Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med 2012;367:2407-18. DOI: 10.1056/NEJMoa1205511

(PDF updated March 28, 2013.)

Supplementary Appendix:

Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease: The TEMPO 3:4 Trial

Vicente E. Torres, MD, PhD, Arlene B. Chapman, MD, Olivier Devuyst, MD, PhD, Ron T. Gansevoort, MD, PhD, Jared J. Grantham, MD, Eiji Higashihara, MD, PhD, Ronald D. Perrone, MD, Holly B. Krasa, MS, John Ouyang, PhD, Osamu Sato, MS, and Frank S. Czerwiec MD, PhD, for the TEMPO 3:4 Trial Investigators

Table of Contents

TEMPO 3:4 Investigators and Committee Members

In addition to the authors, the following investigators and committee members participated in the Tolvaptan Efficacy and Safety in Management of Polycystic kidney disease and it's Outcomes 3:4 (TEMPO 3:4) trial:

***Steering Committee**:* V. Torres, *Mayo Clinic, Rochester, USA (Chair)*; A. Chapman, *Emory University, Atlanta, USA*; O. Devuyst, *Université catholique de Louvain, Brussels, Belgium, and University of Zürich, Zürich, Switzerland*; R. Ganservoort, *University of Groningen, Groningen, Netherlands*; E. Higashihara, *Kyorin University, Mitaka, Japan*; R. Perrone, *Tufts Medical Center, Boston, MA*; J. Ouyang, *Otsuka, Rockville, MD*; F. Czerwiec, *Otsuka, Rockville, MD*.

Independent Data Monitoring Committee: S. Goldstein, Henry Ford, Detroit, MI (Chair); B. Cowley, *University of Oklahoma College of Medicine, Oklahoma City, OK;* M. Fukagawa, *Tokai University School of Medicine, Kanagawa, Japan*; R. Torra, *Fundacio Puigvert, Barcelona, Spain;* L.J. Wei, *Harvard University School of Public Health, Boston, MA;* T. Cook, *University of Wisconsin Statistical Data Analysis Center, Madison, WI.*

Clinical Events Committee: R.Toto, M.D (Chair), *UT Southwestern Transplant Program, Dallas, TX*; R. Agarwal, *Indiana University & Purdue University Indianapolis, IN;* P. August, *Cornell University Medical Center, New York City, NY;* G. Bakris, *University of Chicago Medical Center, Chicago, IL;* S. Beddu, *University of Utah, UT; H. Corwin, MD & Dartmouth-Hitchcok Medical Center, Lebanon, NH;* L. Ruilope, *Universidad Autónoma de Madrid, Madrid, Spain*

Clinical Sites and Investigators:

Argentina: G. Rosa-Diez, *Hospital Italiano de Buenos Aires, Gascon, Buenos Aires;* De La Fuente, *Hospital Privado — Centro Médico de Córdoba Naciones Unidas, Córdoba;* R. Martin*, Hospital Universitario Austral, Buenos Aires;* P. Massari, *Hospital Privado — Centro Médico de Córdoba, Córdoba;* P. Novoa, *Sanatorio Allende Hipólito, Córdoba;* M. Rial*, Instituto de Nefrología, Buenos Aires;* A. Wasserman*, Hospital Municipal de Vicente López, Dr. Bernardo, Houssay, Buenos Aires.* ***Australia:*** R. Faull, *Royal Adelaide Hospital, Adelaide, SA;* I. Fraser*, Melbourne Renal Research Group, Melbourne, VIC;* D Johnson, *Princess Alexandra Hospital, Woolloongabba, QLD;* E. Pedagagos, *Royal Melbourne Hospital Grattan, Melbourne, VIC;* C. Pollock*, Royal North Shore Hospital, Sydney, NSW;* G. Rangan*, Westmead Hospital, Sydney, NSW;* S. Roger*, Renal Research, Gosford, NSW;* G. Russ*, Queen Elizabeth Hospital, Adelaide,*

SA; M. Thomas, *Royal Perth Hospital, Perth, WA;* R. Walker, *Royal Melbourne Hospital Grattan, Melbourne, VIC.* ***Belgium:*** O. Devuyst, *UCL-Saint-Luc, Brussels;* P. Peeters*, UZ Gen, Ghent;* P. Van der Niepen, *UZ-VUB Brussels, Brussels.* ***Canada:*** P. Barre, *Royal Victoria Hospital, Montréal, Québec;* D. Bichet, *Hôpital du Sacre-Coeur de Montréal, Montréal, Québec;* S. Soroka, *Queen Elizabeth II Health Science Centre, Nova Scotia.* ***Denmark:*** H. Dieperink, *Odense Universitets Hospital, Odense;* S. Strandgaard, *Herlev Amtssygehus, Herlev.* ***France:*** F. Berthoux, *CHU — Hôpital Nord, Saint-Etienne;* B. Canaud, *CHU — Hôpital Lapeyronie, Montpellier;* D. Chauveau, *Hôpital Rangueil, Toulouse;* C. Combe, *CHU-Hôpital Pellegrin, Bordeaux;* B. Dussol, *Hôpital de la Conception, Marseille;* M. Laville*, Hôpital Edouard Herriot, Lyon;* F. Mignon*, Hôpital Bichat-Claude Bernard, Paris;* P. Rieu*, Centre Hospitalier Universitaire, Reims Cedex;* J. P. Ryckelynck*, CHU — Hôpital Clemenceau, Clemenceau.* ***Germany:*** F. H. Dellanna, *Nephrologische, Düsseldorf;* P. Gross*, Universitätsklinikum Carl Gustav Carus, Dresden;* T. Feldkamp*, Klinik für Nephrologie, Essen;* J. Nurnberger, *Klinik für Nephrologie, Essen;* B. D. Schulze*, UH Erlangen/Nuernberg, Nuernberg;* G. Walz*, Universitätsklinikum Freiburg, Freiburg;* M. Zeier*, Nierenzentrum Heidelberg, Ruprecht-Karls-Universität, Heidelberg.* ***Italy:*** S. Bianchi, *UO Nefrologia, Livorno;* G. Capasso, *Policlinico, Napoli;* R. Magistroni*, Policlinico di Modena, Modena;* P. Manunta; *Università Vita e Salute, Milano;* G. Remuzzi, *Ospedali Riuniti di Bergamo, Bergamo;* G. Villa*, IRCCS Fondazione Salvatore Maugeri, Pavi.* ***Japan:*** K. Asahi*, Fukushima Medical University Hospital, Fukushima;* M. Endo*, Tokai University Hospital, Kanagawa;* Y. Fujigaki*, Hamamatsu University School of Medicine, Shizuoka;* A. Fukatsu, *Kyorin University Hospital, Tokyo;* H. Hasegawa, *Saitama Medical Center, Saitama;* S. Horie, *Teikyo University Hospital, Tokyo;* T. Hosoya, *The Jikei University Hospital, Tokyo;* N. Iehara, *Kyorin University Hospital; Tokyo,* Y. Iino, *Nippon Medical School Hospital, Tokyo;* E. Imai, *Osaka University Hospital, Osaka;* Y. Isaka*, Osaka University Hospital, Osaka;* E. Ishimura, *Osaka City University Hospital, Osaka;* S. Ito*, Tohoku University Hospital, Miyagi;* K. Kamata*, Kitasato University Hospital, Kanagawa;* K. Kamura*, National Hospital Organization, Chiba;* T. Kato, *Fukushima Medical University Hospital, Fukushima;* E. Kusano*, Jichi Medical School Hospital, Tochigi;* M. Kuwahara*, Shuwa General Hospital, Saitama;* A. Matsubara*, Hiroshima University Hospital, Hiroshima;* T. Mochizuki, *Hokkaido University Hospital, Hokkaido;* I. Narita, *Niigata University Medical and Dental Hospital, Niigata;* Y. Naya, *Chiba University Hospital, Chiba;* N. Nihei, *Chiba University Hospital, Chiba;* S. Nishio, *Hokkaido University Hospital, Hokkaido;* K. Nitta*, Tokyo Women's Medical, Tokyo;* K. Nutahara*, Kyorin University Hospital, Tokyo;* M. Okamura, *Ohno Memorial Hospital, Osaka;* S. Sasaki,

Tokyo Medical and Dental University, Tokyo; K. Seta*, National Hospital Organization, Kyoto;* S. Shibazaki*, Hokkaido University Hospital, Hokkaido;* A. Sugawara, *National Hospital Organization, Kyoto;* M. Sugawara, *Fujita Health University Hospital, Aichi;* S. Sugiyama, *Fujita Health University Hospital, Aichi;* K. Tabei*, Saitama Medical Center, Saitama;* K. Takaichi*, Toranomon Hospital, Tokyo;* K. Tomita, *Kumamoto University Hospital, Kumamoto;* Y. Tsukamoto, *Shuwa General Hospital, Saitama;* K. Tsuruya*, Kyusyu University Hospital, Fukuoka;* Y. Ubara*, Toranomon Hospital Kajigaya, Kangawa;* T. Watanabe, *Fukushima Medical University Hospital, Fukushima;* N. Yorioka, *Hiroshima University Hospital, Hiroshima;* K. Yoshida*, Kitasato University Hospital, Kanagawa;* H. Yoshiyuki, *Fujita Health University Hospital, Aichi;* Y. Yuzawa*, Fujita Health University Hospital, Aichi.* ***Netherlands:*** R. Gansevoort*, UMCG Groningen, Gronigen;* M. Vervloet, *VU Medisch Centrum, Amsterdam.* ***Poland:*** K. Ciechanowski, *Samodzielny Publiczny Szpital Kliniczny, Szczecin.* M. Gutowska-Jablonska, *Szpital Praski, Samodzielny, Warszawa;* W. Klatko, *Oddział Nefrologiczny Stacja Dializ, Ciechanow;* M. Klinger*, Akademicki Szpital Kliniczny im J Mikulicza, Wroclaw;* A. Ksiazek, *SPSzK nr 4 w Lublinie, Klinika Nefrologii, Lublin;* R. Malecki*, Międzyleski Szpital Specjalistyczny w Warszawie, Warszawa;* M. Nowicki, *SPSzk nr 4 w Lublinie, Lublin;* B. Rutkowski*, Akademickie Centrum Kliniczne AMG, Gdansk;* A. Rydzewski, *Klinika Chorób Wewnętrznych I Nefrologii, Warszawa;* W. Sulowicz*, Szpital Uniwersytecki w Krakowie, Krakow.* ***Romania:*** A. Covic, *Spitalul Clinic, Iasi,* G. Mircescu*, Spitalul Clinic de Nefrologie, Bucharest,* M. Voiculescu*, Institutul Clinic Fundeni, Bucuresti;* ***Russian Federation:*** O. Barbarash, *Kemerovo Medical Academy, Kemerovo,* S. Borovoy, *Leningrad Regional Clinical Hospital, St.Petersburg,* L. Demina, *The Municipal Health Institution, Municipal Clinical Hospital, Novosibirsk,* G. Shostka*, City Mariinskiy Hospital, St. Petersburg,* L. Tkalich*, Tomsk Regional Clinical Hospital, Tomsk,* N. Tomilina*, City Clinical Hospital, Moscow;* ***United Kingdom:*** L. Foggensteiner*, Queen Elizabeth Hospital, Birmingham,* S. Holt, *Brighton and Sussex University Hospitals, Brighton;* J. Kingswood, *Brighton and Sussex University Hospitals, Brighton,* S. Lambie*, Raigmore Hospital, Inverness,* I. MacDougall*, King's College Hospital, London,* I. MacPhee*, St. George's Hospital Medical School, London,* A. Maxwell*, Belfast City Hospital, Belfast,* A. Mikhail*, Morriston Hospital, Swansea,* N. Turner, *Royal Infirmary, Edinburgh,* D. Wheeler*, Center for Nephrology, University College Medical School, London,* M. Wilkie*, Royal Hallamshire Hospital, Sheffield,* D. Zehnder*, UHCW MHS TRUST, Coventry;* ***United States of America:*** S. Adler, *Nephrology Associates of Westchester, Hawthorne, NY,* D. Battle, *Northwestern University, the Feinberg School of Medicine, Chicago, IL,* W. Bennett, *Northwest*

Renal Clinic, Inc., Portland, OR, B. Berger, *University Hospitals of Cleveland, Cleveland, OH,* J. Blumenfeld, *The Rogosin Institute, New York, NY,* P. Bolin, *East Carolina University, Greenville, NC,* R. Browder, *Charleston Nephrology Associates, N. Charleston, SC,* A. Chapman, *Emory University Hospital, Atlanta, GA,* M. Culpepper, *University of South Alabama, Mobile, AL,* N. Dahl, *Yale University School of Medicine, New Haven, CT,* C. Edelstein, *University of Colorado Health Sciences Center, Aurora, CO,* D. Fischer*, Kidney & Hypertension Center, Cincinnati, OH,* S. Goral*, University of Pennsylvania, Philadelphia, PA,* M. Kaplan*, Nephrology Associates, Nashville, TN,* K. Kaveh*, Coastal Nephrology Associates, Port Charlotte, FL,* M. Koren*, Jacksonville Center for Clinical Research, Jacksonville, FL,* R. Lafayette*, Stanford University Medical Center, Stanford, CA,* W. Bibb Lamar, *Coastal Clinical Research, Mobile, AL,* J. Lee, *Apex Research of Riverside, Riverside, CA,* R. Mahnensmith, *Yale University Medical Schoo, New Haven, CT,* P. Nachman, *University of North Carolina, UNC Kidney Center, Chapel Hill, NC,* R. Perrone*, Tufts Medical Center, Boston, MA,* J. Petersen, *Stanford University Medical Center, Stanford, CA,* J. Radhakrishnan*, Columbia University Medical Center, New York, NY,* M. Roppolo*, Renal Associates of Baton Rouge, Baton Rouge, LA,* M. Rosner, *University of Virginia, Nephrology Clinical Research Center, Charlottesville, VA,* G. Schulman*, Vanderbilt University Medical School, Nashville, TN,* L. Steed*, Northwest Renal Clinic, Inc., Portland, OR,* T. Steinman*, Beth Israel Deaconness Medical Center, Boston, MA,* V. Torres*, Mayo Clinic, Rochester, MN,* J. Tuazon, *Northwestern University, Chicago, IL,* R. Venuto*, Erie County Medical Center, Buffalo, NY,* T. Watnick*, Johns Hopkins School of Medicine, Baltimore, MD,* F. Winklhofer*, University of Kansas Medical Center, Kansas City, KS*

Figure S1: Annual Treatment Effects of Tolvaptan on Total Kidney Volume Differences in least-squares (LS) mean TKV changes for tolvaptan versus placebo groups by year. “ITT, within treatment period” includes data from subjects having TKV measurements within the protocol-specified 14-day since last dose window while the “ITT, on-drug” includes subjects having their MRI while taking drug. The larger improvement over placebo within Year 1, where tolvaptan actually reduces mean TKV, is consistent with prior reports of 2-4% reductions in TKV within 1-3 weeks of starting treatment. In-vivo and ex-vivo measurements of the effect of tolvaptan on human cysts implicate reduced fluid secretion into the cysts as the most likely mechanism.[1-4] This effect on TKV partially reverses within 3 weeks of drug discontinuation, explaining the difference between the “ITT, within treatment period” and “ITT, on-drug” analysis for Year 3. Over 3 years, an accumulating non-secretory difference of about 6% can be attributed to slower and more persistent tolvaptan effects. This difference, averaging approximately 2% per year, is consistent with inhibition of cyst cell proliferation, which has also been demonstrated in animal and ex-vivo human models.[4,5-8]

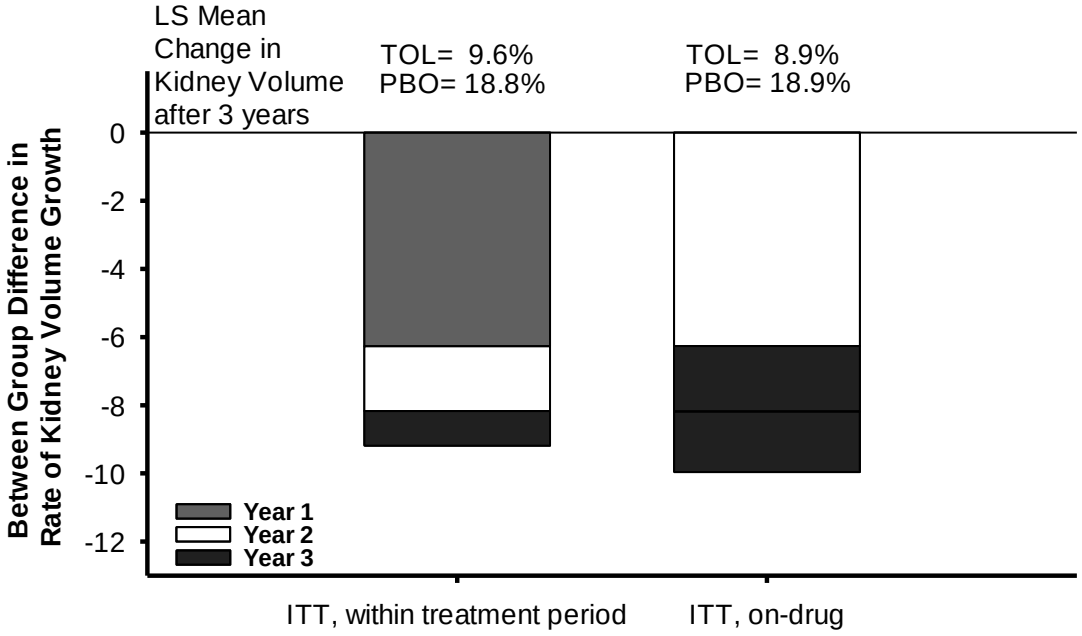
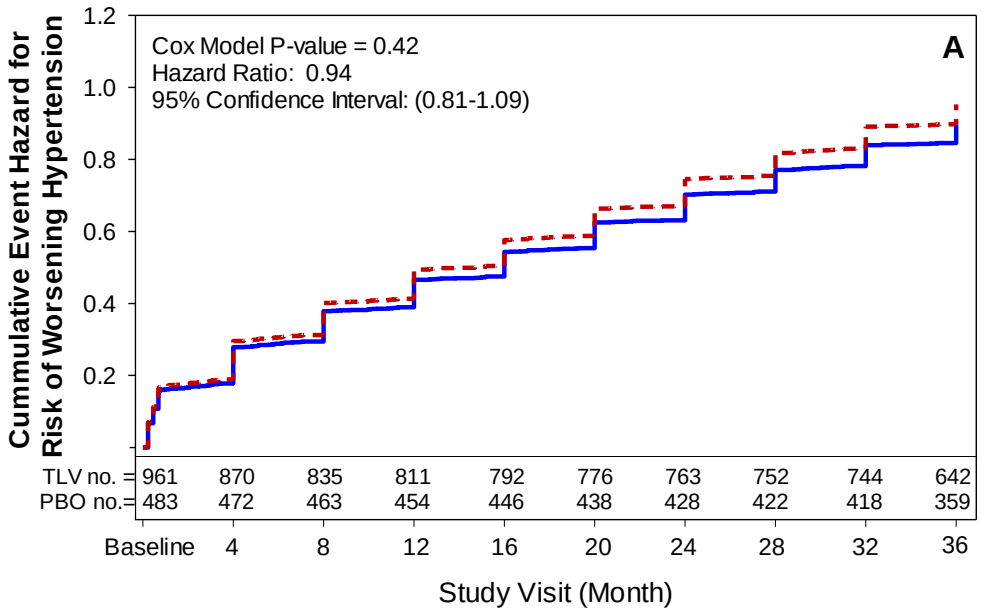


Figure S2. Effect of Tolvaptan on Time to Multiple Worsening Hypertension or Albuminuria Outcomes. Cumulative hazard function of time to multiple events of worsening hypertension (Panel A). Cumulative hazard function of time to multiple events of worsening albuminuria (Panel B). TOL denotes tolvaptan (blue), PBO denotes placebo (red).



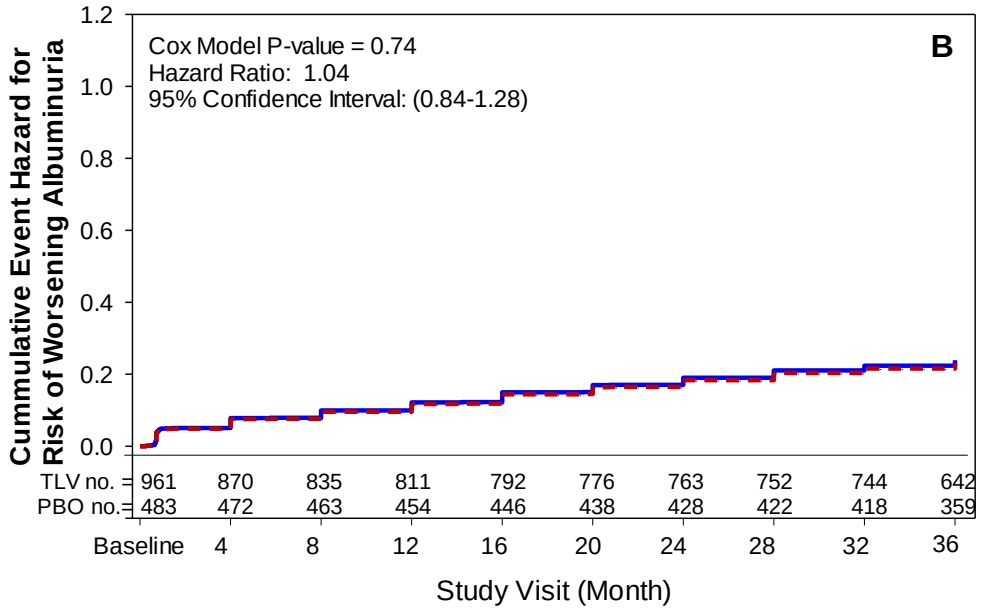
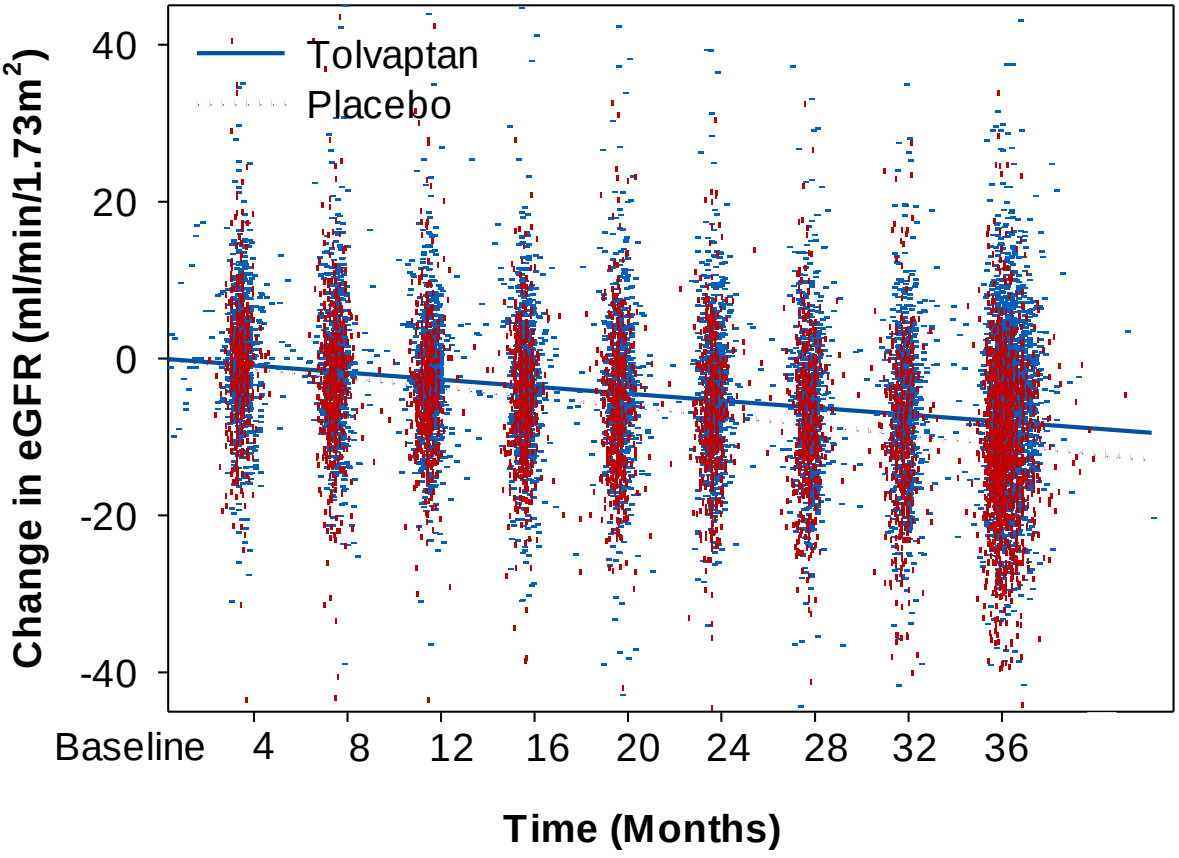


Figure S3. Effect of Tolvaptan on Annual Slope of Estimated Glomerular Filtration Rate (eGFR). Annual slope of eGFR estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation; intent-to-treat, within-treatment period, and individual patient data included in slope calculations; annual difference in slope (95% CI) = 0.98 ml/min/1.73 m^2 (0.60 to 1.36); P<0.001.



Other Secondary End Points

Other protocol-specified secondary endpoints are summarized below. The non-composite secondary endpoints were tested after the key composite secondary endpoint using a two-sided alpha level of 0.05. These were tested in the sequence presented without adjustment for multiplicity. Results are presented in Table S1.

The secondary endpoint tested first following the slope of kidney function was the change from Baseline for resting mean arterial pressure (MAP) at scheduled clinic visits up to point of exposure to antihypertensive therapy for any reason for subjects who were nonhypertensive at baseline. The analysis was similar to the analysis of the primary endpoint, except that the MAP value, instead of its $\log_{10}$ scale, was used and applied to all the subjects with nonhypertensive status and without taking antihypertensive therapy for any reason at baseline. All the observations, from Baseline up to the values observed just prior to the start of antihypertensive therapy for the subjects who start antihypertensive therapy during the trial, and from Baseline up to the last visit for the subjects who do not need antihypertensive therapy during the trial, were used in the analysis. The analysis of the rate of change in MAP did not yield any trends or statistically significant results in favor of tolvaptan. There was a mean increase in BP of 2.6% in both treatment groups. Subjects had to be nonhypertensive (defined as sBP < 140 mm Hg and dBP < 90 mm Hg and not taking antihypertensive medications at baseline), so the number of subjects included in this analysis was small.

Change from Baseline in kidney pain (Average AUC) as assessed by asking the patient at each trial visit, to rate their kidney pain from the last trial visit on a scale from 0 to 10. All results were incorporated as an average AUC between Baseline and the last visit or the last visit prior to initiating medical or surgical therapy) was analyzed by analysis of covariance (ANCOVA) with factors of treatment and Baseline stratification factors and covariate Baseline pain scale, based on the ITT dataset. The analysis of change from baseline in kidney pain did not yield any trends or statistically significant results in favor of tolvaptan or placebo. While 50.9% of the overall population reported a medical history of kidney pain, only a small proportion of subjects reported pain on this scale at

baseline, with the population mean score mean score <1. This method of assessing kidney pain over an extended time period (4 months between visits) was not sufficient to detect kidney pain in ADPKD, possibly due to the more episodic nature of pain events for most patients with ADPKD.

The next secondary endpoint was time to progress to a) high-pre-hypertension (sBP > 129 and/or dBP > 84), b) hypertension (sBP > 139 and/or dBP > 89 mm Hg), or c) requiring antihypertensive therapy for subjects who were nonhypertensive at Baseline. Analysis of time to recurrent events similar to that used for the key composite secondary endpoint was applied for a comparison of tolvaptan to placebo using nonhypertensive subjects without antihypertensive therapy at Baseline. No difference between treatment groups was observed in the time to hypertensive events in nonhypertensive subjects, similar to what was observed in the change in MAP endpoint.

The final secondary endpoint was the percentage of subjects with clinically sustained decreases of BP leading to a sustained reduction in antihypertensive therapy compared with Baseline at Month 12, 24, and 36 visits for hypertensive subjects taking antihypertensive therapy at Baseline. This endpoint was analyzed by the Cochran-Mantel-Haenszel (CMH) statistic stratified by Baseline stratification factors at Months 12, 24, and 36. All subjects who were hypertensive and took antihypertensive therapy before randomization were included in the analysis. The last observation carried forward dataset was used for this analysis. The primary visit for this endpoint was Month 36. The analyses at Months 12 and 24 were conducted in this order if the analysis at Month 36 was significant. No difference between treatment groups was observed in the percentage of hypertensive subjects with a sustained reduction in antihypertensive therapy.

Table S1. Other Secondary End Point Results		
End Point	**Tolvaptan (N = 961)**	**Placebo (N = 483)**
Change in MAP in Non-hypertensive Subjects		
Number of subjects	129	74
Mean	2.56	2.59
Estimated slope[a]	0.84	1.08
Estimated treatment effect[b]	−0.25	
95% CI	−1.06, 0.57	
P-value[a]	0.55	
Change from Baseline in Average AUC of Kidney Pain Score		
Number of subjects	926	467
LS mean	0.00	0.08
Mean	0.06	0.09
Difference[c]	−0.08	
95% CI[c]	−0.20, 0.03	
P-value[c]	0.16	
Hypertensive Progression Events in Nonhypertensive Subjects		
Number of subjects	174	79
Events/100 follow-up years	31.80	29.60
HR[d]	0.99	
95% CI[d]	0.81, 1.23	
P-value[d]	0.97	
Reduction in Antihypertensive Therapy in Hypertensive Subjects at Month 36		
Number of subjects	481	267
Number of decreases in BP (%)	30 (6.24)	15 (5.62)
Relative risk of reduction[e]	1.10	
95% CI[e]	0.60, 2.02	
P-value[e]	0.75	

[a] Derived from testing the time treatment interaction using linear mixed model in which both intercept and slope are fixed and random effects.

[b] An estimate of the difference between the slopes of tolvaptan and placebo.

[c] Derived from analysis of covariance with factors of treatment and baseline stratification factor interaction and covariate kidney pain baseline

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

[e] Derived using Cochran-Mantel-Haenszel test stratified by trial center.

MAP denotes mean arterial pressure. AUC denotes area under the curve.

Table S2 presents the adverse events reported in at least 2% of subjects during the course of the 3-year trial as classified using the Medical Dictionary for Regulatory Activities (MedDRA).

Table S2: Incidence of Adverse Events in at Least 2% of Subjects in Any Group by System Organ Class and MedDRA Preferred Term in the TEMPO 3:4 Trial

System Organ Class MedDRA Preferred Term	Tolvaptan (N = 961) n (%)	Placebo (N = 483) n (%)
Blood and Lymphatic System Disorders		
Anaemia	27 (2.8)	24 (5.0)
Cardiac Disorders		
Palpitations	34 (3.5)	6 (1.2)
Ear and Labyrinth Disorders		
Vertigo	24 (2.5)	18 (3.7)
Gastrointestinal Disorders		
Abdominal discomfort	29 (3.0)	10 (2.1)
Abdominal distension	47 (4.9)	16 (3.3)
Abdominal pain	62 (6.5)	32 (6.6)
Abdominal pain upper	63 (6.6)	42 (8.7)
Constipation	81 (8.4)	12 (2.5)
Diarrhoea	128 (13.3)	53 (11.0)
Dry mouth	154 (16.0)	60 (12.4)
Dyspepsia	76 (7.9)	16 (3.3)
Gastrooesophageal reflux disease	43 (4.5)	16 (3.3)
Nausea	98 (10.2)	57 (11.8)
Toothache	10 (1.0)	12 (2.5)
Umbilical hernia	21 (2.2)	7 (1.4)
Vomiting	79 (8.2)	40 (8.3)
General Disorders and Administration Site Conditions		
Asthenia	57 (5.9)	27 (5.6)
Chest pain	42 (4.4)	12 (2.5)
Fatigue	131 (13.6)	47 (9.7)
Malaise	24 (2.5)	10 (2.1)
Oedema peripheral	81 (8.4)	46 (9.5)
Pyrexia	45 (4.7)	42 (8.7)
Thirst	531 (55.3)	99 (20.5)
Hepatobiliary Disorders		
Hepatic cyst	13 (1.4)	10 (2.1)
Immune System Disorders		
Seasonal allergy	26 (2.7)	10 (2.1)
Infections and Infestations		
Bronchitis	58 (6.0)	33 (6.8)
Cystitis	11 (1.1)	12 (2.5)
Ear infection	22 (2.3)	7 (1.4)
Gastroenteritis	54 (5.6)	21 (4.3)

Table S2: Incidence of Adverse Events in at Least 2% of Subjects in Any Group by System Organ Class and MedDRA Preferred Term in the TEMPO 3:4 Trial

System Organ Class MedDRA Preferred Term	Tolvaptan (N = 961) n (%)	Placebo (N = 483) n (%)
Gastroenteritis viral	20 (2.1)	6 (1.2)
Influenza	75 (7.8)	38 (7.9)
Nasopharyngitis	211 (22.0)	111 (23.0)
Pharyngitis	16 (1.7)	16 (3.3)
Renal cyst infection	9 (0.9)	13 (2.7)
Rhinitis	14 (1.5)	11 (2.3)
Sinusitis	53 (5.5)	23 (4.8)
Upper respiratory tract infection	82 (8.5)	42 (8.7)
Urinary tract infection	81 (8.4)	61 (12.6)
Viral infection	21 (2.2)	13 (2.7)
Injury, Poisoning and Procedural Complications		
Ligament sprain	14 (1.5)	11 (2.3)
Investigations		
Alanine aminotransferase increased	39 (4.1)	17 (3.5)
Aspartate aminotransferase increased	36 (3.7)	16 (3.3)
Blood creatinine increased	135 (14.0)	71 (14.7)
Blood urea increased	10 (1.0)	12 (2.5)
BUA increased	24 (2.5)	6 (1.2)
Gamma-glutamyl transferase increased	23 (2.4)	11 (2.3)
Weight decreased	46 (4.8)	16 (3.3)
Weight increased	46 (4.8)	19 (3.9)
Metabolism and Nutrition Disorders		
Decreased appetite	69 (7.2)	5 (1.0)
Dehydration	18 (1.9)	11 (2.3)
Gout	28 (2.9)	7 (1.4)
Hypercholesterolaemia	26 (2.7)	12 (2.5)
Hyperglycaemia	6 (0.6)	10 (2.1)
Hypernatraemia	27 (2.8)	5 (1.0)
Hyperuricaemia	37 (3.9)	9 (1.9)
Polydipsia	100 (10.4)	17 (3.5)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	69 (7.2)	28 (5.8)
Back pain	133 (13.8)	88 (18.2)
Flank pain	11 (1.1)	10 (2.1)
Muscle spasms	35 (3.6)	17 (3.5)
Musculoskeletal pain	37 (3.9)	17 (3.5)
Myalgia	50 (5.2)	16 (3.3)
Neck pain	25 (2.6)	12 (2.5)
Pain in extremity	42 (4.4)	27 (5.6)
Tendonitis	16 (1.7)	10 (2.1)
Nervous System Disorders		
Dizziness	109 (11.3)	42 (8.7)

Table S2: Incidence of Adverse Events in at Least 2% of Subjects in Any Group by System Organ Class and MedDRA Preferred Term in the TEMPO 3:4 Trial		
System Organ Class MedDRA Preferred Term	**Tolvaptan (N = 961) n (%)**	**Placebo (N = 483) n (%)**
Dysgeusia	21 (2.2)	7 (1.4)
Headache	241 (25.1)	121 (25.1)
Hypoaesthesia	15 (1.6)	12 (2.5)
Migraine	22 (2.3)	10 (2.1)
Paraesthesia	19 (2.0)	13 (2.7)
Psychiatric Disorders		
Anxiety	30 (3.1)	8 (1.7)
Depression	42 (4.4)	21 (4.3)
Insomnia	55 (5.7)	21 (4.3)
Stress	9 (0.9)	10 (2.1)
Renal and Urinary Disorders		
Haematuria	75 (7.8)	68 (14.1)
Nephrolithiasis	15 (1.6)	14 (2.9)
Nocturia	280 (29.1)	63 (13.0)
Pollakiuria	223 (23.2)	26 (5.4)
Polyuria	368 (38.3)	83 (17.2)
Renal pain	260 (27.1)	171 (35.4)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	77 (8.0)	38 (7.9)
Dyspnoea	22 (2.3)	6 (1.2)
Oropharyngeal pain	46 (4.8)	18 (3.7)
Skin and Subcutaneous Tissue Disorders		
Dry skin	47 (4.9)	8 (1.7)
Eczema	19 (2.0)	3 (0.6)
Pruritus	33 (3.4)	13 (2.7)
Rash	40 (4.2)	9 (1.9)
Vascular Disorders		
Hypertension	310 (32.3)	174 (36.0)
Hypotension	30 (3.1)	15 (3.1)

Table S3. Summary of Laboratory Parameters							
Parameter, mean (SD), range	**Baseline**	**End of Titration**	**Month 12**	**Month 24**	**Month 36**	**Follow-up #2**	**PCS Change n (%)**
Serum Sodium (mEq/L)							
Tolvaptan	140.4 (2.1) 132-150	142.6 (2.6) 136-160	141.9(2.6) 131-162	141.7 (2.5) 131-153	141.6 (2.6) 128-156	140.0 (2.3) 128-148	Decreased: 1 (0.1) Increased: 38 (4.0)
Placebo	140.2 (2.0) 134-149	140.3 (2.2) 135-150	140.5(2.1) 133-150	140.3 (2.4) 131-151	140.3 (2.3) 131-148	140.3 (2.3) 134-151	Decreased: 1 (0.2) Increased: 7 (1.4)
Serum Creatinine (mg/dL)							
Tolvaptan	1.05 (0.3) 0.38-2.29	1.11 (0.3) 0.52-2.55	1.16 (0.4) 0.50-3.25	1.19 (0.4) 0.53-3.13	1.25 (0.5) 0.50-4.09	1.21 (0.5) 0.49-3.79	Increased: 159 (16.7)
Placebo	1.04 (0.3) 0.20-2.82	1.06 (0.3) 0.48-3.44	1.13 (0.4) 0.28-4.33	1.17 (0.5) 0.23-4.34	1.26 (0.6) 0.50-5.07	1.27 (0.6) 0.50-5.38	Increased: 101 (21.0)
Blood Urea Nitrogen (mg/dL)							
Tolvaptan	19.4 (5.4) 7-46	15.2 (5.7) 4-48	15.9 (6.0) 5-41	17.0 (6.6) 3-59	18.3 (7.6) 5-61	21.0 (7.4) 7-65	Increased: 150 (15.6)
Placebo	19.3 (5.4) 8-52	18.9 (5.7) 8-56	19.8 (5.7) 7-49	20.6 (6.6) 8-64	21.8 (7.9) 8-75	22.0 (7.6) 8-67	Increased: 142 (29.4)
Uric Acid (mg/dL)							
Tolvaptan	5.7 (1.7) 1.8-13.1	6.4 (1.8) 2.5-12.9	6.5 (1.8) 2.1-11.7	6.5 (1.8) 2.5-13.2	6.5 (1.7) 2.7-12.6	5.9 (1.7) 2.3-11.5	Increased: 59 (6.2)
Placebo	5.5 (1.5) 1.9-10.9	5.6 (1.6) 2.0-10.7	5.7 (1.6) 2.4-13.0	5.8 (1.6) 2.3-11.6	5.9 (1.6) 2.2-10.6	5.9 (1.6) 2.2-11.6	Increased: 8 (1.7)
ALT (SGPT) (IU/L)							
Tolvaptan	21.3 (12.7) 6-140	26.5(106.4) 4-3179	22.8(16.6) 5-213	21.6 (13.0) 5-122	20.8 (12.3) 6-138	21.4 (11.5) 6-100	Increased: 47 (4.9)
Placebo	21.0 (13.0) 5-188	20.4 (10.1) 6-76	20.7(11.7) 6-130	20.7 (11.7) 6-119	20.1 (9.0) 5-58	19.7 (10.0) 6-108	Increased: 6 (1.2)
AST (SGOT) (IU/L)							
Tolvaptan	20.9 (6.7) 9-78	25.8(120.6) 10-3624	22.1 (9.4) 10-207	21.5 (7.4) 10-89	21.9 (15.6) 10-399	21.4 (6.6) 11-72	Increased: 31 (3.2)
Placebo	21.0 (9.6) 10-181	20.3 (5.6) 9-52	20.8 (6.7) 8-68	21.3 (8.0) 9-120	20.8 (5.8) 8-45	20.9 (6.6) 8-62	Increased: 4 (0.8)
Bilirubin, Total (mg/dL)							
Tolvaptan	0.54 (0.27) 0.2-2.5	0.50 (0.25) 0.2-2.4	0.52(0.24) 0.2-2.2	0.51 (0.25) 0.2-2.7	0.50 (0.25) 0.20-3.0	0.50 (0.24) 0.2-2.8	Increased: 9 (0.9)

Table S3. Summary of Laboratory Parameters							
Parameter, mean (SD), range	**Baseline**	**End of Titration**	**Month 12**	**Month 24**	**Month 36**	**Follow-up #2**	**PCS Change n (%)**
Placebo	0.57 (0.32) 0.2-2.9	0.54 (0.32) 0.2-3.1	0.55(0.33) 0.3-3.7	0.53 (0.30) 0.2-2.6	0.51 (0.27) 0.2-2.8	0.51 (0.24) 0.2-2.0	Increased: 9 (1.9)
Albumin/Creatinine Ratio (mg/mmol)							
Tolvaptan	7.2 (14.3) 0.5-207.9	7.4 (15.2) 0.3-235.8	7.0 (11.8) 0.3-127.1	7.2 (13.3) 0.0-128.9	8.3 (20.7) 0.3-290.6	7.5 (18.7) 0.0-219.3	Not Applicable
Placebo	8.6 (21.7) 0.4-220.8	7.1 (15.8) 0.0-189.6	8.9 (23.1) 0.5-232.5	9.2 (25.1) 0.0-296.4	9.4 (19.0) 0.5-209.6	9.1 (20.1) 0.0-219.3	Not Applicable

PCS denotes Potentially Clinically Significant. ALT (SGPT) denotes alanine transaminase (serum glutamic pyruvic transaminase). AST (SGOT) denotes aspartate transaminase (serum glutamic oxaloacetic transaminase), Plus–minus values are mean ±SD.

References

1. Higashihara E, Torres VE, Chapman AB, et al; TEMPO 2:4 and 156-05-002 Study Investigators. Tolvaptan in autosomal dominant polycystic kidney disease: three years experience. Clin J Am Soc Nephrol. 2011;6:2499–507.
2. Irazabal MV, Torres VE, Hogan MC, et al. Short-term effects of tolvaptan on renal function and volume in patients with autosomal dominant kidney disease. Kidney Int 2011;80:295–301.
3. Clinicaltrials.gov trial #NCT01336972: Short-term renal hemodynamic effects of tolvaptan in subjects with autosomal dominant polycystic kidney disease. Boertien WE, Meijer E, de Jong PE, et al. Short-term effects on efficacy parameters with tolvaptan in subjects with ADPKD at various levels of kidney function. Kidney Week 2012, San Diego (abstract).
4. Reif GA, Yamaguchi T, Nivens E, Fujiki H, Pinto CS, Wallace DP. Tolvaptan inhibits ERK-dependent cell proliferation, Cl secretion, and in vitro cyst growth of human ADPKD cells stimulated by vasopressin. Am J Physiol Renal Physiol 2011;301:F1005–13.
5. Gattone VH, Maser RL, Tian C, Rosenberg JM, Branden MG. Developmental expression of urine concentration–associated genes and their altered expression in murine infantile-type polycystic kidney disease. Develop Gen 1999:24;309–18.
6. Gattone VH, Wang X, Harris PC, Torres VE. Inhibition of renal cystic disease development and progression by a vasopressin V2 receptor antagonist. Nature Med 2003:9:1323–6.
7. Torres VE, Wang X, Qian Q, Somlo S, Harris PC, Gattone VH II. Effective treatment of orthologous model of autosomal dominant polycystic kidney disease. Nature Med 2004;10:363–4.
8. Wang X, Gattone V II, Harris PC, Torres VE. Effectiveness of vasopressin V2 receptor antagonists OPC-31260 and OPC-41061 on polycystic kidney disease development in the PCK rat. J Am Soc Nephrol 2005;16:846–51.