Tolvaptan: Slowing Progression of Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Cardiovascular and Renal Drugs Advisory Committee

August 5, 2013

Otsuka

Introduction

Robert McQuade, PhD

Executive Vice President and Chief Strategic Officer
Otsuka Pharmaceutical Development & Commercialization, Inc.

Autosomal Dominant Polycystic Kidney Disease

- A relentlessly progressive, hereditary illness that in most (~80%) patients takes decades to reach End-Stage Renal Disease (ESRD)
- ADPKD is characterized by:
  1. Increasing cyst growth leading to increase of total kidney volume
  2. Increasing kidney fibrosis and damage by fluid-filled cysts
  3. Worsening kidney function
  4. Worsening patient clinical outcomes
  5. Reaching end stage renal disease
- **There are no treatments targeting the underlying pathophysiology of the disease**

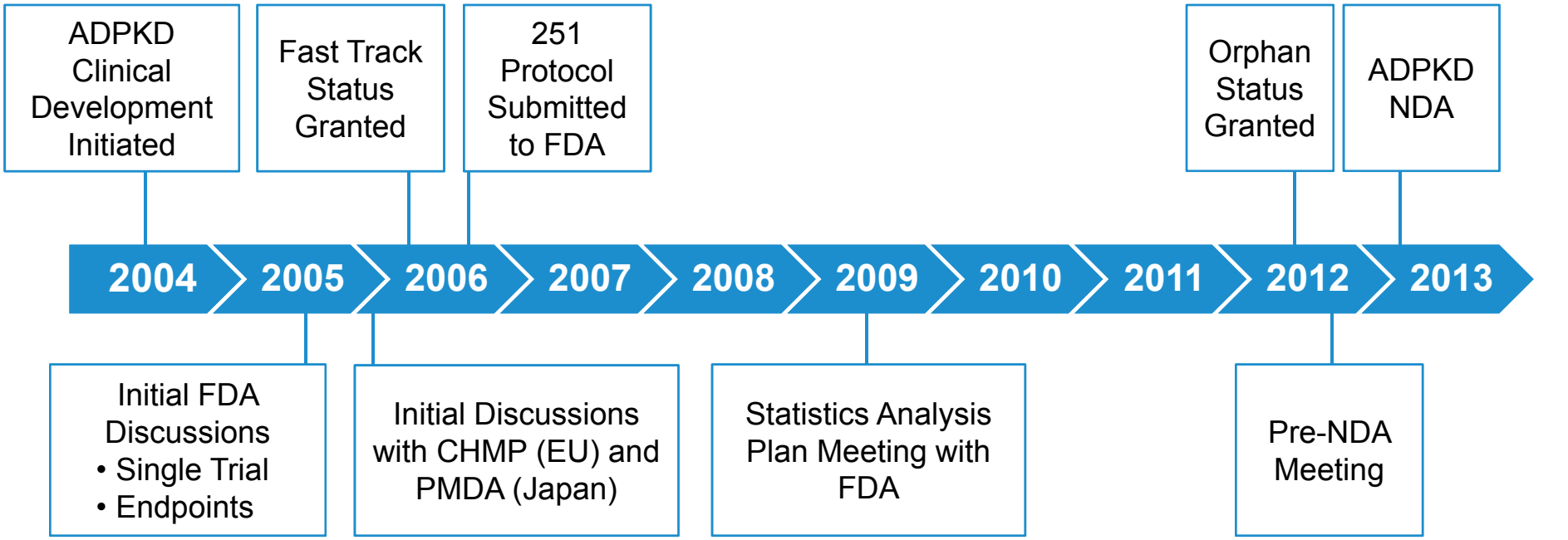
Challenges of Studying ADPKD

- **ADPKD is an orphan condition**
  - Estimated prevalence in US is 1:2000
- **Kidney damage is widespread before renal functional decline is evident**
  - *"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, 2006)"*
    – FDA Briefing Document, p. 25
- **Without prior positive interventional trials, there are no validated endpoints to use in a study of practical duration**

Tolvaptan slows disease progression

- Tolvaptan blocks vasopressin at V_2 receptors in the kidney
  - Vasopressin promotes the number and growth of kidney cysts
  - Blockade of V_2 receptors reduces disease severity in five pre-clinical animal models
- Tolvaptan (Samsca) is approved by FDA for the treatment of clinically significant hyponatremia (2009)
- **Tolvaptan trial 156-04-251 (Study 251) is the largest and longest placebo-controlled study in ADPKD patients**
  - Randomized 1445 patients for 3 years in the Americas, Europe and Japan

Key Regulatory Milestones



Phase 3 Study 251

Supportive Tolvaptan ADPKD Studies

PKD Outcomes Consortium

Tolvaptan Proposed Indication

- **Tolvaptan is a selective vasopressin V_2-receptor antagonist indicated to slow kidney disease in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD)**
  - Efficacy was established in patients with enlarged kidneys who were in chronic kidney disease (CKD) stages 1-3 at initiation of treatment

Agenda

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Pathophysiology of Autosomal Dominant Polycystic Kidney Disease	**Vicente Torres, MD, PhD** *Professor of Medicine, Mayo Clinic*
Measuring Patient Burden and Renal Progression in ADPKD	**Arlene Chapman, MD** *Professor of Medicine, Emory University*
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Conclusion: Risk Evaluation/Mitigation and Net Benefit	**Robert McQuade, PhD**

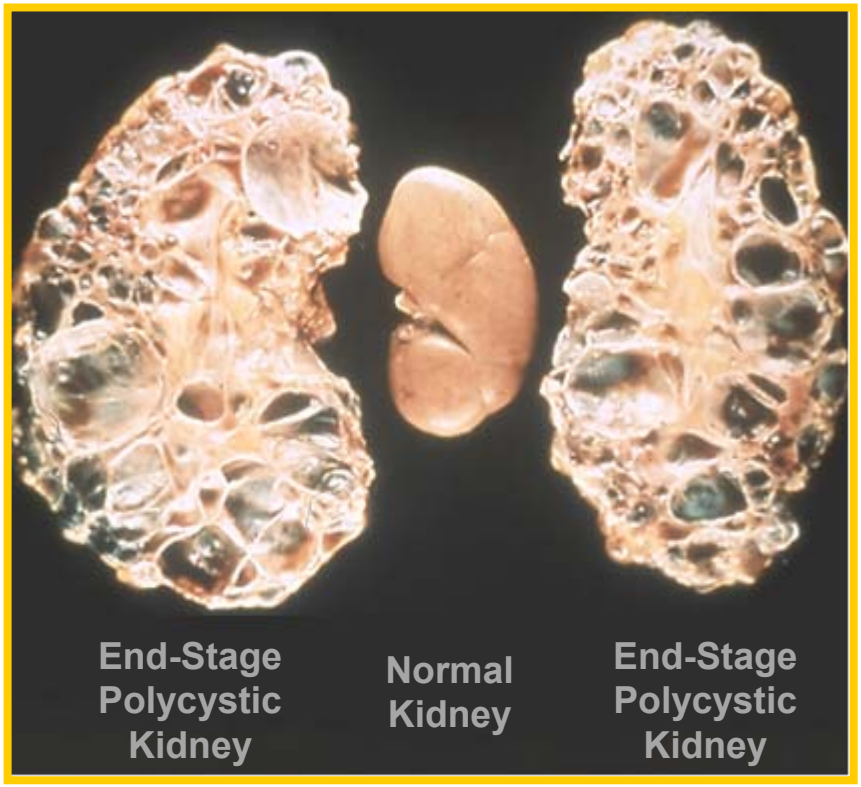
Additional Responders

- **Daniel Bichet, MD**
  - Université de Montréal
  - Nephrology and Genetics
- **Sidney Goldstein, MD**
  - Henry Ford Hospital
  - Independent Data Monitoring Committee
- **Jared Grantham, MD**
  - University of Kansas
  - ADPKD and Patients
- **Keith Flaherty, MD**
  - Massachusetts General Hospital
  - Neoplasm
- **Gary Koch, PhD**
  - University of North Carolina
  - Biostatistics
- **Willis Maddrey, MD**
  - University of Texas Southwestern
  - Hepatotoxicity
- **Ronald Perrone, MD**
  - Tufts University
  - ADPKD and Clinical Trial Endpoints
- **Paul Watkins, MD**
  - University of North Carolina
  - Hepatotoxicity

Pathophysiology of Autosomal Dominant Polycystic Kidney Disease

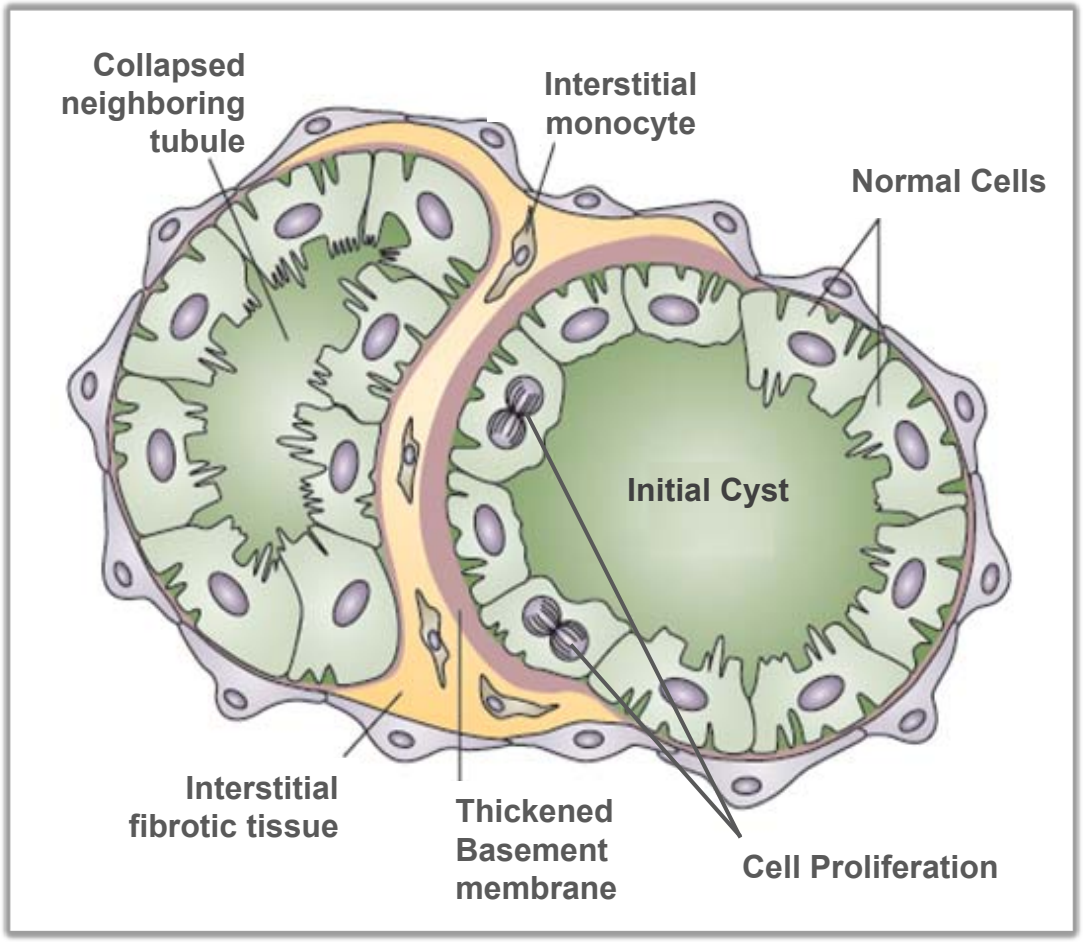
Vicente Torres, MD, PhD
Professor of Medicine
Mayo Clinic

Autosomal Dominant PKD



- Characterized by multiple bilateral kidney cysts
- Affects all races, ethnicities and genders
- Progressive kidney enlargement with symptomatic episodes (eg, renal pain, bleeding, stones, UTI)
- Fourth most common cause of End Stage Renal Disease (ESRD)
- Genetically heterogeneous (PKD1 more frequent and severe than PKD2)

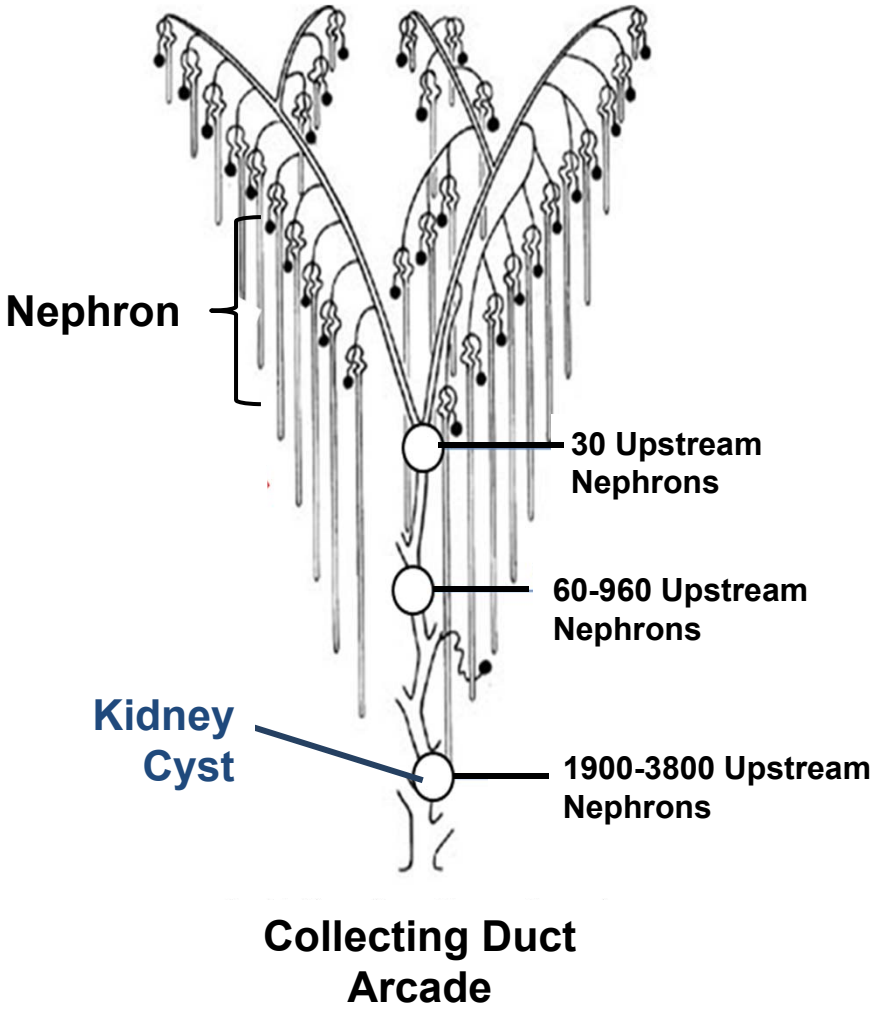
Cysts damage the kidney through multiple mechanisms



- Structural compression by cyst growth
- Obstruction of urine flow
- Interstitial inflammation and fibrosis from cyst chemokines and cytokines

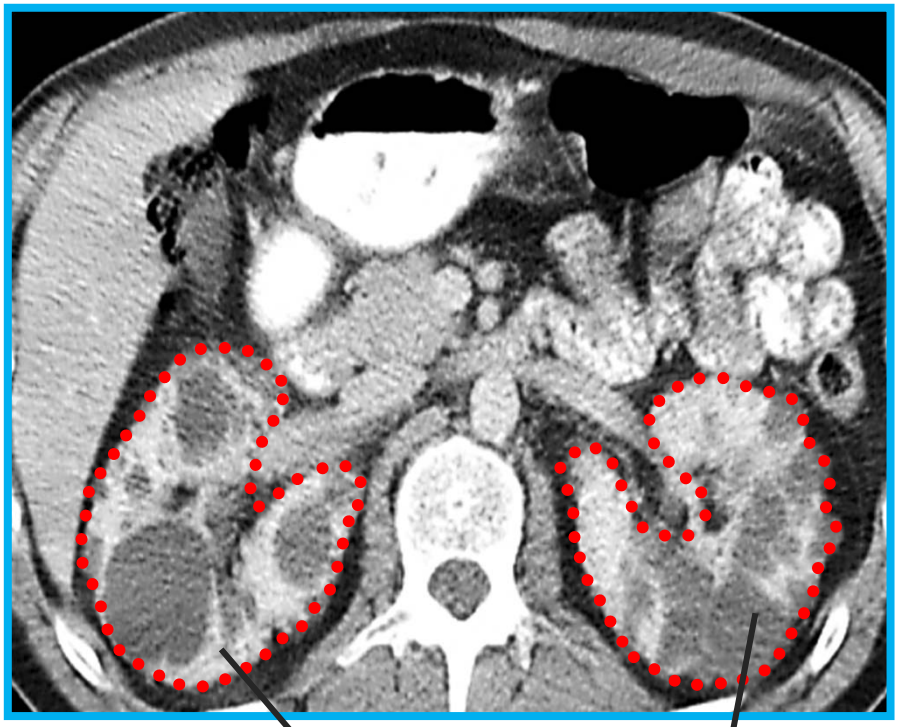
Adapted from Grantham JJ. *Nat. Rev. Nephrol.* 7, 556–566 (2011)

Kidney Structure Magnifies Impact of Tubular Obstruction by Cysts



- Cysts originate from collecting duct and distal nephrons
- Each papillary collecting duct drains up to 4000 nephrons
- An individual cyst can render functionless a larger number of nephrons

Kidney Volume is Increased while Kidney Function Remains Normal



30 Year Old Male

Total Kidney Volume (TKV)= 1441 ml

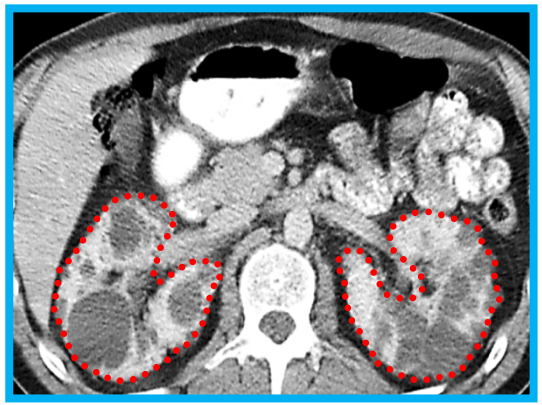
CKD Stage 1

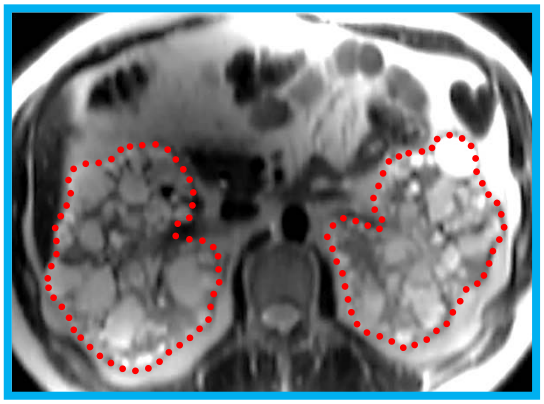
Glomerular Filtration Rate (GFR)= 93 ml/min

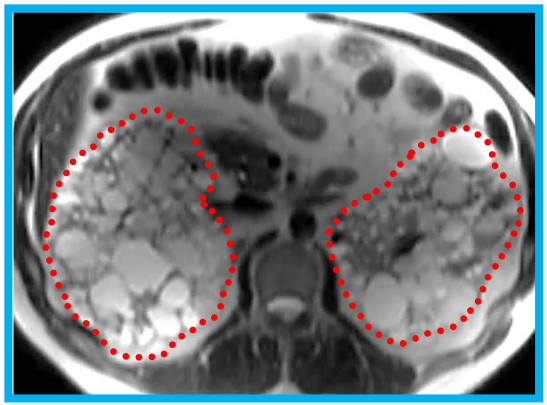
CKD=Chronic Kidney Disease; Normal TKV for men is 300 ml

Over time Cysts Develop and Expand Resulting in Loss of Kidney Function

Over 13 years, TKV increased by 300%
with a 53% loss of kidney function







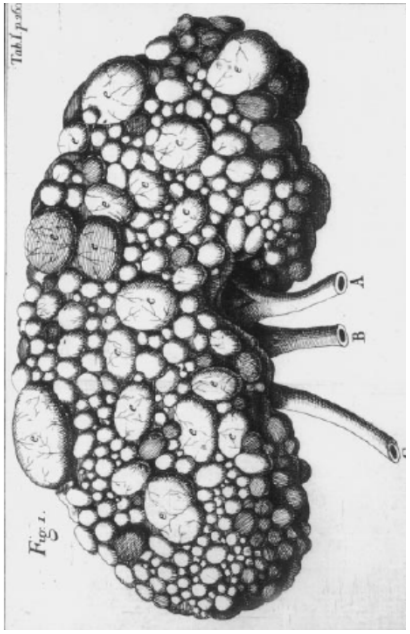
Age 30	→	Age 37	→	Age 43
CKD Stage 1		*CKD Stage 2*		*CKD Stage 3*
GFR 93 ml/min		GFR 61 ml/min		GFR 44 ml/min
TKV 1441 ml		TKV 2775 ml		TKV 4459 ml

GFR=Glomerular Filtration Rate; CKD=Chronic Kidney Disease; TKV=Total Kidney Volume

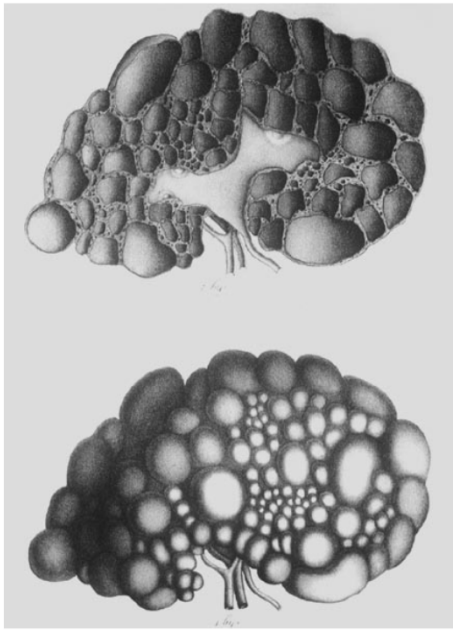
Cyst growth and fibrosis: Primary causes of renal insufficiency

- Cysts are dynamic, proliferative, secretory tumors
- Damage results from both structural compression, tubular obstruction, inflammation and fibrosis (eg, due to chemokines and cytokines)
- Cyst development and growth over decades destroy the structure and function of kidneys
- GFR decline becomes evident at late stage when most of the tissue has been destroyed

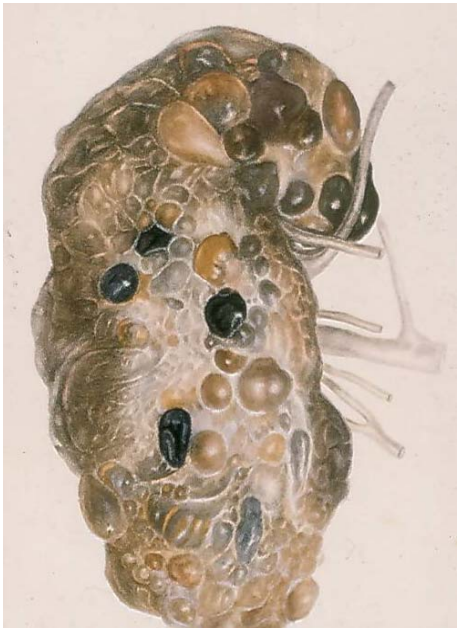
An unmet medical need:
For Centuries…an illness without cure



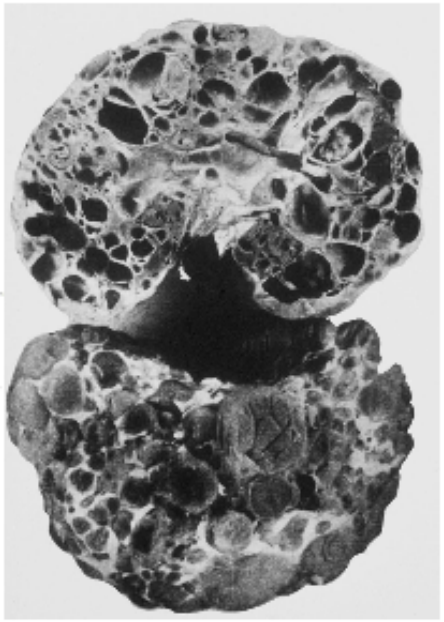
Galeazzi
1757



Cruveilhier
1835



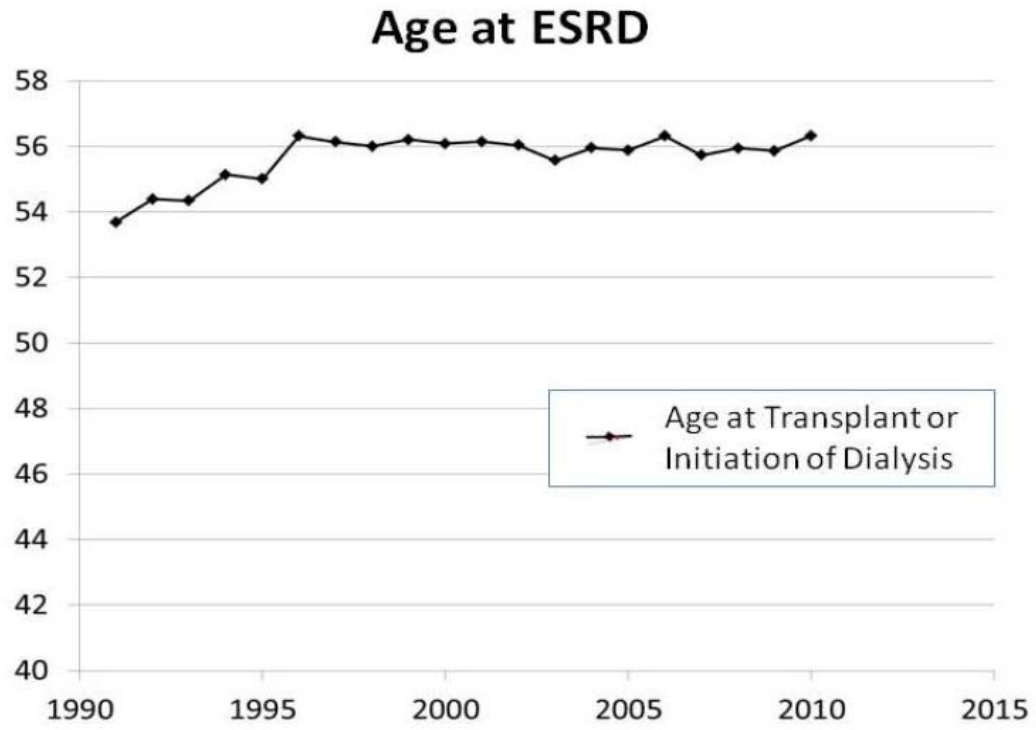
Rayer
1841



Dalgard
1957

"The cystic degeneration of the kidneys, once it reaches the point where it can be detected or suspected during life, is an illness without cure."
Rayer 1841

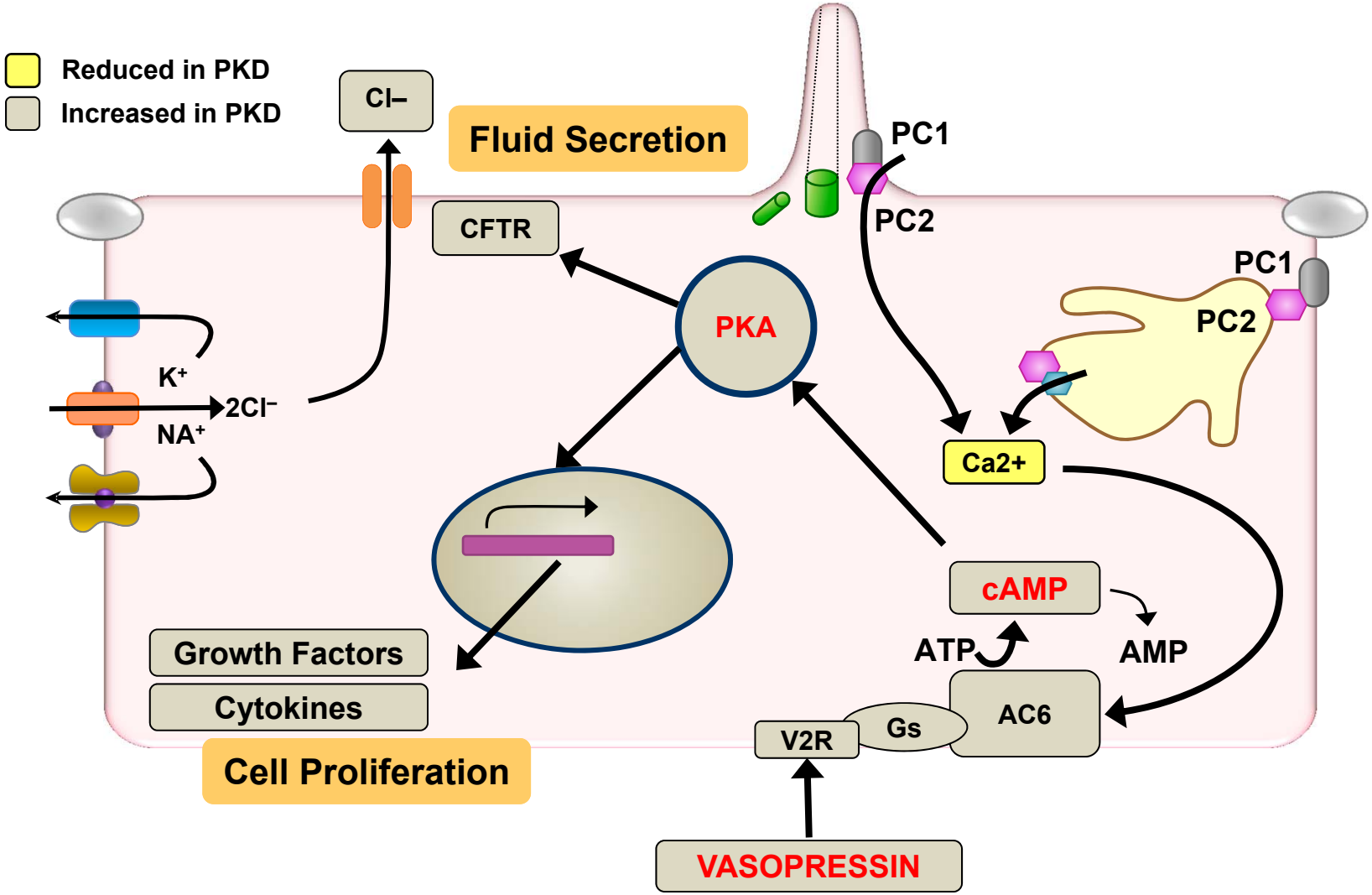
Outcomes for ADPKD patients have not substantially changed in decades



- ADPKD accounts for approximately 5% of the U.S. ESRD population
- The cost of renal replacement therapy for ADPKD alone exceeds 1 billion dollars annually

USRDS, courtesy of Eric Weinhandl and Ronald Perrone 3/2013

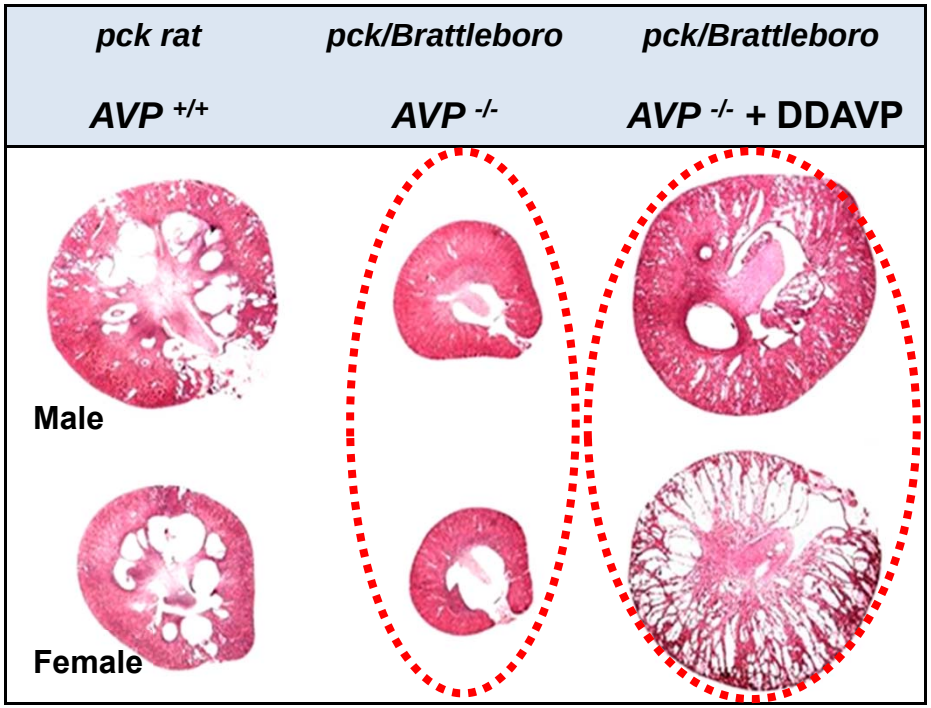
Increased cAMP drives cystogenesis



Vasopressin is crucial for cyst development

Vasopressin is

- The major stimulus of cAMP production in collecting duct and distal nephron
- Constantly present in circulation acting on kidney
- Associated with disease progression in ADPKD patients (copeptin)

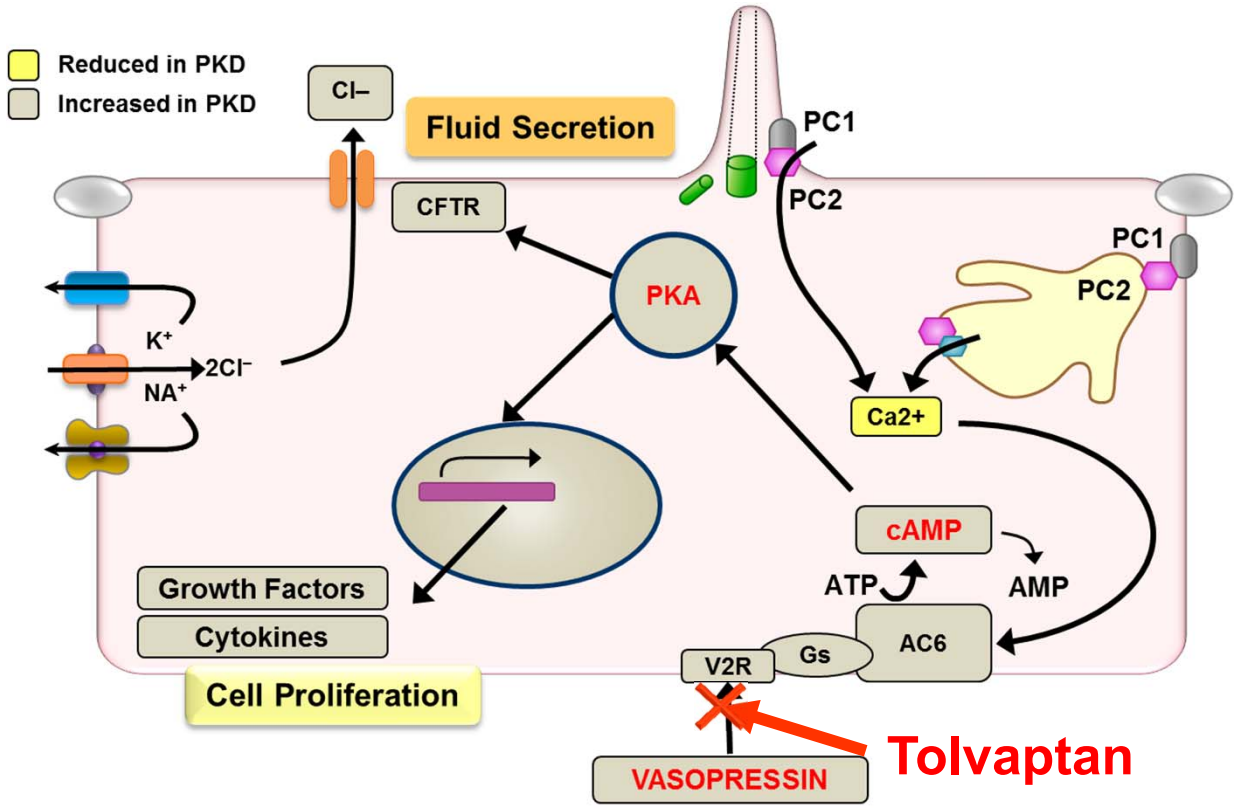


pck rat: animal model of PKD; Brattleboro rat: animal model without vasopressin

Reif *Am. J. Physiol. Renal Physiol*. 2011; Wang. *JASN* 19:102-108, 2008; Meijer, E. *Kidney Blood Press Res* 34:235–244, 2011

Rationale for Tolvaptan in ADPKD

- Consistently reduces disease severity in pre-clinical animal models
- Reduces ADPKD cell proliferation and secretion in human *ex vivo* cysts
- Restricted localization of V2R limits the potential for side effects



Summary

- For centuries, an unmet medical need
- New opportunities based on solid science
- Cysts directly and indirectly damage the kidney
- Cyclic AMP drives cyst growth
- Tolvaptan inhibits the production of cAMP at the main sites of renal cystogenesis

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Measuring Patient Burden and Renal Progression in ADPKD

Arlene Chapman, MD
Professor of Medicine
Emory University

Outline

- Describe the natural history of ADPKD
- Demonstrate the results of CRISP regarding the importance of Total Kidney Volume in ADPKD
- Describe how the natural history of ADPKD informed CRISP, which has informed the Study 251 design

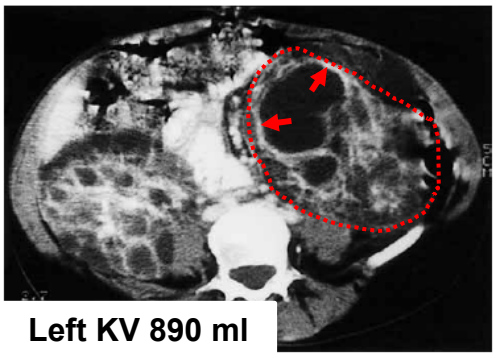
Kidney Volume and Cysts are Determinants of Renal Outcomes in ADPKD

- Renal cysts are the first verifiable primary manifestation of ADPKD
- Cyst formation always precedes:
  - flank pain
  - hypertension
  - gross hematuria
  - nephrolithiasis
  - kidney infections
  - reduced GFR
- Inverse correlation between kidney volume and function is well established[1-6]

[1]Thomsen *Urol Rad* 3:85, 1981; [2]Chapman *Kid Int* 64:1035, 2003; [3]Fick-Brosnahan *AJKD* 39:1127, 2002; [4]Lee *Nephron Clin Pract* 103:c173, 2006; [5]Tokiwa Clin Exp Neph March 2011; [6]*Meijer CJASN* 5:1091, 2010;

Renal Events in ADPKD Result in Clinically Meaningful Pain

Cyst Infection

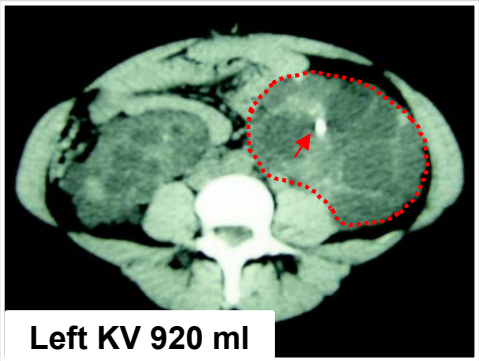


Left KV 890 ml

- 20 Y Female
- Acute left flank pain
- eGFR 106

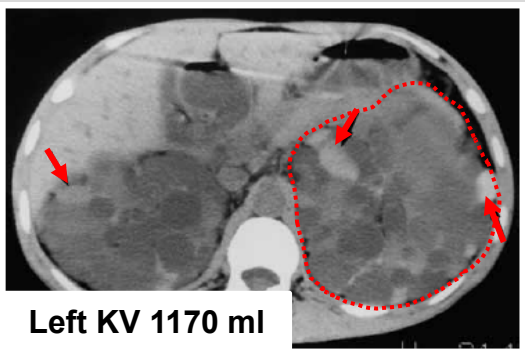
Nephrolithiasis

- 35 Y Male
- Acute left flank pain



Left KV 920 ml

Cyst Hemorrhage

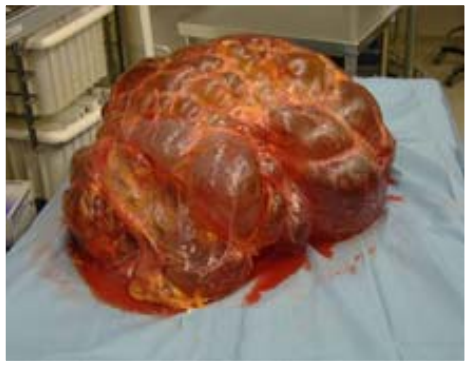


Left KV 1170 ml

- 32 Y male
- Acute onset left flank pain
- eGFR 80

Nephrectomy for Pain

- 52 Y Male
- Chronic pain
- Kidney Weight: 21.5 kg



KV= Single Kidney Volume; Normal Single Kidney Volume ~ 150 ml; Normal Weight of 1 kidney ~ 0.15 kg

Increased Kidney Volume Associates with Renal Complications

		Mean Volume per Kidney mLs ± SD		
Renal Complication	**N**	**Complication Present**	**Complication Absent**	**P-value**
Loss of GFR	220	598 ± 368	366 ± 168	<0.0001
Hypertension	241	628 ± 48	352 ± 33	<0.0001
Gross Hematuria	191	820 ± 87	588 ± 52	<0.03
Microalbuminuria	49	853 ± 87	535 ± 52	<0.01
Proteinuria	270	1190 ± 93	578 ± 32	<0.0001

Grantham *Clin J Am Soc Nephrol* 1:148–157, 2006.

Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP)

Sponsored by the National Institutes of Health

- Observational study to develop imaging techniques and determine markers of ADPKD disease progression for treatment evaluation
- 241 ADPKD patients with “normal” kidney function
  - Age range 15–45 y
  - Creatinine clearance >70 mL/min
  - 2/3 with a risk factor for renal progression
- Up to 14 years of follow-up
  - CRISP 1: First 3 years
  - CRISP 2: through year 8
  - CRISP 3: through 14 years (ongoing)

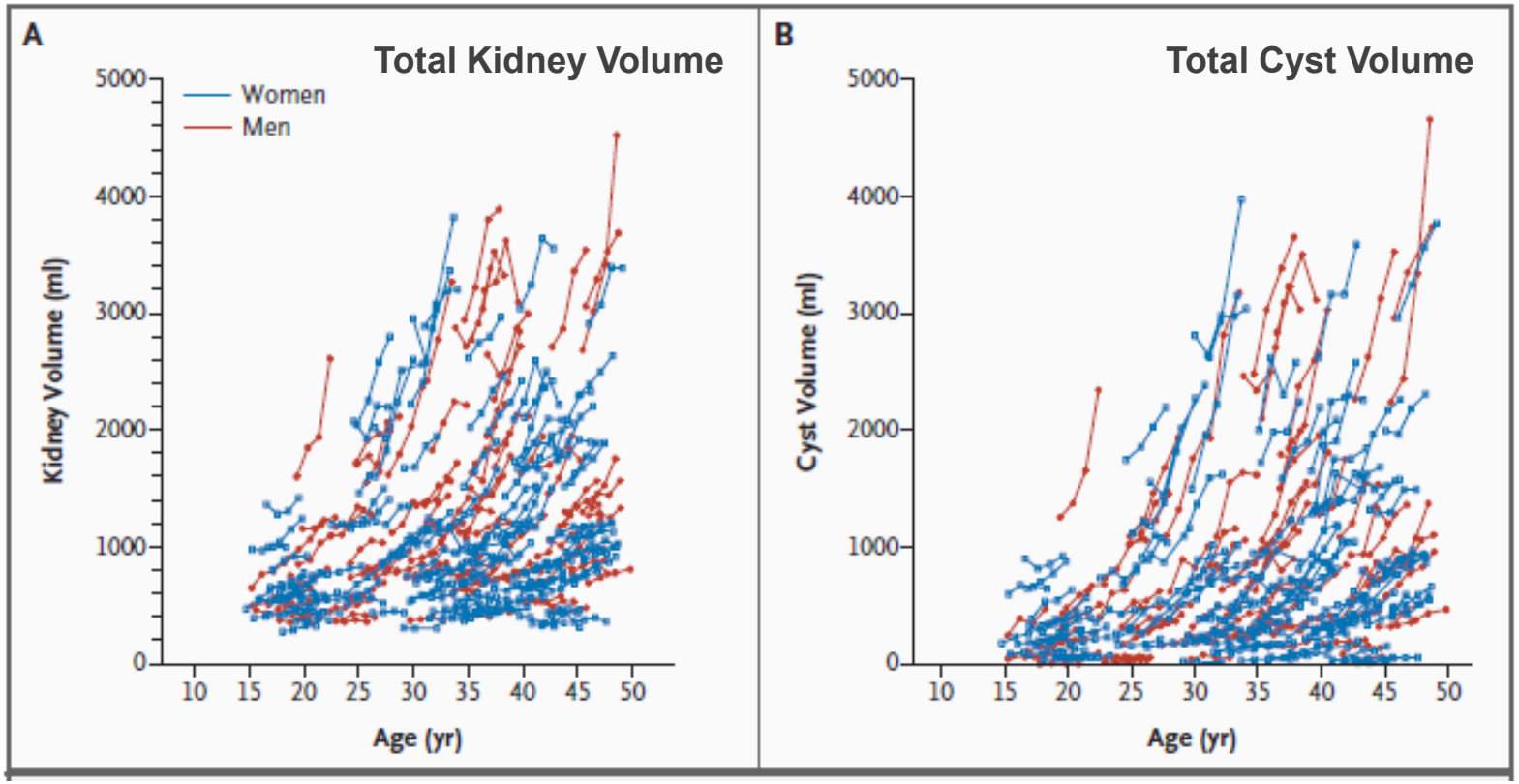
Chapman AB et al. *Kidney Int*. 64:1035-45. 2003

CRISP Participants Demonstrate Frequent Renal Complications

Baseline Parameter	N=241
Mean Age	33.8 (± 9) years
Mean Age of Diagnosis	24.5 (± 9) years
Mean TKV	1076 (± 670) ml
Mean Serum Creatinine Concentration	1.0 (± 0.2) mg/dl
Mean Glomerular Filtration Rate	98.2 (± 24.9) ml/min/1.73m²
Baseline Medical History	
Hypertension	69.3 %
Gross Hematuria	40.7 %
Nephrolithiasis	16.2 %
Flank/Kidney Pain	80.1 %

Chapman, *Kidney Int.* CRISP 2003; Grantham, *NEJM* CRISP 2006

Increased Kidney Volume is Due to Increased Cyst Volume

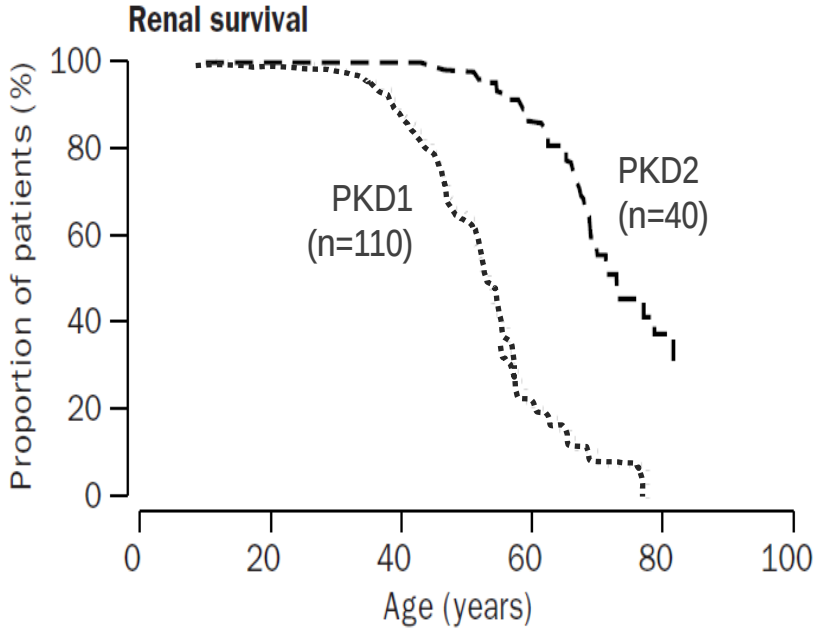


Kidney growth is highly variable and each individual has their own growth curve

Measurement variability= Inter-observer 2.1%, Intra-observer 2.4%, Day-to-Day 2.4%

Grantham, *NEJM* CRISP 2006; Chapman *Kidney Int* 64; 1035–1045, 2003

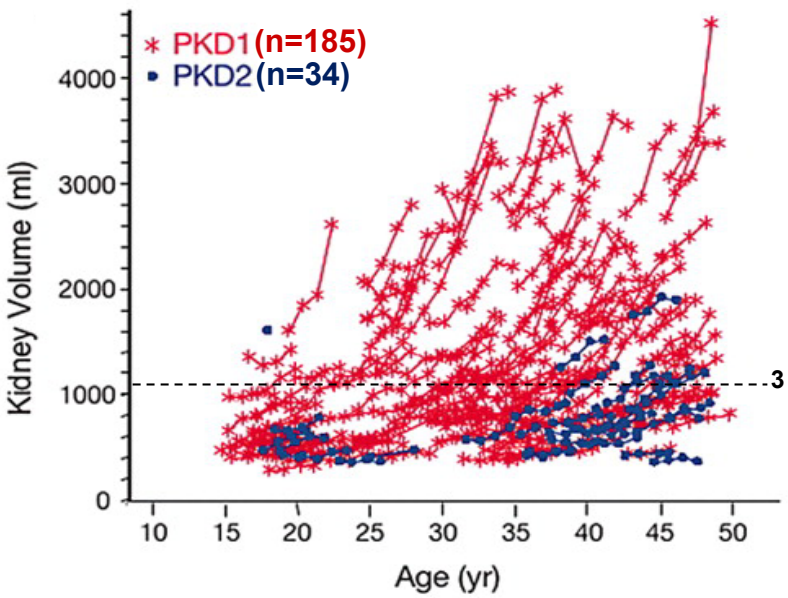
The Best Predictor of Renal Failure is Kidney Volume



EU Cohorts[1] followed to ESRD

PKD1 Mean Age 54

PKD2 Mean Age 74



CRISP Cohort[2]

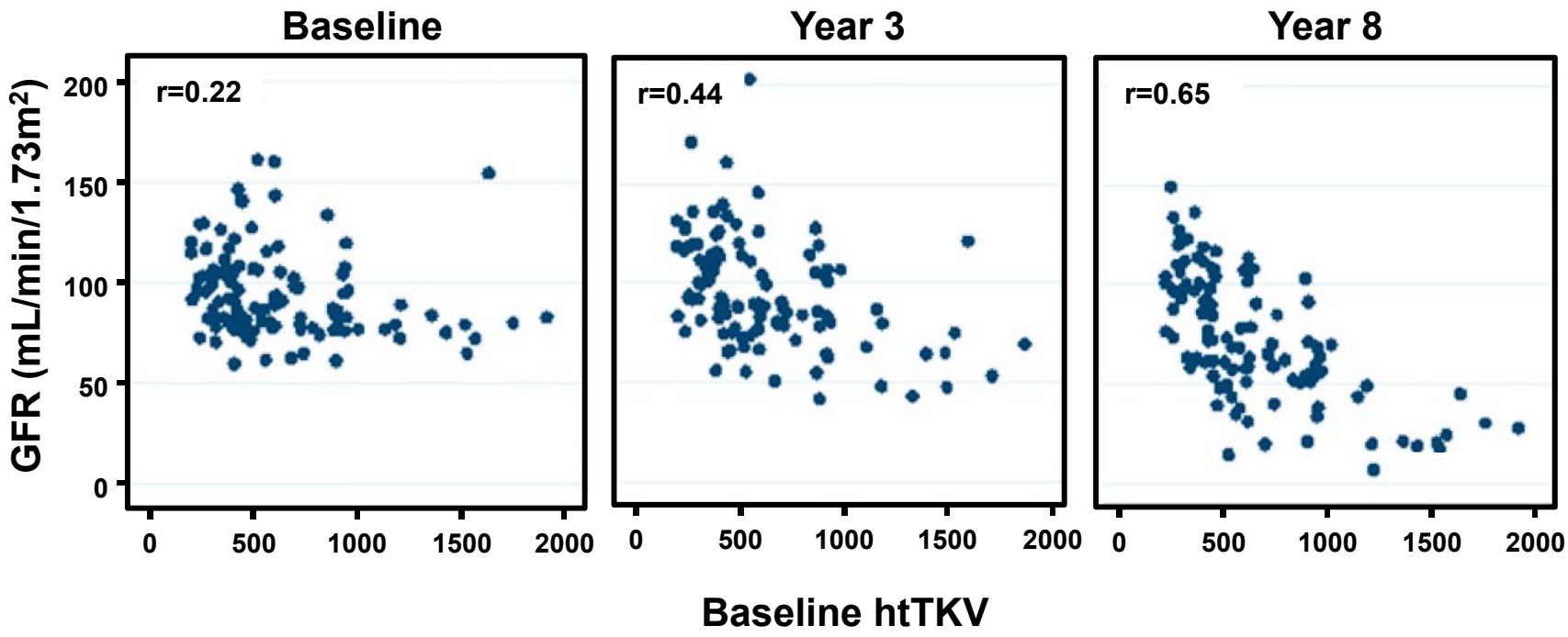
TKV: PKD1 =1011 ml vs PKD2 TKV =688 ml

Cyst Number: PKD1=30.8 vs PKD2=18.8

P<0.0001 for both comparisons

[1]Hateboer *Lancet* 353:103, 1999; [2]Harris P. *J Am Soc Nephrol* 17: 3013–3019, 2006; [3]Chapman *CJASN* 7:479, 2012

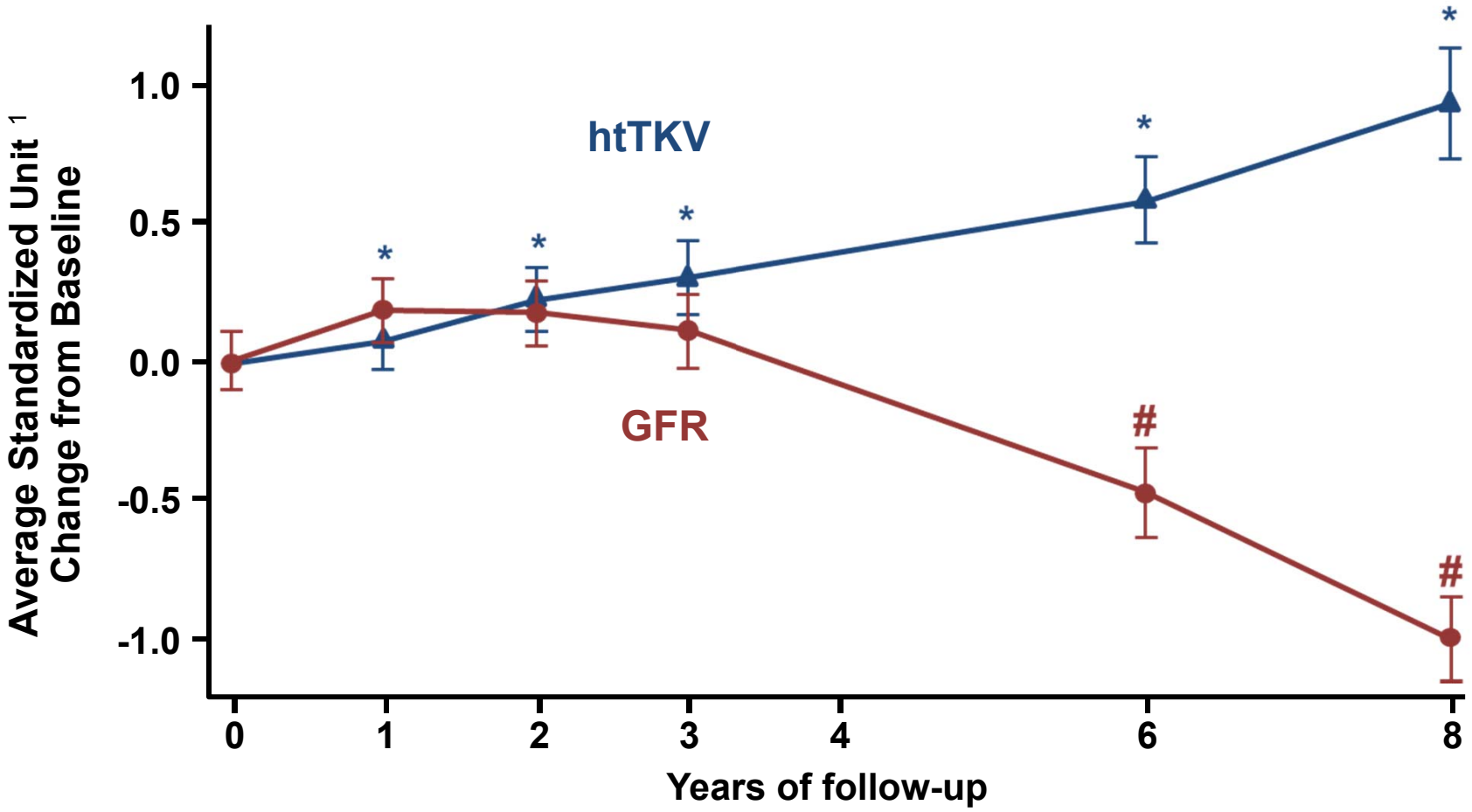
Future Decline in Renal Function is Predicted by Baseline Kidney Volume



The relationship improves significantly with longer follow-up time

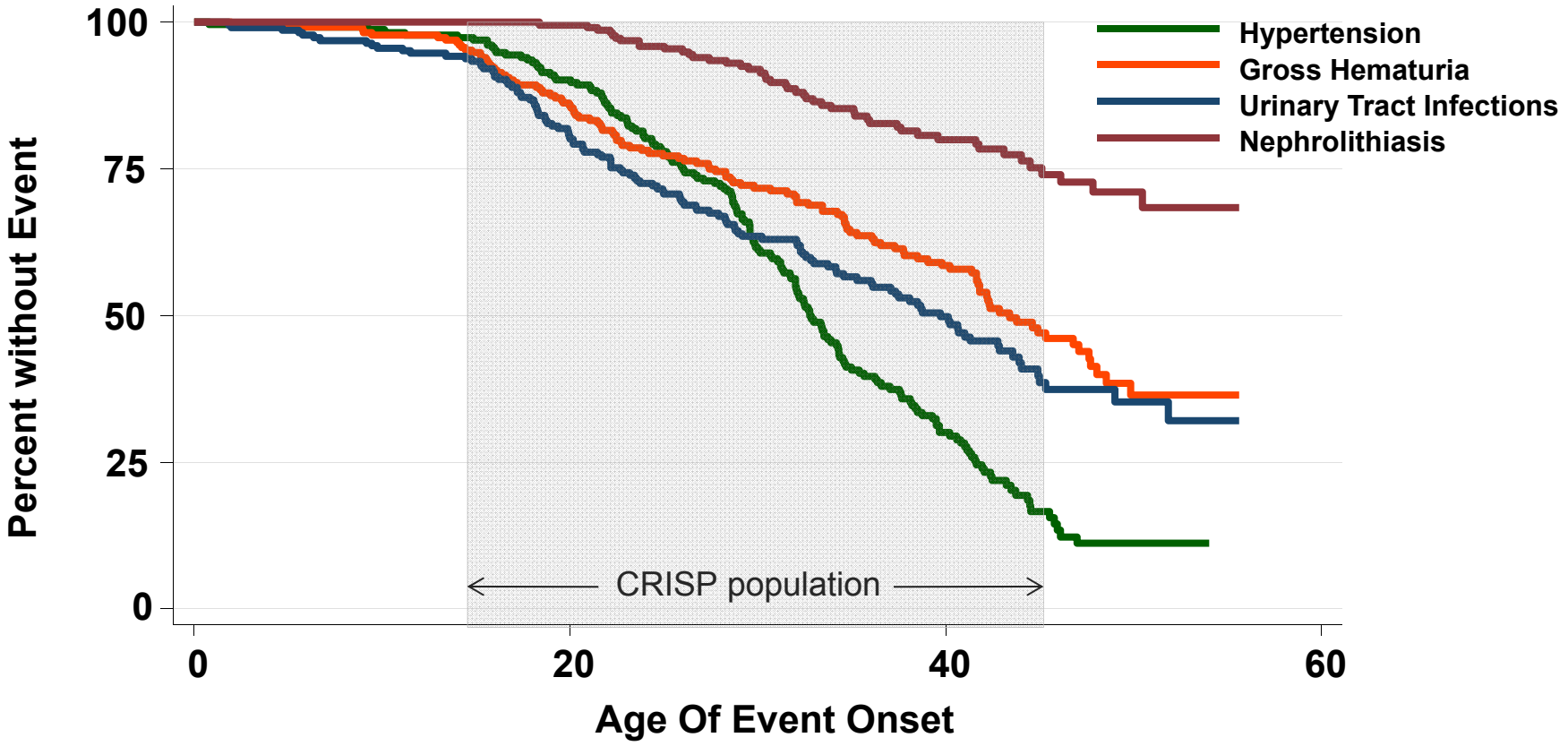
NIH CRISP Studies; htTKV=height-adjusted total kidney volume; GFR by iothalamate clearance
Chapman *CJASN* 7:479, 2012

Change in Kidney Volume Precedes Change in Kidney Function



p<0.05 for htTKV change from baseline; # p<0.05 for GFR change from baseline; htTKV=Height-adjusted total kidney volume; [1] Percent Change Standardized to a common unit;
NIH CRISP Studies; Chapman CJASN 7:479, 2012

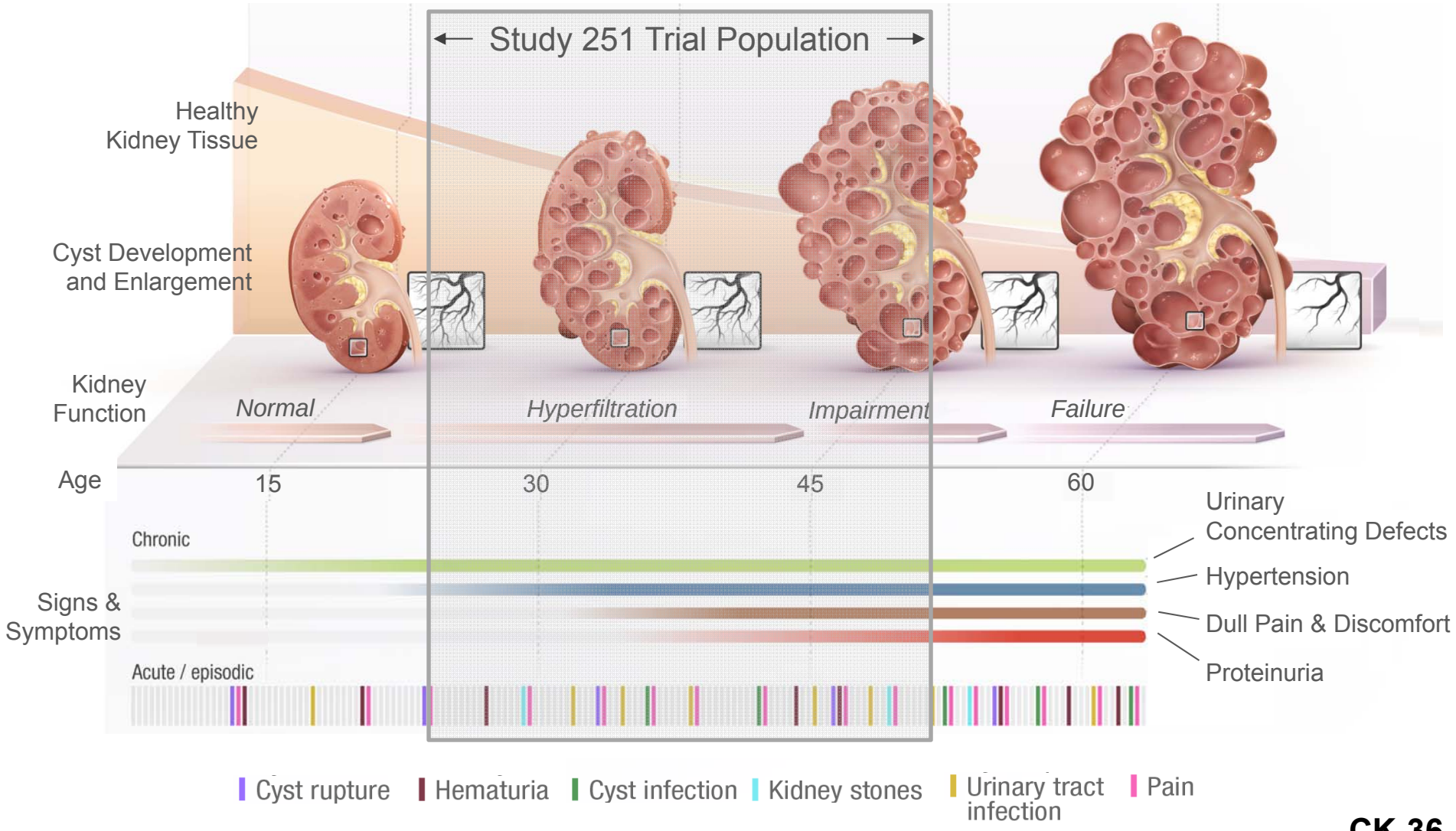
ADPKD patients experience renal complications prior to loss of kidney function



By age 30, over 50% have at least one complications

NIH CRISP Studies; Chapman *J. Amer. Soc. Neph*, 21:384A, 2010.

Cyst Burden and Patient Complications in ADPKD



Conclusions

- The natural history of ADPKD is well understood
  - The CRISP study helped define the population and endpoints for interventional trials
- Total Kidney Volume is the most important predictor of loss of kidney function and renal complications
- The tolvaptan 251 trial design is appropriate given the natural history of ADPKD

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Relevant FDA Questions
will be highlighted here

Efficacy of Tolvaptan in Delaying ADPKD Progression

Frank S. Czerwiec, MD PhD

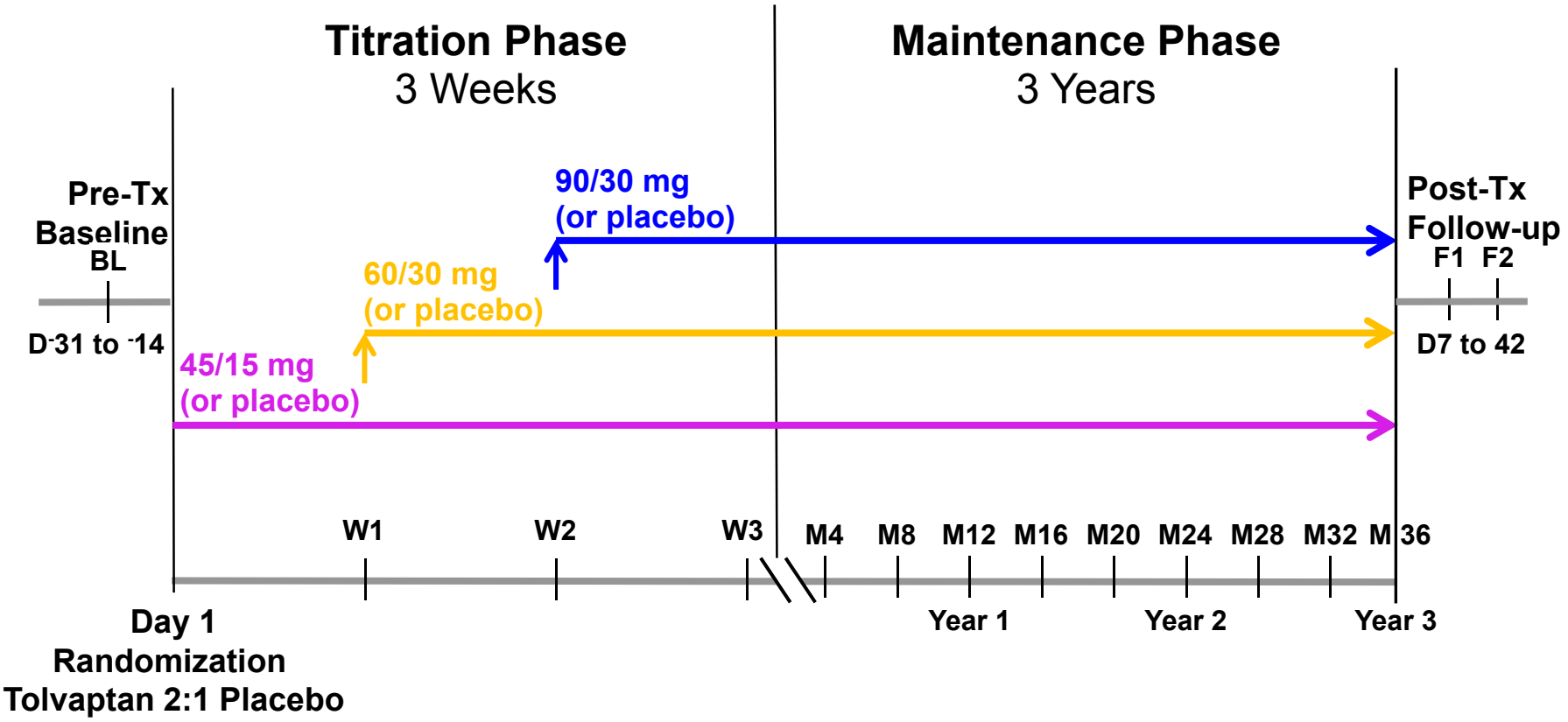
Sr. Director, Global Clinical Development
Otsuka Pharmaceutical Development & Commercialization, Inc.

Study Design and Demographics

FDA Questions
(Trial Design, Patient Population)

156-04-251 (Study 251)

The Pivotal Trial Design



Treatment Regimen: Subjects could interrupt, down- or up-titrate therapy as needed.

Study 251

Follow-up of Subjects Discontinuing Trial Participation

- FDA recommended that Otsuka encourage patients to continue with monitoring and follow-up (including MRIs)… even if they choose to discontinue study drug or placebo

- Based on prior experience, Otsuka believed that requiring in-person follow-up would not be accepted by most patients who discontinued

- Otsuka did, however, make a commitment to encourage all patients who dropped out to permit continuing contact by telephone to assess outcomes of ADPKD

Study 251

The Pivotal Trial Key Inclusion Criteria

- ADPKD by Ravine's Radiologic Criteria (Modified)
- Men and women age 18-50
- Total kidney volume (TKV) >750 mL by MRI
- Estimated creatinine clearance (eCrCL) >60 mL/min
- Stratification factors
  - By region (Japan, Americas, Europe/Australia)
  - TKV >1000 mL
  - eCrCL >80 mL/min
  - Presence of hypertension

Population at risk for rapidly progressing disease

Study 251

Key Endpoints Measure ADPKD Progression

Endpoint	Endpoint Description
Primary (Structure & Cause)	**Annualized Rate of Change in Total Kidney Volume (TKV)**
Key Secondary Composite (Symptoms & Signs)	**Time to Multiple Events of Clinical Progression** • **Clinically Significant Kidney Pain** • **Worsening Kidney Function*** • **New or Worsening Hypertension** • **New or Worsening Albuminuria**
Next Secondary (Function Decline)	**Annualized Rate of Change* in Kidney Function (Serum Creatinine)**

* Measured from Week 3/End of Titration Visit.

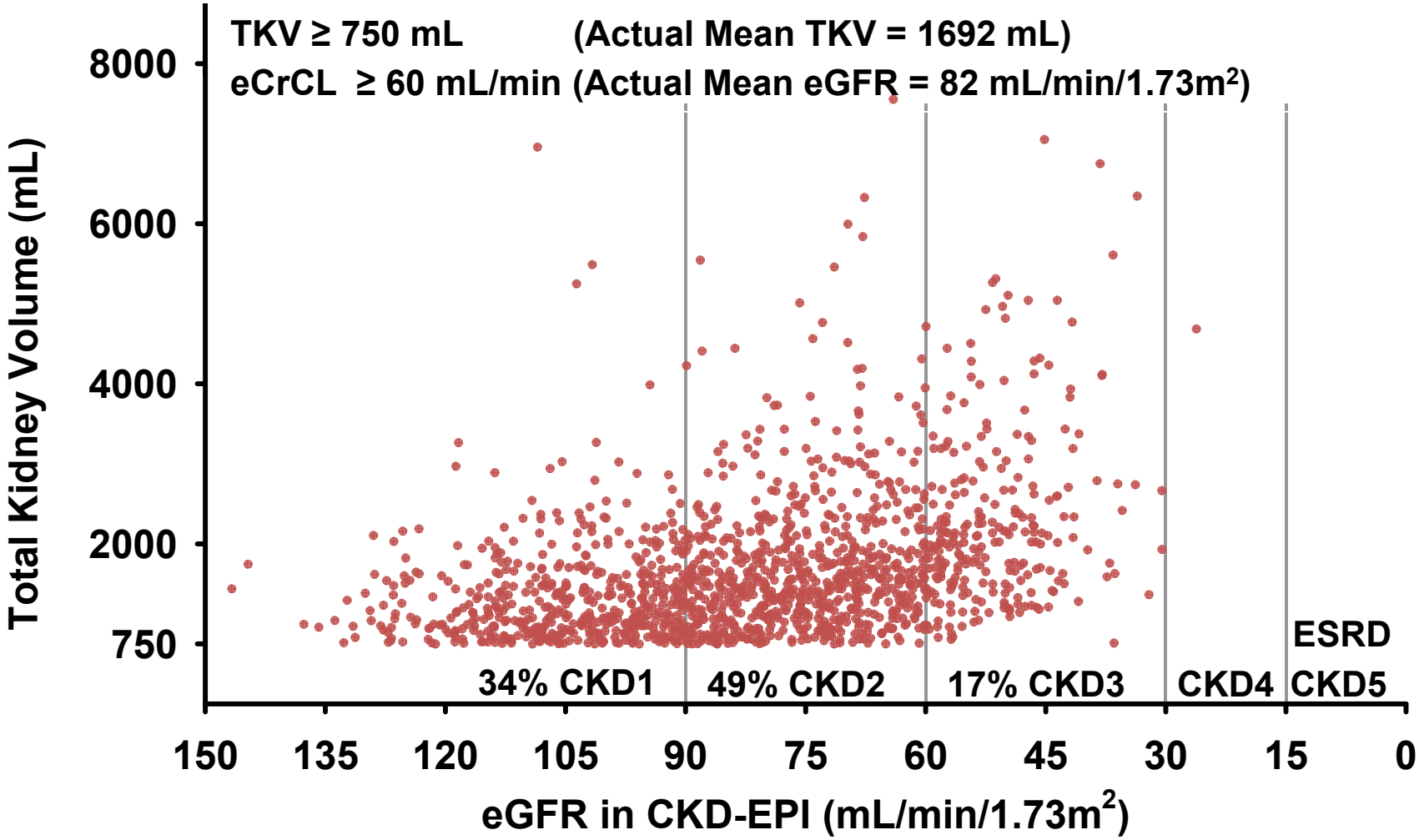
Study 251

Subject Region and Demographics

	Tolvaptan (N=961)	Placebo (N=484)
Region, n (%)		
Americas	316 (32.9)	159 (32.8)
USA	255 (26.5)	124 (25.6)
Japan	118 (12.3)	59 (12.2)
Europe/Australia	527 (54.8)	266 (55.0)
Demographics		
Race, n (%)		
Caucasian	810 (84.3)	408 (84.3)
Asian	121 (12.6)	62 (12.8)
Other	30 (3.1)	14 (2.9)
Female gender, n (%)	476 (48.5)	233 (48.1)
Mean age, yr. (±SD)	39 (±7)	39 (±7)

Study 251

Entry Criteria Led to Selection of an Appropriate ADPKD Population



Study 251

Burden of ADPKD by Baseline Medical History

Subject History	Tolvaptan (N=961) %	Placebo (N=484) %
Hypertension	79.6	78.8
Kidney pain	51.6	49.4
Hematuria	35.2	33.9
Upper urinary tract infection	30.2	33.9
Nephrolithiasis	19.5	22.5
Proteinuria	24.2	24.0

Enrollment criteria have selected a well-balanced cohort of subjects in early to mid-stages of ADPKD. The population is appropriate for studying a potentially disease-modifying agent.

Study Results

FDA Questions

(Subject Follow-up, Effectiveness)

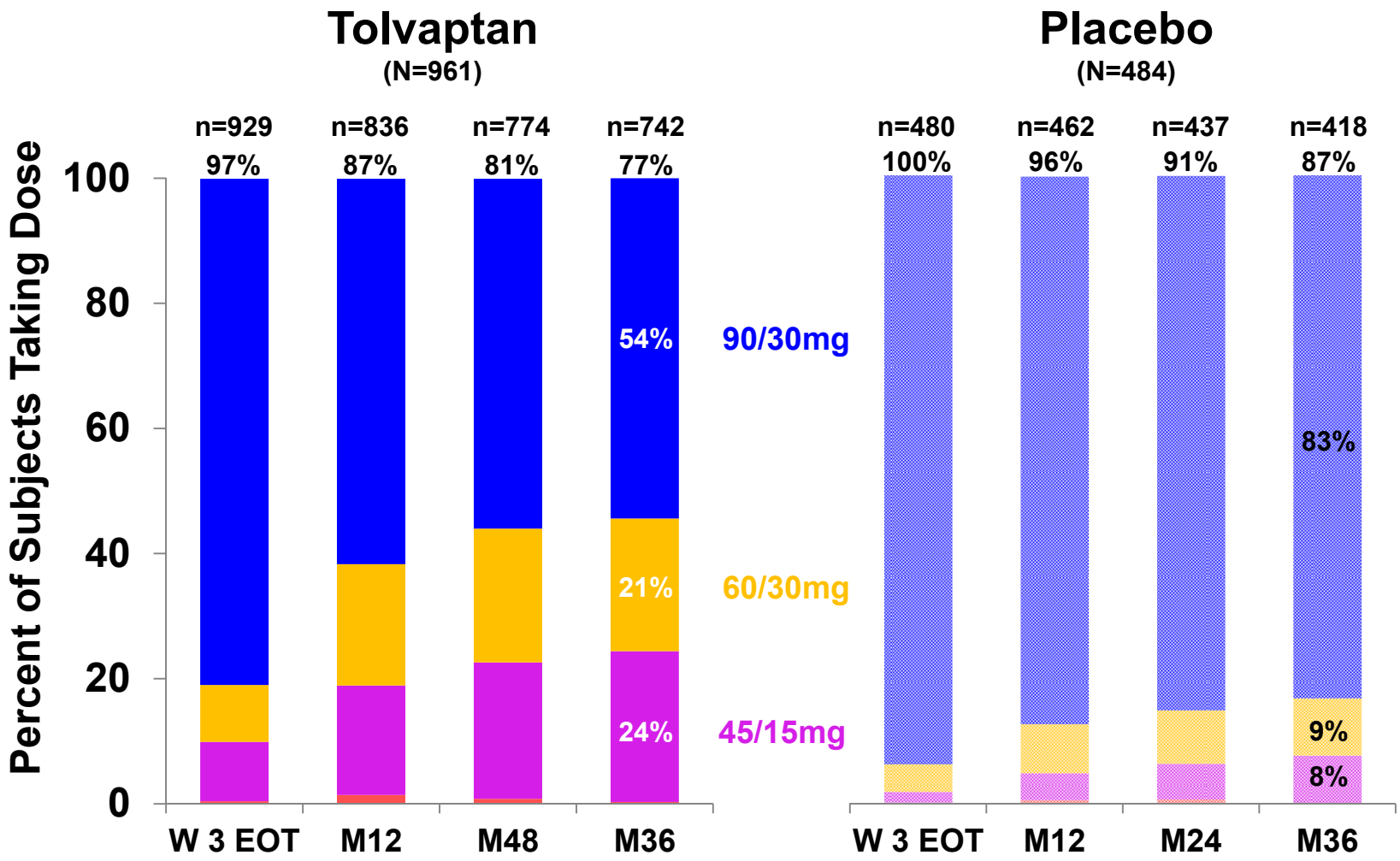
Study 251

Trial Population Disposition: 80% of Subjects Completed 3 Years of Therapy

Number of Subjects	Tolvaptan (N=961) n (%)	Placebo (N=484) n (%)
Randomized	961 (100.0)	484 (100.0)
Completed 36 month visit on treatment	740 (77.0)	417 (86.2)
Discontinued study treatment	221 (23.0)	67 (13.8)
Adverse event (AE)	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)
Other	8 (0.8)	5 (1.0)
Discontinued Patients with Telephone follow up at 36 months	70 (7.4)	19 (3.9)

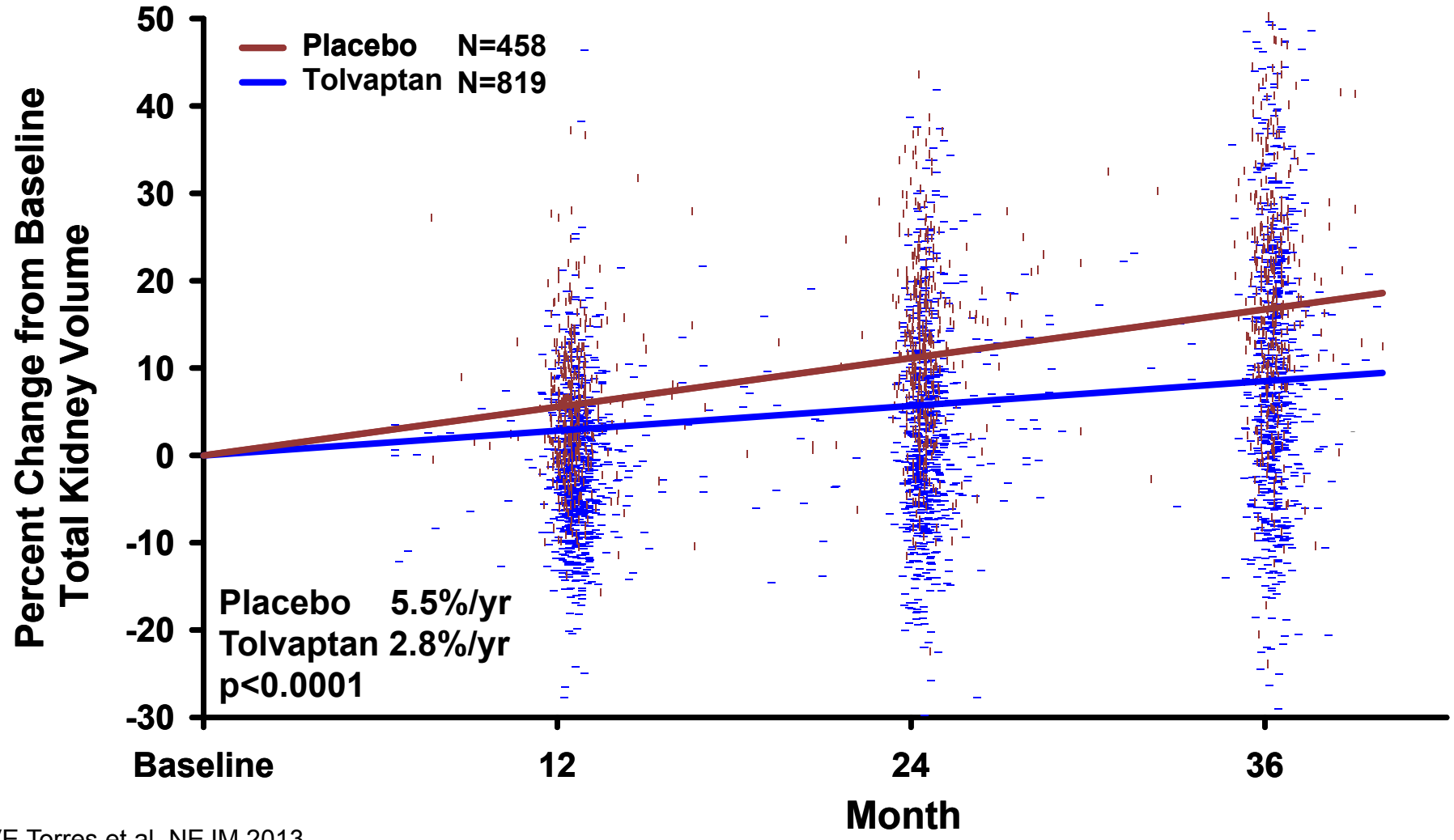
Study 251

Majority of Completers Maintained on Highest Dose



Study 251: Primary Endpoint

Tolvaptan Slows Polycystic Kidney Growth

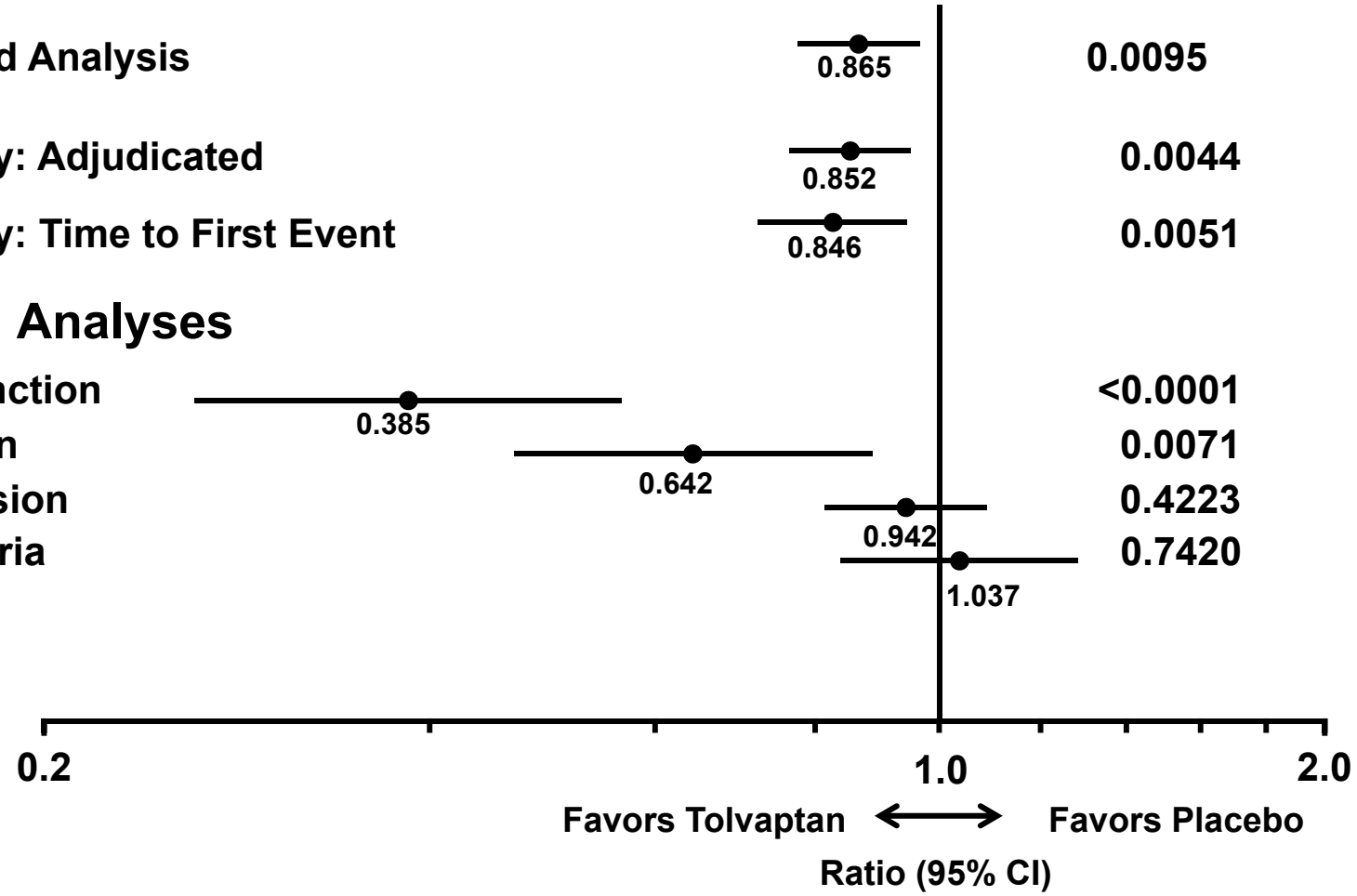


VE Torres et al, NEJM 2013
6/1315 (0.5%) placebo and 3/2370 (0.1%) tolvaptan outlier data points are not shown

Study 251

Key Secondary Composite Endpoint of Clinical Progression Events: Tolvaptan Reduces Signs and Symptoms of Progression

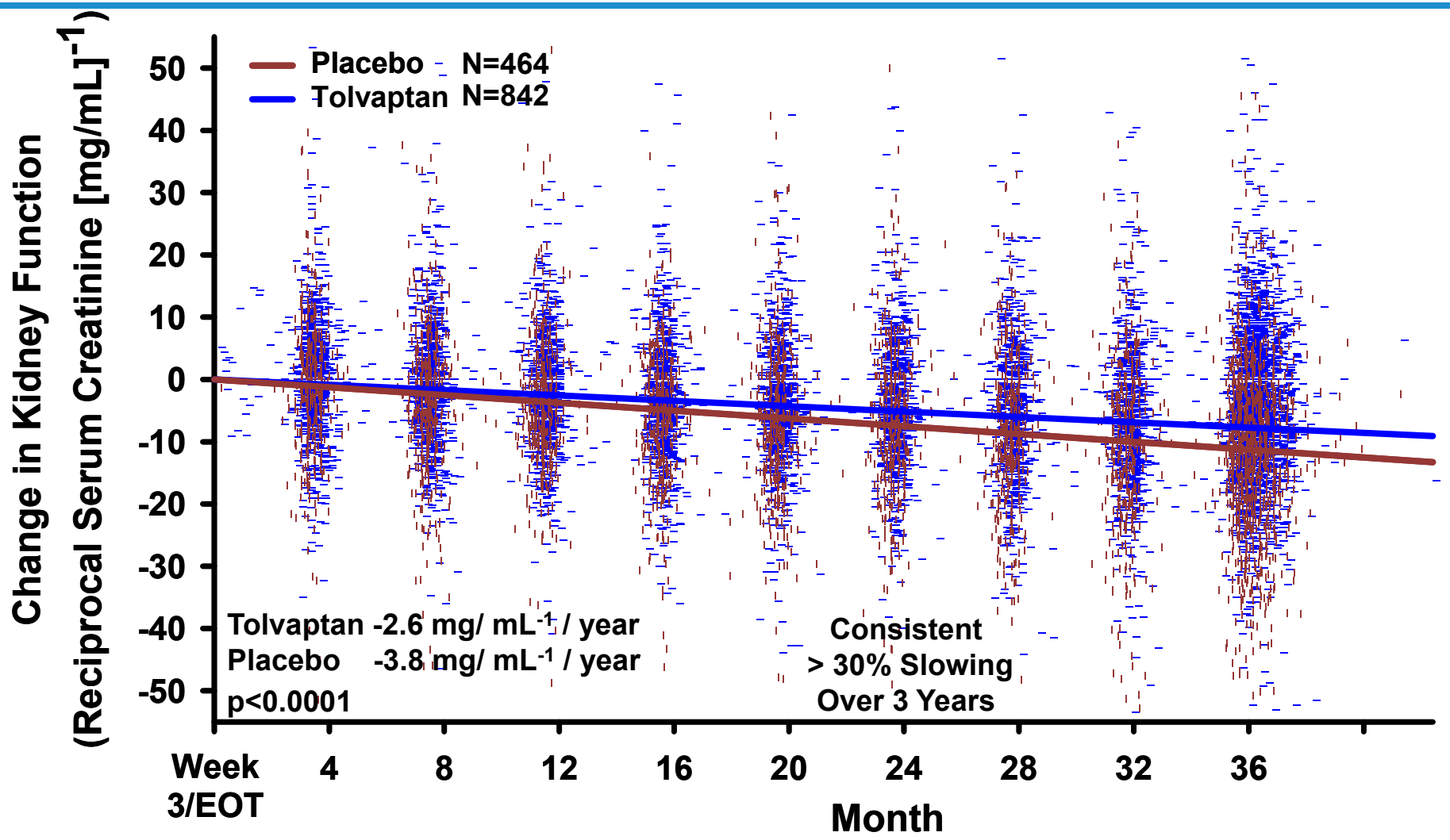
Composite Analyses



Component Analyses

Study 251:Next Secondary Endpoint

Tolvaptan Slows Renal Function Decline



VE Torres et al, NEJM 2013
19/4759 (0.4%) placebo and 16/8564 (0.2%) tolvaptan outlier data points are not shown

FDA's Questions

- Use of post-titration serum creatinine for baseline
- Impact of missing data
- Effectiveness of tolvaptan on…
  - …reducing ADPKD clinical progression events?
  - …slowing the loss of renal function?
  - …reducing severe renal pain events?

FDA's Questions

- Use of post-titration serum creatinine for baseline
- Impact of missing data
- Effectiveness of tolvaptan on…
  - …reducing ADPKD clinical progression events?
  - …slowing the loss of renal function?
  - …reducing severe renal pain events?

Study 251: Renal Function Analysis

Use of Post-titration Serum Creatinine

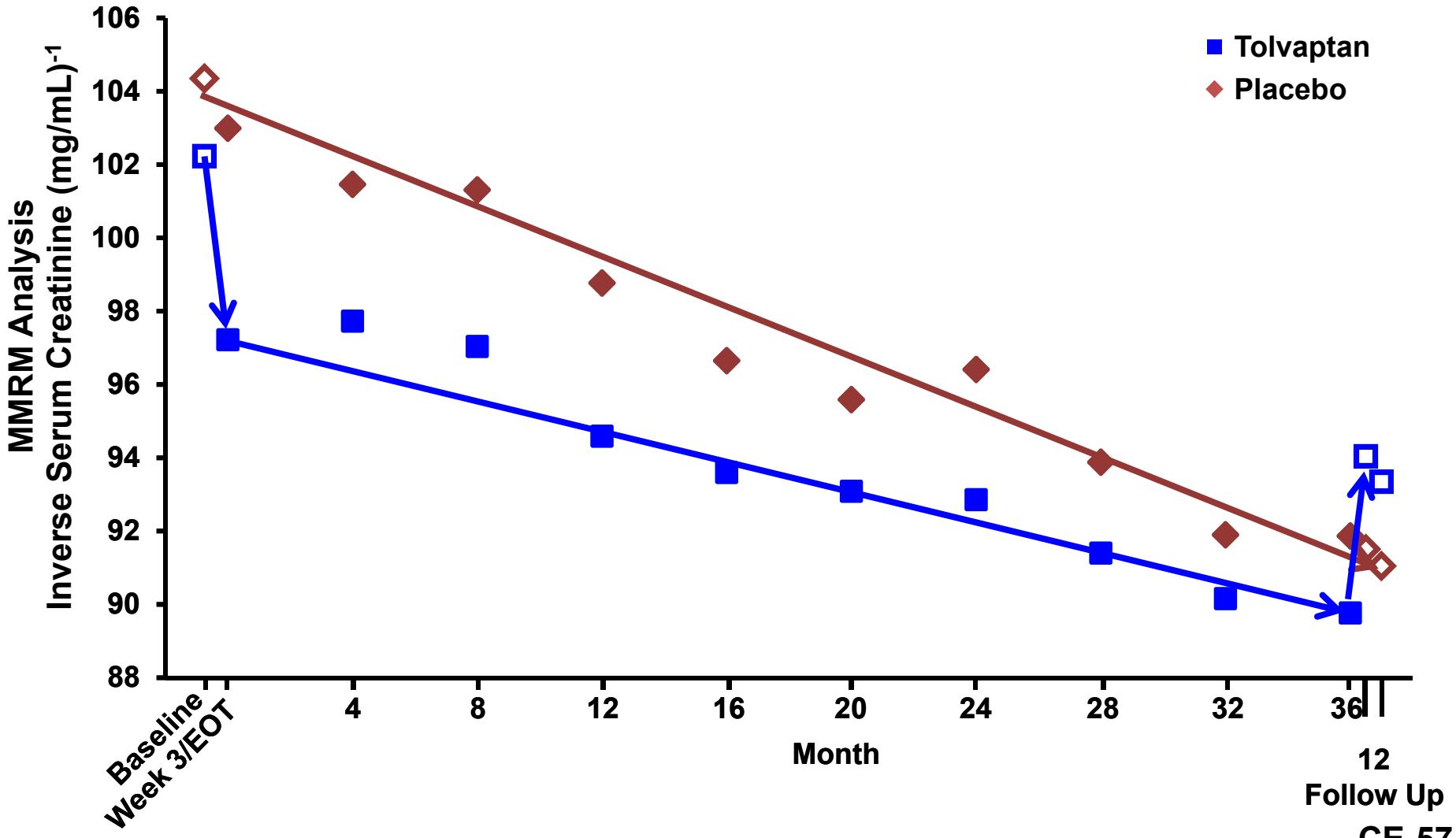
28Mar2007 Protocol:
"Baseline for the Composite Secondary Efficacy endpoint will be defined as the value obtained at Week 3 (or End of Titration) visit because some shifts of serum creatinine level are expected with tolvaptan administration *and with placebo administration* in the context of a prescribed fluid regimen."
The same baseline was to be used for renal function slope.

FDA Briefing Document, Page 58:
"…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 the change from baseline to the post-therapy period when any potential 'hemodynamic effect' had worn off."

Study 251

Acute, Sustained, Reversible Effects of Tolvaptan on Renal Function

FDA Questions:
(Creatinine Baseline)

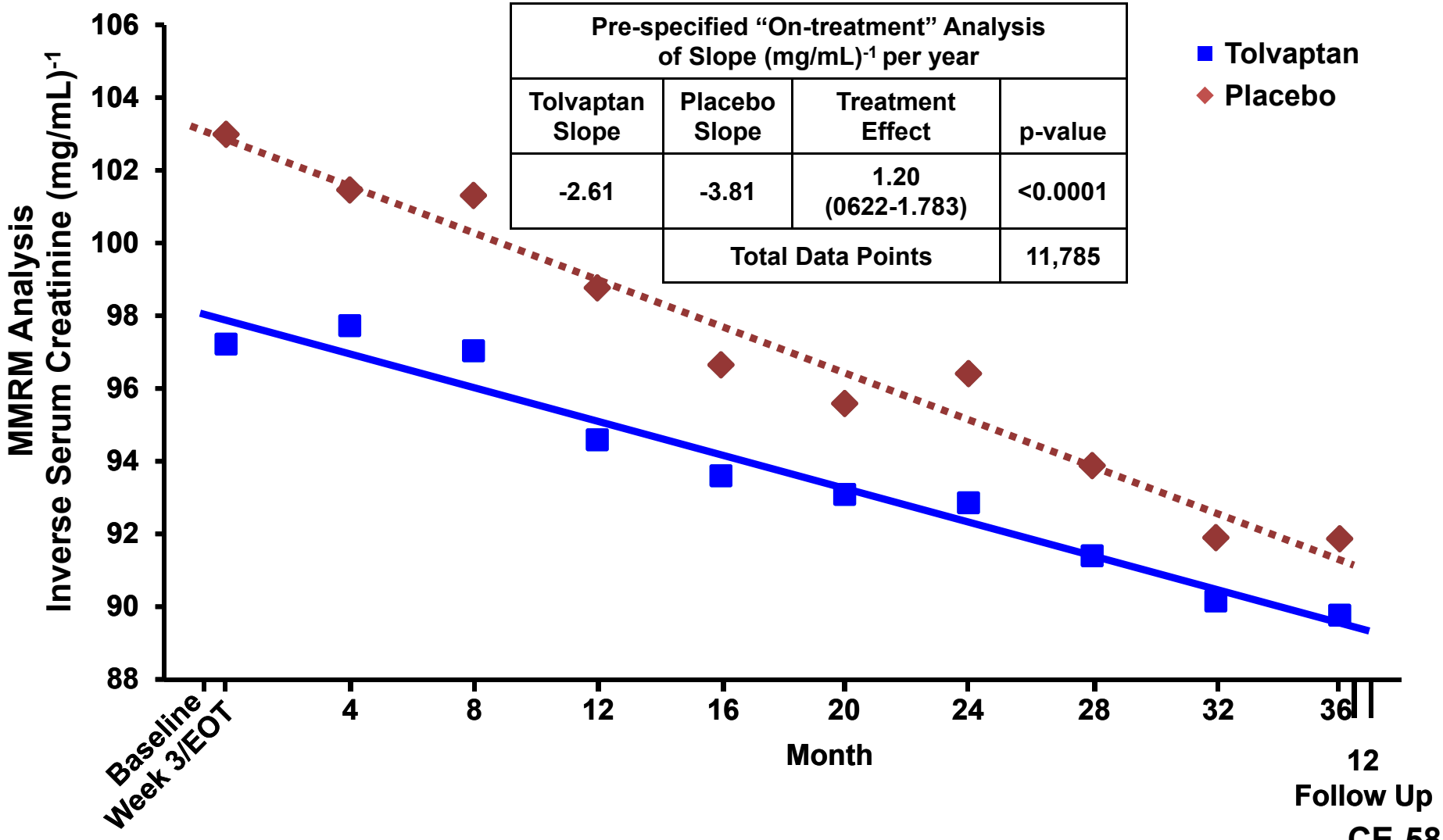


CE-57

Study 251: Renal Function Slope

Pre-specified Analysis

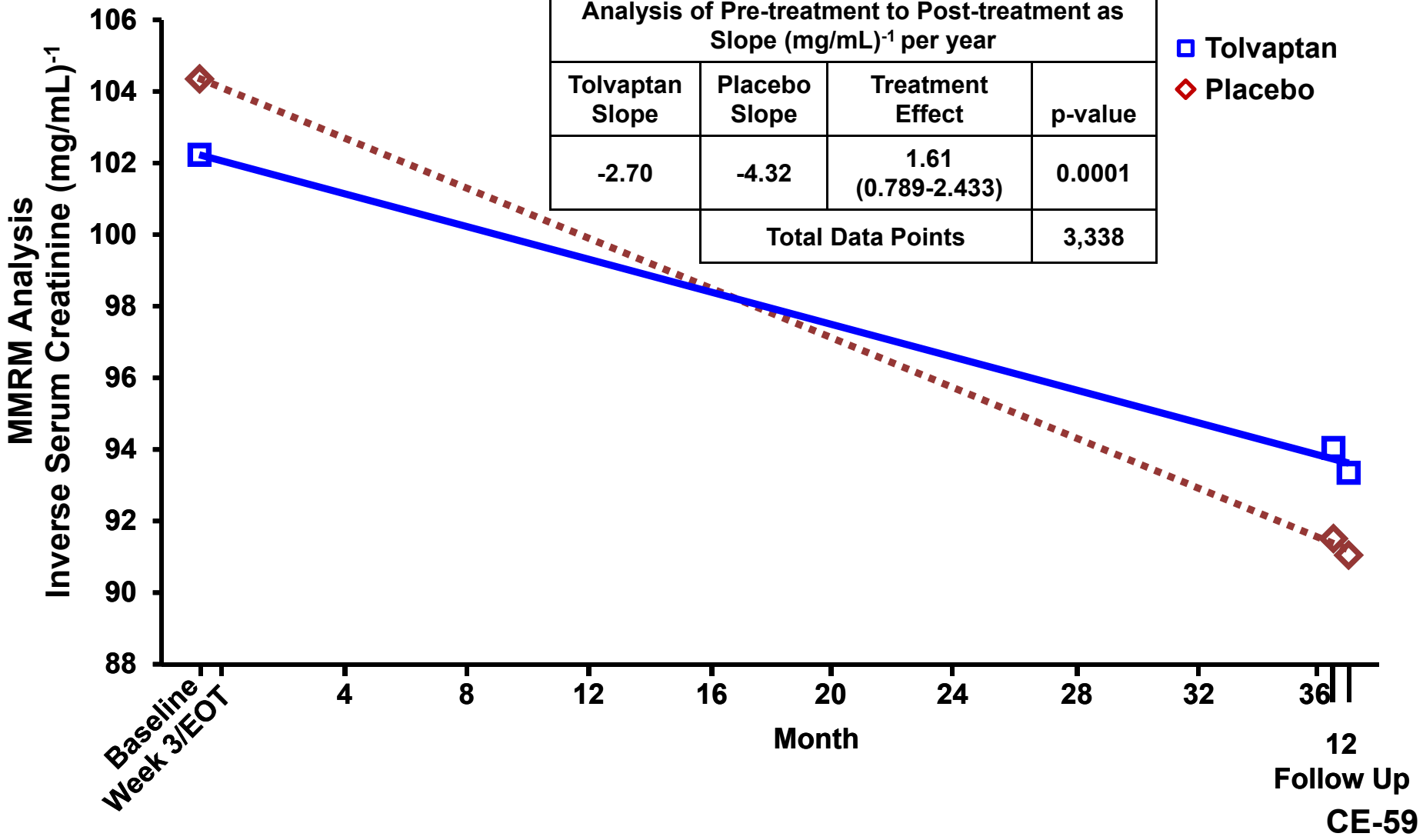
Pre-specified "On-treatment" Analysis of Slope $(mg/mL)^{-1}$ per year			
Tolvaptan Slope	Placebo Slope	Treatment Effect	p-value
-2.61	-3.81	1.20 (0622-1.783)	<0.0001
	Total Data Points		11,785



Study 251: Renal Function Slope

Pre-treatment to Post-treatment Analysis

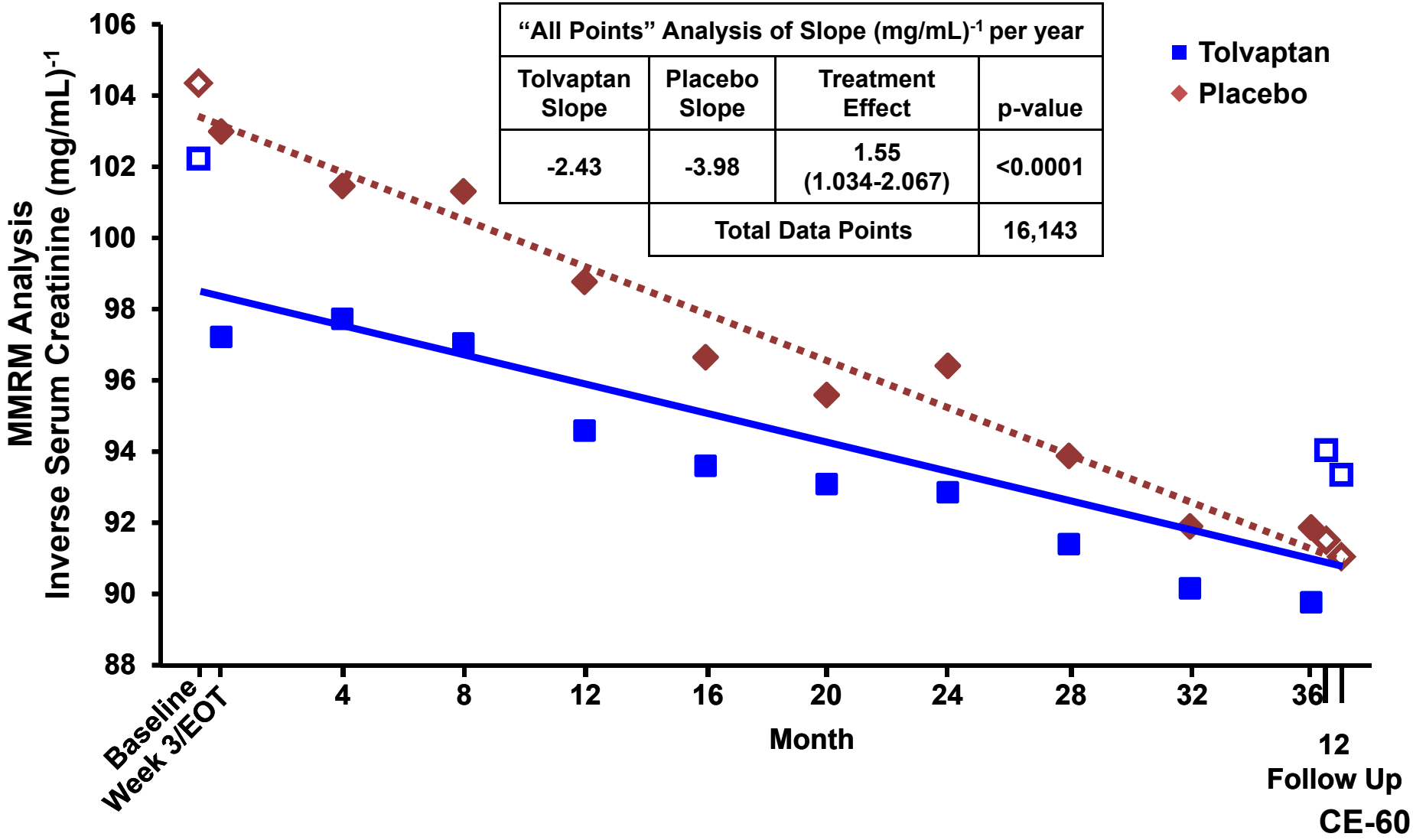
Analysis of Pre-treatment to Post-treatment as Slope $(mg/mL)^{-1}$ per year			
Tolvaptan Slope	Placebo Slope	Treatment Effect	p-value
-2.70	-4.32	1.61 (0.789-2.433)	0.0001
	Total Data Points		3,338



Study 251: Renal Function Slope

All Points Analysis

"All Points" Analysis of Slope $(mg/mL)^{-1}$ per year			
Tolvaptan Slope	Placebo Slope	Treatment Effect	p-value
-2.43	-3.98	1.55 (1.034-2.067)	<0.0001
	Total Data Points		16,143



156-04-251 Renal Function Slope:

Summary of Treatment Effect by Analysis

Analysis	**Treatment Effect** $(mg/mL)^{-1}$ per year	**95% CI**	**p-value**
Pre-specified: End of Titration to Month 36 (Only on-treatment data)	1.20	0.622-1.783	<0.0001
Sensitivity: Pre- to Post-treatment (No on-treatment data)	1.61	0.789-2.433	0.0001
Sensitivity: All Points, Pre- to Post-treatment (Including on-treatment data)	1.55	1.034-2.067	<0.0001

Each slope analysis has a similar treatment effect and significance.

Tolvaptan consistently slows the decline of renal function regardless of which starting point is used.

FDA's Questions

- Use of post-titration serum creatinine for baseline
- Impact of missing data
- Effectiveness of tolvaptan on…
  - …reducing ADPKD clinical progression events?
  - …slowing the loss of renal function?
  - …reducing severe renal pain events?

Sensitivity Analyses to Assess the Impact of Missing Data

- The SAP prespecified Mixed Model Repeated Measures (MMRM) analyses to account for missing data (assumption was data missing at random) for TKV and renal function
  - MMRM analyses for both TKV and renal function $p < 0.0001$
- Upon unblinding, analyses to account for data missing not at random were performed
  - The approach used placebo imputation with a penalty for tolvaptan-group subjects with missing data
  - FDA agreed with sponsor's approach to use a conservative imputation method (FDA Briefing Package)

Study 251

Missing Data Analysis by 30-Iterations of Placebo/Multiple Imputation

% of Placebo Group Response Imputed for Missing Tolvaptan Data	p-value by Endpoints Tested				
	TKV	Key Secondary Composite	Renal Function	Renal Pain	eGFR Slope
Placebo response	<0.01	<0.04	<0.01	<0.03	<0.01
10% worse than placebo	<0.01	≤0.05	<0.01	<0.03	<0.01
20% worse than placebo	<0.01	0.11	<0.01	<0.04	<0.01
30% worse than placebo	<0.01	0.16	<0.01	0.06	<0.01
	Significant to 110% worse than placebo		Significant to 90% worse than placebo		Significant to 50% worse than placebo

Study 251: Missing Data Sensitivity Analysis
Responder Analysis Based on Power Assumption Thresholds

Response Definition Completers Only	Group	Subjects (N)	Responders (n)	Responders (%)	OddsRatio (95% CI)	p-value[a]
Completers with 20% better than placebo's TKV slope	Tolvaptan	961	481	50.1	2.0 (1.6-2.5)	<0.0001
	Placebo	484	162	33.5		
Above AND: 20% better than placebo's eGFR slope	Tolvaptan	961	302	31.4	2.0 (1.5-2.6)	<0.0001
	Placebo	484	90	18.6		
Above AND: no renal pain or worsening renal function events	Tolvaptan	961	272	28.3	2.1 (1.6-2.8)	<0.0001
	Placebo	484	76	15.7		
Above AND: no hypertension or albuminuria events	Tolvaptan	961	127	13.2	2.1 (1.4-3.1)	0.0003
	Placebo	484	33	6.8		

[a] Derived from chi square test.

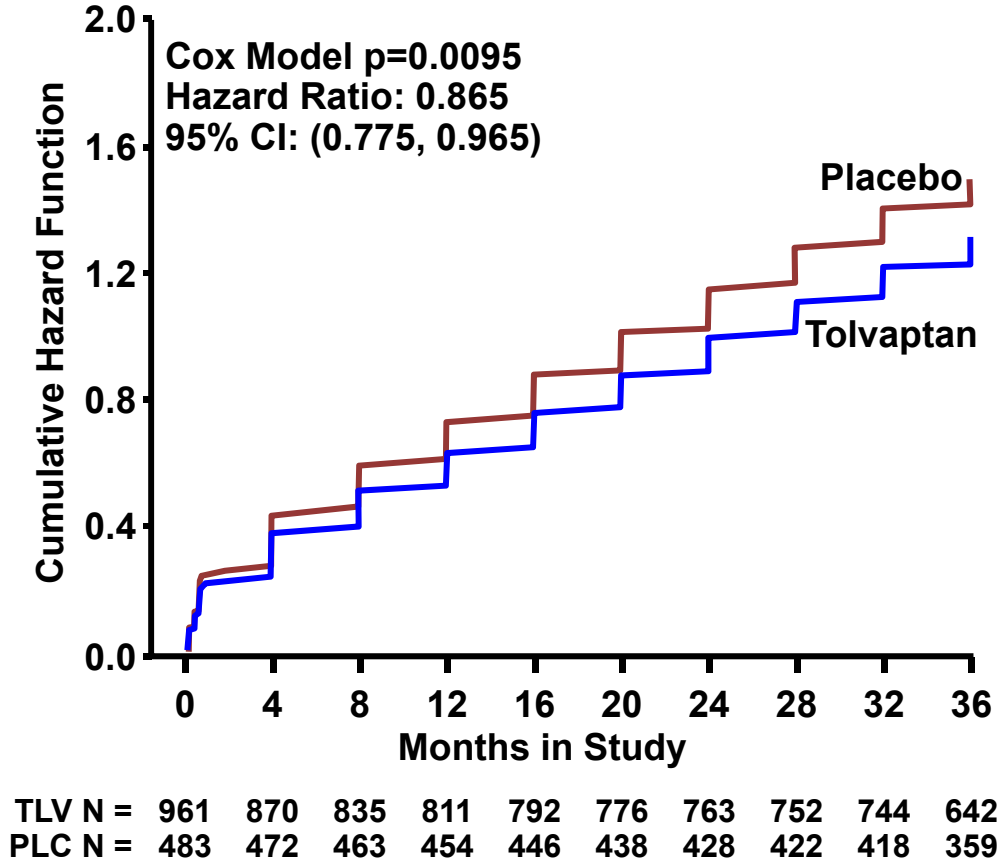
Missing Data Conclusions

- As predicted in the protocol's power calculations, the amount of missing data was ~20% in this 3-year long trial and this is comparable to similar trials
- Analyses accounting for data missing at random and data missing not-at-random both support the conclusion that tolvaptan is effective in slowing the progression of ADPKD
- "*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 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.*" - FDA Briefing Document, p 35

FDA's Questions

- Use of post-titration serum creatinine for baseline
- Impact of missing data
- Effectiveness of tolvaptan on…
  - …reducing ADPKD clinical progression events?
  - …slowing the loss of renal function?
  - …reducing severe renal pain events?

Study 251: Key Secondary Composite Endpoint
Tolvaptan Reduced Clinical Events of Disease Progression*

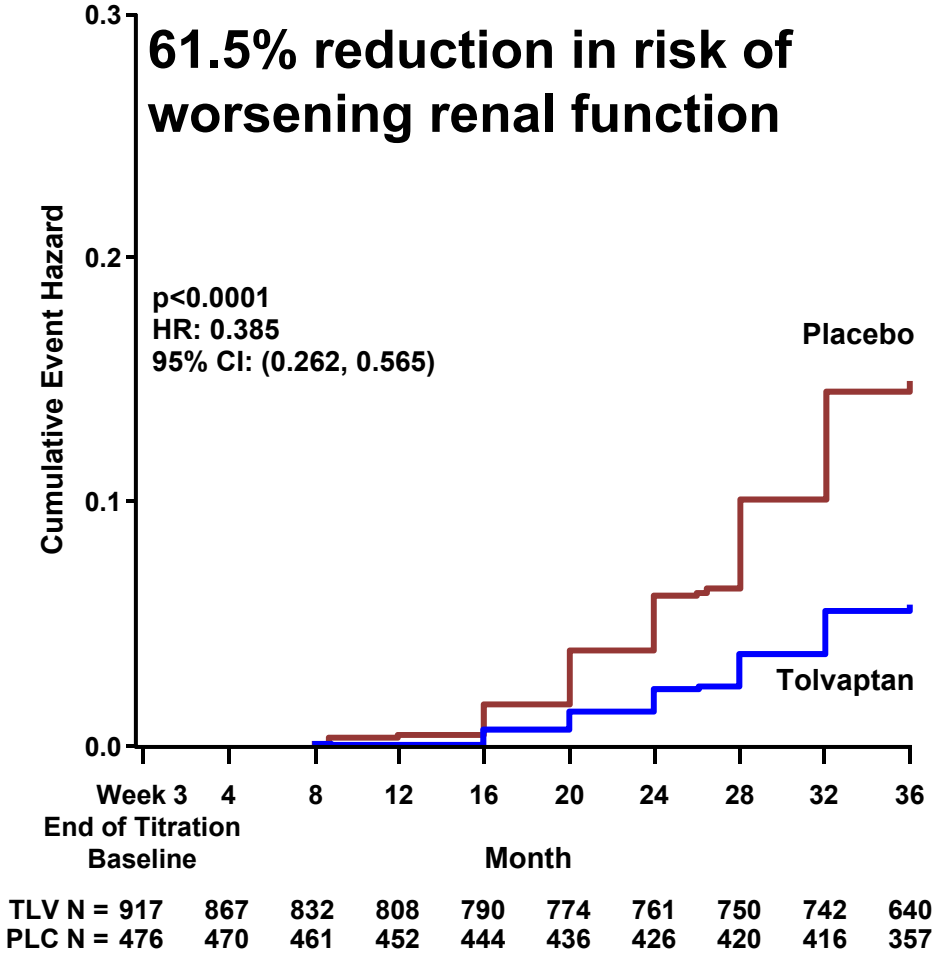


*Clinical Events of Disease Progression include:

- **Worsening renal function**
- **New or worse renal pain**
- New or worse hypertension
- New or worse albuminuria

Study 251: Key Secondary Composite Components

Tolvaptan Reduces the Risk of Worsening Renal Function



46% relative percent reduction

Sensitivity Analysis:
Percent of subjects with worsening renal function from Day 1 Pre-treatment to Post-treatment Follow-up Visits 1 or 2

Group	N	n	%	p-value
Tolvaptan	679	56	8.25	0.0003
Placebo	383	59	15.4	

Study 251: Renal Function Slope Endpoint

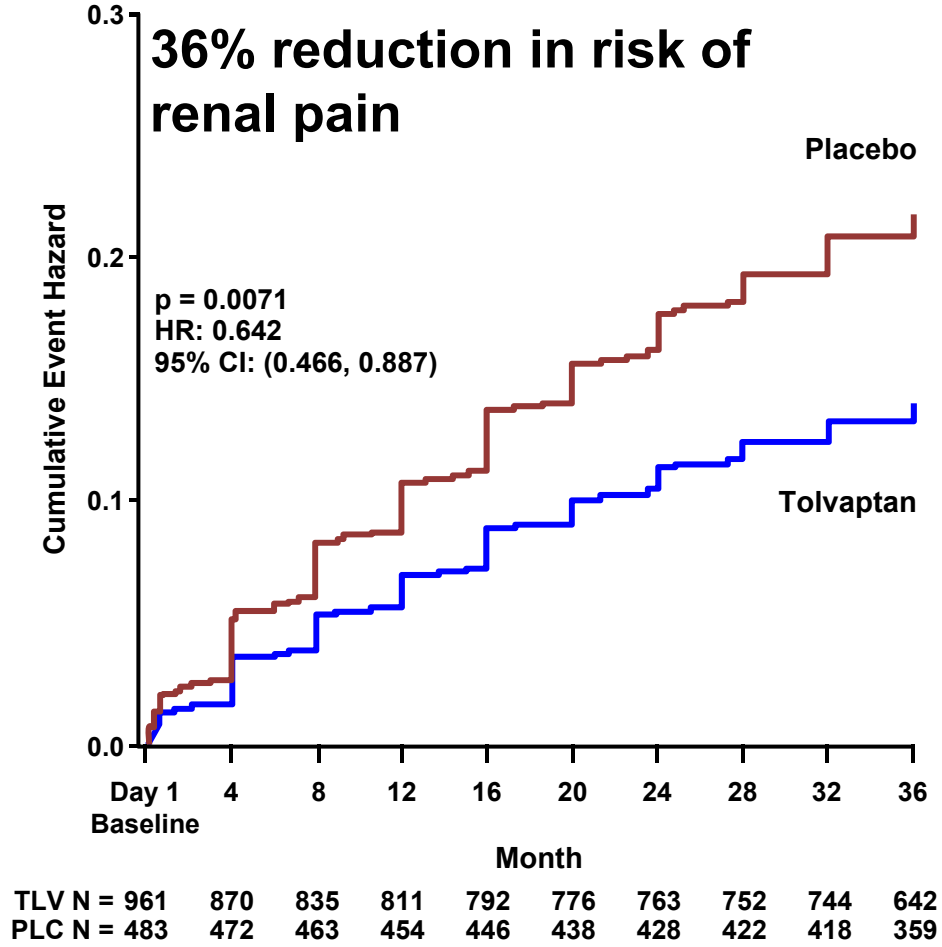
Tolvaptan Effect is Consistent in CKD Stages 1 to 3

CKD Stage By $eGFR_{CKD-EPI}$ ($mL/min/1.73m^2$)	eGFR Slope Placebo	eGFR Slope Tolvaptan	Effect Size	Relative Effect Size
Stage 1 (≥90)	-2.860	-1.926	0.935*	33%
Stage 2 (60-90)	-3.850	-2.640	1.209*	31%
Stage 3 (30-60)	-5.315	-3.582	1.733*	33%

*All p<0.005

Study 251: Key Secondary Composite Components

Tolvaptan Reduces the Renal Pain Events Hazard



Study 251: Exploratory PKD Outcomes Endpoint

Tolvaptan Selectively Reduces Renal Complications

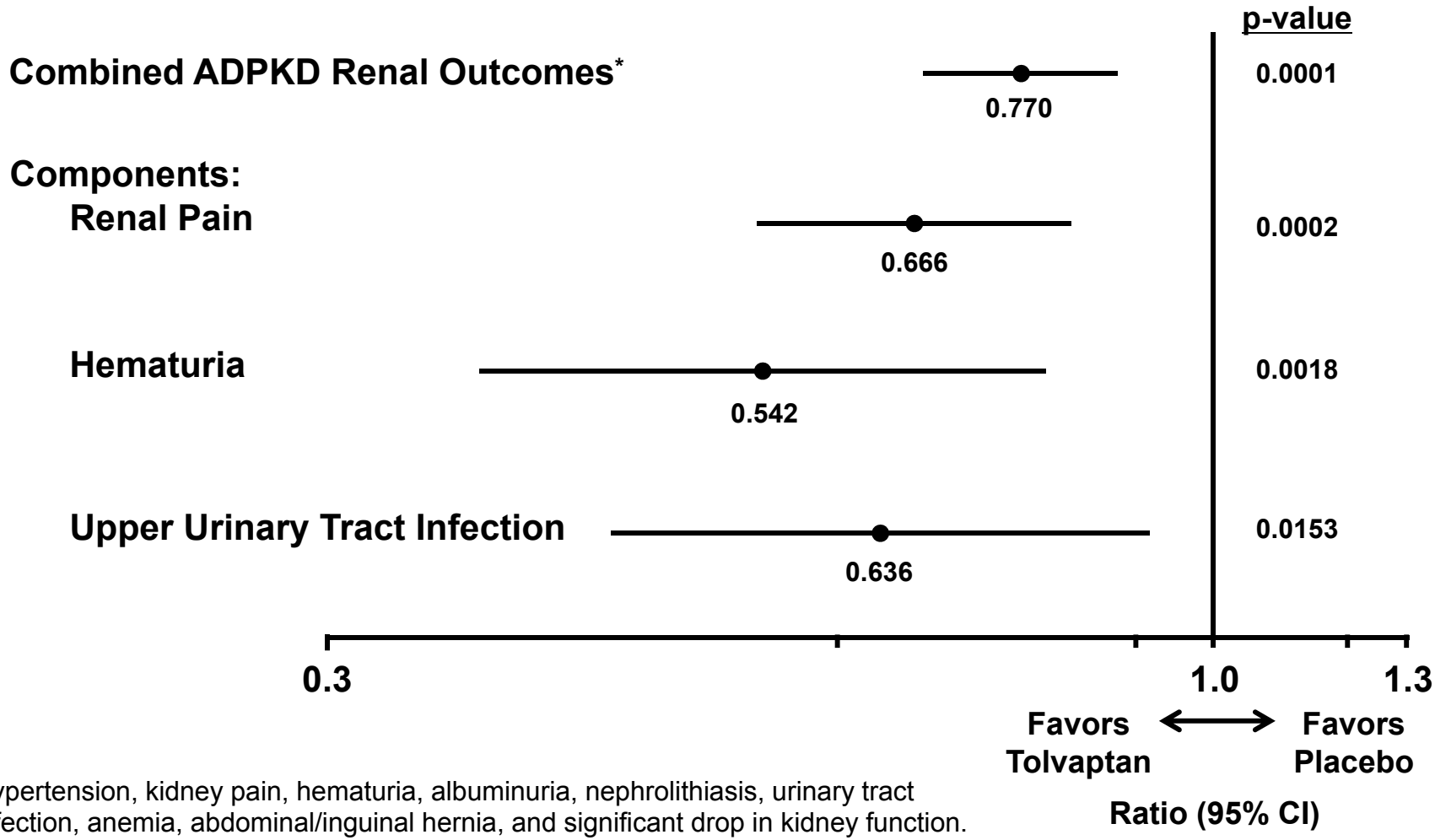
PKD Renal Outcomes

PKD Outcome	Tolvaptan Subjects (%)	Placebo Subjects (%)
Kidney pain	27	39
Hypertension	36	36
Upper urinary tract infection	11	15
Hematuria	8.0	14
Anemia	2.6	4.5
Abdominal/inguinal hernia	3.3	3.7
Nephrolithiasis	2.1	3.5
Albuminuria	0.7	1.6
Renal function*	0.9	1.2

*Significant drop e.g., dialysis, transplant.

Study 251: Exploratory Renal Outcomes

Clinically Relevant Outcome Improvements are Driven by Components Related to Renal Pain



* Hypertension, kidney pain, hematuria, albuminuria, nephrolithiasis, urinary tract infection, anemia, abdominal/inguinal hernia, and significant drop in kidney function.

Study 251: Exploratory Renal Outcomes

Tolvaptan Subjects had Fewer Hospitalizations Due to Renal Complications, Including Renal Pain

Hospitalizations Due to:	Group	Subjects (N)	Subjects with Hospitalization (n)	Subjects with Hospitalization %	OddsRatio* (95% CI)	p-value
Any kidney complications	Tolvaptan	961	31	3.23	0.403 (0.238-0.677)	0.0004
	Placebo	484	37	7.65		
Renal pain	Tolvaptan	961	9	0.94	0.232 (0.092-0.542)	0.0004
	Placebo	484	19	3.93		

*Exact Test (Exact Logistic Regression).
Subjects with multiple events counted only once.

Summary of Efficacy

Tolvaptan demonstrated efficacy in delaying ADPKD progression…

- Tolvaptan slowed polycystic kidney growth by up to 50% over 3 years
- Tolvaptan lowered the risk of composite events of clinical progression events by 14%, driven by a reduced risk of events of worsening renal function (by 61%) and of renal pain (by 36%)
- Tolvaptan's renal pain benefits were immediate and meaningful to patients
- Renal function declined at a 32% slower rate, accumulating benefits each year, and with comparable relative efficacy in CKD stages 1-3

Agenda

Introduction	**Robert McQuade, PhD** *Executive VP & Chief Strategic Officer, Otsuka*
Pathophysiology of Autosomal Dominant Polycystic Kidney Disease	**Vicente Torres, MD, PhD** *Professor of Medicine, Mayo Clinic*
Measuring Patient Burden and Renal Progression in ADPKD	**Arlene Chapman, MD** *Professor of Medicine, Emory University*
Efficacy of Tolvaptan to Delay ADPKD Progression	**Frank Czerwiec, MD, PhD** *Sr. Director, Global Clinical Development, Otsuka*
Sponsor Response to FDA Comments	**Robert McQuade, PhD**
Safety of Tolvaptan in ADPKD: Signal Identification and Interpretation	**Christopher Zimmer, MD** *Sr. Director, Global Clinical Development, Otsuka*
Conclusion: Risk Evaluation/Mitigation and Net Benefit	**Robert McQuade, PhD**

Sponsor Response to FDA Comments

Robert McQuade, PhD

Executive Vice President and Chief Strategic Officer
Otsuka Pharmaceutical Development & Commercialization, Inc.

FDA Guidance on Study 251

Patient Population and Dosing

Otsuka and FDA discussions on the design of Study 251 resulted in the following understandings:

1. **Target Population:** Patients with relatively preserved renal function (eGFR > 60 ml/min/1.73 m^2) and rapidly progressive kidney growth (total volume >4%/year)

   FDA response: *"We believe the enrollment criteria to be reasonable"*
   -FDA SPA Comments, September 2005

2. **Dose Selection:** Titration to the highest dose

   FDA response: *"…we recognize that it will be difficut to conduct a randomized, fixed dose, dose-response study and the best use of available patients is to titrate them to the highest dose. The design is therefore acceptable."* - FDA SPA Comments, September 2005

FDA Guidance on Study 251

Primary Endpoint of Total Kidney Volume

FDA Briefing Document Comment: *"…there is no intervention to alter renal volume that is known to affect renal function, and so it is hard to accept renal volume as a surrogate."* – FDA, September 2005

FDA Study Design Proposal: *"…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."* - FDA, September 2005

- TKV was accepted as the primary endpoint by Europe (CHMP) in 2005 and Japan (PMDA) in 2006

Clinical Relevance of Total Kidney Volume in ADPKD in 2013

- ✓ The prognostic value of TKV for predicting renal function decline and ESRD has been confirmed
  - NIH-sponsored CRISP studies (2003-Ongoing) & the PKD Outcomes Consortium (2007-2013)
- ✓ A 30% decrease in GFR (ie, 33% increase in SCr) is a clinically meaningful measure of progressive renal function decline
  - NKF-Sponsored CKD Outcomes Consortium (2012-Ongoing)
- ✓ **The results of Study 251 demonstrate that tolvaptan treatment slowed the rate of kidney growth and eGFR decline thereby addressing the 2005 concern and confirming TKV is an acceptable endpoint**

Otsuka Response to FDA Briefing Document

Clinical Relevance of Effect on eGFR

FDA Clinical Reviewer Risk-Benefit Comment:

- *"…the effect on renal function observed in the phase 3 trial was small (an ~1 mL/min/1.73 m^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"*
  – FDA Briefing Document, p. 9

Otsuka response: Preserving 1 mL/min/1.73 m^2 per year of renal function in ADPKD is a clinically meaningful outcome with precedent

- Trials of losartan and irbesartan showed similar results (0.8 and 1.2 mL/min/1.73m^2 per year), which translated to a delay in time to ESRD (doubling of SCr, ESRD or death) in patients with diabetic nephropathy

Otsuka Response to FDA Briefing Document

Tolvaptan's Safety Profile

FDA Clinical Reviewer Risk-Benefit Comment:

- *"If tolvaptan's safety profile had been reassuring, we think the available data, despite the aforementioned limitation, might have been sufficient to support approval. However, tolvaptan's safety profile was not reassuring."*
  - FDA Briefing Document, p. 10

Otsuka response: Tolvaptan's safety profile and risk for liver injury are well-defined.

- A REMS for liver injury (proposed in the NDA and revised based on FDA recommendations) includes:

✓ Monthly monitoring of liver function

✓ Monthly physician attestation that the patient's liver function is appropriate for continued therapy

✓ A closed distribution system will ensure that drug shipment from a specialty pharmacy will only occur following monthly testing and attestation

Otsuka Response to FDA Briefing Document

Additional Safety Information

FDA Clinical Reviewer Risk-Benefit Comment:

– *"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."*
– FDA Briefing Document, p. 10

Response: Otsuka agrees that additional clinical trials are unlikely to further our understanding of the true nature of the hepatic risk. Implementation of a closed-distribution REMS to mitigate the risk and to protect patient safety is necessary.

- ✓ Otsuka will ensure that all out-patients are enrolled in the Tolvaptan REMS Program
- ✓ Otsuka will initiate a Phase 4 Registry to collect data for hepatic functioning to provide greater insight into the risk of liver injury.

Otsuka Response to FDA Briefing Document

Additional Efficacy Information

FDA Clinical Reviewer Risk-Benefit Comment:

- *"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."* – FDA Briefing Document, p. 10

Otsuka Response: Additional data from extension or new trials in different populations are unlikely to change the conclusions from Study 251

- Study 271, the ongoing open-label extension trial (n=1000), will only yield 2 more years of data in relatively early stage patients not expected to reach ESRD
- Studies in CKD4 will not further inform the efficacy of tolvaptan in early disease.

Agenda

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Conclusion: Risk Evaluation/Mitigation and Net Benefit	**Robert McQuade, PhD**

Safety of Tolvaptan in ADPKD: Signal Identification and Interpretation

Christopher A. Zimmer, MD

Sr. Director, Global Clinical Development
Otsuka Pharmaceutical Development & Commercialization, Inc.

Clinical Development Program Overview
ADPKD Exposed: 1533 Subjects

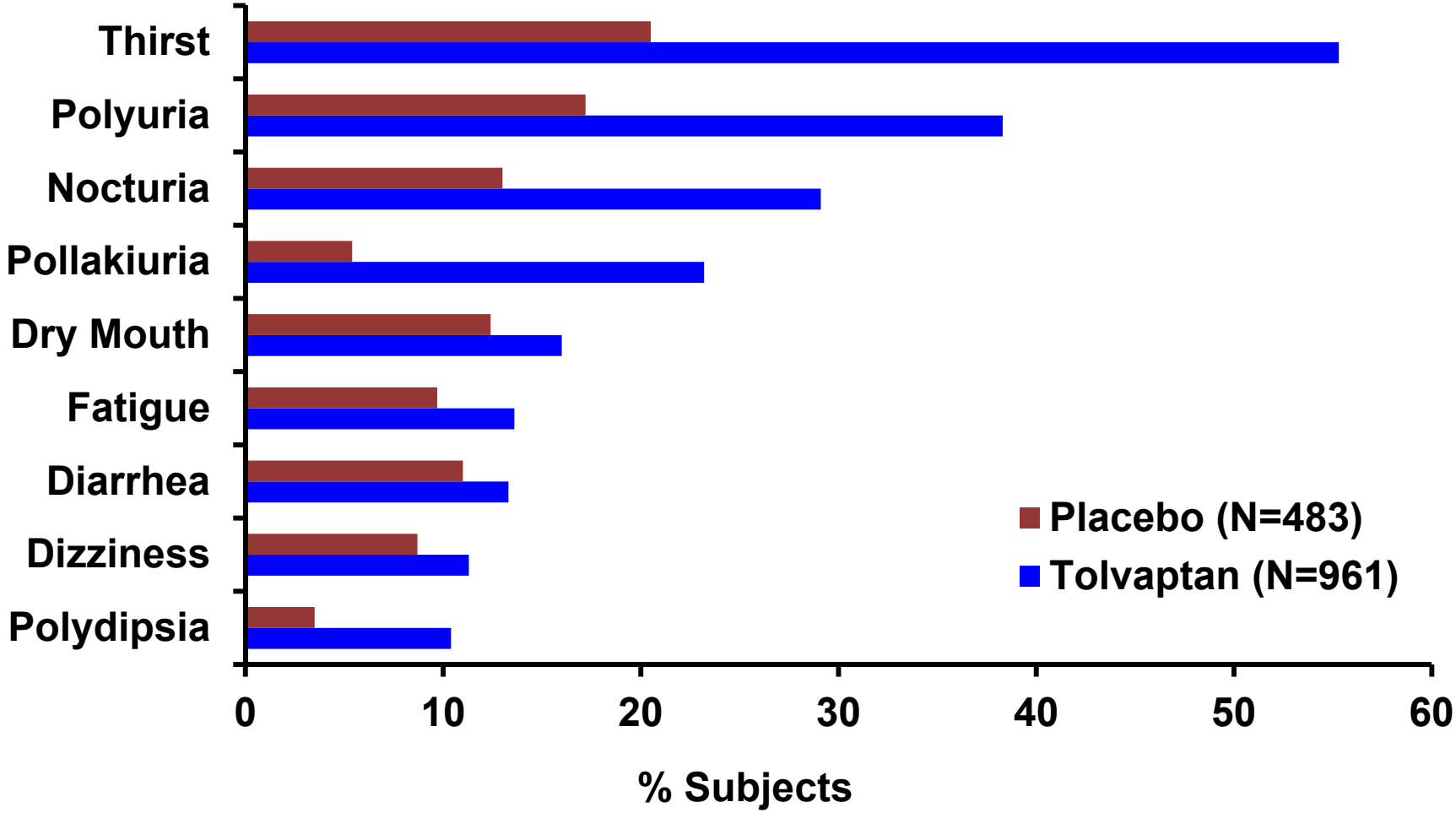
Subjects with ADPKD			Non-ADPKD Subjects	
Phase 3 Pivotal	Open Label	Phase 1/2	Prior NDA	Other Indications
156-04-251 N=961	156-08-271 (5 Trials) N=448	6 Trials N=124	Heart Failure Hyponatremia N=3294	N=2724
Total = 1533			**Total = 6018**	

Duration of Exposure in ADPKD Population (Number of Subjects)

Total	1533
1 Year	1208
1.5 Years	1067
3 Years	801
4 Years	537
5 Years	196

Study 251

Incidence of Adverse Events Greater Than 10% and Greater Than Placebo



Study 251

Overall Safety Profile: AEs/SAEs Balanced Except for Withdrawals

	Primary ADPKD Safety Population	
Subjects Experiencing	Tolvaptan N=961 %	Placebo N=483 %
Adverse events (AE)	97.9	97.1
Serious AE	18.4	19.7
Withdrawal due to AE	15.4	5.0
Aquaretic AE	7.3	0.5
Hepatic AE	2.2	0
Death	0	0

Study 251

Adverse Events of Special Interest More Common with Tolvaptan

	Tolvaptan (N=961) %	Placebo (N=483) %
Expected Adverse Events of Special Interest		
Serum sodium >150 mEq/L	4.0	1.4
Serum uric acid >7.5 mg/dL	6.2	1.7
New Adverse Events of Special Interest		
Glaucoma*	0.7	0.4
Skin neoplasms (basal cell/melanoma)*	1.0	0.2
ALT >3x ULN	4.4	1.0

* From FDA Briefing Document:

"While these risks should be described in labeling…they do not pose a barrier to approval." (Page 62)

"Most of the cancers were pre-malignant or occurred after a relatively short time… suggesting that it was unlikely that tolvaptan played a role." (Page 95)

Study 251

Hepatic Injury with Tolvaptan: Transaminase Elevations and Hy's Lab Criteria

	Tolvaptan			Placebo		
Abnormality	**Subjects**	**Subjects Meeting Criteria**	**%**	**Subjects**	**Subjects Meeting Criteria**	**%**
ALT >3x ULN	**961**	**42**	**4.4**	**483**	**5**	**1.0**
Hy's Lab Criteria*	**961**	**2‡**	**0.2**	**483**	**0**	**0**
Death or Liver Failure	**961**	**0**	**0**	**483**	**0**	**0**

* Hy's Lab Criteria: ALT >3x ULN with bilirubin >2x, but ALP <2x ULN

‡ 1 additional Hy's Lab case in the Open-Label Trial (156-08-271)

Study 251

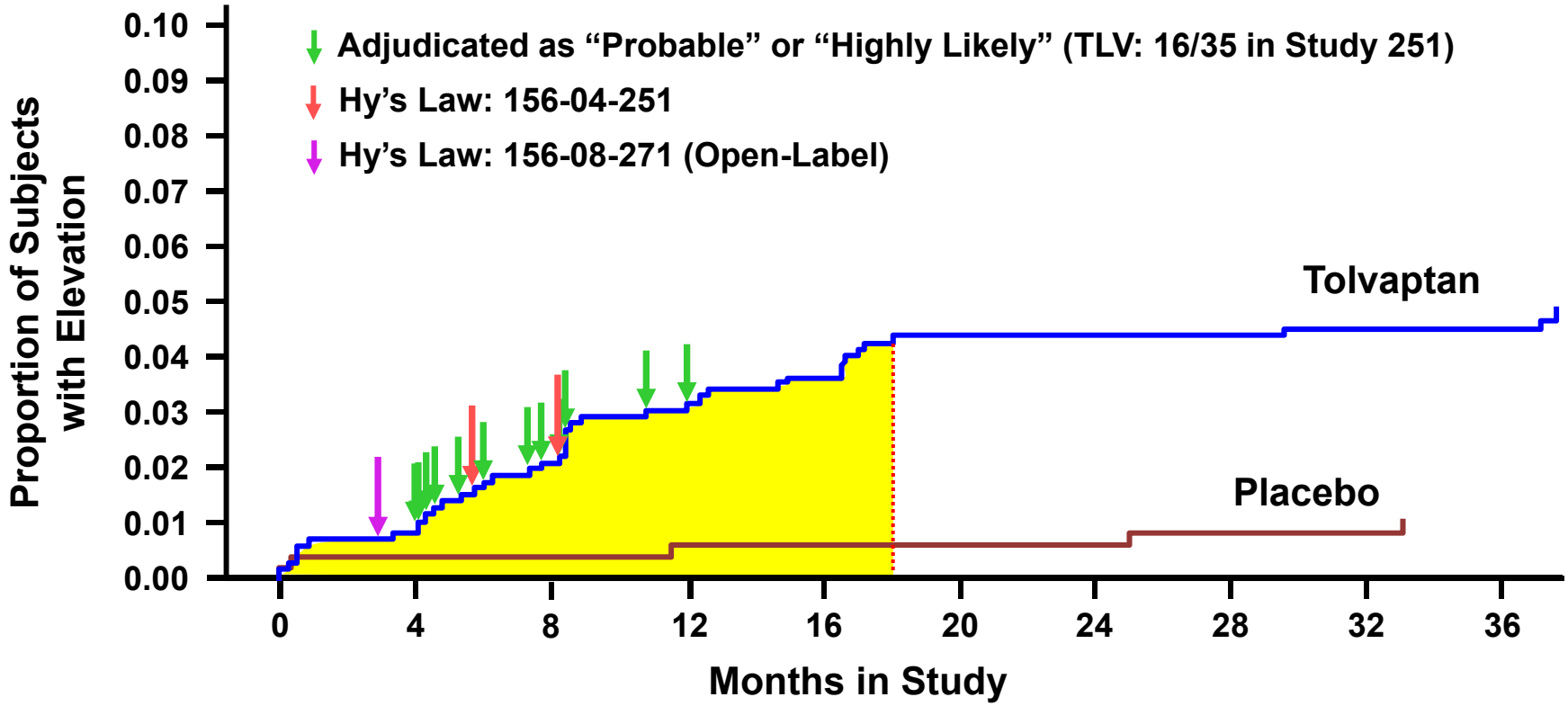
Tolvaptan is Causally Associated with Hepatic Injury

- Independent Hepatic Adjudication Committee to determine causality
  - Dr. Paul Watkins, Dr. Neil Kaplowitz, Dr. James H. Lewis, Dr. David Alpers
- 35 tolvaptan-treated cases from 156-04-251 met the criteria for review
  - 16 likely attributed to tolvaptan
  - 3 Hy's Law (1 from open-label extension trial)
- Evaluations confirmed DILI to be associated with tolvaptan in ADPKD
- Committee estimated theoretical risk of hepatic failure to be 1:3000

3	÷	1000	×	10%	≈	1/3000
Hy's Cases		Number of Subjects Treated Through 18 Months		Risk of Outcome of Liver Failure/Mortality (Registries)		Theoretical Risk of Liver Failure/Mortality

Study 251, Study 271

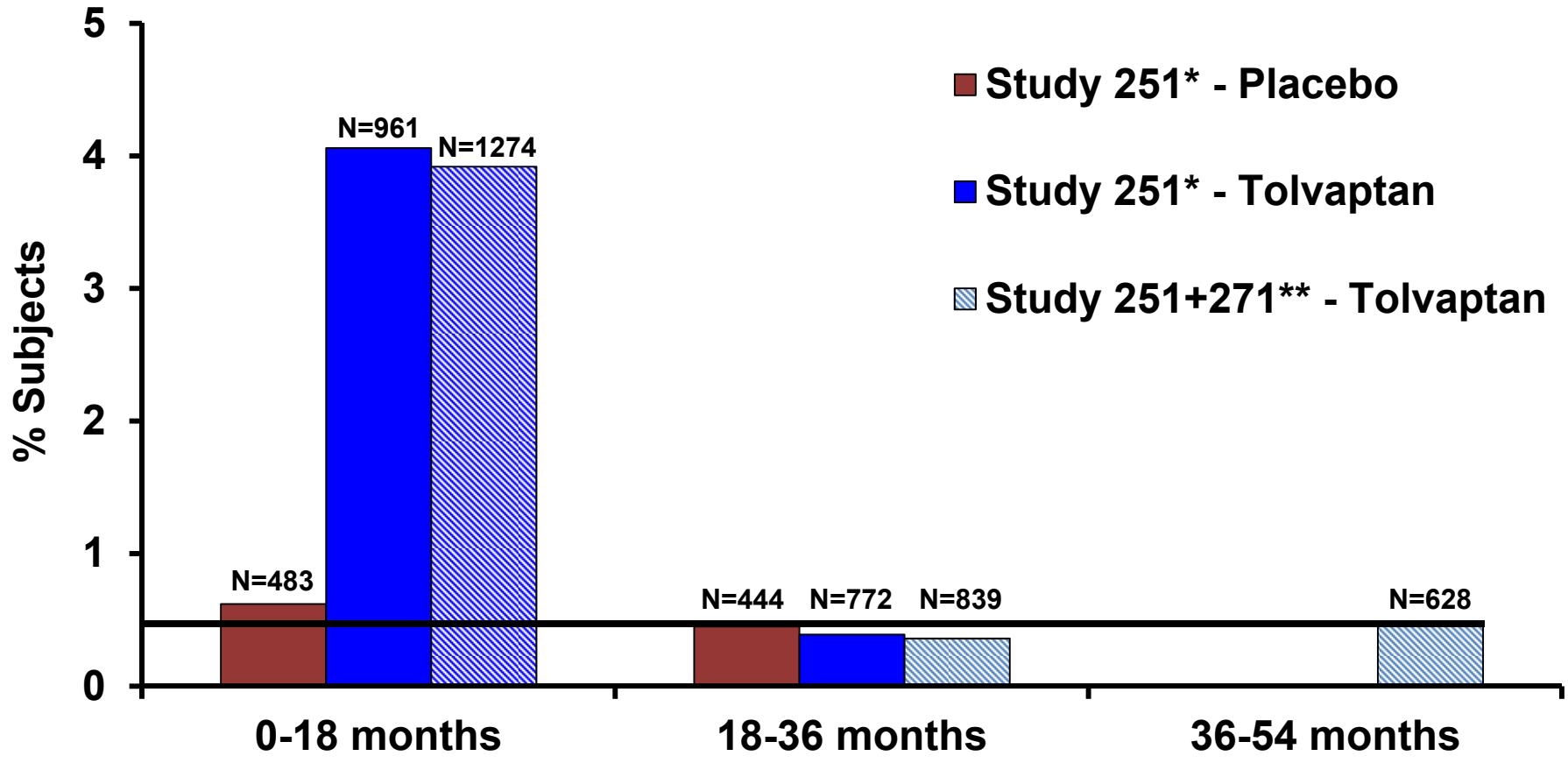
Time to First Elevation in ALT (>3x ULN): 18-Month "Window of Susceptibility"



Days in Study	0	100	200	300	400	500	600	700	800	900	1000	1100
Tolvaptan N=	961	884	836	812	796	774	765	751	740	734	726	268
Placebo N=	483	476	468	459	452	445	442	433	425	422	415	147

Study 251

Risk of ALT Elevation After 18 Months is Comparable to Placebo



* Study 251 is the pivotal ADPKD trial; ** Study 271 is an open-label extension trial

Study 251, Adjudicated Population

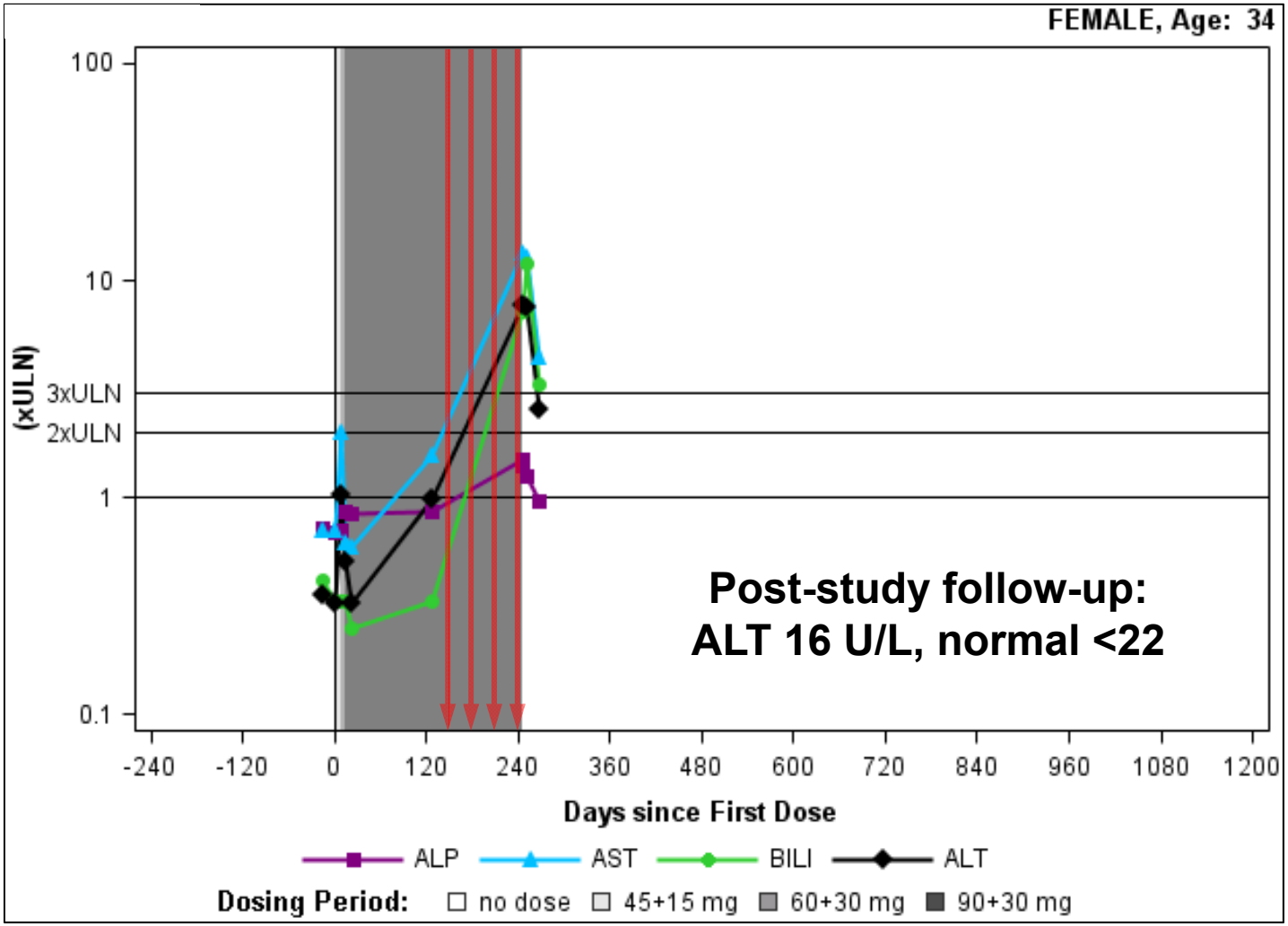
Reversibility of ALT Elevations

- All 35 subjects returned to ≤3x ULN
  - Discontinued therapy (14/35): the majority of subjects returned to ≤3x ULN within 40 days
  - Continued therapy (21/35): the majority of subjects returned to ≤3x ULN within 4 months
- All 3 Hy's cases returned to <1x ULN

- ***ALT elevations are reversible***
- ***Recovery is faster in patients who discontinue therapy***
- ***Some patients (10/21) were able to continue therapy with ALT levels that remained <3x ULN after recovery***

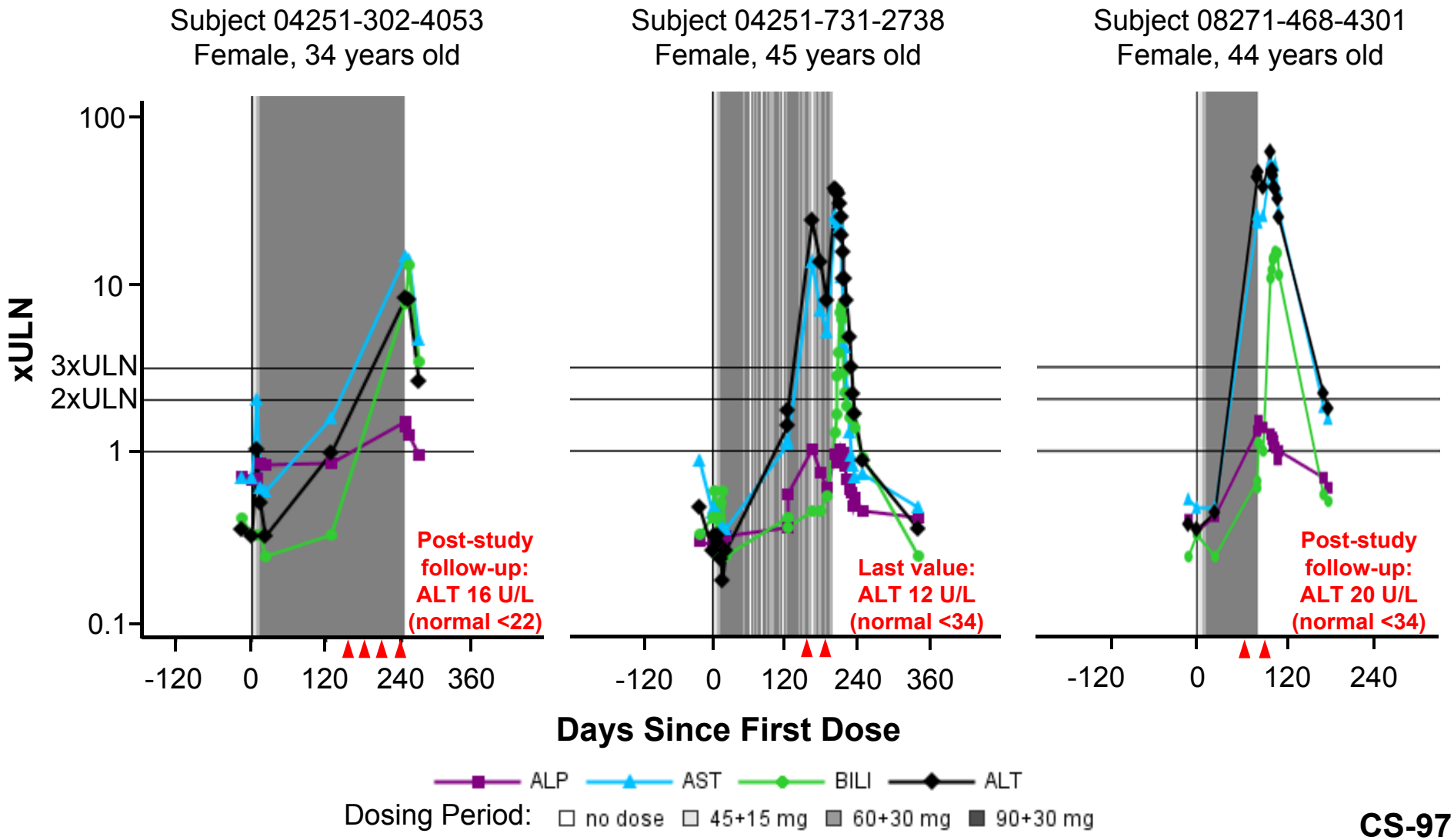
Study 251

Subject 04251-302-4053
Hy's Law Case, Treatment: Tolvaptan



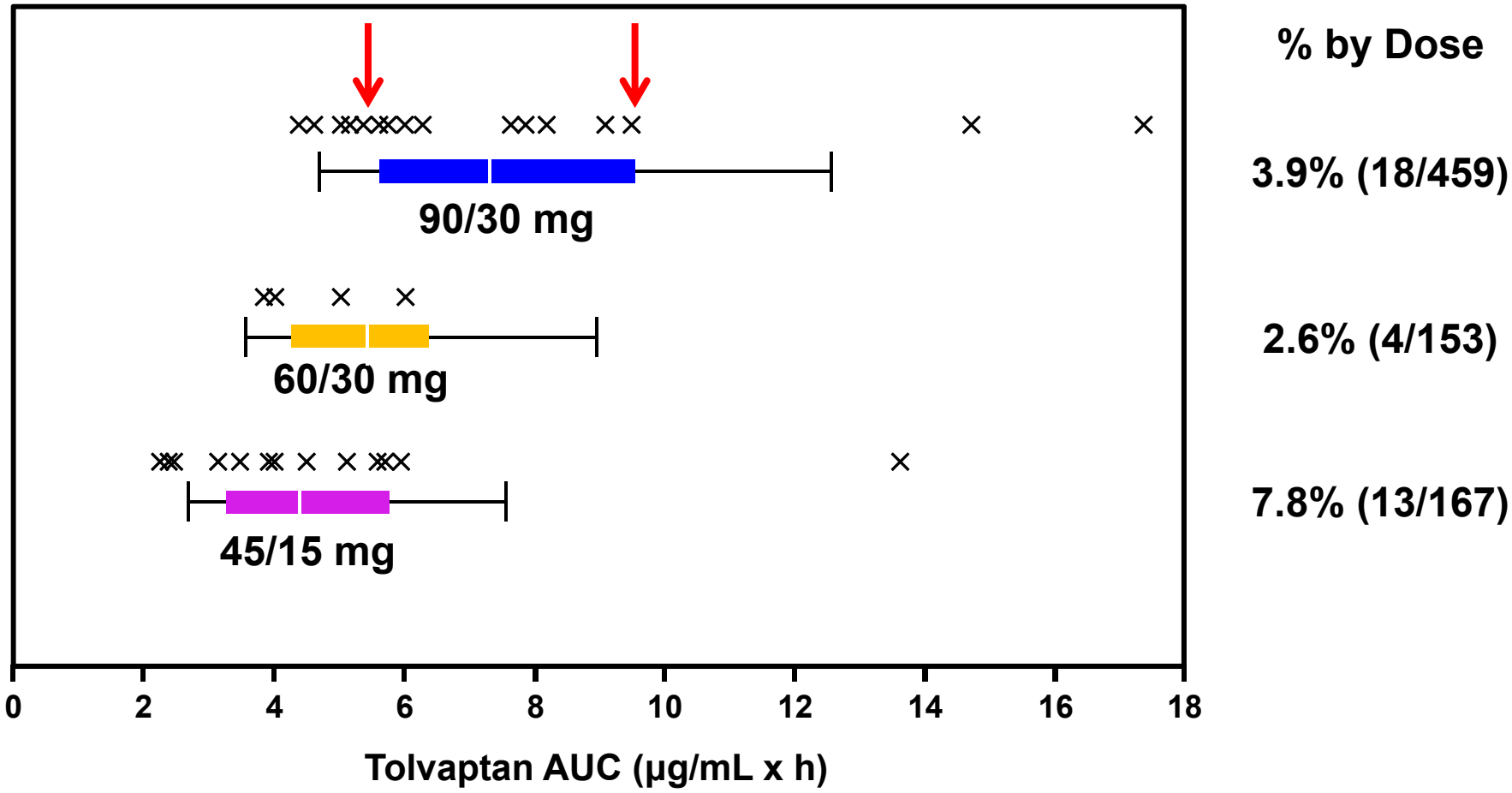
Study 251, Study 271

Hy's Law Cases, Signature Pattern



Study 251

Hepatotoxicity in Adjudicated Subjects Is Not Associated with Dose or Exposure



X = exposures for adjudicated subjects at or near time of event
Red arrows indicate Hy's cases in 251; The third Hy's Law subject was on 90/30 but no PK is available.
The whiskers represent the 10th to 90th percentile.

Tolvaptan Proposed Label: Boxed Warning

WARNING: IDIOSYNCRATIC HEPATIC TOXICITY
See full prescribing information for complete boxed warning.

Tolvaptan has been associated with idiosyncratic elevations of blood alanine and aspartate aminotransferases (ALT & AST) with infrequent cases of concomitant elevations in bilirubin-total (BT). To mitigate the risk of liver injury, blood testing for hepatic transaminases is required prior to initiation of tolvaptan, continuing monthly for 18 months and at regular intervals (e.g., 3-6 months) thereafter.

Tolvaptan Proposed Label: Guidelines for Hepatic Injury

- Interrupt treatment and repeat tests within 48-72 hours if:
  - ALT or AST are abnormal
  - Onset of signs or symptoms of hepatic injury
- Continue testing at increased frequency until resolution/stabilization
- Cautious continuation of treatment and frequent monitoring if ALT remains below 3x ULN
- Permanent discontinuation if ALT or AST levels are:
  - Greater than 8x ULN
  - Greater than 5x ULN for more than two weeks
  - Greater than 3x ULN and BT >2x ULN or INR >1.5
  - Greater than 3x ULN with persistent symptoms of hepatic injury

Note: Based on FDA Guidance for Industry: Drug-Induced Liver Injury: Pre-Marketing Clinical Evaluation (July 2009)

Safety Profile is Well-Characterized

- Commonly-occurring AEs are related to mechanism of action and are manageable
- Identified risk of reversible liver injury which could be fatal if left unrecognized
- No dose response relationship to liver injury
- Risk for liver injury can be addressed by careful language in the label and a comprehensive REMS plan

Agenda

Introduction	**Robert McQuade, PhD** *Executive VP & Chief Strategic Officer, Otsuka*
Pathophysiology of Autosomal Dominant Polycystic Kidney Disease	**Vicente Torres, MD, PhD** *Professor of Medicine, Mayo Clinic*
Measuring Patient Burden and Renal Progression in ADPKD	**Arlene Chapman, MD** *Professor of Medicine, Emory University*
Efficacy of Tolvaptan to Delay ADPKD Progression	**Frank Czerwiec, MD, PhD** *Sr. Director, Global Clinical Development, Otsuka*
Sponsor Response to FDA Comments	**Robert McQuade, PhD**
Safety of Tolvaptan in ADPKD: Signal Identification and Interpretation	**Christopher Zimmer, MD** *Sr. Director, Global Clinical Development, Otsuka*
Conclusion: Risk Evaluation/Mitigation and Net Benefit	**Robert McQuade, PhD**

Risk Evaluation/Mitigation and Net Benefit

Robert McQuade, PhD

Executive Vice President and Chief Strategic Officer
Otsuka Pharmaceutical Development & Commercialization, Inc.

REMS Program Goals

To Mitigate the Risk of Serious Outcomes Associated with Hepatotoxicity

- Inform healthcare providers (HCPs) and patients about the risk of hepatotoxicity associated with the use of tolvaptan
- Provide education to all patients who will be prescribed tolvaptan about the signs and symptoms of hepatotoxicity
- Ensure compliance with hepatic laboratory testing prior to and monthly during out-patient therapy
- Periodic review of hepatotoxicity events reported in patients enrolled in the Tolvaptan REMS to further establish long-term safety

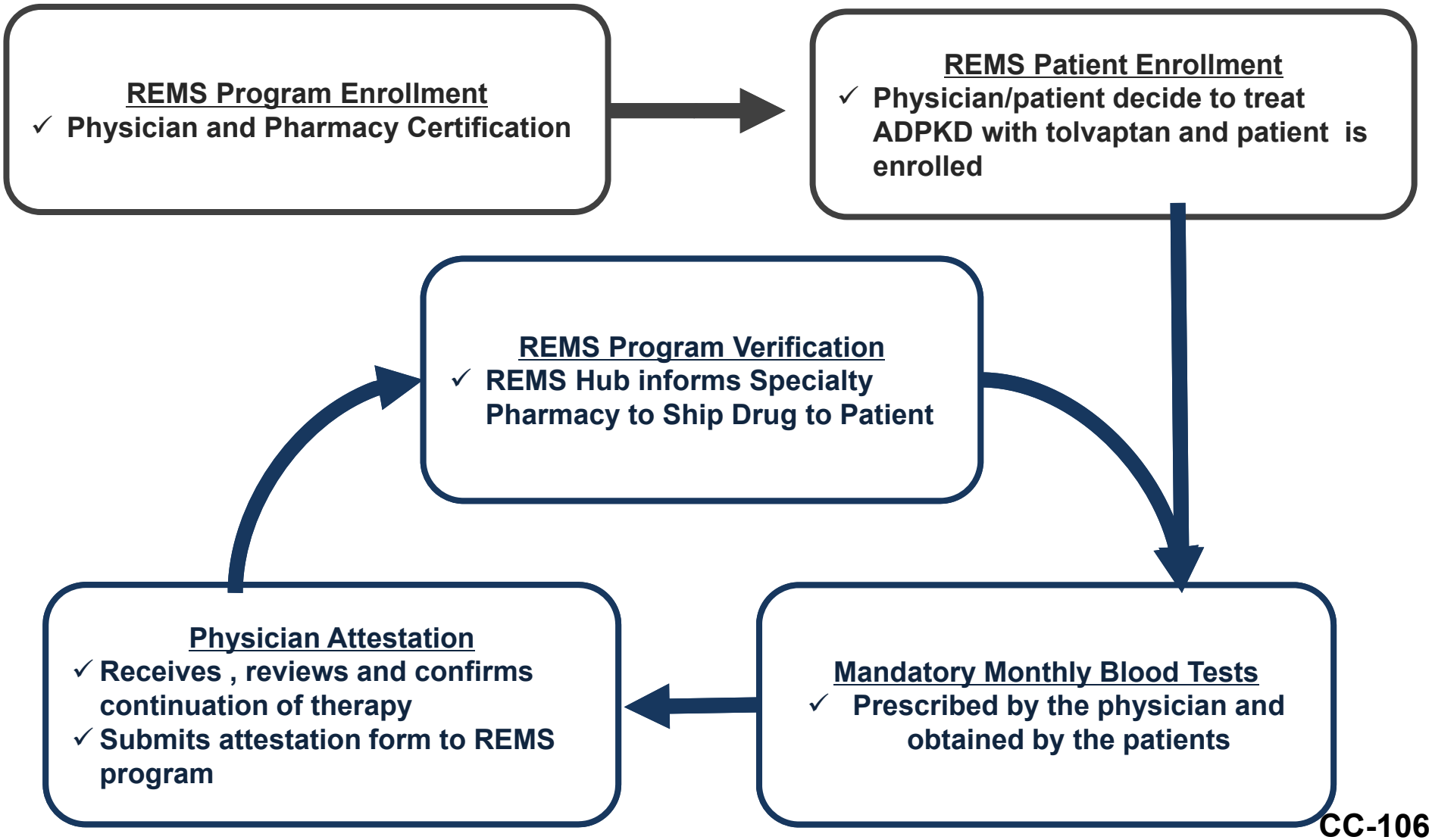
Based on current discussions with FDA

Hepatic Risk Can Be Mitigated: REMS Elements to Assure Safe Use (ETASU)

Mandatory Prescriber/Pharmacy Certification and Registration	1. Prescribers and specialty pharmacies complete mandatory training and certification prior to prescribing or dispensing privileges
Mandatory Patient Education	1. Patients are educated by HCP to recognize signs and symptoms of hepatotoxicity 2. All out-patients are enrolled in the REMS Program
Mandatory hepatic monitoring confirmed by HCP as completed and reviewed prior to drug dispensing every month	1. Physician orders baseline and monthly liver testing 2. Patients must obtain monthly liver test 3. Physicians must review liver test results and recommend continuation of tolvaptan 4. Physicians must submit attestation form to REMS vendor
All Safe Use conditions must be verified before dispensing – closed out-patient distribution from a small number of specialty pharmacies	1. REMS vendor verifies to pharmacy that: physician is certified, patient is enrolled, physician attestation recommends continuation of treatment 2. Ship up to 30 day supply of tolvaptan

Mandatory Reporting of All Adverse Events Associated with Hepatotoxicity

Tolvaptan REMS Process



Additional Risk Mitigation

- Boxed Warning regarding liver injury risk and need for monthly monitoring
- Enhanced pharmacovigilance activities
  - Otsuka follow-up on reported cases to obtain additional relevant information
  - Adjudication committee of hepatic experts to review cases consistent with possible severe liver injury (cases with an ALT > 5xULN)
- Post-marketing Patient Registry collecting monthly liver monitoring test results on tolvaptan-treated out-patients to provide comprehensive risk assessment

REMS System Quality Assurance

- Audit certified out-patient pharmacies, contracted distributors and REMS Program Call Center at least annually for the first three years and then at least every two years thereafter
- REMS database will record the documentation of drug dispensing and attestation; submission of this assessments to FDA at 9 months, 18 months, and then annually
- REMS collect Questionnaires (physician and patient) on understanding of risk of hepatotoxicity
- Otsuka will conduct chart audits with select group of nephrologists as well as estimation of LFT compliance based on health insurance claims data, in order to confirm monthly liver function test are conducted

Efforts to Ease Potential REMS Burden

- The following potential options are being explored by Otsuka to reduce the burden for physicians/patients*:
  - As part of the REMS (if approved by FDA):
    - Proactive communication to remind HCPs of monthly hepatic monitoring
    - Home health nursing visits for blood draws
  - Additional efforts outside the REMS
    - Proactive reminders to patients of monthly hepatic monitoring
    - Additional informational brochures and materials for prescribers and patients

* In compliance with applicable laws and regulations

Net Benefit of Tolvaptan for Patients with ADPKD

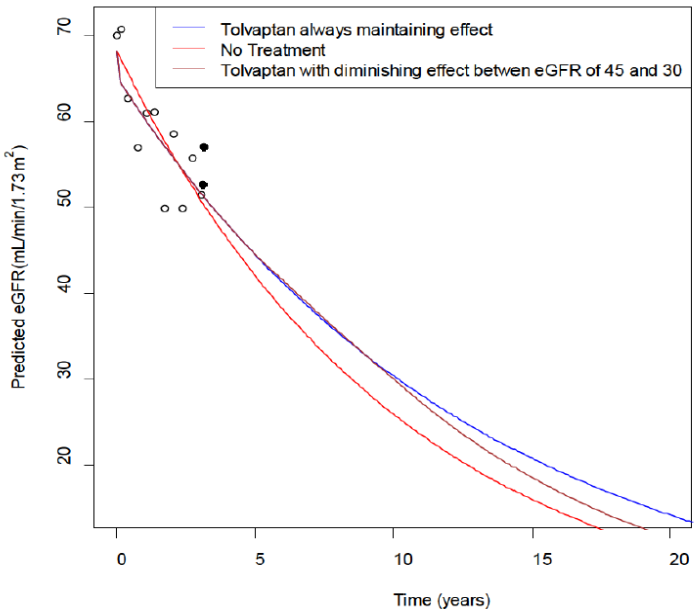
Tolvaptan Benefits in ADPKD

Tolvaptan is the first medication to demonstrate significant effects for slowing the pathophysiology and progression of ADPKD

- **Kidney structure:** 50% reduction in TKV growth
  - 182 ml vs. 342 ml
- **Patient outcomes:** 14% relative risk reduction for ADPKD clinical progression events
  - 61% relative risk reduction for worsening renal function events
  - 34% relative risk reduction for events of renal pain
- **Kidney function:** 33% reduction in rate of eGFR decline

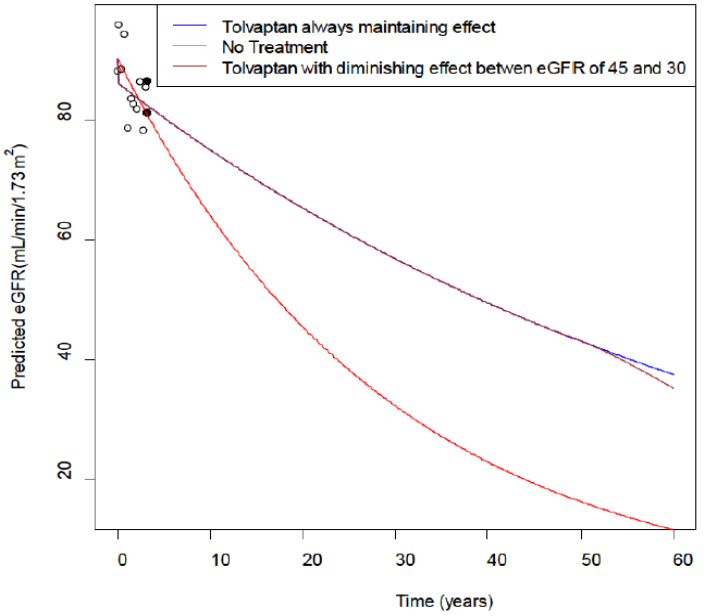
FDA Estimates of Benefit on Kidney Function
Example Patient Projections

46 year old
eGFR = 70 mL/min/1.73 m^2



ESRD Projection: 1.5 – 3.6 year delay

20 year old patient
eGFR = 88.3mL/min/1.73 m^2



ESRD Projection: > 10 year delay

FDA Briefing Document Statistical Review pp. 28-33

FDA Estimate of Benefit on Kidney Function
Overall Study 251 Population

- Model Assumptions:
  - 10% risk of withdrawal of tolvaptan in first 4 months
  - 5% annual risk of withdrawal thereafter

- **Estimated 4 year delay in time to eGFR < 15 mL/min/1.73 m^2 (ie dialysis or transplant)***

*If there is no benefit of tolvaptan after 3 years, there is no benefit on time to ESRD

FDA Briefing Document Statistical Review pp. 28-33

Otsuka Commitment to ADPKD Patients

- Dedicated over **30 years** to vasopressin research and **15 years** to the research of V_2 antagonists in ADPKD
- Responsible for the largest ADPKD research program in history
  - Largest, longest placebo-controlled trial (Study 251)
  - Ongoing long-term trials in over **1100 patients** (Study 271 & 003)
  - Ongoing natural history study in over **3400 patients** (Study 291)
- Clinical development program for pediatric patients in both hyponatremia and ADPKD
- Continued collaboration with PKD Outcomes Consortium
- Potential to refer patients with hepatotoxicity to U.S. Drug Induced Liver Injury Network (DILIN)
- Additional research to understand potential genetic, biochemical and metabolic factors that may be predictive of hepatotoxicity

Otsuka Post-Approval Research Commitments

- Post-marketing Patient Registry to provide greater insight into the risk of liver injury
- Extend Study 271 for additional 5 years to confirm the longer-term benefits of tolvaptan
  - 10 years follow-up for tolvaptan patients from Study 251
  - 7 years follow-up for patients who received placebo
- Post-approval commitment to conduct a study in CKD 4 patients measuring the time to a doubling of serum creatinine or ESRD

Conclusions

- ADPKD is a life-threatening disease without a treatment
- Tolvaptan is the first drug to prove beneficial effects slowing kidney disease progression in ADPKD
- The closed-distribution REMS with mandatory monthly attestation will mitigate the risk for drug-induced liver injury
- Tolvaptan should be approved now to allow physicians and patients a therapeutic option that targets ADPKD progression

Tolvaptan: Slowing Progression of Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Cardiovascular and Renal Drugs Advisory Committee

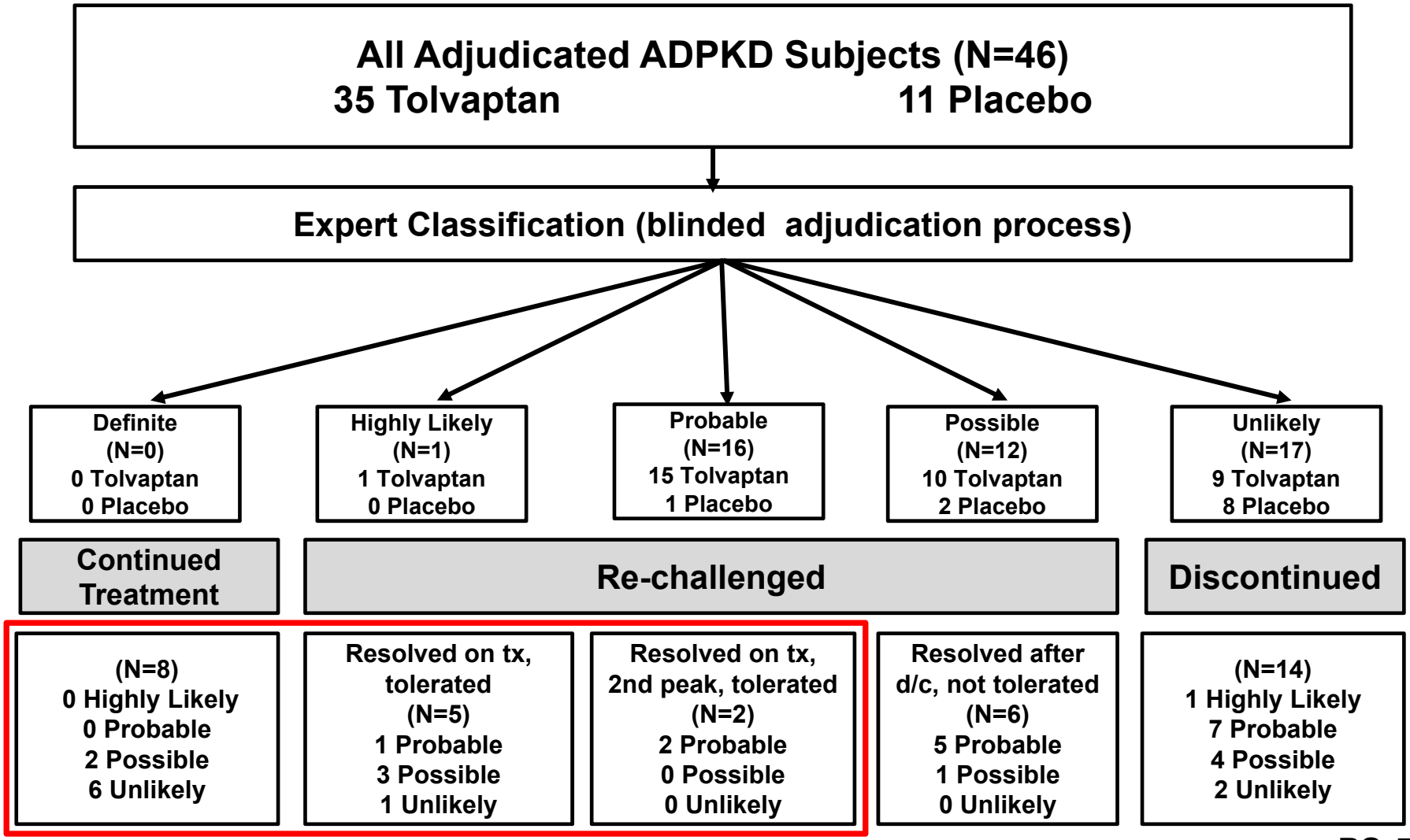
August 5, 2013

Otsuka

Backup slides shown during Q&A

Study 251

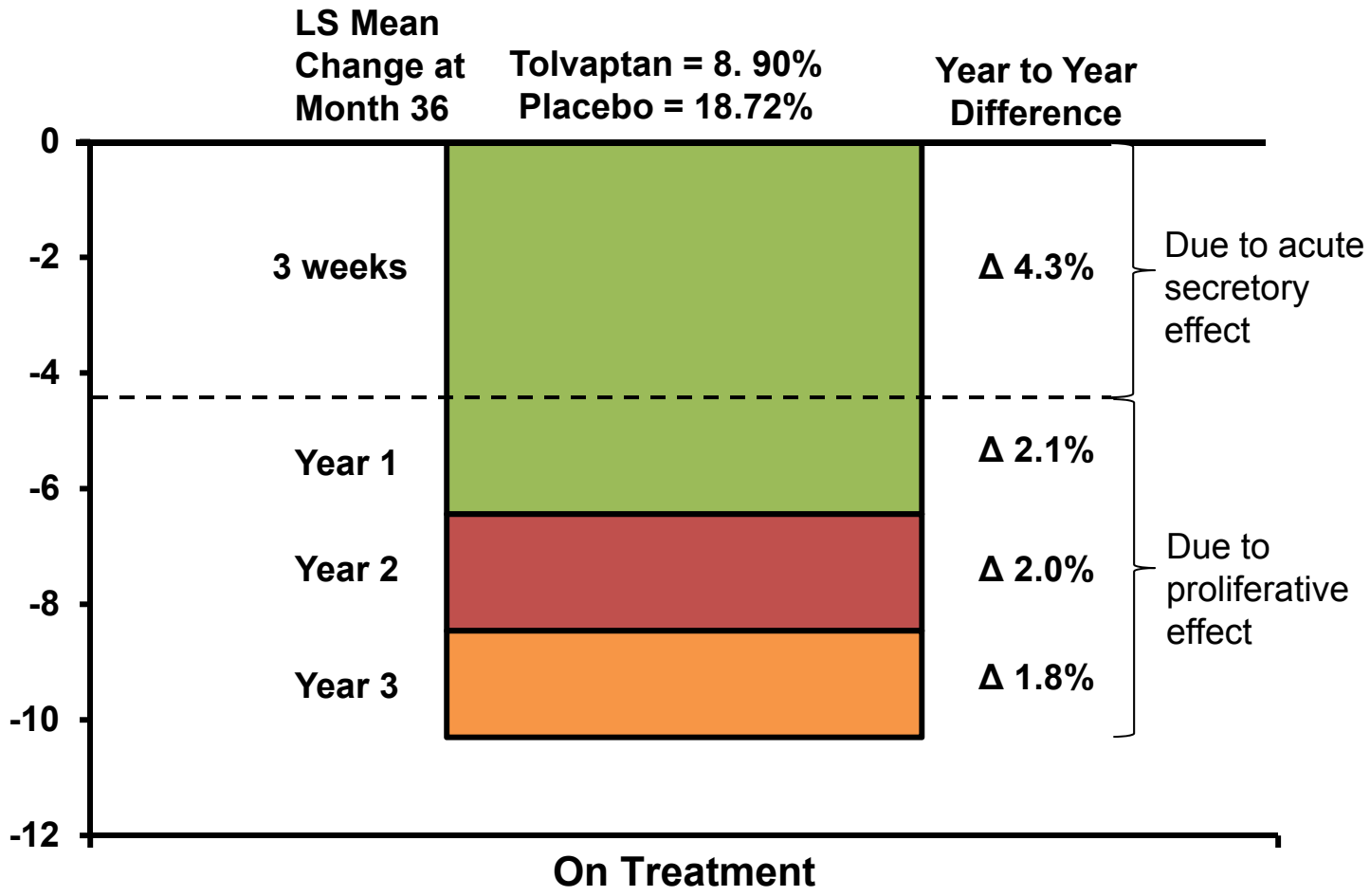
Adjudication Results for the 46 Subjects Meeting Criteria for Adjudication



PS-518

156-04-251

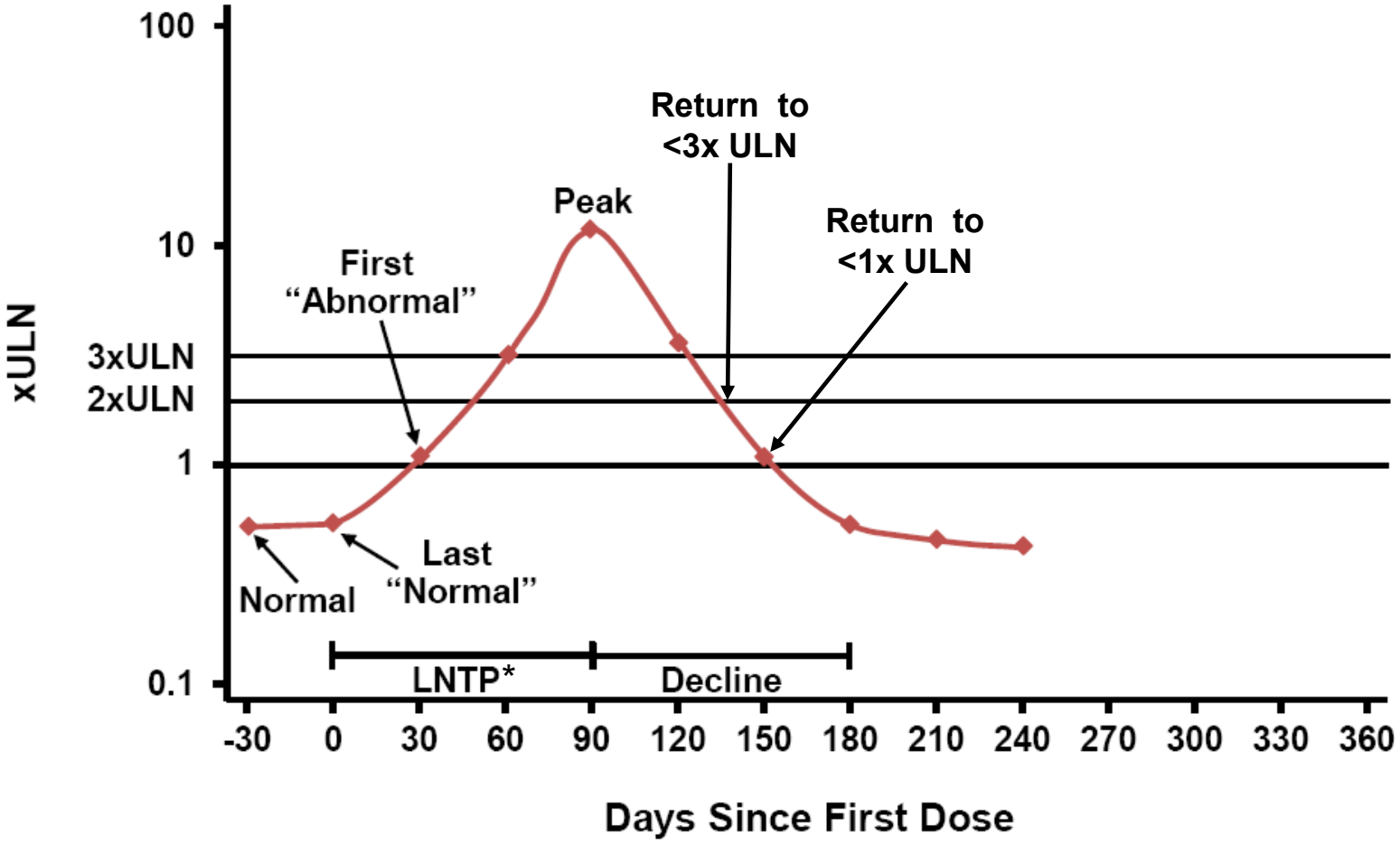
Annual Treatment Effects of Tolvaptan Relative to Placebo on Total Kidney Volume



PE-1077

Study 251

Illustration of ALT Elevation and Decline

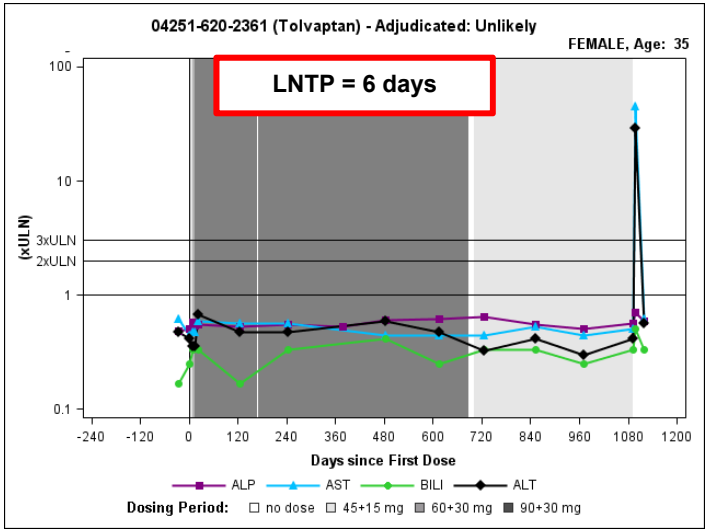


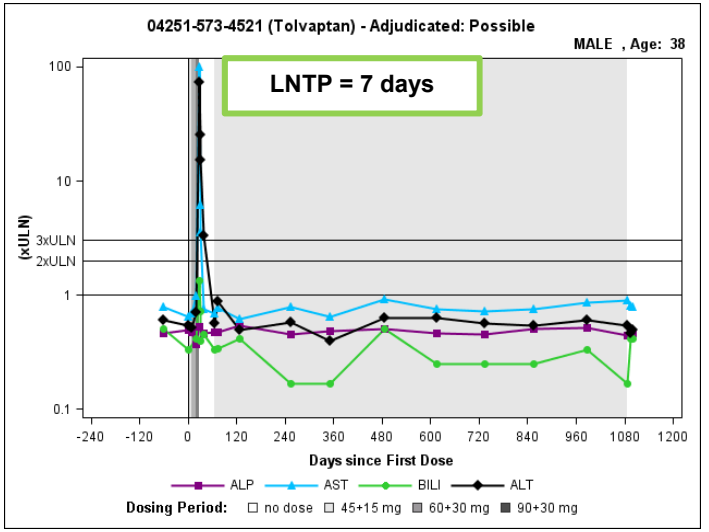
* Last normal to peak. Mean = 150 days (+/- 100)

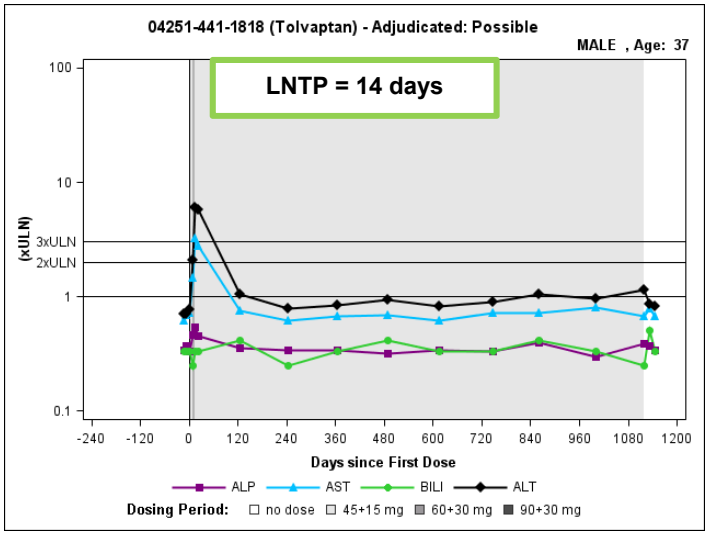
PS-732

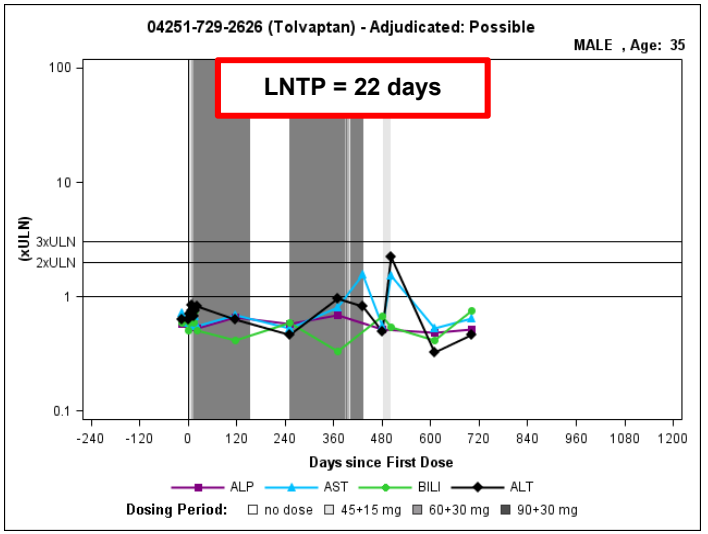
Study 251

LNTP Less Than 30 Days







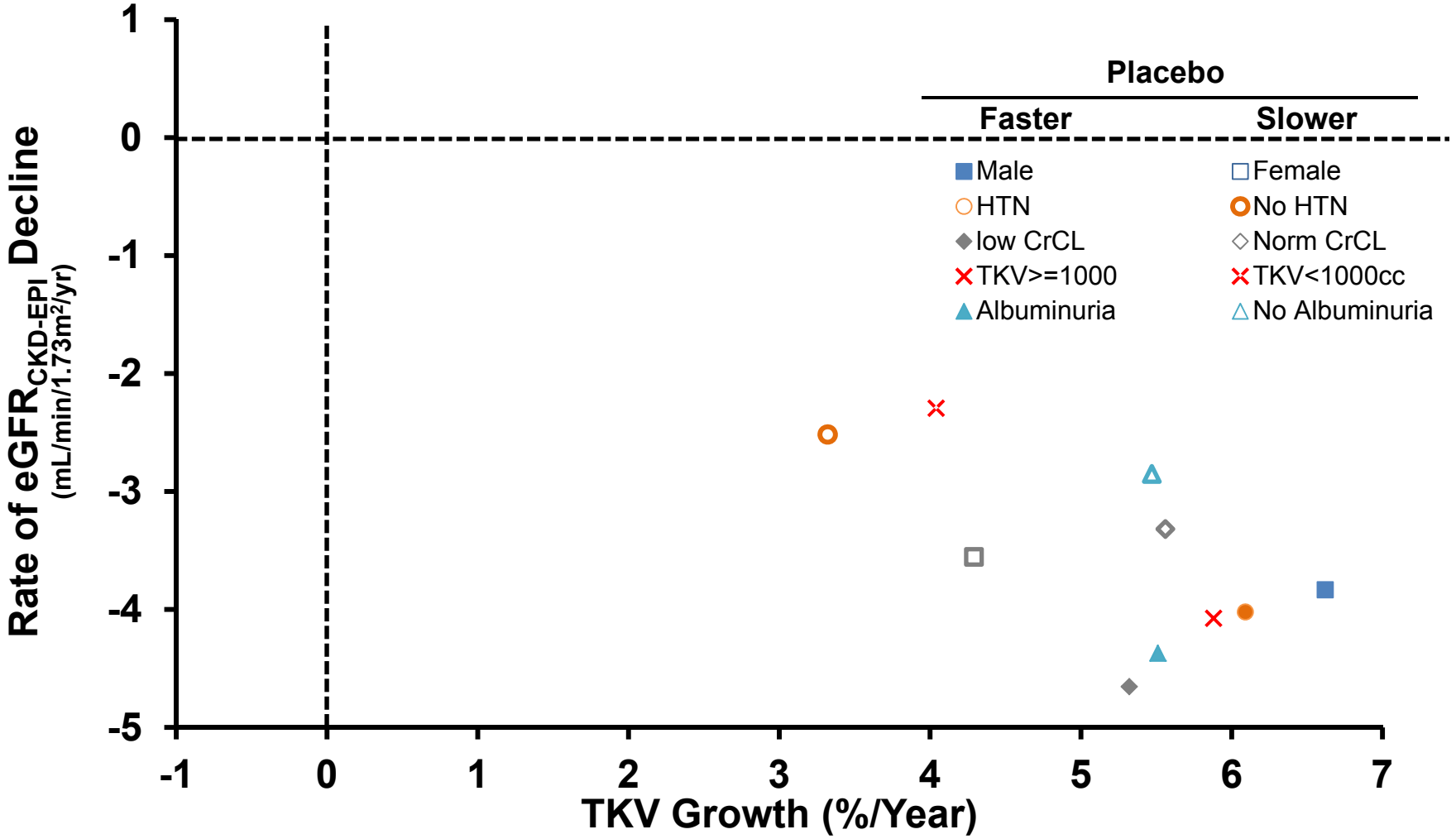


PS-740

156-04-251

Tolvaptan Subpopulation Benefit

Total Kidney Volume (TKV) and Renal Function (eGFR)



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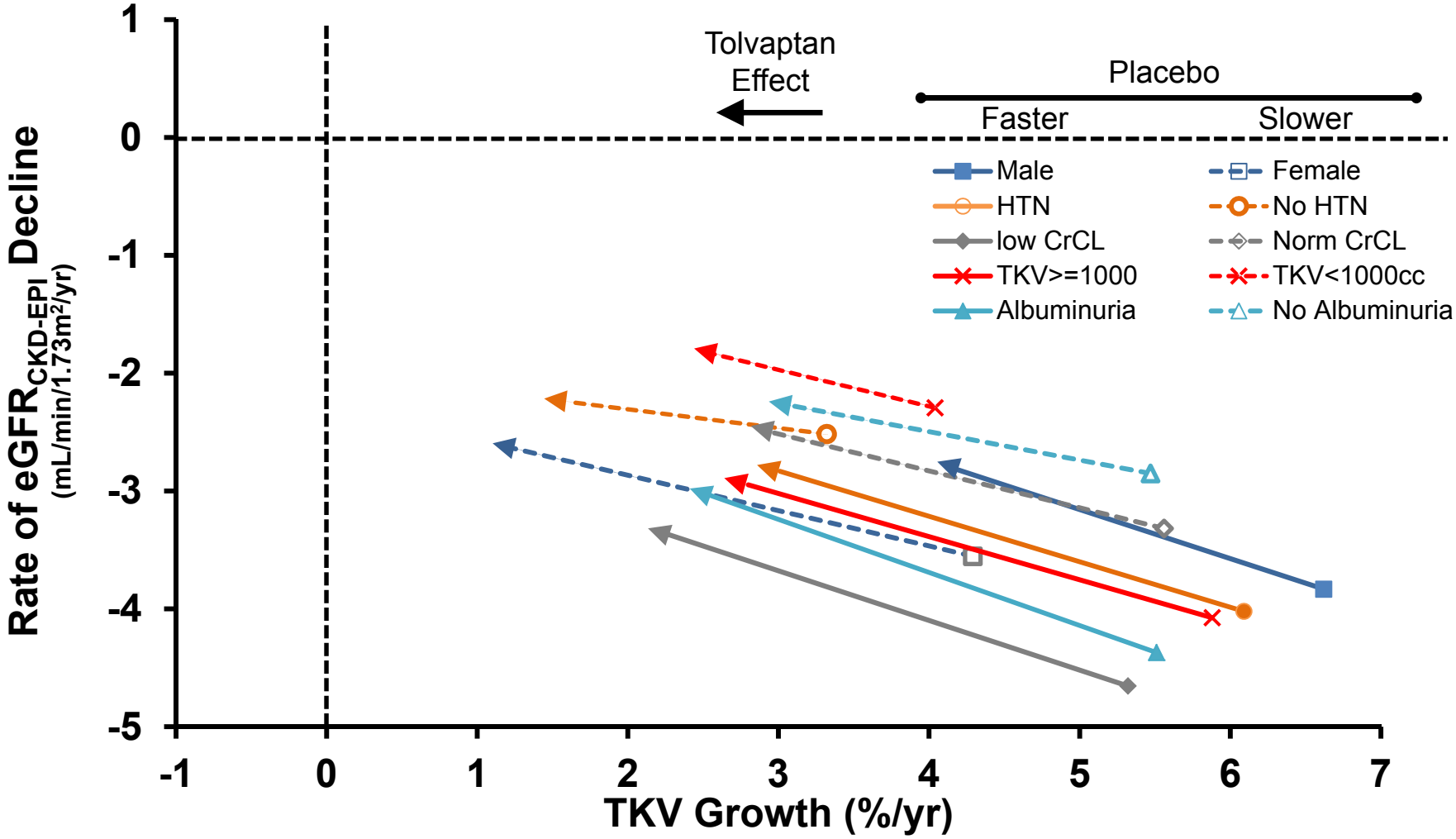
156-04-251

Tolvaptan Subpopulation Benefit

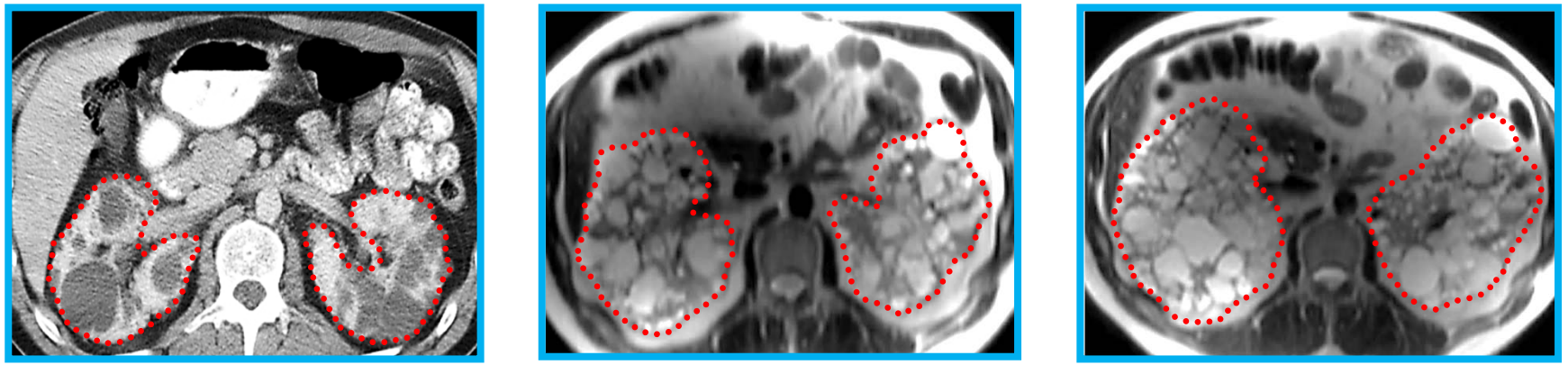
Total Kidney Volume (TKV) and Renal Function (eGFR)



PE-1120

Over time Cysts Develop and Expand Resulting in Loss of Kidney Function

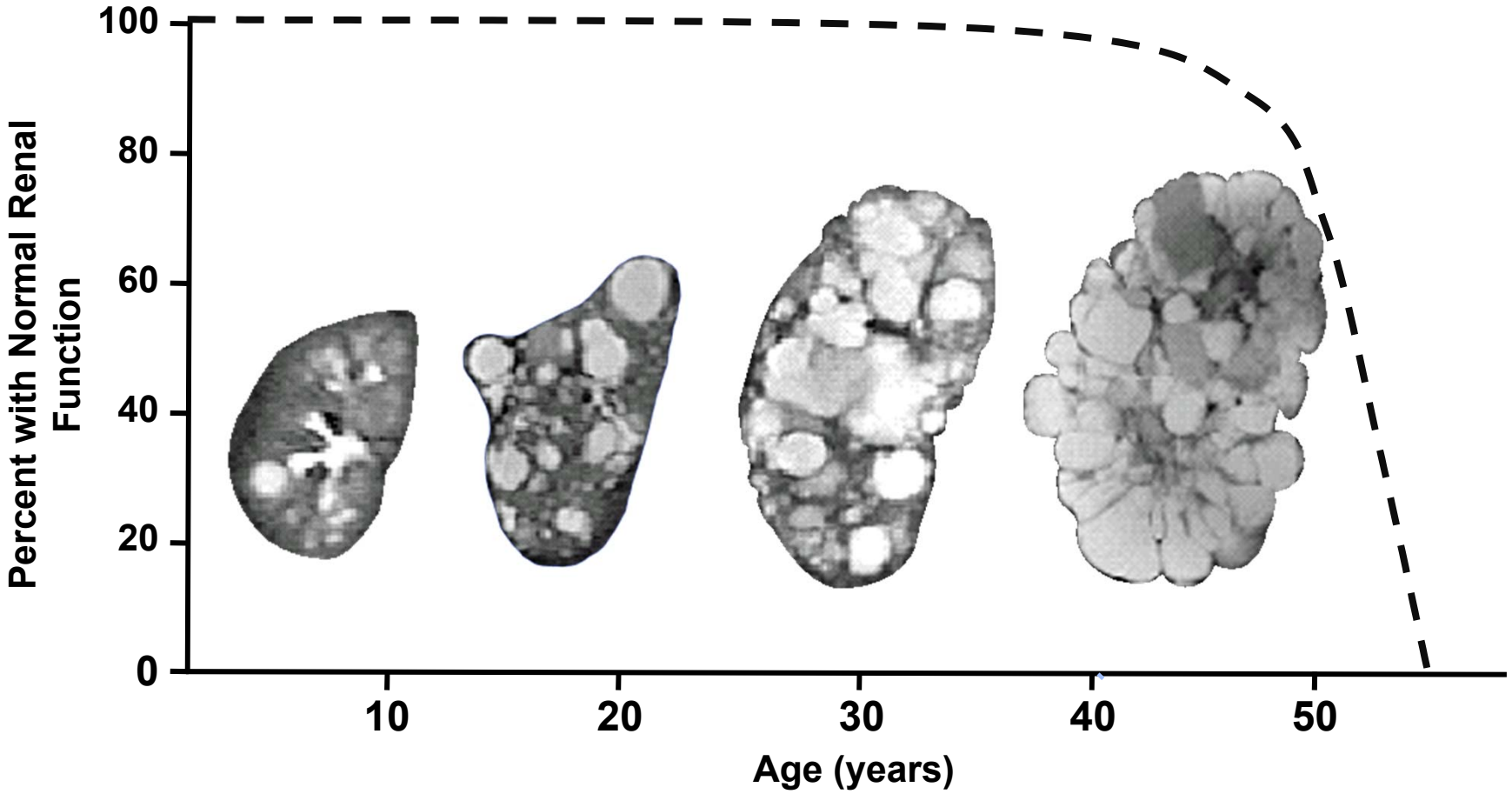
Over 13 years, TKV increased by 300%
with a 53% loss of kidney function



Age 30	→	Age 37	→	Age 43
CKD Stage 1		*CKD Stage 2*		*CKD Stage 3*
GFR 93 ml/min		GFR 61 ml/min		GFR 44 ml/min
TKV 1441 ml		TKV 2775 ml		TKV 4459 ml

GFR=Glomerular Filtration Rate; CKD=Chronic Kidney Disease; TKV=Total Kidney Volume

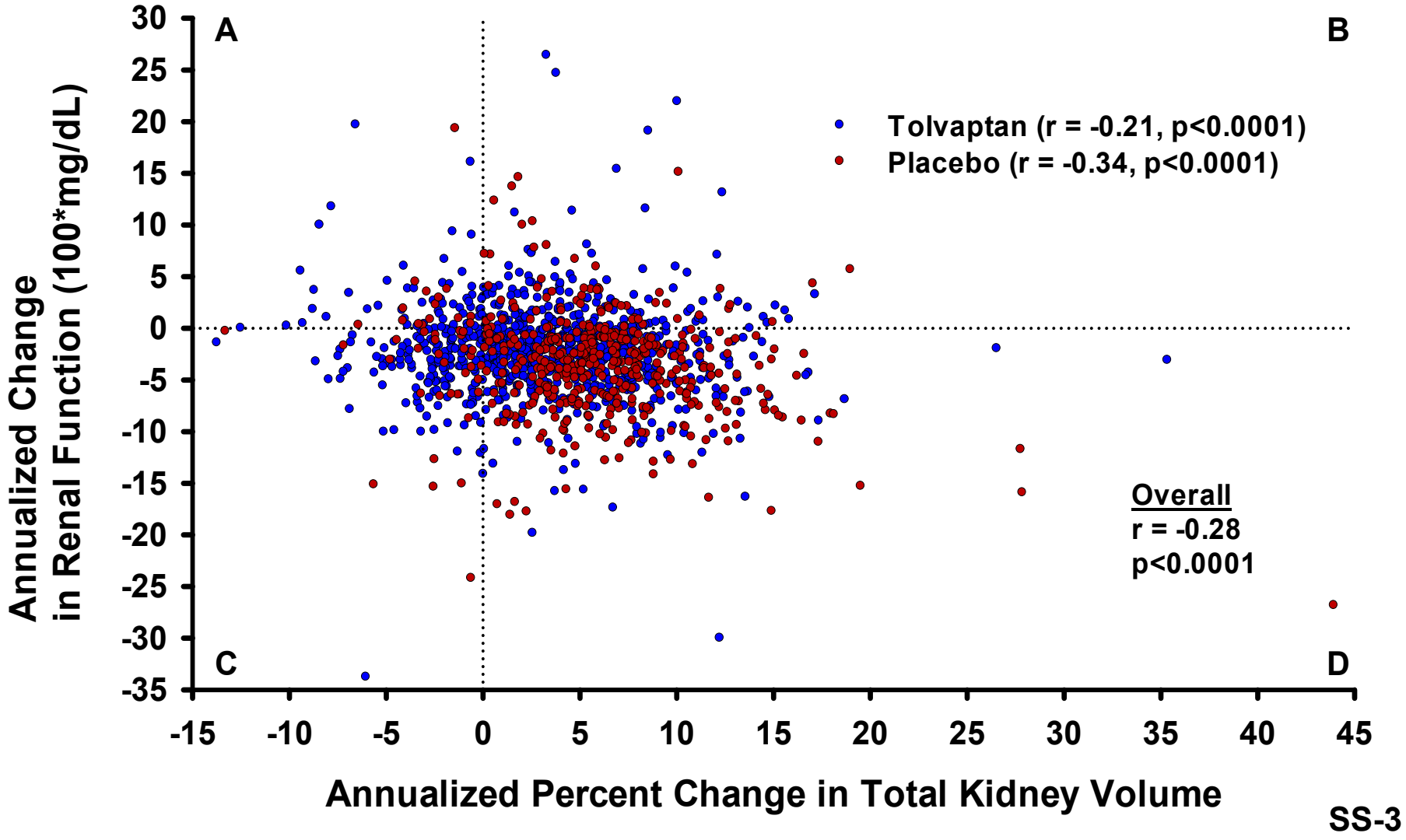
This compensatory capacity accounts for the natural history of ADPKD



SS-2

156-04-251

Annualized Change in Renal Function (100/Scr) vs Total Kidney Volume Pearson's Correlations



SS-3

156-04-251, ITT, Regardless of Treatment Period

Sensitivity Analysis: Time to Multiple Renal Function Events and 50% Increase in Serum Creatinine

	Recurrent Events								
Group	# of Subjects	# of Events	Total F/U Years	Events per 100 F/U Years	Mean F/U Years	HR[1]	95% CI Limit Lower[1]	95% CI Limit Upper[1]	p-value[1]
Tolvaptan	917	19 (2.1%)	2398	0.79	2.62	0.411	0.228	0.741	0.0031
Placebo	476	26 (5.5%)	1333	1.95	2.80				

[1] Derived from rate and mean model of time to recurrent event analysis with factor treatment

156-04-251

Hospitalization by Treatment (ITT) From Serious Adverse Event Reports

	Tolvaptan (N=961) n (%)	Placebo (N=484) n (%)	P-value
Subjects treated	**961 (100.0)**	**483 (99.9)**	
Subjects with hospitalizations	**143 (14.9)**	**83 (17.2)**	**=0.26**
Total events of hospitalization	**198 (20.6)**	**138 (28.5)**	
Subject years of drug exposure	**2334.5**	**1305.5**	
Hospitalizations per subject year of exposure	**0.085**	**0.106**	**=0.033**

Source: ARGUS data review on Aug 5, 2013

Study 251: Exploratory Renal Outcomes

Tolvaptan Subjects had Fewer Hospitalizations Due to Renal Complications, Including Renal Pain

Hospitalizations Due to:	Group	Subjects (N)	Subjects with Hospitalization (n)	Subjects with Hospitalization %	OddsRatio* (95% CI)	p-value
Any kidney complications	Tolvaptan	961	31	3.23	0.403 (0.238-0.677)	0.0004
	Placebo	484	37	7.65		
Renal pain	Tolvaptan	961	9	0.94	0.232 (0.092-0.542)	0.0004
	Placebo	484	19	3.93		

*Exact Test (Exact Logistic Regression).
Subjects with multiple events counted only once.

Study 251: Missing Data Sensitivity Analysis

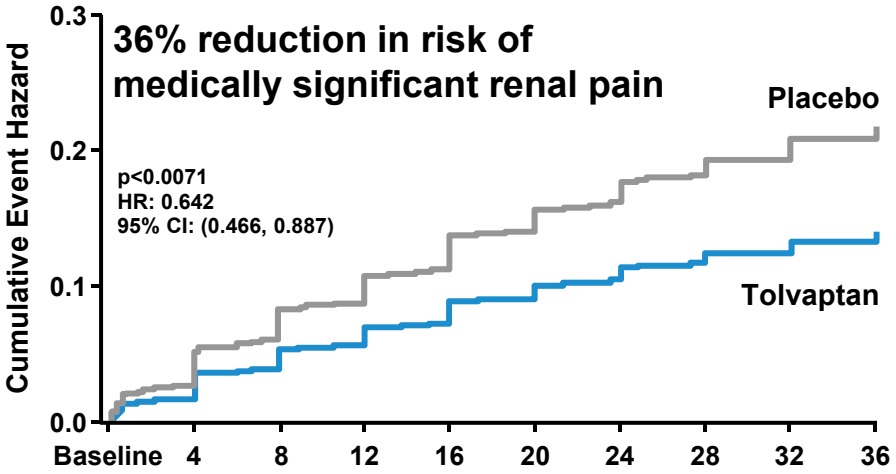
Responder Analysis Based on Power Assumption Thresholds

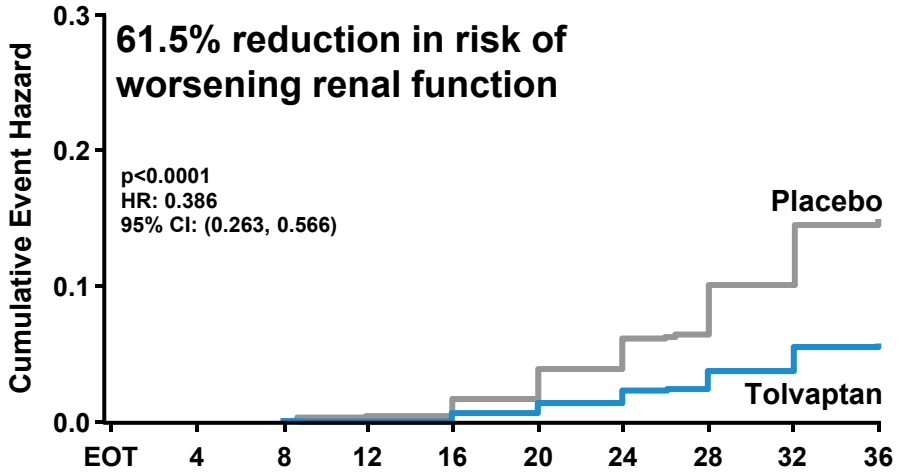
Response Definition Completers Only	Group	Subjects (N)	Responders (n)	Responders (%)	OddsRatio (95% CI)	p-value[a]
Completers with 20% better than placebo's TKV slope	Tolvaptan	961	481	50.1	2.0 (1.6-2.5)	<0.0001
	Placebo	484	162	33.5		
Above AND: 20% better than placebo's eGFR slope	Tolvaptan	961	302	31.4	2.0 (1.5-2.6)	<0.0001
	Placebo	484	90	18.6		
Above AND: no renal pain or worsening renal function events	Tolvaptan	961	272	28.3	2.1 (1.6-2.8)	<0.0001
	Placebo	484	76	15.7		
Above AND: no hypertension or albuminuria events	Tolvaptan	961	127	13.2	2.1 (1.4-3.1)	0.0003
	Placebo	484	33	6.8		

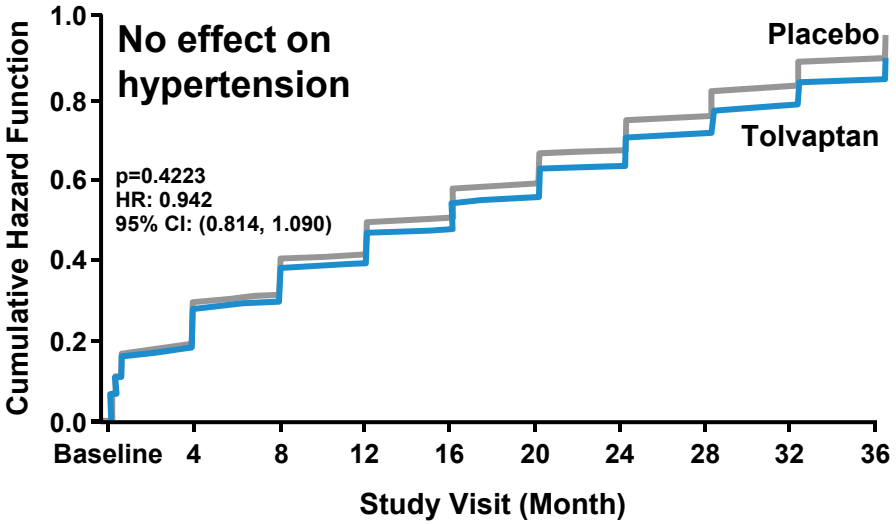
[a] Derived from chi square test.

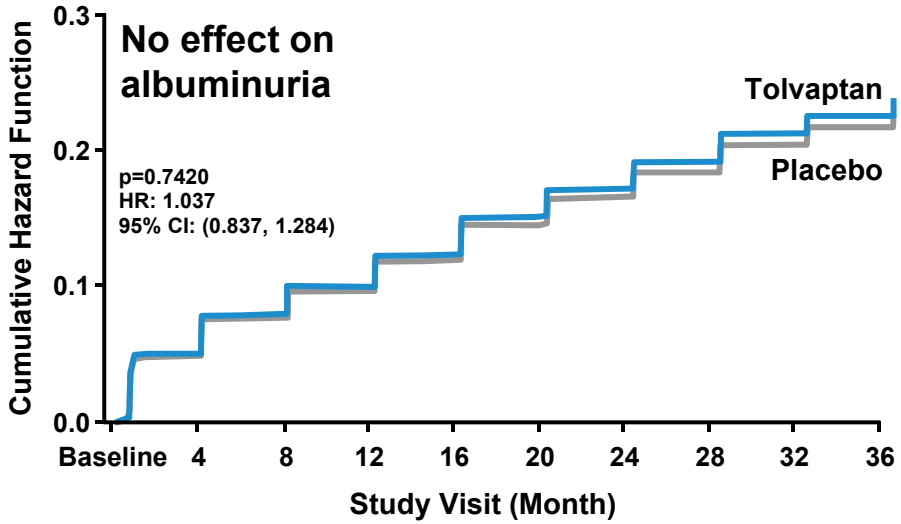
156-04-251 TEMPO$^{3}_{4}$

Composite Components Indicate Benefit due to Reduced Renal Dysfunction and Renal Pain with No Negative Effects









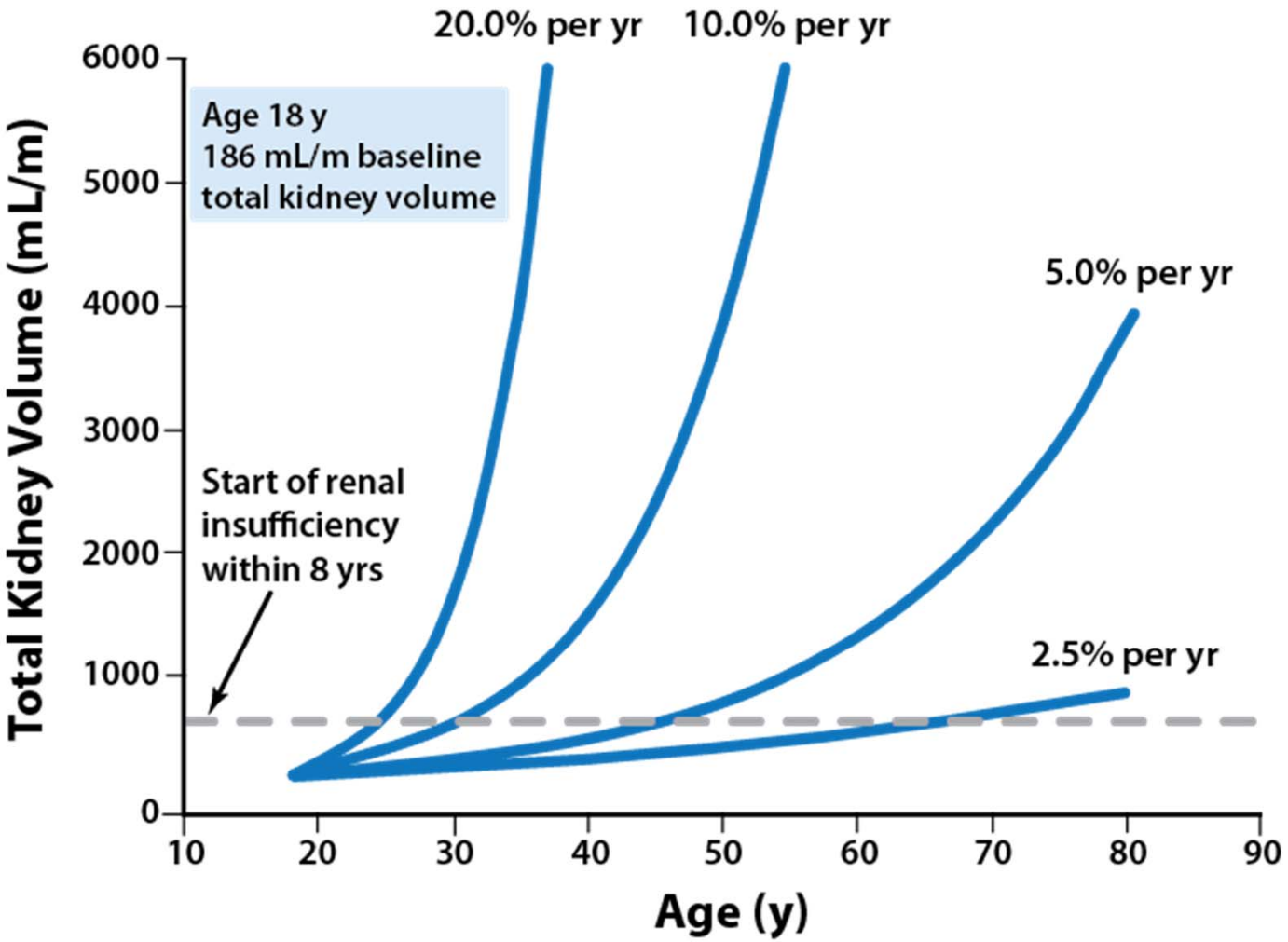
156-04-251, ITT, Regardless of Treatment Period

Sensitivity Analysis: Time to Multiple Composite ADPKD Events

	Recurrent Events								
Group	# of Subjects	# of Events	Total F/U Years	Events per 100 F/U Years	Mean F/U Years	HR[1]	95% CI Limit Lower[1]	95% CI Limit Upper[1]	p-value[1]
Tolvaptan	961	1080	2408	44.84	2.51	0.874	0.784	0.974	0.0147
Placebo	484	678	1339	50.63	2.77				

[1] Derived from rate and mean model of time to recurrent event analysis with factor treatment

Effect of Kidney Growth Rate on Development of ESRD



Study 251

Dropouts vs Completers: Rate of Change in Renal Function, Estimated by 100/Serum Creatinine (1/(mg/dL))[3]

Treatment Group		N	Slope[1]	Treatment Effect[1]	95% Lower CI	95% Upper CI	p-value[2]
Tolvaptan	Dropout	129	-2.374	0.244	-1.317	1.805	0.7592
	Completer	713	-2.618				

Data from 88% of enrolled subjects

[1] Derived from testing the time treatment interaction using linear mixed model in which both intercept and slope are fixed and random effects.
[2] An estimate of the difference between the slopes of dropout and completer.
[3]Subjects with at least 4-month follow-up, excluding observations deemed unreliable by investigators, within treatment period.