Synopsis

Clinical Report Synopsis for Protocol 156-04-251
EudraCT No. 2006-002768-24

Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc (OPDC)

Name of Investigational Medicinal Product: Tolvaptan (OPC-41061)

Protocol Title: A Phase 3, Multi-center, Double-blind, Placebo-controlled, Parallel-arm Trial to Determine Long-term Safety and Efficacy of Oral Tolvaptan Tablet Regimens in Adult Subjects with Autosomal Dominant Polycystic Kidney Disease

Coordinating Investigator and Trial Site:

Vicente Torres, MD, PhD	Mayo Clinic 200 First Street SW Rochester, MN 55905, USA

A total of 135 trial sites were initiated for this trial; of these, 132 trial sites screened at least 1 subject and 129 trial sites randomized at least 1 subject. This trial was conducted in 1445 subjects at 129 trial sites in the following 15 countries: United States (379 subjects at 29 sites), Canada (44 subjects at 3 sites), Argentina (52 subjects at 5 sites), Australia (72 subjects at 8 sites), Belgium (69 subjects at 3 sites), Denmark (10 subjects at 2 sites), France (115 subjects at 9 sites), Germany (158 subjects at 5 sites), Italy (70 subjects at 5 sites), Netherlands (68 subjects at 2 sites), Poland (93 subjects at 9 sites), Romania (35 subjects at 3 sites), Russia (31 subjects at 5 sites), United Kingdom (72 subjects at 11 sites), and Japan (177 subjects at 30 sites).

Publications: Torres VE, Meijer E, Bae KT, Chapman AB, Devuyst O, Gansevoort RT, et al. Rationale and design of the TEMPO (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes) 3-4 Study. Am J Kidney Dis. 2011;57(5):692-9.

Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, et al for the TEMPO 3:4 Trial Investigators. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med. 2012 Nov 3. [Epub ahead of print.] doi:10.1056/NEJMoa1205511.

Trial Period:

Date of first signed informed consent: 25 Jan 2007

Date of last trial observation: 23 Jan 2012

Clinical Phase/Trial Type: Phase 3/therapeutic confirmatory

Objectives: The primary objective of this trial was to evaluate the long-term efficacy of tolvaptan in autosomal dominant polycystic kidney disease (ADPKD) through the rate of kidney volume change (%) for tolvaptan subjects compared with placebo subjects. The key secondary objective was to evaluate long-term efficacy of tolvaptan in slowing the progression of ADPKD through a composite of clinical outcome events (ie, progressive hypertension, renal pain, albuminuria, and renal function).

Other secondary objectives were to evaluate long-term efficacy of tolvaptan in ADPKD using noncomposite clinical markers of ADPKD progression; to evaluate the long-term safety of tolvaptan through standard clinical measures; and to evaluate the pharmacokinetic (PK), pharmacodynamic (PD), and exploratory parameters for tolvaptan in ADPKD.

Methodology: This was a phase 3, multicenter, double-blind, placebo-controlled, parallel-arm trial to determine long-term safety, tolerability, and efficacy of split-dose oral regimens of tolvaptan tablets in adult subjects with ADPKD. After trial eligibility was determined and baseline events were established, subjects were stratified, randomized (2:1 tolvaptan:placebo), and began treatment. During the 3-week titration phase, tolvaptan or placebo tablets (as multiples of 15 mg or 30 mg) were titrated in weekly intervals from lowest to highest tolerated levels given in split-dose regimens of 45 mg AM/15 mg PM (45/15 mg), 60 mg AM/30 mg PM (60/30 mg), or 90 mg AM/30 mg PM (90/30 mg). As soon as a subject could not tolerate a dose, the titration phase was considered complete and the maintenance phase began at the dose level tolerated for up to Month 36. Subjects were allowed to down-titrate at any time, as indicated for safety or tolerability. During the maintenance phase, investigators could increase a subject's dosage up to the maximum dose of 90/30 mg with medical monitor approval if a change in clinical status, lifestyle, or concomitant treatment suggested that a higher dose could be tolerated.

Number of Subjects: This trial was planned to enroll between 1200 and 1500 men or women with a diagnosis of ADPKD in the Americas, Japan, Europe, and the rest of the world. The sample size needed for the key secondary composite endpoint was unknown at the planning stage of this trial. Since no reliable information on the event rates of the key secondary composite endpoint, or its components, was available in the scientific literature, this provided the rationale for the planned, blinded sample size recalculation. Blinded sample size recalculation was prospectively defined in the protocol to occur after either 1000 subjects had been enrolled or when at least 200 subjects had completed their 12-month visit, whichever came first. Recalculation was conducted on 20 Oct 2008 based on available data after 1000 subjects had been enrolled. This recalculation suggested that a total of 1400 subjects would be an appropriate sample size for this trial. This sample size falls into the sample size range of 1200 to 1500 subjects originally specified in the protocol.

Of 2122 subjects screened at 132 investigative sites, 1445 subjects were enrolled at 129 investigative sites and randomly assigned in a 2:1 ratio to the tolvaptan and placebo treatment groups.

Diagnosis and Main Criteria for Inclusion: Men and women (age of legal adulthood [minimum of 18] to 50 years) with a confirmed clinical diagnosis of ADPKD, relatively preserved renal function (glomerular filtration rate [GFR], approximated as creatinine clearance derived from serum creatinine, ≥ 60 mL/min, estimated using the Cockcroft-Gault formula), and a total kidney volume (TKV; both kidneys;) of ≥ 750 mL were enrolled.

Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration, Batch or Lot No(s): Tolvaptan was supplied as 15 mg and 30 mg tablets. Placebo was supplied as matching tablets. Tablets were round and white and provided on blister cards. Tolvaptan (or placebo) tablets were given orally twice daily for 3 years. Dosing was to occur on waking and approximately 9 hours later, regardless of meals. Tolvaptan and placebo tablets were manufactured by Otsuka Pharmaceutical Company, Ltd, and were supplied to Almac Clinical Services (Souderton, PA) as bulk for packaging and site distribution.

Tolvaptan placebo lot numbers packaged for the trial:
09L70P000C, 09L70P000B, 09F71P000B, 09F71P000A, 09D70P000A, 09D70P000B, 09D70P000C, 08E88P000A, 08E88P000B, 08E88P000C, 07I95P000, 06H90P000A, 06H90P000B, 06H90P000C, 06H90P000D, 06L80P000B, 06L80P000C, 05I84P000C, 06B75P000A, 06B75P000B, 04H00P000F, 06L80P000A

Tolvaptan 15 mg lot numbers packaged for the trial:
10D85A015D, 09F78A015A, 09F78A015B, 07A74A015B, 07A74A15C, 09D77A015A, 09D77A015B, 09D77A015C, 08E98A015A, 08E98A015B, 08E98A015C, 07I96A015, 06H90A015A, 06H90A015B, 06H90A015C, 04J88A015B, 05D73A015B, 07A74A015A

Tolvaptan 30 mg lot numbers packaged for the trial:
10D97A030C, 10D97A030A, 09F85A030B, 09F85A030A, 09D84A030C, 08F80A030A, 06H90A030A, 06H90A030B, 07A88A030B, 06B75A030C, 08F80A030C, 07I97A030, 06B75A030A, 08F80A030B, 09D84A030B, 09D84A030A, 07A88A030C, 07A88A030A

Of the lots packaged for the trial, there are 3 lot numbers (10D85A015D, 10D97A030C, and 09L70P000C) that were not dispensed to any subjects.

Reference Product, Dose, Dosage Regimen, Formulation, Mode of Administration, Batch or Lot No(s): Not applicable

Trial Assessments:

- Screening: Medical history (non-ADPKD related), self and family history of ADPKD (confirming diagnosis)
- Efficacy: Magnetic resonance imaging (MRI) of both kidneys, blood pressure (BP), serum creatinine, spot urine albumin/creatinine ratio, renal pain scale, and polycystic kidney disease (PKD) clinical outcomes
- Safety: Vital signs, adverse events (AEs), clinical laboratory tests, electrocardiograms (ECGs), and pregnancy tests for women of childbearing potential
- Pharmacokinetic: Blood samples for tolvaptan and its DM-4103 and DM-4107 metabolites
- Pharmacodynamic: Urine samples for trough spot urine osmolality and monocyte chemoattractant protein-1 (MCP-1), blood samples for serum cystatin C and uric acid, and urine and blood samples for exploratory development of other biomarkers of ADPKD disease progression

Criteria for Evaluation:

Primary Efficacy Endpoint:

Rate of kidney volume (total, both kidneys) change (normalized as percentage) for tolvaptan (combining all doses) relative to placebo.

Secondary Outcome Endpoints:

Key Secondary Composite Efficacy Endpoint: Time to multiple investigator-reported ADPKD clinical progression events for tolvaptan (combining all doses) relative to placebo while on treatment, including:

- Onset or progression of hypertension (HTN; BP measurement, need for intensification of HTN treatment),
- Severe renal pain (requiring medical intervention),
- Worsening albuminuria (by category), and
- Worsening renal function (25% decrease in 1/serum creatinine as a measure of renal function from steady-state postdose baseline value).

Other Secondary Efficacy Endpoints (tested sequentially for tolvaptan compared with placebo):

1) Rate of renal function change from postdose baseline value (End of Titration [EOT]) to last on-drug trial visit. The primary measure was 1/serum creatinine. Additional exploratory measures were based on estimates using demographic and/or anthropomorphic variables, ie, creatinine clearance by Cockcroft-Gault ($CrCL_{CG}$), and estimated GFR by Modification of Diet in Renal Disease ($eGFR_{MDRD}$) or Chronic Kidney Disease Epidemiology Collaboration ($eGFR_{CKD\text{-}EPI}$).

2) For subjects who were nonhypertensive at baseline, change from baseline for resting mean arterial pressure at scheduled clinic visits up to the point of exposure to antihypertensive therapy for any reason.
3) Change from baseline in renal pain as assessed by a 0 to 10 pain scale as average area under the concentration-time curve between baseline and the last trial visit or the last visit prior to initiating medical (eg, narcotic or antinociceptives [eg, tricyclic antidepressants]) or surgical therapy for pain.
4) For subjects who were nonhypertensive at baseline, time to progress to a) high-pre-HTN (systolic blood pressure [sBP] > 129 mmHg and/or diastolic blood pressure [dBP] > 84 mmHg), b) HTN (sBP > 139 mmHg and/or dBP > 89 mm Hg), or c) requiring antihypertensive therapy.
5) For subjects who were taking antihypertensive therapy at baseline, percentage with clinically sustained decreases of BP leading to a sustained reduction in antihypertensive therapy compared with baseline (while taking investigational product [IMP]) at visits on Months 12, 24, and 36 for hypertensive subjects.

Safety Endpoints:

Safety endpoints analyzed included a descriptive summary of:
1) Reported treatment-emergent AEs (TEAEs)
2) Vital signs
3) Clinical laboratory tests
4) ECGs

Pharmacokinetic Endpoint:

Sparse samples were taken for determination of tolvaptan and metabolite plasma concentrations (DM-4103 and DM-4107).

Pharmacodynamic Endpoints:

For tolvaptan compared with placebo:
5) For urine, trough spot osmolality and MCP-1 concentrations
6) For blood, cystatin C and uric acid concentrations

Exploratory Endpoints:

7) Fasting urine osmolality (at randomization and Follow-up Visit 2 only)
8) PKD Outcomes and medical resource utilization. Analysis of additional events attributed to ADPKD for tolvaptan subjects compared with placebo subjects

Statistical Methods:

Efficacy:

Primary Endpoint: The prospectively defined primary endpoint in this trial was the rate of TKV change (normalized as percentage) from baseline. In order to derive the primary endpoint, MRI was performed to evaluate TKV at baseline (31 to approximately 14 days prior to randomization) and at Month 12, 24, and 36/Early Termination (ET) visits. All data of intent-to-treat subjects who had kidney volume observations both at baseline and postbaseline during the double-blind treatment period were used in the analysis of efficacy. For the purpose of statistical modeling, time to MRI from randomization was treated as a continuous variable, expressed as years from the date of the baseline MRI visit to the date of the MRI visit, ie, (date of MRI visit – date of baseline MRI visit)/365.25. To reduce heterogeneity in variance and achieve linearity over time, $\log_{10}$ transformation was applied to the TKV data. The log-transformed TKV repeated-measures data were fitted to a linear mixed-effect model, which has fixed effects of treatment, time, treatment time interaction, and covariate $\log_{10}$ transformed baseline, and random effects of intercept and time. The variance-covariance matrix of the random effects was assumed to have unknown structure. A "sandwich" variance-covariance estimator was used in statistical testing. The test of the primary null hypothesis was provided by testing the contrast of the treatment time interaction using the Wald test. A significance level of 0.05 (two-sided) was used to declare statistical significance. In addition, estimates of the contrast and its 95% confidence interval (CI) were obtained.

In addition to the primary analysis provided above, a mixed model repeated measures (MMRM) sensitivity analysis was applied to the repeated measures of percent change from baseline in TKV. A least squares mean difference of the 2 treatment groups at Year 3 under the MMRM was used to estimate the treatment effect at Year 3. The MMRM included stratification factors (hypertensive status, kidney volume status, baseline creatinine clearance status, and by geographic regions), visit, treatment, and treatment visit interaction as class variables and baseline kidney volume as a covariate. The observed cases (OC) dataset within the treatment period was used in this MMRM analysis. The OC dataset consists of data obtained from subjects who were evaluated at the Baseline visit, postbaseline visits during the trial, and the end of treatment (Month 36)/ET visit. Other sensitivity analyses, including imputation to account for data missing at random or missing not at random (MNAR), were performed and confirmed the robustness of the principal analysis.

Key Secondary Composite Endpoint: Clinically important complications of progressing ADPKD likely to be influenced by reducing the rate of cyst development and expansion were grouped into a composite endpoint. The prospectively defined key secondary composite endpoint was time to multiple ADPKD clinical progression events: onset of or progressing HTN, severe renal pain, worsening albuminuria, and worsening renal function. Analysis of time to multiple (recurrent) events following the Anderson-Gill approach of an extended Cox model was utilized for the key secondary composite endpoint to provide a point estimate of the hazard ratio (ie, intensity ratio) and its p-value

with the p-value provided by the Wald test using a sandwich estimate of the covariance matrix. Treatment was the sole variable in the model. The primary analysis of the key secondary composite endpoint included all renal function events observed from Week 3/EOT to the end of double-blind treatment, and all other events observed during double-blind treatment starting from the date of first dose of IMP. The second analysis was a sensitivity analysis of all events observed during double-blind treatment from Week 3/ EOT to the end of double-blind treatment, using Week 3/EOT as the new baseline for all components. A significance level of 0.05 (two-sided) was used to declare statistical significance for the key secondary composite endpoint, for the purpose of subsequent sequential hierarchical analysis.

An independent Clinical Events Committee reviewed ADPKD clinical progression events to determine if changes were consistent with a clinically meaningful definition of disease progression. A sensitivity analysis used all adjudicated events observed during double-blind treatment. Several sensitivity analyses were performed regarding robustness and missing data for the renal function and pain clinical event data, such as subgroup analyses, using subject outcome data and multiple imputation method for missing data, and confirmed the robustness of the principal analysis.

Other Secondary Endpoints: The other secondary efficacy endpoints were tested sequentially after the key secondary composite efficacy endpoint using a two-sided alpha level of 0.05. Where positive, additional sensitivity analyses were performed to confirm the robustness of the principal result. Once a negative result ($p > 0.05$) was obtained, further analyses were considered nominal and not otherwise statistically meaningful.

Safety: Safety analyses were conducted based on the safety dataset, which is defined as all subjects who consumed at least 1 dose of trial medication. Safety variables analyzed included clinical laboratory tests, vital signs, and AEs. In general, summary statistics of changes from baseline were provided for safety variables based on all available data. Since this Clinical Study Report represents the core of primary safety data for this indication, additional post-hoc analyses were performed. Analyses of TEAEs were conducted to assess frequency of TEAEs, temporal onset of TEAEs, and important subgroups.

Pharmacokinetics: Tolvaptan and metabolite (DM-4103 and DM-4107) concentrations were determined using high-performance liquid chromatography with tandem mass spectrometry detection. For each PK sample, the time postdose was calculated using the sampling time and the time of the previous dose. The highest concentration of DM-4107 was determined. DM-4103 has a long half-life, approximately 180 hours, making DM-4103 concentrations a good marker of compliance; a concentration (PK) analysis of compliance was conducted.

Pharmacodynamics: Descriptive statistics of absolute values at each visit and change from the last predose value were determined for trough urine osmolality, urine MCP-1 to creatinine concentration ratios, and plasma concentrations of cystatin C and uric acid. The predose fasting spot urine osmolality was used as the baseline value for the trough spot urine osmolality assessments. Additionally, serum creatinine concentrations and urine albumin to urine creatinine concentration ratios were analyzed as PD endpoints using descriptive statistics.

Results:

Demographics and Disposition: The trial screened 2122 subjects. Of these, 1445 subjects were randomized, of whom 1444 received at least 1 dose of IMP. A total of 961 subjects received tolvaptan and 483 subjects received placebo. Overall, 1157/1445 (80.1%) subjects completed the 3-year trial, with 77.0% and 86.2% completion in the tolvaptan and placebo groups, respectively. The difference in completion rates between tolvaptan and placebo subjects was predominantly accounted for by discontinuations due to TEAEs. Of the 221/961 (23.0%) tolvaptan and 67/484 (13.8%) placebo subjects who discontinued IMP early, 102/961 (10.6%) subjects and 27/484 (5.6%) subjects, respectively, agreed to further follow-up of polycystic kidney disease (PKD) Outcomes via telephone. Subjects who agreed to telephone follow-up to assess PKD Outcomes represent 46.2% (102 of 221 subjects) and 40.3% (27 of 67 subjects), respectively, of those who discontinued. For subjects who discontinued tolvaptan early, the primary reason for discontinuation was AEs. A total of 1307/1445 (90.4%) subjects were included in the primary efficacy analysis.

A minimum interval of 6 months from a prior MRI scan was required, meaning many subjects who terminated participation in the first 6 months of the trial could not be included in the primary efficacy analysis. All 1445/1445 (100%) subjects were included in the analysis of the key secondary composite endpoint, and the 1444/1445 (99.9%) subjects who took at least 1 dose of IMP were included in the safety analysis.

Subject Disposition and Reasons for Discontinuation

Number of Subjects	Tolvaptan (N = 961) n (%)	Placebo (N = 484) n (%)	Total (N = 1445) n (%)
Screened	-	-	2122
Randomized	961 (100.0)	484 (100.0)	1445 (100.0)
Treated	961 (100.0)	483 (99.8)	1444 (99.9)
Completed	740 (77.0)[a]	417 (86.2)[b]	1157 (80.1)
Discontinued IMP	221 (23.0)	67 (13.8)	288 (19.9)
Lost to follow-up	15 (1.6)	8 (1.7)	23 (1.6)
AE	148 (15.4)	24 (5.0)	172 (11.9)
Subject met withdrawal criteria	4 (0.4)[c]	0 (0.0)	4 (0.3)
Investigator withdrew subject	3 (0.3)	4 (0.8)	7 (0.5)
Subject withdrew consent	50 (5.2)	30 (6.2)	80 (5.5)
Protocol deviation	1 (0.1)[d]	1 (0.2)[d]	2 (0.1)
Discontinued and followed for PKD Outcomes	102 (10.6)	27 (5.6)	129 (8.9)
Analyzed for primary efficacy[e]	842 (87.6)	465 (96.1)	1307 (90.4)
Analyzed for secondary efficacy[f]	961 (100.0)	484 (100.0)	1445 (100.0)
Analyzed for safety[g]	961 (100.0)	483 (99.8)	1444 (99.9)

[a] A total of 740 tolvaptan subjects completed the study, but 742 tolvaptan subjects received IMP for 36 months. Subject 04251-100-0291, Subject 04251-143-4067, Subject 04251-510-1870, and Subject 04251-530-4225 were considered completers but only received IMP for 921, 962, 966 and 827 days, respectively; these were not counted as 36 months. Subject 04251-105-0257, Subject 04251-143-4094, Subject 04251-302-0523, Subject 04251-462-1862, Subject 04251-573-4522, and Subject 04251-732-3005 were not considered completers, but received IMP for 986, 1004, 1106, 1009, 982, and 1024 days, respectively.

[b] A total of 417 placebo subjects completed the study, but 418 placebo subjects received IMP for 36 months. Subject 04251-160-0727 was a completer but only received IMP for 959 days; this was not counted as 36 months. Subject 04251-461-4149 and Subject 04251-670-4294 were not considered completers, but received IMP for 1018 and 1028 days, respectively.

[c] Withdrawal criteria included pregnancy (n=3) and "inability to adhere to trial proceeding" (n=1)

[d] Required chronic use of diuretics

[e] Subjects were analyzed for the primary efficacy endpoint if they were randomized and had baseline and postbaseline observations on TKV. Subjects withdrawing from the trial early would have an MRI during the ET visit only if the subject's most recent MRI was greater than 6 months prior to withdrawal. The number of subjects presented in this table represents the analysis based on the intent-to-treat dataset, regardless of treatment period dataset.

[f] Subjects were analyzed for the key secondary composite efficacy endpoint if they were randomized.

[g] Subjects were analyzed for safety if they received at least one dose of IMP.

Demographics were well balanced between the groups randomized to tolvaptan or placebo. Approximately half of the subjects were male (746/1445, 51.6%) and the majority of subjects were Caucasian (1218/1445, 84.3%). The mean age of randomized subjects was 38.7 years (range 18 to 51 years). The 2 treatment groups were well matched for stratification factors. There are some regional differences when comparing Japanese subjects to the subjects from the Americas and Europe/rest of world (in Japan, lower percentage of hypertensive subjects, worse renal function [higher percentage of

subjects with eCrCL < 80 mL/min], and smaller kidney volumes [higher percentage of subjects with TKV < 1000 mL]).

Estimates of creatinine clearance and GFR were consistent between treatment groups but varied based on the formula used. Total kidney volume was positively skewed, with a mean TKV greater than the median.

Pretitration Baseline Renal Function and Total Kidney Volume

Parameter	Tolvaptan (N = 961)	Placebo (N = 484)	Total (N = 1445)
1/serum creatinine ([mg/mL]$^{-1}$)			
Number of subjects	958	482	1440
Mean	102.27	104.30	102.95
SD	27.21	33.87	29.61
Median	100.00	100.00	100.00
Minimum	43.7	35.5	35.5
Maximum	263.2	500.0	500.0
$eGFR_{CKD-EPI}$ (mL/min/1.73 m^2)			
Number of subjects	958	482	1440
Mean	81.35	82.14	81.61
SD	21.02	22.73	21.60
Median	80.76	80.40	80.74
Minimum	32.3	26.4	26.4
Maximum	132.8	186.7	186.7
TKV (mL)			
Number of subjects	961	483	1444
Mean	1704.8	1667.5	1692.3
SD	921.27	873.11	905.31
Median	1456.7	1468.5	1458.8
Minimum	750.0	751.1	750.0
Maximum	7555.4	6751.1	7555.4
Height-adjusted TKV (mL/m)			
Number of subjects	960	482	1442
Mean	978.56	958.18	971.75
SD	514.84	483.27	504.43
Median	858.70	849.30	857.00
Minimum	394.7	408.7	394.7
Maximum	4317.4	3750.6	4317.4

SD = standard deviation.

Pretreatment PKD Outcomes, including progressing HTN and renal pain, reported between the Screening or Baseline visits and reported between the Baseline and Day 1 visits were consistent between treatment groups. Baseline ADPKD history characteristics were well balanced between the tolvaptan and placebo groups.

Efficacy Results: The rate of TKV increase over 3 years was significantly less for tolvaptan subjects than for placebo subjects: 2.80% per year vs 5.51% per year, respectively, for a difference of −2.71% per year with a 49.2% reduction in growth rate in the tolvaptan group compared with the placebo group ($p < 0.0001$). Subgroup results

supported the efficacy of tolvaptan across all populations regardless of intrinsic and extrinsic factors such as demographic profiles, disease stage, comorbidities, or concomitant therapies.

Primary Endpoint (Random Effect Intercept): TKV Rate of Growth (%/yr); ITT, Within Treatment Period

Parameter	Tolvaptan (N = 961)	Placebo (N = 483)
Rate of percent growth per year[a]		
Number of subjects	819	458
Mean	2.777	5.608
Median	2.265	5.585
SD	5.659	5.330
Minimum	−23.129	−20.634
Maximum	64.270	43.948
Estimated slope[b]	0.0280	0.0551
Treatment effect		
Difference (%)	-2.708	
95% CI[c]	-3.269, -2.147	
Slope reduction (%)	49.2	
Ratio of geometric mean[d]	0.974	
95% CI	0.969, 0.980	
p-value[e]	< 0.0001	

ITT = intent-to-treat.

Note: Subjects with baseline and postbaseline MRI results are included in the primary efficacy analysis. "Within the treatment period" was defined as the period starting from the first dosing day to 14 days after the last dose of IMP.

[a] Summary statistics were derived by regressing logarithm transformed kidney volume data against time, then displaying regression slope exponentials. Time variable used in the regression was equal to (MRI date - baseline MRI date)/365.25.

[b] Slope was estimated by subtracting 1 from the geometric mean of annualized growth rate.

[c] Derived from delta method assuming independence between the estimates of the slope between the 2 treatments. Difference in slope produced post-hoc to facilitate clinical interpretation.

[d] An estimate of the ratio of geometric mean of annualized growth rate of tolvaptan and placebo.

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

Sensitivity analyses and subgroup analyses of the primary endpoint were consistent with the overall population result and support the robustness of results and broad applicability of these data. The MMRM approach confirmed the primary analysis. Baseline TKV was similar for tolvaptan (1705 ± 921 mL) and placebo (1668 ± 873 mL) subjects. Least-squares mean TKV growth at month 36 for tolvaptan (9.56%) was halved relative to the placebo (18.75%), for a treatment group difference of −9.19% (95% CI −11.1 to −7.32, $p < 0.0001$). The MMRM analysis also showed that the effect of tolvaptan treatment on TKV growth was greatest in the first year and included negative cyst growth for the tolvaptan group or a treatment effect of −6.27%, a statistically significant difference between groups

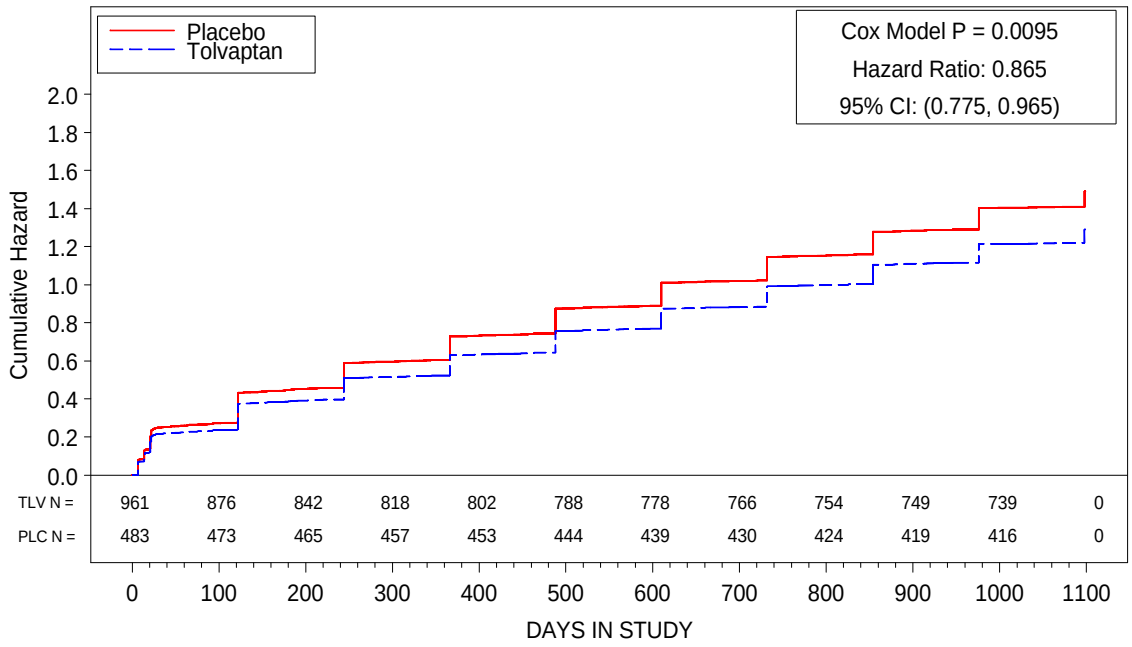
($p < 0.0001$). During the second and third years, kidney enlargement progressed in both groups; this progression was significantly slower in tolvaptan subjects compared with placebo subjects (2.93% vs 11.10% for a treatment effect of −8.17% by Month 24 and 9.56% vs 18.75% for a treatment effect of −9.19% by Month 36; each, $p < 0.0001$). The effects of tolvaptan persisted into the second and third year of therapy, with a year-to-year accrual of effect over time, leading to continued incremental separation from placebo over the entire 3-year duration of therapy. Wu-Bailey analysis, a shared-parameter approach to account for MRI data MNAR, was statistically significant ($p < 0.0001$). Further analyses suggest that it is unlikely that missing data could impact this finding.

The key secondary composite endpoint also favored tolvaptan, reflecting a reduction in the rate of composite events of 13.5%. The number of recurrent events per 100 follow-up years (E/100 follow-up years) was 43.94 for tolvaptan and 50.04 for placebo, producing a hazard ratio (HR; ie, intensity ratio) of 0.865 (95% CI 0.775 to 0.965, $p = 0.0095$). This result was confirmed by analysis of time to first event with an HR of 0.826 (95% CI 0.722 to 0.944, $p = 0.0051$). Adjudication results also confirmed the results of the key secondary composite endpoint (HR 0.852, 95% CI 0.764 to 0.951, $p = 0.0044$). For an overall effect size of 13.5%, which was robustly statistically significant, subgroup analyses produced nominal point estimates that consistently favored tolvaptan. Statistical significance for every subgroup was not demonstrated given the power for this endpoint.

Key Secondary Composite Endpoint: Time to Multiple Composite ADPKD Events; ITT, Within Treatment Period

Parameter	Nonadjudicated Composite Events		Adjudicated Composite Events	
	Tolvaptan (N = 961)	Placebo (N = 483)	Tolvaptan (N = 961)	Placebo (N = 483)
Number of events	1049	665	1067	688
Total follow-up years	2387	1329	2387	1329
Events/100 follow-up years	43.94	50.04	44.69	51.77
Mean follow-up years	2.48	2.75	2.48	2.75
HR[a]	0.865		0.852	
95% CI[a]	0.775, 0.965		0.764, 0.951	
p-value[a]	0.0095		0.0044	

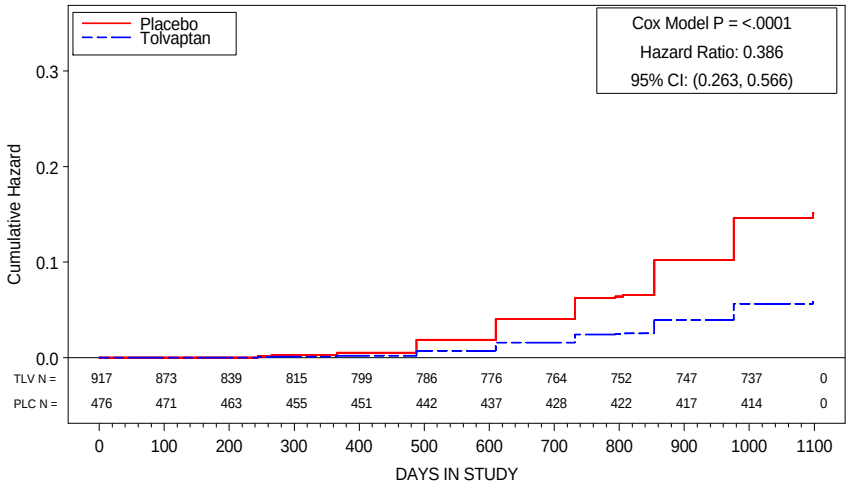
[a]Derived from rate and mean model of time to recurrent event analysis with factor treatment.



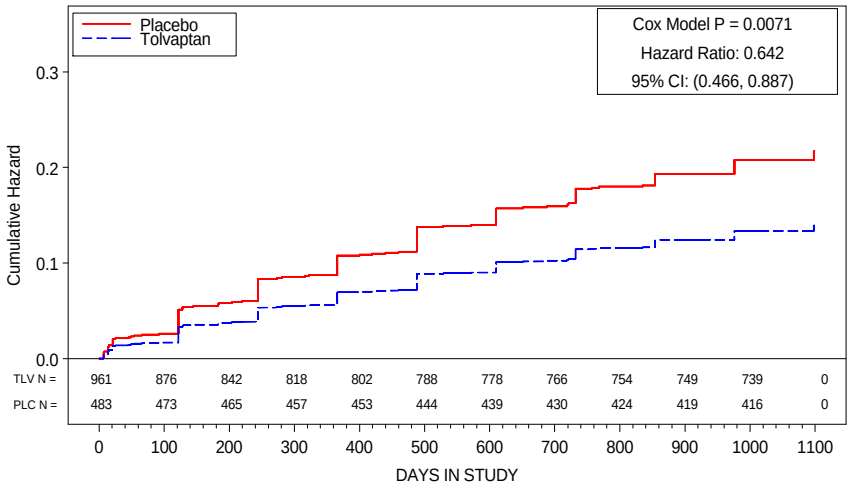
Cumulative Hazard Functions of Time to Multiple Events for the Key Secondary Composite Endpoint

PLC = placebo; TLV = tolvaptan.

Individual components of the key secondary composite endpoint differed in their contribution to this positive result. The result was driven predominantly by clinical events directly attributable to ADPKD, ie, renal function decline (HR 0.386, 95% CI 0.263 to 0.566, $p < 0.0001$) and renal pain (HR 0.642, 95% CI 0.466 to 0.887, $p = 0.0071$). No evidence for an effect of treatment was seen in HTN (HR 0.942, 95% CI 0.814 to 1.090, $p = 0.4223$) or albuminuria events (HR 1.037, 95% CI 0.837 to 1.284, $p = 0.7420$), The effect of tolvaptan on renal pain was observed early in treatment, with continuing separation between the tolvaptan and placebo groups over the remaining 3 years. By contrast, renal function decline events were delayed in both groups until approximately Month 18, potentially due to the time needed for a subject to lose 25% of estimated baseline renal function. Hazard ratios for the subgroup analyses for time to multiple events of worsening renal function and worsening renal pain generally favored tolvaptan. A reduction in multiple events of worsening renal function and multiple events of renal pain in subjects with TKV smaller than 1000 mL (or height-adjusted TKV less than 600 mL/m) is consistent with recently published findings from the CRISP cohort study. (Torres, et al Study. Am J Kidney Dis. 2011; Chapman, et al, Clin J Am Soc Nephrol. 2012)



Worsening Renal Function



Worsening Renal Pain

Cumulative Hazard Functions of Time to Multiple Events for Worsening Renal Function and Worsening Renal Pain Components of the Key Secondary Composite Endpoint

PLC = placebo; TLV = tolvaptan.

The statistical analysis plan stipulated that statistical testing could be considered valid for other secondary endpoints until a null hypothesis could not be rejected with 95% confidence. This allowed testing of the third prospectively-defined endpoint for the trial, slope of renal function decline using 1/serum creatinine. This endpoint assesses tolvaptan's overall effect on renal function and not just a progression of subjects who were declining most rapidly. The slope of renal function decline across the entire population also permits a projection of treatment effect over time. This endpoint also favored tolvaptan treatment with an estimated slope of −2.609 $(mg/mL)^{-1}$ $year^{-1}$ versus an estimated slope for placebo of −3.812 $(mg/mL)^{-1}$ per $year^{-1}$ for a treatment effect of +1.203 $(mg/mL)^{-1}$ per year (95% CI 0.622 to 1.783, $p < 0.0001$). This result, which

represents a relative improvement of 31.6%, was confirmed using other methods of estimating renal function, $CrCL_{CG}$, $eGFR_{MDRD}$, and $eGFR_{CKD\text{-}EPI}$. These results complement the findings of the key secondary composite endpoint, which demonstrated that tolvaptan decreased the proportion of subjects experiencing significant declines in renal function. Additionally, MMRM sensitivity analysis of estimated renal function as change from post-titration baseline suggested that the treatment effect is evident early and maintained throughout 3 years of treatment. The treatment effect for the subgroup analyses of the rate of renal function change was generally consistent with the results of the primary analyses of change in renal function, and although the subgroup analyses were generally underpowered to detect statistically significant differences, they support efficacy in each subgroup tested. Other sensitivity and supportive analyses confirmed the robustness of the original analysis as well as suggested it is unlikely that missing data impacted the result.

Secondary Endpoint: Rate of Change in Renal Function; ITT Subjects with at Least 4-month Follow-up, Excluding Observations Deemed Unreliable by Investigators, Within Treatment Period

Endpoint	Tolvaptan (N = 961)	Placebo (N = 483)
1/serum creatinine ($[mg/mL]^{-1}$)		
Number of subjects	842	464
Mean rate of change per year[a]	−2.555	−3.682
Estimated slope[b]	−2.609	−3.812
Treatment effect[c]	1.203	
95% CI	0.622, 1.783	
p-value[b]	< 0.0001	
$eGFR_{CKD\text{-}EPI}$ ($mL/min/1.73\ m^2$)		
Number of subjects	842	464
Mean rate of change per year[a]	−2.680	−3.568
Estimated slope[b]	−2.723	−3.700
Treatment effect[c]	0.977	
95% CI	0.597, 1.357	
p-value[b]	< 0.0001	

[a] Summary statistics were based on slope of change, obtained by regressing renal function data (Week 3/EOT and beyond) against time by subject. Time variable used in the regression was equal to (observation date - Week 3/EOT date)/365.25.

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

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

Beyond the third endpoint, none of the other planned secondary endpoints yielded notable trends or statistically significant results, although several planned and unplanned exploratory analyses suggested benefits of tolvaptan therapy might be found in each of the composite components, as well as other ADPKD outcomes.

Tolvaptan led to favorable reductions in the rate of total kidney volume growth and rate of renal function decline. The percent change in total kidney volume and renal function slope were moderately and increasingly correlated over the 3-year trial period.

Exploratory Efficacy Endpoints: Follow-up of PKD Outcomes was obtained for the trial population, including 40.3% to 46.2% of subjects who elected to discontinue the investigational medicinal product early. Thirteen prespecified ADPKD self-reported outcomes were evaluated in a time-to-event analysis individually and in groups representing "all" events and only those events that might be theoretically related to progressing renal cystic disease. Analysis of time to multiple events of PKD Outcomes and time to first events of PKD Outcomes using all 13 components both individually nominally favored tolvaptan ($p = 0.0003$ and $p = 0.0160$, respectively). On a time to multiple event basis, the rate of ADPKD progression events per the 13-item composite was lowered by 20.8% in tolvaptan subjects.

The components of the PKD Outcomes exploratory endpoint were examined to determine the impact of evaluating the 4 components of the key secondary composite endpoint. In the 4 prospectively defined most frequent components among the 9 ADPKD related outcomes, 3 of them (renal pain, hematuria, and urinary tract infection [UTI]) were highly significant in the analysis of time to multiple events. Like the component of the key secondary composite endpoint, HTN was not significantly improved. Events such as renal pain, UTI, hematuria, anemia, and nephrolithiasis were also nominally or significantly reduced in those who received tolvaptan in support of main endpoints for the trial.

Pharmacokinetic Results: Tolvaptan concentrations from sparse samples were reviewed and are included in a population PK analysis, which is reported separately. The highest DM-4107 concentration was 1094 ng/mL, a value similar to peak concentrations observed in ADPKD clinical pharmacology trials. In tolvaptan subjects, most (94.6%) subject self-reports of dosing compliance were accurate based on DM-4103 concentrations.

Pharmacodynamic Results: Tolvaptan treatment elevated mean creatinine, cystatin C, and uric acid concentrations shortly after the start of dosing (Week 3/EOT) and mean values for all analytes decreased upon cessation of tolvaptan treatment. All mean changes from baseline at Follow-up Visit 2 were lower for tolvaptan subjects with the difference from placebo subjects statistically significantly lower for creatinine ($p < 0.0001$) and trending for cystatin C ($p = 0.0574$).

In tolvaptan subjects, mean changes from baseline in urine MCP-1 to creatinine ratios were negative at Months 12, 24, and 36 and returned to baseline following the end of tolvaptan treatment; in placebo subjects, the mean change from baseline was negative at Month 12 but increased steadily to Month 36 and remained positive following the end of tolvaptan treatment. Statistically significant differences were seen at Months 24 and 36.

When log-transformed, urine albumin to creatinine ratios at Month 12 to the end of the trial and through the follow-up visits were statistically significantly lower in tolvaptan subjects compared with placebo subjects.

Urine concentration defects are one of the earliest manifestations of ADPKD, and many subjects were unable to concentrate their urine to a level above plasma osmolality during an overnight fast at baseline. Approximately, 15% of subjects in this trial had a urine osmolality of < 300 mOsm/kg at baseline. Decreases in trough urine osmolality were observed in both treatment groups. The decrease from baseline observed in the placebo group, approximately 26 to 85 mOsm/kg, may likely be due to trial-prescribed increases in water consumption during the trial. In tolvaptan subjects, urine osmolality was approximately 250 mOsm/kg lower than the placebo group. While on treatment, significantly more tolvaptan subjects, 76% to 85%, had a trough urine osmolality of < 300 mOsm/kg compared with placebo subjects, 22% to 24%.

For tolvaptan subjects, subjects with the greatest mean decreases in urine osmolality (ie, −252 to −300 mOsm/kg) had lower rates of TKV growth and slower declines in renal function. In placebo subjects, subjects with lowest average urine osmolality had lower rates of TKV growth and slower declines in renal function.

Novel biomarker identification and analysis is planned.

Safety Results: A total of 1444 of the 1445 randomized subjects received at least 1 dose of IMP during trial participation, of whom 961 subjects received tolvaptan and 483 subjects received placebo. A total of 742/961 tolvaptan subjects and 418/483 placebo subjects were still receiving treatment with any dose of IMP at the end of the trial (ie, Month 36). Cumulative exposure to tolvaptan over the duration of the trial was 2334.5 subject years.

Overall, 97.6% of subjects (1410/1444) reported TEAEs, and proportions were similar between treatment groups. The incidence of serious TEAEs was nominally lower on tolvaptan. The proportion of subjects who experienced TEAEs that resulted in discontinuation of IMP was approximately 3.5 times higher in the tolvaptan group (15.0%) compared with the placebo group (4.3%). There were no deaths in the trial.

Adverse Events (All Causalities) Within the Treatment Period

	Tolvaptan (N = 961)	Placebo (N = 484)	Total (N = 1445)
Number of subjects treated	961	483	1444
Subject years of drug exposure	2334.5	1305.5	3640.0
Subjects with AEs, n (%)	941 (97.9)	469 (97.1)	1410 (97.6)
Number of AEs	10909	4968	15877
Subjects with TEAEs, n (%)	941 (97.9)	469 (97.1)	1410 (97.6)
Number of TEAEs[a]	8544	3775	12319
Subjects with serious TEAEs, n (%)	177 (18.4)	95 (19.7)	272 (18.8)
Subjects with severe TEAEs, n (%)	203 (21.1)	88 (18.2)	291 (20.2)
Subjects who discontinued IMP due to an AE, n (%)	144 (15.0)	21 (4.3)	165 (11.4)
Number of subjects who died	0	0	0

Note: AEs were censored 7 days after IMP end date.

[a]All AEs that began after start of IMP, or if the event was continuous from baseline and was serious; related to the IMP; or resulted in death, discontinuation, interruption, or reduction of IMP.

The most frequently reported TEAEs (≥ 10% of subjects in either treatment group) were: Thirst (55.3% on tolvaptan vs 20.5% on placebo), Polyuria (38.3% vs 17.2%), Hypertension (32.3% vs 36.0%), Nocturia (29.1% vs 13.0%), Renal Pain (27.1% vs 35.4%), Headache (25.1% vs 25.1%), Pollakiuria (23.2% vs 5.4%), Nasopharyngitis (22.0% vs 23.0%), Dry Mouth (16.0% vs 12.4%), Blood Creatinine Increased (14.0% vs 14.7%), Back Pain (13.8% vs 18.2%), Fatigue (13.6% vs 9.7%), Diarrhoea (13.3% vs 11.0%), Dizziness (11.3% vs 8.7%), Polydipsia (10.4% vs 3.5%), Nausea (10.2% vs 11.8%), Urinary Tract Infection (8.4% vs 12.6%), and Haematuria (7.8% vs 14.1%) (CT-8.2.4).

Treatment-emergent AEs reported at an incidence at least 5% higher in tolvaptan subjects than in placebo subjects were Thirst (55.3% on tolvaptan vs 20.5% on placebo), Polyuria (38.3% vs 17.2%), Nocturia (29.1% vs 13.0%), Pollakiuria (23.2% vs 5.4%), Polydipsia (10.4% vs 3.5%), Constipation (8.4% vs 2.5%), and Decreased Appetite (7.2% vs 1.0%). Treatment-emergent AEs that were reported at a lower incidence (≥ 5% difference) in the tolvaptan group as compared with the placebo group included Renal Pain (27.1% vs 35.4%) and Haematuria (7.8% vs 14.1%). Notably, other TEAEs related to ADPKD outcomes reported less frequently on tolvaptan than placebo included Urinary Tract Infection (8.4% vs 12.6%), Anaemia (2.8% vs 5.0%), and Nephrolithiasis (1.6% vs 2.9%).

Some notable differences in the incidence of TEAEs between subgroups based on age, gender, race or baseline stratification factors were observed (eg, Nocturia reported less frequently in Japanese subjects versus Americans or Europeans). In general, these differences were considered to be predominantly due to cultural influences (eg, differences in AE reporting practices), and were not concluded to be clinically important.

Analysis of TEAEs of special interest using Standardised or Customised Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs or CMQs) yielded

several notable safety findings. The incidence of TEAEs in the hypernatremia CMQ was higher on tolvaptan (5.2%) than on placebo (1.4%). Likewise, TEAEs in the blood uric acid increased CMQ were more frequently reported on tolvaptan (5.1%) as compared with placebo (2.7%). These differences were confirmed in laboratory test results (see below), and generally expected based on the mechanism of action of tolvaptan. In addition, there was a higher incidence of glaucoma-related TEAEs (Glaucoma, Open Angle Glaucoma, and Intraocular Pressure) noted in the tolvaptan group (0.7%) than in the placebo group (0.4%), which was considered clinically important. Additionally, after database lock, it was determined that one subject (Subject 04251-614-4264, a 40-year old Caucasian female randomized to tolvaptan) was diagnosed with open angle glaucoma while enrolled in Trial 156-04-251; however this event was not captured as an AE for this trial. Thus, in total there were 8 glaucoma-related cases in the tolvaptan group, including this case of open angle glaucoma which was not reported as an AE in this trial. Although there is no direct evidence for a causal association between tolvaptan and glaucoma, the possibility of such an association could not be excluded. There was also an increased incidence of malignant neoplasm diagnoses (malignant tumor SMQ) (1.7% vs 0.4%), and basal cell carcinoma in particular (0.8% vs 0.2%), on tolvaptan. It is not clear whether there is a causal association between these observations and tolvaptan use.

Clinical laboratory results during the trial were routinely monitored, and potentially clinically significant abnormalities were summarized using pre-specified thresholds based on established criteria. Consistent with TEAE results reported above, the incidence of potentially clinically significant increased sodium abnormalities was higher in the tolvaptan group (4.0%) compared with the placebo group (1.4%). Likewise, potentially clinically significant increased uric acid was reported in a higher proportion of tolvaptan subjects (6.2%) than placebo subjects (1.7%). In contrast, potentially clinically significant increased creatinine (16.7% vs 21.0%) and increased BUN (15.6% vs 29.4%) were reported at a lower incidence in tolvaptan subjects as compared with placebo subjects. Of note, the incidence of TEAEs in the blood creatinine increased CMQ (analyzed as a TEAE of special interest) was similar between treatment groups (14.2% vs 14.9%). Overall, there were no serious TEAEs reported in association with the potentially clinically significant laboratory changes noted above. Likewise, laboratory abnormalities related to serum sodium, creatinine, BUN, or uric acid concentrations rarely resulted in discontinuation of IMP during the trial.

Based on central laboratory data, the incidence of elevated transaminase levels for tolvaptan subjects ($> 3 \times$ ULN) was approximately 3- to 4-fold higher than for placebo subjects. Elevations of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $> 10 \times$ ULN or $> 20 \times$ ULN were observed only in the tolvaptan group. In a combined analysis of local and central laboratory data, 2 tolvaptan subjects were identified who met Hy's laboratory criteria. Evidence for transient hepatocellular injury in tolvaptan subjects was confirmed by an expert Hepatic Adjudication Committee. The overall incidence of serious hepatic TEAEs was higher for tolvaptan subjects (2.3%) than for placebo subjects (1.0%). However, few hepatic TEAEs led to permanent discontinuation of IMP. No events of hepatic failure or liver transplant were reported in either the tolvaptan or placebo group during the trial, and no hepatic TEAEs were fatal.

While liver function testing was conducted infrequently during the trial (ie, on a quarterly basis), subjects with plausibly related abnormalities were characteristically identified within a 3 to 14-month window, and the majority experienced resolution of elevations during ongoing therapy or after discontinuation of IMP.

No clinically significant trends or potentially clinically important abnormalities were observed for vital signs or ECG parameters.

Conclusions:

Autosomal dominant polycystic kidney disease represents a large and unmet medical need among genetic renal diseases. Animal models implicate arginine vasopressin as an important cystogenic driver in ADPKD. Tolvaptan blocks arginine vasopressin's effects in these models and in humans, suggesting that it may slow the development of APDKD cysts. This trial was designed to study the effects of tolvaptan treatment on cystogenesis and its effects on outcomes important to ADPKD patients and their physicians. The totality of evidence evaluated in this trial indicates that tolvaptan slows the progression of the kidney-related effects of ADPKD. The benefits of slowing ADPKD progression must be weighed against commonly observed aquaretic adverse events and rarer signals such as hepatic toxicity.

- In this 3-year, placebo-controlled trial, tolvaptan was shown to reduce the total kidney volume growth rate by half in comparison with placebo, for a difference of 2.71%/year. These findings were robust ($p < 0.0001$) and were confirmed by multiple sensitivity analyses, including a recommended mixed model repeated measures analysis and a conservative approach using placebo slope to impute missing MRI data in the tolvaptan group. The mixed model repeated measures analysis also showed a year-to-year accrual of the effect of tolvaptan treatment over time, leading to continued incremental separation from treatment with placebo. Further analyses suggest it is unlikely that missing data could impact this finding.
- The findings of the key secondary composite endpoint were consistent with the results of the primary endpoint. The key secondary composite endpoint measured tolvaptan's effects on 4 clinically relevant complications important to ADPKD patients and their physicians (worsening of renal function, renal pain, hypertension, and albuminuria). Tolvaptan reduced the rate of the pooled composite events by 13.5%. These findings were robust ($p = 0.0095$), a result that was replicated when using outcomes that had been independently adjudicated ($p = 0.0044$). Additional sensitivity and supportive analyses were performed to test the robustness of the key secondary composite endpoint and each of these analyses produced results consistent with the primary analysis. Notably, follow-up of PKD Outcomes was obtained for the trial population, including 40.3% to 46.2% of subjects who elected to discontinue the investigational medicinal product early. In analysis of a 13-item composite of complications most related to ADPKD progression, tolvaptan reduced the rate of ADPKD progression events by 20.8%, a significant difference between groups ($p = 0.0003$), that corroborated the findings of the key secondary composite endpoint.
- Changes in serum creatinine were prespecified as the key measure to estimate renal function rate of change and this was the third prespecified endpoint in the hierarchical

analysis of this trial following the primary endpoint of TKV and the key secondary composite endpoint. The slope of estimated renal function decline improved by approximately one third with tolvaptan therapy, reflecting a preservation of renal function due to reduction of cystogenesis and/or other mechanisms. This effect was robust ($p < 0.0001$) and confirmed by sensitivity analyses including mixed model repeated measures, which demonstrated an early and durable effect. Other sensitivity and supportive analyses were performed, which confirmed the robustness of the primary analysis as well as suggested it is unlikely that missing data impacted the result

- Consistent results of subgroup analyses across the first 3 trial endpoints (rate of change in total kidney volume, key secondary composite, and renal function rate of change) support broad applicability of these efficacy results to patients with ADPKD. Evidence of efficacy was observed in all subgroups. For the primary endpoint all relevant subgroups yielded statistically significant favorable results for tolvaptan treatment.
- Beyond the third endpoint, none of the other planned secondary endpoints yielded trends or statistically significant results, although several planned and unplanned exploratory analyses suggested benefits of tolvaptan therapy might be found in each of the composite components, as well as other ADPKD outcomes.
- Planned exploration of the components of the key secondary composite endpoint revealed that favorable effects of tolvaptan treatment were evident in renal function and renal pain components while no effects were apparent for hypertension or albuminuria. The impact on renal function and renal pain events was clinically significant and had nominal statistical significance at $p < 0.0001$ and $p < 0.01$, respectively. The beneficial separation in renal function required at least 18 months of tolvaptan therapy whereas a reduced number of medically significant renal pain events was observed early in treatment with tolvaptan. Multiple sensitivity and supportive analyses of the renal pain and renal function components confirmed the results of the primary analyses.
- In an exploratory analysis, treatment with tolvaptan was associated with an improvement in clinically relevant ADPKD-related conditions. A smaller proportion of subjects on tolvaptan reported renal pain, urinary tract infection, hematuria, anemia, and nephrolithiasis compared with subjects on placebo, with nominally statistically significant differences in renal pain, urinary tract infection, and hematuria.
- Post-hoc analysis of albuminuria suggested a potential difference appearing late in the trial. It is unclear whether this was related to the late intergroup difference clearly demonstrated for renal function.
- Tolvaptan led to favorable reductions in the rate of total kidney volume growth and rate of renal function decline. The percent change in total kidney volume and renal function slope were moderately and increasingly correlated over the 3-year trial period. Tolvaptan's proposed mechanism of action involves slowing cyst cell proliferation and secretion, and can be directly linked to total kidney volume growth; however, a mechanism for improvement in renal function has not been demonstrated other than through cystogenesis.

- Changes in plasma cystatin C concentrations were consistent with changes in serum creatinine concentrations and, therefore, this biomarker is supportive of tolvaptan efficacy.
- At Month 36, urine MCP-1 to creatinine ratios were significantly lower in tolvaptan subjects compared with placebo subjects, but the variability in this endpoint would make it difficult to use to monitor disease progression.
- The tolvaptan split-dose regimens of 45/15 mg to 90/30 mg significantly inhibited the activity of arginine vasopressin at the V_2 receptor, as 76% to 85% of tolvaptan subjects had trough urine osmolality < 300 mOsm/kg compared with 22% to 24% of placebo subjects, and mean trough urine osmolality was about 250 mOsm/kg lower for tolvaptan compared with placebo subjects.
- Tolvaptan subjects with the slowest rates of total kidney volume growth or decline in renal function had the greatest mean decreases (ie, −252 to −300 mOsm/kg) in urine osmolality.
- Approximately 80% of subjects completed the 3-year trial. The difference in completion rates between tolvaptan and placebo subjects was predominantly accounted for by discontinuations due to adverse events. The majority of discontinuations were due to adverse events related to the aquaretic actions of tolvaptan and unrelated to ADPKD progression.
- Comprehensive safety analyses focused on an evaluation of treatment-emergent adverse events by frequency, temporal onset, standardized groupings of medical concepts, intrinsic or extrinsic subgroups (eg, age, gender, race, geographic region, and baseline stratification factors), laboratory/vital sign/electrocardiogram trends, and individual case review. Important findings included:
    - The most frequently reported treatment-emergent adverse events included known side effects associated with vasopressin antagonists (eg, polyuria, pollakiuria, nocturia, thirst, dry mouth) or treatment-emergent adverse events typically observed during the course of a 3-year trial (eg, headache, nasopharyngitis).
    - Other less frequently reported, but predictable, adverse events attributable to tolvaptan use, included hypernatremia, which is also considered a class effect of vasopressin antagonists, and hyperuricemia/gout. The increased reporting of events of hyperuricemia/gout was expected due to decreased uric acid clearance by the kidney caused by tolvaptan treatment.
    - Among the subgroups of subjects examined (eg, age, gender, race, baseline stratification factors), none appeared to be more or less susceptible to frequently reported adverse events. Some differences noted were consistent with age, gender, or regional cultural differences, as noted by variable reporting frequencies in the placebo group.
    - No subject died in this trial. The incidence of serious treatment-emergent adverse events was nominally lower on tolvaptan.
    - Based on central laboratory data, the incidence of elevated transaminase levels for tolvaptan subjects (> 3 times the upper limit of normal) was approximately

3- to 4-fold higher than for placebo subjects. In a combined analysis of local and central laboratory data, 2 tolvaptan subjects were identified who met "Hy's Law" laboratory criteria. Evidence for transient hepatocellular injury in tolvaptan subjects was confirmed by an expert Hepatic Adjudication Committee; however, the sponsor considers the potential risk of permanent injury to be clinically manageable and balanced by the potential benefit for this population, as supported by the efficacy results observed in this trial.

- The incidence of potentially clinically significant increased sodium and increased uric acid laboratory abnormalities was higher in tolvaptan subjects as compared with placebo subjects. These effects are attributable to tolvaptan's mechanism of action, and are considered clinically manageable. In contrast, the proportion of subjects with potentially clinically significant increased creatinine abnormalities was lower in the tolvaptan group compared with the placebo group, which was consistent with the trial's efficacy findings.
- No clinically significant trends or potentially clinically important abnormalities were observed for vital signs or electrocardiogram parameters.
- There was a higher incidence of glaucoma-related treatment-emergent adverse events (Glaucoma, Open Angle Glaucoma, and Intraocular Pressure Increased) in the tolvaptan group than in the placebo group, which was considered potentially clinically important. Although there is no direct evidence for a causal association between tolvaptan and glaucoma, the possibility of such an association could not be excluded.
- There was an increased incidence of malignant neoplasm diagnoses (ie, in the malignant tumors Standardized MedDRA Query analysis) (1.7% vs 0.4%), in particular basal cell carcinoma (0.8% vs 0.2%), on tolvaptan compared with placebo. It is not clear whether there is a causal association between this observation and tolvaptan use.
- Consistent with efficacy results, tolvaptan treatment was associated with a reduction in the reporting of adverse events related to ADPKD conditions or complications. A smaller proportion of subjects on tolvaptan reported renal pain, urinary tract infection, hematuria, anemia, and nephrolithiasis.

Overall, tolvaptan treatment slowed the rate of TKV growth and renal function decline, and reduced the risk of medically significant renal pain and dysfunction, in subjects with ADPKD, a rare disease with significant morbidity/mortality and unmet medical need. Tolvaptan therapy was associated with a clinically manageable safety profile, supporting a favorable risk/benefit assessment.