigated to improve the benefit-risk balance, and if so, how?

Outline

- Introduction to Risk Evaluation and Mitigation Strategies (REMS)
- Overview of proposed tolvaptan REMS requirements
- Impact of the REMS on burden and access
- Limitations of the proposed REMS for tolvaptan
- Conclusions

Food and Drug Administration Amendments Act (FDAAA) of 2007

- FDAAA authorizes the FDA to require a Risk Evaluation and Mitigation Strategy (REMS)

- Risk Evaluation and Mitigation Strategy (REMS)
  - A risk management plan that utilizes strategies beyond labeling to ensure that the benefits of a drug outweigh the risks
  - Designed to achieve specific goals to mitigate the serious risk(s) associated with use of a drug

Components of a REMS

- A REMS *may* include:
  - Medication Guide or Patient Package Insert
  - Communication Plan
  - Elements to Assure Safe Use (ETASU)
  - Implementation Plan

- A REMS *must* include:
  - Timetable for Submission of Assessments

Elements to assure safe use (ETASU)

One or more activities required to assure the safe use of a drug – may include "restricted distribution":

1. Prescribers have particular training or special certification
2. Pharmacies that dispense the drug have particular training or special certification
3. The drug may be dispensed only in certain healthcare settings
4. The drug may be dispensed to patients with evidence of safe-use conditions
5. Each patient may be subject to monitoring
6. Patients may be enrolled in a registry

Drugs that require ETASU

- The drug can only be approved or would be withdrawn unless such elements (to assure safe use) are required
- Assuring access and minimizing burden
  - Must be commensurate with specific serious risk(s) listed in the labeling
  - Cannot be unduly burdensome on patient access
  - To minimize the burden on the healthcare delivery system, must, to the extent practicable, conform with elements for other drugs with similar serious risks and be designed for compatibility with established distribution, procurement, and dispensing systems for drugs

Purpose of a REMS

A REMS is necessary when a serious risk outweighs the benefit of a drug unless specific counter measures (REMS requirements) are implemented to improve the benefit-risk balance.

Risk of concern for tolvaptan: Severe tolvaptan-induced liver injury

- A panel of experts on drug-induced liver injury (DILI) concluded the following:
  - tolvaptan has the potential to cause liver injury capable of progression to liver failure.
  - a rough incidence of liver failure in about 1:3000 patients who receive long term treatment with tolvaptan.
- No treatment for idiosyncratic DILI has been demonstrated to be effective.

Overview of tolvaptan REMS requirements

- Prescribers must be informed of the risk and enrolled in the tolvaptan REMS program.
- Patients must be informed of the risk by completing a *Patient-Prescriber Agreement Form*.
- Monthly hepatic laboratory monitoring must be completed, reviewed and documented by prescribers.
- Patients must be enrolled in the tolvaptan registry.
- Prior to dispensing tolvaptan, pharmacies must verify:
  - prescriber and patient enrollment
  - documentation of monthly hepatic laboratory monitoring

How can the tolvaptan REMS mitigate the risk of severe liver injury?

- Provide a mechanism to detect DILI at a time when it may be reversible by:
  - Requiring monthly hepatic laboratory monitoring
  - Ensuring prescribers are informed of the risk of DILI
  - Ensuring patients are informed how to recognize DILI and actions to take if it occurs

Impact of the tolvaptan REMS: Burden

- Prescribers
  - Enrollment of patients in the tolvaptan registry
  - Documentation of monthly monitoring

- Pharmacists
  - Verification of prescriber certification
  - Verification of patient enrollment
  - Verification of documented monthly monitoring

Impact of the tolvaptan REMS: Patient Access

- Potential interruptions in therapy due to REMS verification process

- Prescribers may choose not to become certified in the tolvaptan REMS, thus limiting patient access

Limitation of a REMS for tolvaptan

Any REMS for tolvaptan will not prevent all progression to severe liver injury caused by tolvaptan.

Conclusions

- The risk of severe tolvaptan-induced liver injury requires risk mitigation strategies beyond labeling.
- Multiple strategies are needed to address the risk.
- The proposed tolvaptan REMS will increase burden and has the potential to limit patient access.
- No REMS will prevent all severe liver injury associated with tolvaptan.