Protocol

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

Protocol for: 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

This supplement includes the final protocol for the TEMPO Trial.

As such, it includes:

- A final version ICH and GCP mandated sections (including descriptions of the statistical analyses)

- A listing (after page 106) of all changes made during protocol implementation (Amendments 1 and 2 as well as administrative changes)

Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational New Drug

Tolvaptan (OPC-41061)

REVISED PROTOCOL

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

Protocol No. 156-04-251
IND No. 72,975
EudraCT No. 2006-002768-24

CONFIDENTIAL – PROPRIETARY INFORMATION

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Protocol Synopsis

Name of Company: Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) Name of Product: Tolvaptan (OPC-41061)	Protocol No. 156-04-251 IND No. 72,975 EudraCT No. 2006-002768-24
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
Clinical Phase:	3
Treatment Indication:	Autosomal Dominant Polycystic Kidney Disease (ADPKD)
Objective(s):	Primary Objective: • Evaluate long-term efficacy of tolvaptan in ADPKD through rate of renal volume change (%) for tolvaptan-treated compared to placebo-treated subjects Secondary Objectives: • Evaluate long-term efficacy of tolvaptan in ADPKD through a composite of ADPKD progression clinical markers (ie, hypertension, renal pain, albuminuria and renal function) • Evaluate long-term efficacy of tolvaptan in ADPKD using single clinical markers of ADPKD progression • Evaluate long-term safety of tolvaptan through standard clinical measures • Evaluate pharmacokinetic (PK), pharmacodynamic (PD) and exploratory parameters for tolvaptan in ADPKD
Trial Design:	• This is a multi-center, double-blind, placebo-controlled, parallel-arm trial in adult subjects with ADPKD • After determining eligibility, and monitoring of the available data from screening subjects for Baseline event rates, tolvaptan or placebo will be titrated from lowest to highest tolerated levels when given in split dose regimens of 45/15, 60/30 or 90/30 mg by mouth (PO), given twice per day (BID), on awakening and approximately 9 hours later for up to 36 months
Subject Population:	Approximately 1200-1500 adult male and female subjects (age of legal adulthood to 50 years) meeting standardized, diagnostic criteria for ADPKD stratified by glomerular filtration rate (GFR), renal size and presence of hypertension.

Inclusion/Exclusion Criteria:	Inclusion: • GFR estimated at ≥60 mL/ min • Rapidly progressive kidney growth (total volume ≥750 cc) by Magnetic Resonance Imaging (MRI) at randomization Exclusion: • Safety contraindications including: non-compliance with therapies, reproductive precautions, unawareness of thirst, severe allergic reactions to compounds with similar chemical structure as tolvaptan • Contraindications to or interference with MRI assessments • Concurrent conditions or taking therapies likely to confound endpoint assessments or prevent completion of the trial
Trial Sites:	Approximately 100 enrolling sites in the following regions: the Americas, Europe, Japan and Rest of World (ROW)
Investigational Product (s), Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration:	Tolvaptan (using 15 or 30 mg strengths) or matching placebo (randomized in 2:1 ratio) will be self-administered for 36 months, as oral tablets given in split-dose separated by approximately 9 hours, first dose being given on awaking. Regimens include 45/15, 60/30 and 90/30 mg of the standard tolvaptan formulation and will be titrated to tolerability. Treatment duration on this trial is 3 years
Trial Assessments:	Screening: medical history (non-ADPKD related), self and family history of ADPKD (confirming diagnosis) Efficacy: MRI, blood pressure, serum creatinine, spot urine albumin/creatinine ratio, renal pain scale, and Polycystic Kidney Disease (PKD) Outcomes Safety: vital signs, adverse events, clinical laboratory tests, electrocardiogram (ECG), pregnancy tests for women of child-bearing potential (WOCBP) PK: blood samples for tolvaptan and its DM-4103 and DM-4107 metabolites PD: Urine samples for trough spot urine osmolality and monocyte chemoattractant protein-1 (MCP-1), blood samples for cystatin C and blood uric acid (BUA), urine and blood sample for exploratory development of other biomarkers of ADPKD disease progression
Criteria for Evaluation:	**Primary Outcome Endpoint:** <u>Primary Efficacy Endpoint:</u> Rate of renal volume (total, both kidneys) change (normalized as percentage) for tolvaptan

(combining all doses) relative to placebo

Secondary Outcome Endpoints:

Composite Secondary Efficacy Endpoint: Time to multiple ADPKD clinical progression events (ie, onset or progression of hypertension (HTN) [blood pressure measurement, need for HTN treatment], severe renal pain [requiring medical intervention], worsening albuminuria [by category], worsening renal function [25% change in reciprocal serum creatinine as a measure of glomerular filtration rate from steady-state post-dose Baseline]) for tolvaptan (combining all doses) relative to placebo while on treatment

Non-composite Secondary Efficacy Endpoints:

For tolvaptan compared to placebo:

1) Rate of GFR change from post-dose Baseline (End of Titration) to last on-drug trial visit (using 1/serum creatinine as primary measure while Cockcroft-Gault results will be exploratory)
2) For subjects who are non-hypertensive at Baseline, change from Baseline for resting mean arterial pressure (MAP) at scheduled clinic visits up to point of exposure to anti-hypertensive therapy for any reason
3) Change from Baseline in kidney pain as assessed by 1-10 pain scale as average area under the concentration - time curve (AUC) between Baseline and last trial visit or last visit prior to initiating medical (eg, narcotic or tricyclic) or surgical therapy for pain
4) For subjects who are non-hypertensive at Baseline, time to progress to a) high-pre-hypertension (sBP > 129 and/or dBP > 84) or b) hypertension (sBP >139 and/or dBP >89 mm Hg) or c) requiring anti-hypertensive therapy
5) For subjects who are taking anti-hypertensive therapy at Baseline, percentage with clinically sustained decreases of BP leading to a sustained reduction in anti-hypertensive therapy compared to Baseline (while taking investigational product) at visit Months 12, 24 and 36 for hypertensive subjects

Safety Endpoints:

Safety endpoints to be analyzed will include a descriptive

	summary of: 1) Reported Adverse Events 2) Vital signs 3) Clinical laboratory tests 4) ECG <u>Pharmacokinetic Endpoint:</u> 1) Sparse samples will be taken for determination of tolvaptan and metabolite plasma concentrations (DM-4103 and DM-4107) <u>Pharmacodynamic Endpoints:</u> For tolvaptan compared to placebo: 1) For urine, trough spot osmolality, and MCP-1 concentrations 2) For blood, cystatin C and BUA concentrations <u>Exploratory Endpoint:</u> 1) Fasting urine osmolality (at randomization and Follow-up visit #2 only) 2) ADPKD outcomes and medical resource utilization. Analysis of additional events attributed to ADPKD for tolvaptan-treated subjects as compared to placebo, including their health-economic outcomes
Statistical Methods:	The analysis of the primary endpoint is to fit the $\log_{10}$ transformed total renal volume data to a linear mixed-effect Laird-Ware model, with p-value derived by applying the "sandwich" estimator of the covariance matrix to the Wald test of the treatment-time interaction of the model, using observed cases of all intent to treat (ITT) subjects Secondary composite efficacy will be analyzed using the Andersen-Gill approach of the extended Cox model for analysis of time to multiple events, with p-value provided by the robust Wald test using "sandwich" estimate for the covariance matrix
Trial Duration:	Up to 6 Months initial screening and secondary endpoint frequency observation, 3 years treatment, 2-6 weeks follow-up, 5 years total to last subject complete (estimated completion date 2012)

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List of Abbreviations and Definitions of Terms

ABPM	ambulatory blood pressure monitoring
ACEi	angiotensin converting enzyme inhibitor
ADR	adverse drug reaction
AE	adverse event
ADPKD	autosomal dominant polycystic kidney disease
AHA	American Heart Association
ALP	alkaline phosphatase
ALT	alanine transaminase
aPTT	activated partial thromboplastin time
ARB	angiotensin receptor blocker
ARPKD	autosomal recessive polycystic kidney disease
AST	aspartate transaminase
AUC	area under the concentration-time curve
AUC_{∞}	area under the concentration-time curve from time 0 to infinity
AUC_t	area under the concentration-time curve calculated to the time of the last observable concentration
AUC_{τ}	area under the concentration-time curve during the dosing interval at steady state
AVP	arginine vasopressin
BID	twice per day
BP	blood pressure
BUA	blood uric acid
BUN	serum urea nitrogen
cAMP	adenosine 3', 5'-cyclic monophosphate
CBPM	conventional blood pressure monitoring

CFR	code of federal regulations
CHF	congestive heart failure
CL/F	apparent clearance of drug from plasma following extravascular administration of drug
C_{max}	maximal (peak) plasma concentration
CRF	case report form
CT	computed tomography
dBP	diastolic blood pressure
DCF	data clarification form
DDAVP	desmopressin, a synthetic analogue of arginine vasopressin
DSMB	data safety monitoring board (equivalent to IDMC)
EC	ethics committee
ECG	electrocardiogram
EDC	electronic data capture
EOT	end of titration
ESH	European Society of Hypertension
ET	early termination
EudraCT	European clinical trial data base
FDA	Food and Drug Administration (United States of America)
GCP	good clinical practice
GFR	glomerular filtration rate
GGT	gamma glutamyl transferase
hERG	human ether-à-go-go related gene
HR	heart rate
HTN	hypertension
IB	investigator's brochure
ICF	informed consent form
ICH	international conference on harmonization

IDMC	independent data monitoring committee (equivalent to DSMB)
IEC	independent ethics committee
IMP	investigational medicinal product (interchangeable with IP)
INR	international normalized ratio
IP	investigational product (interchangeable with IMP)
IRB	institutional review board
IRE	immediately reportable event
ITT	intent to treat
IVRS	interactive voice response system
IUD	intra-uterine device
Ki	inhibition constant
LDH	lactate dehydrogenase
LOCF	last observation carried forward
MAP	mean arterial pressure
MAPK	mitogen-activated protein kinase
MedDRA	medical dictionary for regulatory activities
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MCP-1	monocyte chemoattractant protein-1
MDRD	modification of diet in renal disease
MED	minimal effective dose
MMRM	mixed model repeated measures
MTD	maximal tolerated dose
MRI	magnetic resonance imaging
NIH-CRISP	National Institutes of Health-consortium for radiologic imaging studies of polycystic kidney disease subjects
NPO	nil per os (nothing by mouth)
N/K	not known

OC	observed case
OFRI	Otsuka Frankfurt Research Institute GmbH
OMRI	Otsuka Maryland Research Institute, Inc. (former name of sponsor)
OPC	Otsuka Pharmaceutical Company, Ltd.
OPDC	Otsuka Pharmaceutical Development & Commercialization, Inc (current name of sponsor)
PD	pharmacodynamic
PI	principal investigator
PK	pharmacokinetic
PKD	polycystic kidney disease
PO	per os (by mouth)
PT	prothrombin time
QD	once per day
ROW	rest of world
RBC	red blood cell count
SD	standard deviation
SAE	serious adverse event
sBP	systolic blood pressure
SBPM	self blood pressure monitoring
SGPT	serum glutamate pyruvate transaminase
SGOT	serum glutamic oxaloacetic transaminase
SIADH	syndrome of inappropriate antidiuretic hormone secretion
SmPC	summary of product characteristics
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment emergent adverse event
t_{max}	time of maximal (peak) plasma concentration
US or USA	United States of America

UTI	urinary tract infection
Vk	combined kidney volume
VS	vital signs
WBC	white blood cell count
WOCBP	women of childbearing potential

1 Introduction

Otsuka Pharmaceutical Company (OPC) discovered tolvaptan, (+/-)-4'-[(7-chloro-2,3,4,5- tetrahydro-5-hydroxy-1H-1-benzazepin-1-yl) carbonyl]-o-tolu-m-toluidide, an orally effective, non-peptide arginine vasopressin (AVP) V_2 receptor antagonist. Tolvaptan is being developed as an oral aquaretic agent for the treatment of fluid volume-overload conditions and hyponatremia (in either states of normal or excess fluid volume). The unique mechanism of action differentiates tolvaptan from traditional diuretics, allowing its use to complement available agents for these disorders. This mechanism of action also offers potential benefit in novel indications. Both tolvaptan and a related V_2 -specific AVP receptor antagonist have been shown to delay disease progression in animal models of human polycystic kidney disease (PKD).[1,2,3] The mechanism of these effects is proposed to involve inhibition of the AVP V_2 receptor and the subsequent decrease in adenosine cyclic 3', 5'-monophosphate (cAMP) concentrations in the kidney. Elevated cAMP in the kidney is thought to promote cyst secretion and growth.[4,5,6] Cyclic AMP is elevated in these animals' kidneys and is believed to increase cyst fluid accumulation and epithelial cell growth, thereby displacing normal kidney and accelerating the kidney's failure.[4,6] Human autosomal dominant polycystic kidney disease (ADPKD) subjects have elevated plasma AVP concentrations or exaggerated response of AVP to sodium challenge and their cyst fluid cAMP levels are elevated by AVP suggesting similar mechanisms may be responsible for disease progression across species and causative mutations.[4,7] Three previous trials have shown that human ADPKD subjects respond to tolvaptan with potent renal vasopressin V_2 receptor blockade. The primary objective of this phase 3 trial is to demonstrate that early renal vasopressin V2 receptor blockade will limit the most basic and clinically relevant marker of disease, the progression of renal growth. We postulate that delayed growth will also favorably affect other clinically relevant markers of ADPKD progression, including hypertension, pain, albuminuria and renal function.[8] This single trial is designed to provide definitive evidence of tolvaptan efficacy and safety (benefit/risk ratio) in human ADPKD to support the application for regulatory marketing approval in three major regions (United States of America [USA], Europe, Japan) and other countries.[9,10]

1.1 Nonclinical Data

In vitro binding studies demonstrated that tolvaptan has higher affinity for the human vasopressin V_2 receptors than for V_{1a} receptors, with virtually no binding to V_{1b}

receptors. The receptor selectivity potential of tolvaptan for human V_2 receptors (K_i = 0.43 nM) is approximately 30 times that for human V_{1a} receptors (K_i = 12.3 nM). Several tolvaptan metabolites (DM-4110, DM-4111 and MOP-21826) have affinity, but to a much lesser degree, for the human, rat and canine kidney V_2 and V_{1a} receptors as compared to tolvaptan. None of the metabolites appear to have affinity for V_{1b} receptors. Tolvaptan has approximately twice native-AVP's affinity for the AVP V_2 receptor.[9,10]

Tolvaptan is a potent inhibitor of AVP action at the kidney with little non-specific toxicity. Tolvaptan produces a dose-dependent aquaretic effect (production of dilute urine), with little influence on vascular blood pressure. In several trials recently conducted, vasopressin V_2 receptor antagonist has demonstrated efficacy in animal models of PKD by decreasing levels of intracellular cAMP, which plays a major role in cyst formation by promoting transepithelial fluid secretion and stimulating cyst-derived cell proliferation.[1,2] In PCK rats, an animal model of autosomal recessive PKD (ARPKD), tolvaptan decreased kidney weight and cyst and fibrosis volume, indicating an inhibitory effect on the development of PKD.[9] Furthermore, the Ras/mitogen-activated protein kinase (MAPK) pathway that was proposed to mediate the proliferative response to cAMP in vitro was activated in PCK rats and was inhibited by tolvaptan.[3] These findings support the importance of cAMP in the pathogenesis of PKD and suggest that tolvaptan can also become a useful drug for treating subjects with PKD.

Tolvaptan inhibition of V_2 receptor action can reverse artificially induced (AVP and hypotonic fluid) hyponatremia, leading to a return of blood sodium to normal levels.[9,10] Both tolvaptan and other vasopressin V_2 receptor antagonists have been shown to limit or reverse the progression of cystic kidney changes in a number of rodent models of PKD. These studies confirm the mechanistic hypothesis that such treatment leads to the reduction in renal cAMP, MAPK, cellular proliferation, and renal fibrosis. Studies in rodents were only successful if the suppression of vasopressin action was constant (administration in food, rather than by gavage) suggesting intermittent dosing by gavage cannot sustain the suppression of vasopressin action to prevent the development of PKD in a rodent model.

The safety of tolvaptan has been evaluated in the following nonclinical safety studies: single dose oral toxicity trials on mice, rats and dogs, 4-week and 13-week repeated dose oral toxicity studies in rats and dogs, a 26-week repeated dose oral toxicity trial in rats, a 52-week repeated dose oral toxicity trial in dogs, preliminary carcinogenicity dose-finding and the two year carcinogenicity trials in mice and rats, mechanistic trials in rats

and dogs, reproductive trials (fertility, embryo-fetal development and pre- and post-natal development) in rats and rabbits, an antigenicity trial in guinea pigs and genotoxicity and phototoxicity studies. Based on results from single oral dose toxicity trials, the approximate lethal dose of tolvaptan is higher than 2000 mg/kg in rats and dogs. The nontoxic dose of the compound is estimated to be 1000 mg/kg/day in males and 100 mg/kg/day in females in a 26-week repeated oral dose trial in rats and 100 mg/kg/day in both males and females in a 52- week repeated oral dose trial in dogs. The exposures in animals at these nontoxic dose levels are 4.0- to 13.1-times higher than that in humans following administration of the compound at a dose of 60 mg/day. No cardio-toxic effects have been seen in animals and in studies of isolated guinea pig papillary muscles, tolvaptan (1×10^{-6} to 3×10^{-5} M) showed no effects on any action potential parameters and no indications of after- depolarization. Tolvaptan did not affect the human ether-à-go-go related gene (hERG) channel current at the tested concentrations up to 2×10^{-6} M, which was the solubility limit for the external solution. In studies on anesthetized dogs, there were no significant effects on QRS, QT-intervals, or ST-segments at any doses ranging from 0.3 to 10 mg/kg given intravenously. In 4-, 13- and 52-week oral dose toxicity studies in dogs using 0, 30, 50, 100, 300, or 1000 mg/kg/day, no abnormal changes in electrocardiograms (ECG) were observed at any dose. No carcinogenicity was observed in 104-week studies in mice or rats.[9,10]

No deleterious changes in copulation or fertility were seen in the fertility studies in rats. Delayed fetal growth was seen at 1000 mg/kg/day in embryo-fetal development trials in rats. No developmental toxicity was noted at 100 mg/kg/day. High fetal mortality and increased fetal malformation were noted at 1000 mg/kg/day in the embryo-fetal development in rabbits. Drug exposure in the rabbits based on area under the curve (AUC) values of 3.88 and 16.9 µg·h/mL at doses of 100 and 1000 mg/kg/day, respectively, were approximately 1.2-fold and 5.2-fold higher than the AUC value of 3.24 µg·h/mL seen in man receiving a 60 mg/day dose. Increased perinatal mortality and suppressed offspring body weight were observed at 1000 mg/kg/day in the pre-and postnatal development trial in rats. No antigenicity was evident in guinea pig studies. No genotoxicity of the compound was observed. No phototoxicity was shown in the studies in guinea pigs and rabbits, though in vitro studies have suggested phototoxic potential of tolvaptan and one of its metabolites.[9,10]

These data suggest that tolvaptan is safe in humans. No male-factor effects were seen; however, appropriate precautions should be implemented for the inclusion of women of

childbearing potential in clinical studies. Additional information relating to nonclinical trials conducted with tolvaptan can be found in the current version of the IB.[9,10]

1.2 Clinical Data

Tolvaptan has completed two Phase 3 trials for the treatment of hyponatremia associated with euvolemic and hypervolemic states and one Phase 3 trial in heart failure.[11,12] It has also been studied in phase 2 as an adjunct to diuretic therapy to treat volume overload in patients with decompensated heart failure. Treatment in hyponatremia is limited to those in fluid overload states (eg, CHF and cirrhosis) or with normal fluid status (cancers or other conditions associated with the syndrome of inappropriate anti-diuretic hormone or "SIADH"), but is contraindicated in states of fluid depletion (eg, salt-wasting syndromes). In previously conducted Phase I trials it was shown that tolvaptan produces a dose-related, transient aquaresis, (efflux of free water in the urine).[9,10]

Aquaresis results when blood concentrations of the parent compound OPC- 41061 achieve concentrations adequate to inhibit the kidney AVP V_2 receptor, and appear to persist only as long as maintained above that concentration (approximately 100 ng/mL). The consequence of this dilution of urine includes mobilization and elimination of fluid from extravascular spaces and an increase in serum sodium concentration. Serum creatinine also increases slightly (0.1 mg/dL on average) and transiently. Other electrolytes are unaffected, and sodium will remain in the normal range so long as the subjects are able to drink in response to physiologic thirst.[9,10]

With the current clinical formulation, tolvaptan-mediated inhibition of AVP at the kidney persists for longer than 24 hours after a single dose of 180 mg or greater, but dissipates after shorter periods of time following lower doses. Although these responses are concluded to arise from the prevention of cAMP generation in the renal collecting duct epithelia, clinical trials measuring plasma and urine cAMP levels have been unsuccessful in confirming this step in this drug's mechanism. Trials in subjects with ADPKD between doses of 15 to 120 mg/d suggest the drug is well tolerated and produces both the desired renal vasopressin V2 blockade along with its undesirable side-effects.[9,10]

Limits of clinical safety and tolerability have been explored in healthy volunteers, without significant safety signals, but with evidence that very high doses can simulate severe nephrogenic diabetes insipidus, an uncomfortable but non-lethal condition (with adequate access to water). In a placebo-controlled, parallel-group, ascending dose tolerance trial in healthy volunteers, single oral doses of 180 to 480 mg tolvaptan were administered. All doses were well tolerated and there were no significant changes in

laboratory values, vital signs or ECG (Bazett correction) for any group compared to the pooled placebo population.[3] Tolvaptan given at doses of 10 to 120 mg once daily for up to 13 days was safe and well tolerated in subjects with CHF and extracellular volume expansion. There were no significant differences between groups in laboratory values, vital signs or ECG (Bazett correction). A "thorough QT trial" was conducted and the results indicated that tolvaptan administration, 30 or 300 mg QD for 5 days (steady state), had no effect on cardiac repolarization.[9,10]

Two United States of America (US) phase 2 trials (156-04-248 and 156-04-249) and 1 Japanese trial (156-04-001) were conducted to evaluate the safety, pharmacokinetics, and pharmacodynamics of tolvaptan in adults with ADPKD. A total of 45 subjects in the US and 18 subjects in Japan with ADPKD were given tolvaptan. Eleven subjects with ADPKD were enrolled in trial 156-04-248: 8 subjects received escalating doses of tolvaptan as single oral doses on Days 1, 4, 7, and 10 (15 mg, 30 mg, 60 mg, and 120 mg, respectively), and 3 subjects received matching placebo on these days. Thirty-seven subjects were enrolled in trial 156-04-249 and randomized to receive tolvaptan 15 mg BID (9 subjects); tolvaptan 30 mg AM + 15 mg PM (9 subjects); tolvaptan 30 mg BID (10 subjects); or tolvaptan 30 mg AM + placebo PM (9 subjects) for 5 consecutive days. The 156-04-001 trial was a parallel-arm, 3-period, sequential treatment trial with 9 subjects/group randomized to either a) a single 15 mg dose, a single 30 mg dose, then 15 mg, BID, 5 Days or b) a single 15 mg dose, a single 30 mg dose, then 30 mg, BID, 5 Days. The washout period between treatments was 1-3 weeks. The results from all trials indicated that urine osmolality decreased following administration of tolvaptan and the antagonistic action of tolvaptan on V_2 receptors was confirmed. Additionally, the results of BID and QD administration of the same dose per day indicated that a BID regimen was more effective in suppressing urine osmolality that was a QD regimen. The pharmacokinetic results are described in more detail in Section 1.3.[9,10]

An open-label extension trial of safety is currently ongoing in the US, all 46 of the subjects enrolled in 156-04-248 and 156-04-249 have reached two months of tolvaptan exposure, and 41 of these have continued for greater than one year, with subjects now receiving 60 or 90 mg/day of tolvaptan as a split dose regimen (see also Protocol Section 2.2).[9,10]

1.3 Pharmacokinetics/Pharmacodynamics

Tolvaptan pharmacokinetics were linear for single oral doses ranging from 5 to 480 mg, although peak plasma concentrations (C_{max}) showed a less than proportional increase with increasing dose. Mean C_{max} values were 374 ng/mL and 994 ng/mL for 60 and 300

mg doses, respectively. Following multiple oral doses, QD, tolvaptan pharmacokinetics were dose proportional for daily doses up to 60 mg; for a 300 mg dose compared to a 30 mg dose, mean values of C_{max} and area under the concentration-time curve during the dosing interval at steady state (AUC_{τ}) were only 4.2- and 6.4-fold higher, respectively. After multiple dosing, there is minimal accumulation of tolvaptan as determined by either C_{max} or AUC_{τ}.[9 10]

The median time to reach peak concentration (t_{max}) is 2 h and ranges from 1 to 12 hours. The mean (SD) half-life of tolvaptan is 8.4 (5.3) hours. The mean (SD) apparent total clearance (CL/F normalized for body weight) is 4.7 (2.0) mL/min/kg for single dose trials and 4.4 (2.3) for multiple oral doses of 60 mg or less.[9 10]

In subjects with ADPKD, mean tolvaptan concentrations are very similar to those seen in normal healthy volunteers but are more variable; the percent coefficients of variation for C_{max}, AUC_{∞} and CL/F are twice that of normal healthy subjects.[9]

Tolvaptan administration does not produce clinically significant changes in amiodarone, warfarin (or its 7-hydroxy and 10-hydroxy metabolites), lovastatin, furosemide or hydrochlorothiazide plasma concentrations.

Tolvaptan concentrations are increased ~350% and CL/F is decreased by 87% when co-administered with ketoconazole. Preliminary results indicate that tolvaptan C_{max} and AUC_{∞} are increased 1.9- and 1.6-fold, respectively, when tolvaptan is coadministered with grapefruit juice. Following coadministration with 600 mg QD rifampin at steady state, tolvaptan C_{max} and AUC_t are decreased 83% and 87%, respectively. Lovastatin increases tolvaptan C_{max} by ~20% but CL/F is unchanged.

Steady-state digoxin concentrations (as determined by AUC_{τ}) were increased by approximately 20% C_{max} at steady state was increased by 30%; in vitro trials have shown that tolvaptan is a substrate and competitive inhibitor of P-glycoprotein.[9 10]

Single oral dose trials in healthy volunteers using doses from 60 to 480 mg showed that there were 1) no further increases in urine excretion rate with doses beyond 180 mg; 2) no further increases in 0-24 hour urine excretion with doses beyond 180 mg and 3) as dose is increased, increases in urine excretion are sustained over time. Tolvaptan elevated electrolyte-free water clearance to a positive value, decreased urine osmolality, increased serum sodium and plasma osmolality, and increased plasma AVP concentrations and renin activity, but no dose related increases were observed for any parameter. Preliminary

results in subjects with ADPKD indicate that they exhibit quantitatively similar pharmacodynamic responses when compared to normal healthy volunteers.[9 10]

Following multiple oral doses, the tolvaptan metabolite DM-4103 was found to accumulate. This metabolite has no pharmacological activity at the concentrations expected to be achieved following the doses used in this study and has shown an acceptable toxicity profile. The metabolite has not been shown to accumulate in nonclinical toxicokinetic trials; however, in a 26-week trial in rats, DM-4103 plasma concentrations greater than those expected at the doses to be used in this trial revealed no evidence of time-dependent toxicological effects.[9 10]

1.4 Known and Potential Risks and Benefits

As of 04 August 2006, 531 healthy (non-ADPKD) volunteers have been exposed to tolvaptan in completed single (30 to 480 mg) and multiple dose (30 to 300 mg) Phase 1 trials in the United States, United Kingdom, Europe and Argentina. In addition, 112 healthy volunteers have been exposed to tolvaptan (1 to 120 mg) in trials conducted in Japan. Safety data indicate that tolvaptan is well tolerated in healthy subjects. The most commonly reported adverse events (>10%) in healthy subjects treated with tolvaptan were thirst, dry mouth, frequent urination and non-specific headache.[10]

In congestive heart failure studies, the most frequently reported treatment emergent adverse events (an incidence of ≥10% or greater in the tolvaptan group and greater than that of placebo) were urinary frequency (14.3% in tolvaptan group versus 3.0% in the placebo group); thirst (21.5% versus 3.3%); dry mouth (11.9% versus 2.8%); and fatigue (10.2% versus 7.8%).[10]

In hyponatremia studies, the most frequently reported treatment emergent adverse events (an incidence of ≥10% or greater in the tolvaptan group and greater than that of placebo) were; thirst (15.7% versus 5.3%); dry mouth (11.7% versus 4.5%).[10]

No subjects in any of the Phase 2, randomized, double-blind ADPKD trials experienced serious adverse events (SAEs) or withdrew because of adverse events. Tolvaptan appeared to be well tolerated in single doses up to 120 mg and in multiple doses (5 days) up to 30 mg BID. In the 156-04-248 trial, the common treatment-emergent adverse events (TEAEs) (2 subjects in the all-tolvaptan group) were dry mouth, somnolence, and aggravated headache. Dry mouth was reported by 3 tolvaptan-treated subjects, and somnolence and aggravated headache were reported by 2 tolvaptan-treated subjects each. No clear dose-related trends were observed. Treatment-emergent adverse events reported by only 1 tolvaptan-treated subject were nausea, infusion site swelling, dizziness, vaginal

candidiasis, pain in limb, headache, restless leg syndrome, sinus headache, anxiety, exacerbated insomnia, dry throat, and pruritus. In the placebo group, dizziness was the most common TEAE, reported by 2 placebo subjects versus 1 subject in the tolvaptan 60-mg dose level. Adverse events reported by only 1 subject in the placebo group were chest pain, fatigue, and headache.[9,10]

In the 156-04-249 trial, the most common TEAEs (reported by ≥2 subjects overall) were dry mouth, fatigue, dizziness, dysgeusia, dyspepsia, thirst, and headache. No clear dose- or regimen-related trends were observed. Treatment- emergent adverse events reported by no more than 1 subject overall were abdominal distension, upper abdominal pain, constipation, dry lip, nausea, retching, sensitivity of teeth, toothache, urinary tract infection, nervousness, bladder pain, polyuria, cough, nasal congestion, throat irritation, and vesicular rash. Similar adverse events were reported for the Japanese trial (156-04-001).[9,10]

Preliminary steady-state data from the 156-04-250 open-label trial, indicates that a daily dose of 120 mg (as 90/30 mg split dose) is tolerated in only approximately 40% of subjects.[9 10]

Tolvaptan has been shown to be primarily metabolized by CYP3A4. Peak tolvaptan concentrations are increased approximately 350% and total body clearance is decreased approximately 87% when tolvaptan is co-administered with ketoconazole. Therefore, subjects taking CYP3A4 inhibitors, ingesting grapefruit or Seville orange products would be expected to have higher concentrations of tolvaptan. While not specifically contraindicated, these agents should be avoided (see Section 4.1). If a subject **must** be prescribed a potent CYP3A4 inhibitor or the subject experiences difficulty with polyuria, nocturia or excessive thirst while taking such drugs with tolvaptan, the investigator must contact the medical monitor to discuss options including: a dose reduction, temporary or permanent withdrawal from tolvaptan therapy.[9,10]

Benefits of this trial include the altruistic advancement of knowledge in ADPKD as well as the possibility of a delay in disease progression if this investigational drug's effects in animals can be replicated in humans. Prolonged use of this drug in individuals who have limited access to fluids would be contraindicated as it might produce an artificial form of diabetes insipidus which associated with water deprivation could lead to hypovolemia and hypernatremia.[13] Symptoms of these conditions could include excessive urination, thirst, dizziness and hypotension. Please refer to the IB for a thorough review of the adverse events experienced with this compound during other clinical trials.[10]

2 Trial Rationale and Objectives

2.1 Trial Rationale

Tolvaptan delays development of renal cysts in an animal ortholog of human autosomal recessive polycystic kidney disease (ARPKD), the PCK rat. Preliminary data suggest similar efficacy is also seen in a model of ADPKD, the PKD2$^{WS25/-}$ mouse.[1,9,2,3] The mechanism is believed to involve a reduction in the kidney's levels of intracellular cAMP via specific inhibition of the vasopressin V_2 receptor.[4,6] Vasopressin is a peptide hormone released from the neuronal axons in the posterior pituitary to regulate water reuptake in the kidney. Vasopressin also regulates vascular tone and release of stress hormones, through its V_{1a} and V_{1b} receptors; however water regulation is specific to the V_2 receptor. [4,6] This receptor is primarily localized to the kidney's collecting duct principle cells. Tolvaptan, as a specific V_2 receptor inhibitor, acts selectively on those cells from which ADPKD and ARPKD cysts appear to arise.[8] Animal trials suggest that continuous suppression of vasopressin action at this receptor is critical to achieve the maximal clinical effect.[1,9,2,3]

ADPKD is slowly progressive with a glomerular filtration rate (GFR) decline slope near zero before the appearance of significant renal decline in the 4th through 7th decade of life. This decline is believed to arise from compromise of functioning nephrons by cyst expansion, loss of perfusion and associated fibrosis. With advancing age, over 50% of patients have lost the majority of normal renal parenchyma, but may have relatively normal levels of serum creatinine due to compensation due to hyper-filtration in the residual units. Eventually the proportion of remaining units will decline to 25% and the GFR will decline precipitously in an accelerating and inevitable progression to renal failure. Unfortunately for those who have already reached this stage, the damage is permanent and progression believed to be irreversible and compounded by age, hypertension, infection and continued parenchymal destruction. It has been noted that this usually occurs in those with the most rapidly enlarging kidneys. The rate of kidney growth also seems to correlate with the expression of earlier markers of renal disease, including the earliest manifestations of urinary concentration defects and hypertension.[8]

For these reasons, this trial will evaluate efficacy and safety in subjects with preservation of at least 50% of residual renal function (estimated GFR $\geq$ 60 mL/min) and where recent kidney size is consistent with rapid cystic growth. Efficacy will be indicated by the rate of changes in total kidney volume as assessed by standardized magnetic resonance imaging (MRI).[14,15] The progression of ADPKD is most readily measured by renal

volume increase which from retrospective and prospective trials in humans correlates significantly with other clinical manifestations of the disease, including the ultimate progression to renal failure. While the lack of an effective therapy for ADPKD has precluded demonstration of a causal relationship in humans, this has been seen in a variety of the animal models of PKD. The trial will also focus on evaluation of several composite clinical measures as a composite to gather data to further support the causal relationship of renal volume with other morbidities and evaluate other beneficial and potentially harmful effects.

2.2 Dosing Rationale

Successful treatment of ADPKD is presumed to require early, constant inhibition of the vasopressin V_2 receptor. This treatment paradigm produced decreased rates of growth in kidney size in animal models. Repeated "breakthrough" from inhibition may provide a stimulus for cyst cell division and progression of this disease. However, prolonged and severe inhibition (maximal receptor saturation) will produce a clinical condition equivalent to diabetes insipidus, which may not be well tolerated.[13] The standard formulation of tolvaptan was optimized to increase bioavailability and produce rapid onset and offset of action. While not optimal to maintain suppression of AVP action across 24 hours, dose regimens have been selected to provide as constant and complete an inhibition as would likely be tolerated by individuals taking tolvaptan chronically. The twice-daily (q9h) regimen is designed to produce a maximal inhibition on waking with a gradual fall-off of effect during sleep. To this end, a higher dose is used on awakening, with a lower dose approximately 9 hours later. The ideal interval between doses is 9 hours in order to prevent increased urine production during the sleep period.

Urine osmolality has been used as a surrogate of vasopressin V_2 receptor inhibition in the 156-03-248 and -249 trials to refine these doses. Normally, urine osmolality only increases above plasma osmolality (approximately 290 mOsm/L) when vasopressin is acting at the kidney's distal collecting ducts. When trough spot urine osmolality remains below 300 mOsm, effective V_2 receptor inhibition can be assumed. These trials also confirmed a phenomenon where the first day's therapy produces the most robust aquaresis, which abates to a more tolerable level by the 5th day of repeated dosing.

Dose regimens of 15/15, 30/15, 45/15, 60/30 and 90/30 were available in the titration phase of the ongoing open-label extension trial in ADPKD (156-04-250). During this phase of trial, both the tolerability of tolvaptan regimens and efficacy (as measured by suppression of urine osmolality) were determined in 46 subjects. Preliminary results of this trial confirm that suppression of trough urine osmolality AUC improves with each

higher dose of tolvaptan, and that "breakthrough" occurred less frequently with each regimen (cumulative [at three time-points] breakthrough of 61%, 39%, 26%, 15% for 30/15, 45/15, 60/30 and 90/30 mg doses, respectively).

While optimal efficacy (0% breakthrough) could not be achieved at any of the dose regimens used in the 156-04-250 titration, the limit of tolerability was reached with only 41% tolerating a 90/30 dose. If beginning at 45/15, however, 95% of subjects tolerated the regimen for at least one week.

The 156-04-250 trial also suggests that "real-world" efficacy of tolvaptan might suffer poor compliance with a set dose regimen. In the previous 156-03-249 trial, 100% of subjects were able to be suppressed with doses as low as 30/30 mg, while under observation in a clinical trial unit. It is also notable that a larger degree of variability in subject response was seen.

Therefore, this trial will implement a titration strategy. On Day 1, if subjects can not begin their first dose (on awakening) by 11 AM, they will begin with the afternoon dose. On Day 2, all subjects will begin the full daily dose regimen, starting at the relatively low daily dose of 45/15 and progressing to the highest tolerated dose. The day following their next weekly titration visit, subjects will begin the new titration regimen, provided tolerance at the previous dose was established. All subjects will be encouraged to progress to the highest dose as this is likely to be the most effective. Throughout the trial, subjects will have an option to down titrate, as circumstances warrant. During the maintenance phase, Investigator's may choose to up titrate subjects, with medical monitor approval, if a change in clinical status, lifestyle or concomitant treatment suggest a possibility that a higher dose may be tolerated. Up titration should occur at regularly scheduled office visits unless approved by the medical monitor.

Thus doses of 45/15, 60/30 and 90/30 mg have been selected as the titration range for this (156-04-251) trial. Subjects will begin at a reasonably effective dose of 45/15 mg and after weekly assessments proceed to 60/30 then 90/30 mg in an effort to extend AVP inhibition throughout the night, without producing extended polyuria during the day.

Table 2.2-1 Tolvaptan/Placebo Dosing Schedule Example		
Trial Day	**Nominal Time**	**Dose**
Week 1 (Day 1-7)	8 AM & 5 PM	45/15 given as three 15 mg tablets Q AM and one 15 mg tablet Q PM or matching placebo
Week 2[a] (Day 8-14)	8 AM & 5 PM	60/30 given as two 30 mg tablets Q AM and one 30 mg tablet Q PM or matching placebo
Week 3[a] (Day 15-21)	8 AM & 5 PM	90/30 given as three 30 mg tablets Q AM and one 30 mg tablet Q PM or matching placebo
Week 3 to Month 36[a]	8 AM & 5 PM	Highest tolerated regimen

[a]Actual time may vary depending on sleep cycle

2.3 Trial Objectives

Primary Objective:

- Evaluate long-term efficacy of tolvaptan in ADPKD through rate of renal volume change (%) for tolvaptan-treated compared to placebo-treated subjects

Secondary Objectives:

- Evaluate long-term efficacy of tolvaptan in ADPKD through a composite of ADPKD progression clinical markers (ie, hypertension, renal pain, albuminuria and renal function)
- Evaluate long-term efficacy of tolvaptan in ADPKD using non-composite clinical markers of ADPKD progression
- Evaluate long-term safety of tolvaptan through standard clinical measures
- Evaluate pharmacokinetic (PK), pharmacodynamic (PD) and exploratory parameters for tolvaptan in ADPKD

3 Trial Design

3.1 Type/Design of Trial

This is a multi-center, double-blind, placebo-controlled, parallel-arm trial in adult subjects with ADPKD.

After determining eligibility, and monitoring of Baseline event rates from screening, tolvaptan or placebo will be titrated from lowest to highest tolerated levels when given in split dose regimens of 45/15, 60/30 or 90/30 mg PO, given BID, with 9 hours between the morning and afternoon dose for up to 36 months. A schematic of the dosing scheme is presented in Figure 3.1-1.

The trial will enroll (randomize) approximately 1200-1500 ADPKD subjects naive to tolvaptan to obtain long-term data on approximately 1000-1200 (20% withdrawal). It is estimated that approximately 3000 subjects may need to be pre-screened using available historical information. Those who appear eligible based upon pre-screening will have critical parameters confirmed at a formal screening visit after obtaining informed consent. It is anticipated that approximately 2000 subjects will need to be formally screened in order to obtain 1200-1500 randomized subjects. Critical pre-screening parameters include serum creatinine and estimation of renal volume (by sonography) unless adequate historical radiographic data are available. Informed consent must be obtained from each subject prior to conducting screening assessments. Eligibility will be determined prior to randomization, however, subjects signing Informed Consent may enroll in an optional non-treatment period (up to 6 months) at the Investigator's discretion.

The trial population will be enriched for "rapid progressing renal size" based on data from other trials where a constant accelerated growth rate was found in subjects whose renal volume reached 750 cc.[9,14,16] A Baseline MRI confirming a combined renal volume of at least 750 cc must be performed and judged adequate (by the central reading laboratory) within no less than 14 days prior to randomization Day 1.

At randomization, Baseline assessments will be established and subjects will be randomly assigned to one of the two treatment groups (2:1 ratio, tolvaptan:placebo) stratified on presence of hypertension at Baseline (systolic blood pressure [sBP] > 139 and/or diastolic blood pressure [dBP] > 89 mmHg or anti-hypertensive treatment), Baseline estimated creatinine clearance (<80 ml/min) and Baseline combined renal volume (<1000 cc). Thus there are eight strata in this trial. Centralized randomization will be performed in this trial so that subjects will be stratified by their Baseline hypertensive status, renal function and renal volume. Three doses of tolvaptan (low [45/15 mg], medium [60/30 mg], and high [90/30 mg]) and matching placebo will be tested. Subjects will begin treatment with the lowest dose and after each 1-week safety assessment, titrate to the next higher dose treatment group, on the subsequent day, until a level of intolerability is reached. It is expected that titration may occur as weekly outpatient visits; however standards of care vary by region with more frequent telephone contact or outpatient visits to be used at the Investigator and IRB/IEC discretion. Subjects will be allowed to down-titrate based on intolerance at any time during the trial. Subjects withdrawing from this trial will be offered continued follow-up for outcomes on a telephone contact basis to Month 36 and the additional follow-up period. The treatment phase of this trial is planned to continue for 3 years, unless terminated by the DSMB/IDMC for safety, futility or significant evidence of clinically relevant efficacy. Subjects will be followed in-person

for an additional period after treatment discontinuation to further assess safety and persistence of tolvaptan effects. The IDMC will define appropriate rules for making such recommendations in their charter.

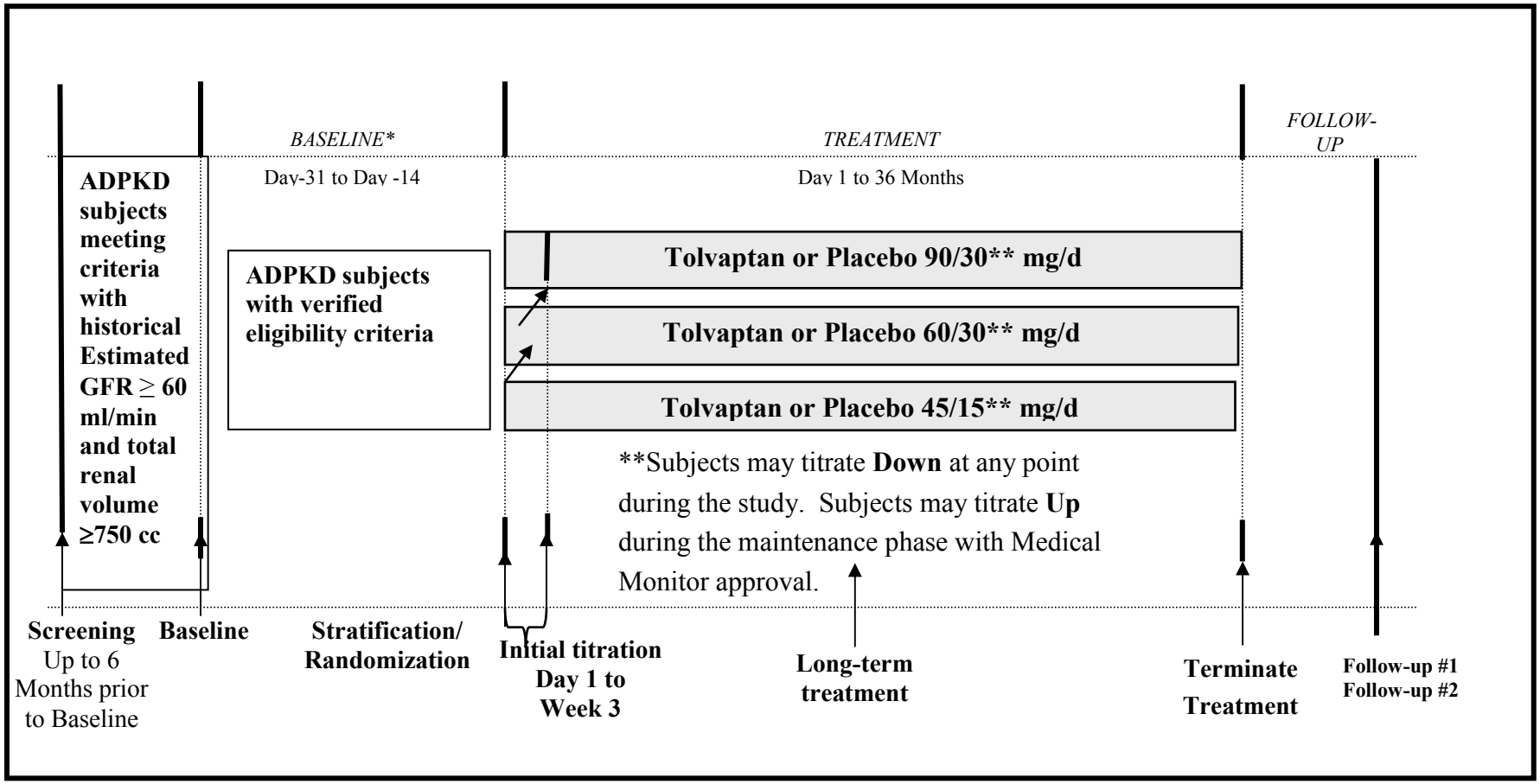

Figure 3.1-1 Trial Design Schematic

3.2 Trial Treatments

3.2.1 Investigational Product

Tolvaptan or placebo tablets (as multiples of 15 or 30 mg) will be given orally twice daily for three years. ***Dosing should occur on waking and approximately 9 hours later, irrespective of meals. Exact timing of dosing may be adjusted based on wake/sleep habits (eg, standard 8 AM and 5 PM may be switched to 10 PM and 7 AM if working a night shift).*** However, dosing times should be consistent for each individual's daily dose to avoid breakthrough. Doses will initially be titrated weekly beginning with a 45/15 mg regimen and progressing to 60/30 mg and 90/30 mg, if tolerated. Subjects may down-titrate at any time, depending on their current dose. During the maintenance phase, Investigator's may choose to up titrate subjects, with medical monitor approval, if a change in clinical status, lifestyle or concomitant treatment suggest a possibility that a higher dose may be tolerated. Up titration should occur at regularly scheduled office visits unless approved by the medical monitor. The Investigator may dechallenge (ie, interrupt use of investigational product) and rechallenge investigational product as needed to aid in assessment of adverse event causality. Subjects unable to tolerate the 45/15 mg dose will be discontinued from investigational product use yet continue with PKD outcomes assessments in the trial, see Section 3.7.3.6

3.2.2 Treatment of Hypertension

Safety of subjects and optimal testing of tolvaptan efficacy will require stratification or standardization of background standard of care. This includes a primary requirement for anti-hypertensive therapy (recommending first-line use of an angiotensin converting enzyme inhibitor [ACEi] or angiotensin receptor blocker [ARB]) in subjects with hypertension (sBP > 139 or dBP >89 mm Hg). Uses of diuretics are not preferred as they may impact certain assessments (eg, urine sodium or osmolality). Therefore, chronic use of diuretics to control hypertension will not be allowed. Subjects using diuretics for this purpose must sign a informed consent and agree to a change in this therapy before being deemed eligible. Blood pressures determined at two consecutive visits will be used to determine blood pressure status. The recommendations for treatment agents have not yet met clinical equipoise in all regions for high-normal blood pressure (pre-hypertensive [sBP 120-139 and/or dBP 80-89 mm Hg), however since ADPKD subjects are at greater risk for developing renal dysfunction, treatment with prescribed medications will be required (unless otherwise contraindicated) in subjects at the higher limit of this range (sBP 130-139 and/or dBP 85-89 mm Hg) and recommended, but optional, at the lower end of this range (sBP 120-129 and/or dBP 80-84 mm Hg. In addition, standard region-

specific recommendations for dietary restrictions (eg, salt [< 5g/day], protein [<1 g/kg/day], and caffeine ≤ 2 coffee equivalents/day (see Section 3.7.2.5), please note these are only examples and may not reflect regional medical practice) and adequate fluid intake (see below) will be reiterated at all visits during the trial (with consideration for cultural differences). Subject compliance, will be noted as stated by subject. If significant or symptomatic decreases in blood pressure are reported to the Investigator, they should first reduce the dose of the current anti-hypertensive therapy, followed by reduction of the investigational product.

3.2.3 Fluid Intake

Potential dehydration with high doses of tolvaptan might induce endogenous vasopressin and counteract the effects of V_2 receptor inhibition, especially at trough. The standard fluid recommendations for subjects will include ingestion of fluid adequate to prevent excessive thirst throughout the daytime period and an additional 1-2 cups of water before bedtime with additional replenishment with each episode of nocturia to prevent dehydration. During the titration phase, dehydration will be monitored by subject self-assessment of changes in body weight and reporting of symptoms. Acute changes of greater than 3% of body weight (increase or decrease) over any 7-day period should be noted. Subjects should be instructed to report acute changes in body weight to the trial physician for further evaluation and recommendations.

3.3 Trial Population

To best evaluate the global applicability of tolvaptan in ADPKD, this trial plans to enroll subjects previously diagnosed with ADPKD in the Americas, Europe, Japan and ROW. Twelve to fifteen-hundred men or women with confirmed clinical diagnosis of ADPKD meeting standardized criteria, but with relatively preserved renal function are expected to be enrolled.

3.3.1 ADPKD Diagnosis Criteria

ADPKD diagnostic criteria have been adapted from that of Ravine et. al. and accepted clinical practices in Japan.[17,18] The criteria require meeting the most stringent of these conditions. Basically, diagnosis for this population (age 18 or 20-50) requires several cysts in each kidney (3 if by sonography, 5 if by computed tomography (CT) or MRI) in those with a family history of ADPKD and 10 cysts (by any radiologic method) in each kidney and exclusion of other cystic kidney diseases if there is no family history. Conditions to be excluded include: multiple simple renal cysts, renal tubular acidosis,

cystic dysplasia of the kidney, multicystic kidney, multilocular cysts of the kidney, medullary cystic kidney and acquired cystic disease of the kidney.

3.3.2 Renal size (volume)

Subjects will have a combined renal volume of ≥ 750 cc as determined by MRI. This will likely exclude early and slowly progressive forms of ADPKD.

3.3.3 Renal function (serum creatinine)

Subjects will have a GFR ≥60 mL/min (by using Cockcroft-Gault with correction for gender and ethnicity). A GFR of 60 mL/min represents Stage 2 kidney disease according to the US National Kidney Foundation (see Figure 3.3.3-1). [18,19,20,21] Beyond this level, less than 50% of functioning nephrons remain, but are already in a state of hyperfiltration and will likely succumb to the progression regardless of intervention.

Figure 3.3.3-1 National Kidney Foundation Disease Outcomes Quality Initiative Classification, Prevalence, and Action Plan for Stages of Chronic Kidney Disease

Table 4. **National Kidney Foundation Kidney Disease Outcomes Quality Initiative Classification, Prevalence, and Action Plan for Stages of Chronic Kidney Disease***

Stage†	Description	GFR, *mL/min per 1.73 m²*	Prevalence, *n* (%)‡	Action§
—	At increased risk	≥60 (with chronic kidney disease risk factors)	—	Screening; chronic kidney disease risk reduction
1	Kidney damage with normal or increased GFR	≥90	5 900 000 (3.3)	Diagnosis and treatment; treatment of comorbid conditions; slowing progression; CVD risk reduction
2	Kidney damage with mild decreased GFR	60–89	5 300 000 (3.0)	Estimating progression
3	Moderately decreased GFR	30–59	7 600 000 (4.3)	Evaluating and treating complications
4	Severely decreased GFR	15–29	400 000 (0.2)	Preparation for kidney replacement therapy
5	Kidney failure	<15 (or dialysis)	300 000 (0.1)	Kidney replacement (if uremia present)

* CVD = cardiovascular disease; GFR = glomerular filtration rate. Modified and reprinted with permission from reference 7.
† Stages 1 to 5 indicate patients with chronic kidney disease; the row without a stage number indicates persons at increased risk for developing chronic kidney disease. Chronic kidney disease is defined as either kidney damage or GFR less than 60 mL/min per 1.73 m^2 for 3 or more months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.
‡ Prevalence for stage 5 is from the U.S. Renal Data System (1998); it includes approximately 230 000 patients treated with dialysis and assumes 70 000 additional patients not receiving dialysis. Prevalence for stages 1 to 4 is from the Third National Health and Nutrition Examination Survey (1988 to 1994). Population of 177 million adults age 20 or more years. Glomerular filtration rate is estimated from serum creatinine measurements by using the Modification of Diet in Renal Disease study equation based on age, sex, race, and calibration for serum creatinine. For stages 1 and 2, kidney damage is estimated by using untimed urine samples to determine the albumin–creatinine ratios; greater than 17 mg/g in men or greater than 25 mg/g in women on two measurements indicates kidney damage. The proportion of persons at increased risk for chronic kidney disease has not been estimated accurately.
§ Includes actions from preceding stages.

Of the 1200-1500 subjects enrolled (actual number to depend on observed early withdrawal rates), it is desirable to nominally have 1000 subjects complete the three-year treatment portion of the trial (20% withdrawal). This rate of withdrawal is based on current experience with tolvaptan in other long-term trials when used at doses >30 mg per day.

3.4 Eligibility Criteria

3.4.1 Informed Consent

Each investigator has both ethical and legal responsibility to ensure that subjects being considered for inclusion in this trial are given a full explanation of the protocol. This shall be documented on a written informed consent form (ICF) that shall be approved by the same institutional review board/independent ethics committee (IRB/IEC) responsible for approval of this protocol. Each ICF shall include the elements required by the ICH Good Clinical Practice (GCP) Guideline and local regulatory requirements and must adhere to the ethical principles that have their origin in the Declaration of Helsinki. The investigator agrees to obtain approval from the sponsor of any written ICF used in the trial, prior to submission to the IRB/IEC.

Written informed consent will be obtained from all subjects (or their guardian or legal representative, as applicable for local laws). Investigators may discuss the availability of the trial and the possibility for entry with a potential subject without first obtaining consent. However, informed consent must be obtained and documented prior to initiation of any procedures that are performed solely for the purpose of determining eligibility for this trial, including withdrawal from current medication(s). When this is done in anticipation of, or in preparation for, the research, it is considered to be part of the research.

Once the appropriate essential information has been provided to the subject and fully explained in layman's language by the investigator (or a qualified designee) and it is felt that the subject understands the implications of participating, the IRB/IEC-approved written ICF shall be personally signed and dated by both the subject and the person obtaining consent (investigator or designee), and by any other parties required by the IRB/IEC. The subject shall be given a copy of the signed ICF; the original shall be kept on file by the investigator. All of the above mentioned activities must be completed prior to the subject's participating in the trial.

In this trial, the subject may have an option to discontinue investigational product administration, yet continue with remote (eg, telephone) outcomes assessments performed during regularly scheduled post-randomization visits.

3.4.2 Inclusion Criteria

Subjects are required to meet the following inclusion criteria:

Table 3.4.2-1 Inclusion Criteria	
1.	Adult subjects providing informed consent: [Defined as men or women ≥ 18 years and ≥ regional legal age of maturity to age 50 years, inclusive who are able to provide informed consent and/or give assent. In the US and Europe, this is generally 18 years, while in Japan it is 20 years, inclusive.]
2.	Adult subjects with a diagnosis of ADPKD: [Diagnosis of ADPKD (age 18 or 20-50) requires several cysts in each kidney (3 if by sonography, 5 if by computed tomography (CT) or MRI) in those with a family history of ADPKD and 10 cysts (by any radiologic method) in each kidney and exclusion of other cystic kidney diseases if there is no family history. Conditions to be excluded include: multiple simple renal cysts, renal tubular acidosis, cystic dysplasia of the kidney, multicystic kidney, multilocular cysts of the kidney, medullary cystic kidney and acquired cystic disease of the kidney.]
3.	Willing to comply with required reproductive precautions: [Limited to women who are capable of becoming pregnant (ie, not abstinent, not surgically sterile by hysterectomy, bilateral oophorectomy nor those who have been postmenopausal for at least 12 consecutive months). These individuals must be willing to remain abstinent or comply with approved birth control (Protocol Section 5.4) from two-weeks prior to, and for 60 days, after taking investigational product. Further, breast-feeding is not permitted while taking tolvaptan in this trial.]
4.	Estimated GFR ≥ 60 mL/min within -31 days of randomization. [Established using Cockcroft-Gault with correction for gender and race where possible]
5.	Rapid estimated rate of renal volume increase based on total renal size ≥750 cc by MRI at randomization. [Excluding those meeting volumetric criteria solely due to six or fewer predominant cysts.]

3.4.3 Exclusion Criteria

Subjects will be excluded if they meet any of the following exclusion criteria prior to randomization.

Table 3.4.3-1 Exclusion Criteria	
1.	Subjects who in the opinion of the trial investigator and/or sponsor present a safety risk. [For example: Subjects having disorders in thirst recognition or inability to access fluids. Subjects who have clinically significant allergic reactions to tolvaptan or chemically related structures such as benzazepines (benzazepril, conivaptan, fenoldopam mesylate or mirtazapine), those with critical electrolyte imbalances, or low blood volume, those with clinically significant anemia, pregnant or breast-feeding women]
2.	Subjects who are unlikely to adequately comply with the trial's procedures. [For example: Subjects having medical conditions likely to require an extended interruption or discontinuation during the first year of trial, with a history of substance abuse (within the last 3 years), with a history of persistent non-compliance with anti-hypertensive or other important medical therapy]
3.	Subjects having contraindications to, or interference with MRI assessments [For example: ferromagnetic metal prostheses, aneurysm clips, severe claustrophobia, large abdominal/back tattoos, etc]
4.	Subjects taking medications or having concomitant illnesses likely to confound endpoint assessments [For example: chronic use of diuretics, advanced diabetes (ie, those with poor glycemic control evidenced by a history of severely elevated hemoglobin A1C, or with evidence of advanced retinopathy, nephropathy or peripheral vascular disease due to micro-or-macro vascular disease), evidence of significant renal disease (ie, currently active glomerular nephritidies), renal cancer, single kidney, recent (within last 3 years) renal surgery etc]
5.	Subjects taking other experimental (ie, non marketed) therapies, or taking approved therapies for the purpose of affecting PKD cysts, or those taking or have a history of taking tolvaptan. [For example: tolvaptan, anti-sense RNA therapies, rapamycin, sirolimus, everolimus, somatostatin analogs (ie, octreotide,sandostatin), recent (within 3 years) or anticipated cyst decompression, etc.]

3.5 Primary and Secondary Outcome Endpoints

3.5.1 Efficacy Endpoints

Measurements of the rate of change in renal volume (total, both kidneys) for subjects randomized to tolvaptan (normalized as percentage) (combining all doses) relative to the rate of change for subjects on placebo.

3.5.2 Secondary Outcome Endpoints

3.5.2.1 Composite Secondary Efficacy Endpoints

Time to multiple Investigator- reported ADPKD clinical progression events, ie, progressing hypertension [blood pressure measurement, need for treatment], severe renal pain [requiring medical intervention], worsening albuminuria [by category], worsening renal function [25% change in reciprocal serum creatinine as a measure of glomerular filtration rate from steady-state post-dose Baseline] for subjects taking tolvaptan

(combining all doses) relative to subjects on placebo. These events will be evaluated by an independent adjudication committee for sensitivity analysis.

3.5.2.2 Non-composite Secondary Efficacy Endpoints

For tolvaptan compared to placebo:

1) Rate of GFR change from post-dose Baseline (End of Titration) to last on-drug trial visit (using one, serum creatinine as primary measure while Cockcroft-Gault results will be exploratory)
2) For subjects who are non-hypertensive at Baseline, change from Baseline for resting mean arterial pressure (MAP) at scheduled clinic visits up to point of exposure to anti-hypertensive therapy for any reason
3) Change from Baseline in kidney pain as assessed by 1-10 pain scale as average AUC between Baseline and last trial visit or last visit prior to initiating medical (narcotic or tricyclic) or surgical therapy for pain
4) For subjects who are non-hypertensive at Baseline, time to progress to a) high-pre-hypertension (sBP > 129 and/or dBP > 84) or b) hypertension (sBP >139 and/or dBP >89 mm Hg) or c) requiring anti-hypertensive therapy
5) For subjects who are taking anti-hypertensive therapy at Baseline, percentage with clinically sustained decreases of BP leading to a sustained reduction in anti-hypertensive therapy compared to Baseline (while taking investigational product) at visit Months 12, 24 and 36 for hypertensive subjects

3.5.2.3 Safety Endpoint

Safety endpoints to be analyzed will include a descriptive summary of:

1) Reported Adverse Events
2) Vital signs
3) Clinical laboratory tests
4) ECG

3.5.2.4 Pharmacokinetic Variables

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

3.5.2.5 Pharmacodynamic Variables

For tolvaptan compared to placebo:

1) For urine, trough osmolality, and monocyte chemoattractant protein-1 (MCP-1) concentrations.
2) For blood, plasma concentrations of cystatin C and Blood Uric Acid (BUA)

Over the course of the trial, it is possible that new biomarkers of ADPKD or renal disease may be reported in the scientific/medical literature. Concentrations of these markers in urine and/or plasma may be determined for subjects in this trial if appropriate assays are available.

3.5.2.6 Exploratory Variables

For tolvaptan compared to placebo:

1) Fasting urine osmolality (at randomization visit and post treatment Follow-up visit #2 only)
2) ADPKD outcomes and medical resource utilization. Analysis of additional events attributed to ADPKD for tolvaptan-treated subjects as compared to placebo, including their health-related conomic outcomes.

3.6 Measures to Minimize/Avoid Bias

This trial will involve stratified parallel randomization to placebo or tolvaptan with forced titration. Randomization will utilize an interactive voice response system (IVRS) to ensure appropriate stratification in main regions (the Americas, Japan and Europe plus ROW) as the ethnic population in Japan will be formally analyzed for registration in that country. Neither subjects nor their principal investigators will be aware of whether the investigational product is active or placebo. Unblinding will only occur when the safety of the subject or local regulations require it, in such cases efforts to maintain the blind will be undertaken to the greatest extent possible. While titration from low to medium and high doses can occur, part of their intent is to limit the physiologic response and minimize major changes in urine volume which might be detected by the subject or physician. Because of urinary concentrating defects, urine volume and osmolality are respectively higher and lower than normal in ADPKD and is unlikely to provide data sufficient to unblind the trial physician. Adherence to a prescription of bedtime fluid ingestion will further obscure investigational product assignment.

All blood and urine chemistry, ECG and MRI endpoint data will be analyzed and read centrally. Local laboratory and local ECG data, collected for safety purposes, will not be included in the clinical database (other than in comments or with findings captured on the CRF as AEs as appropriate). The imaging charter will define measures to be used to limit central reader bias.

While maintaining subject, investigator and sponsor trial personnel blinding, the Bioanalytical laboratory will be unblinded to treatment and the OPDC Bioanalytical

Representative, of the PK/PD and Phase One Department, will be unblinded after the last subject's last visit following completion of all clinical assessments, but prior to database lock.

3.7 Trial Procedures

Trial assessment time points are summarized in 3.7-1

Table 3.7-1 Schedule of Assessments

Assessment	Optional Screening Up to 6 Months prior to Baseline visit[a]	Baseline Day -31 to Day -14	Randomiz-ation Day 1	Titration Wk 1, 2	Wk 3/End of Titration	Mo 4, 8, 16, 20, 28, 32	Mo 12, 24	Mo 36/ET (Early Term)[b]	Follow-up Visit #1 +7 to 21 days post Mo 36/ET	Follow-up Visit #2 +7 to 21 days post Follow-up Visit #1
Informed Consent	X	X								
Inclusion/Exclusion	X	X	X							
Medical/ADPKD History	X	X	X	X	X	X	X	X	X	X
Concomitant meds	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X
Tolerability				X	X	X	X	X		
Physical Exam[c]	D	X	D	D	D	D	D	X	D	D
VS/weight	X	X	X	X	X	X	X	X	X	X
ECG		X	X		X			X		
Blood: PK		X			X		X	X		
Blood/urine: PD		X			X		X	X		X
Blood/urine: Safety	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy	X	X	X	X	X	X	X	X		X

Table 3.7-1 Schedule of Assessments

Assessment	Optional Screening Up to 6 Months prior to Baseline visit[a]	Baseline Day -31 to Day -14	Randomiz-ation Day 1	Titration Wk 1, 2	Wk 3/End of Titration	Mo 4, 8, 16, 20, 28, 32	Mo 12, 24	Mo 36/ET (Early Term)[b]	Follow-up Visit #1 +7 to 21 days post Mo 36/ET	Follow-up Visit #2 +7 to 21 days post Follow-up Visit #1
1° Endpoint MRI		X					X	X[d]		
Composite 2° Efficacy Endpoints Labs/Pain/BP[e]	X	X			X	X	X	X	X	X
PKD Outcomes	X	X	X		X	X	X	X	X	X
Non-fasting spot urine osmolality					X		X	X[f]		
Fasting spot urine osmolality			X							X
IVRS entry	X	X	X	X	X	X	X	X	X	X
Stratify/Randomize			X							
Receive/return drug			X	X	X	X	X	X		
Height	X	X								X

[a] If subject screening period exceeds 6 months, they must be re-screened before moving on to the Baseline visit.

[b] Telephone contact (for outcomes only) will occur through Follow-up Visit #2 for all randomized subjects who permanently discontinue from investigational product administration.

[c] A complete exam is required at Baseline and Month 36/ET. For all other visits, a directed exam should be conducted at the investigators discretion if deemed necessary to assess changes in Medical History, AEs or other medically indicated parameters (D=directed)

[d] MRI will be performed at, or as near to, a clinical ET visit as is practical, MRI will be done only if >6 months has elapsed since last MRI and will not be repeated beyond the ET visit

[e] Blood required for renal function includes serum creatinine, urine for renal function includes spot albumin/creatinine ratio, clinic exam for BP, standardized renal pain score to be assessed in conjunction with confirmation of renal origin of pain by exam and/or history.

[f] Non-fasting spot urine osmolality not done at Early Termination visit

3.7.1.1 Optional Screening (Up to 6 Months prior to Baseline Visit)

At any time, subjects may be pre-screened with review of medical history (per local regulations) but must be consented prior to undergoing any screening assessments. Investigators may pre-screen using existing and recent laboratory or imaging data including sonogram. Subjects' preliminary eligibility will be evaluated formally once obtaining an informed consent, with a complete PKD history and optional screening examination. Subjects may be asked to participate in a screening period for up to 6 months at the Investigator's discretion.

Recent (within last 3 years) results from imaging trials may be used to determine likelihood of eligibility. Based on preliminary data presented for the CRISP trial, a kidney volume of 750 cc or greater indicates a greater likelihood or rapid progression of kidney volume.[14 15 16] Efforts to exclude subjects unlikely to meet trial criteria should be made prior to obtaining a Baseline MRI. Attempts to estimate renal size when using a radiology report should be documented. Copies of films are not required. If an ultrasound measurement is necessary, the report and its measurements will serve as source.

Volume should be calculated using a standard formula for the ellipsoid. Ellipsoid volume is calculated as Volume = length x width x thickness x pi/6, using maximum length in longitudinal plane, and for width and thickness in the transverse plane perpendicular to the longitudinal axis of the kidney at the level of the hilum.[22] This formula should be used if volume is not reported and linear measurements are available. If only coronal plane films are available, the kidney depth may be assumed to be equal to the width at the hilum so that the formula becomes Volume = length x (width) squared x pi/6.

If qualifying based on GFR and other parameters, a subject will have a blood pressure measurement, blood and urine laboratory tests as needed for composite secondary efficacy endpoint. They will be followed for the composite secondary efficacy endpoint but will not be randomized into the trial until a Baseline MRI is obtained to confirm renal volume. Subjects initially consented may have a delay in starting investigational product therapy for a period of up to 6 months.

1) Present, discuss and sign informed consent
2) Confirm diagnosis and assess likelihood of meeting inclusion and exclusion criteria
3) Record medical/ADPKD history, demographic information
4) Record concomitant medications
5) Assess adverse events
6) Perform directed physical exam

7) Assess vital signs (heart rate, blood pressure, body height and weight)
8) Collect blood and/or urine for:
    a) Urine pregnancy test for WOCBP
    b) Baseline clinical safety collection (blood and urine chemistry, hematology, coagulation, urinalysis)
    c) Baseline Composite secondary efficacy (urine albumin/creatinine ratio, serum creatinine for creatinine clearance calculation)
9) Assess hypertension and its therapy, renal pain scale, check for severe renal pain
10) Register subject in IVRS
11) Assess PKD Outcomes and document in source

3.7.1.2 Baseline (Day -31 to day-14)

During this visit, eligibility will be determined and stratification factors assessed: estimated GFR, renal size by MRI and hypertension. For randomization purposes, the renal volume measurement may be performed with a single technician-only measurement, formal replicate measurements using radiologist verification to be performed to determine Baseline volume for primary endpoint as specified in the imaging charter.

1) Present, discuss and sign informed consent
2) Confirm diagnosis and assess likelihood of meeting inclusion and exclusion criteria
3) Record medical/ADPKD history, demographic information
4) Record concomitant medications
5) Assess adverse events (if reported between signing consent and Baseline visit)
6) Perform physical exam
7) Perform 12-lead ECG
8) Assess vital signs (heart rate, blood pressure, body height and weight)
9) Collect blood and/or urine for:
    a) Urine pregnancy test for WOCBP
    b) Baseline clinical safety collection (blood and urine chemistry, hematology, coagulation, urinalysis)
    c) Baseline Composite secondary efficacy (urine albumin/creatinine ratio, serum creatinine for creatinine clearance calculation)
    d) Blood for pre-dose PK, note date and time of PK draw.
    e) Blood for pre-dose cystatin C and blood uric acid and urine for MCP-1.
    f) Blood and urine aliquots for exploratory endpoints.
10) Assess hypertension and its therapy, renal pain scale, check for severe renal pain

11) Baseline renal MRI to be performed to establish Baseline kidney volume
12) Dispense collection vessel and instructions for collecting urine sample for determination of fasting (NPO-nothing by mouth) spot urine osmolality for the morning of Day 1.
13) Register subject status in IVRS
14) Assess PKD Outcomes and document in source

3.7.1.3 Randomization (Day 1)

Assess inclusion and exclusion criteria (confirm MRI is technically acceptable and renal volume by MRI is ≥750 cc)

1) Update medical/ADPKD history
2) Update concomitant medications
3) Assess adverse events
4) Perform directed physical exam as appropriate
5) Assess vital signs (heart rate, blood pressure, body weight)
6) Perform pre-dose ECG
7) Collect blood and/or urine for:
   a) Urine pregnancy test for WOCBP
   b) Clinical safety collection (blood and urine chemistry, hematology, coagulation, urinalysis)
8) Collect fasted (NPO) urine osmolality sample from subject. Dispense collection vessel and instructions for collecting non-fasting trough urine sample for determination of osmolality at Week 3 (or End of Titration).
9) Assess hypertension and its therapy, renal pain scale, check for severe renal pain
10) Assess Baseline PKD Outcomes and document in source
11) Randomize subject in trial through IVRS with stratification
12) If the subject can not begin their first dose (on awakening) by 11 AM, they will begin with the afternoon dose.
13) Instruct subject to begin full dosing on the following day (Day 2).
14) Dispense trial medication (sufficient for 1 Week of dosing). Arrange for next visit.
15) Instruct subjects to note changes in their body weight to aid in compliance with fluid intake recommendations (see Section 3.2.3).

3.7.1.4 Dose Titration Visits (Week 1, 2 and 3 / End of Titration [ie, days 7, 14, 21 ± 2 days])

Subjects will be dispensed investigational product for the next visit. During the weekly interval window, subjects will return to the site each week to report tolerability, have a

directed physical exam as needed and to receive instructions regarding their next dose titration. An interim unscheduled visit or telephone contact may occur to assess wide fluctuations in body weight (ie >3%/week, increase or decrease) or to evaluate AEs. Subjects should assess their weight daily at the same time each day, noting if such changes occur, and reporting them to the trial staff.

At each week's visit, subjects will be asked about tolvaptan tolerability using the following wording exactly, "Could you tolerate taking this dose of investigational product for the rest of your life, please answer only yes or no?" If the answer to this is "Yes" the subject will be prescribed the next available higher dose of investigational product for the next visit, provided clinical assessment of tolerability is also positive. If the answer is "No", the subject will be returned to the next lower dose (if available) and asked to return to the clinic to have protocol specified assessments performed at the next scheduled visit. The doses to be used in this trial are outlined in Figure 3.1-1 and Section 3.2. If the subject cannot tolerate the lowest effective dose (45/15 mg), they will be withdrawn from the trial. Such subjects will still be followed for outcomes via a telephone contact thru month 36/ET. A trial center visit will occur at Weeks 2 and 3 (unless tolerability is reached). Subjects will have a directed physical exam including vital signs. They will return all unused tolvaptan for compliance assessment and long-term storage and be dispensed adequate investigational product supply for the next visit.

1) Update medical/ADPKD history
2) Update concomitant medications
3) Assess adverse events
4) Assess tolerability (medical and subject-driven)
5) Perform directed physical exam as appropriate
6) Assess vital signs (heart rate, blood pressure, body weight)
7) ECG (12-lead) (Week 3 or End of Titration visit only)
8) Collect blood and/or urine for:
    a) Urine pregnancy test for WOCBP
    b) Clinical safety (blood and urine chemistry, hematology, coagulation, urinalysis)
    c) Composite secondary efficacy (urine albumin/creatinine ratio, serum creatinine) (Week 3 or End of Titration visit only)
    d) Blood for PK (Week 3 or End of Titration visit only, note date and time of PK draw and date and time of last dose taken)
    e) Blood for cystatin C and blood uric acid and urine for MCP-1 and blood and urine aliquots for exploratory endpoints (to be taken as close to PK draw as possible). (Week 3 or End of Titration visit)

9) Collect trough urine sample for osmolality from subject (Week 3 or End of Titration only)
10) Assess hypertension and its therapy, renal pain scale, check for severe renal pain (Week 3 or End of Titration visit only)
11) Document PKD Outcomes in source (Week 3 or End of Titration visit only)
12) Register subject status in IVRS
13) Dispense and/or return investigational product and perform compliance assessment

3.7.1.5 Renal MRI Visits (Baseline [Day -31 to day -14] and Months 12, 24, & 36 [± 2 weeks] / Early Termination [+2 weeks])

MRI evaluation of kidney volume will be conducted at Baseline and at Months 12, 24, 36/Early Termination (ET) with a window of +2 weeks. If needed due to early termination, the MRI will be performed at, or as near to the clinical ET visit as is practical. Thus, four MRIs in total may be performed. Discontinuation of investigational product administration will be treated as an ET visit, including if possible acquisition of final MRI data. For ET visits, MRI will not be performed if the ET visit occurred within 6 months of a prior MRI.

3.7.1.6 Safety & Efficacy Clinical Maintenance Visits (Months 4, 8, 12, 16, 20, 24, 28, 32, & 36 [± 2 weeks]/Early Termination [+2 weeks])

Subjects will return for assessments of safety and secondary efficacy endpoints at Months 4, 8 12, 16, 20, 24, 28, 32, 36/ET. If the subject withdraws from the trial early for any reason, every effort to collect the data listed below should be made at that time in an ET visit. If withdrawal occurs at a regularly scheduled visit, those measures, plus the ET measures should be taken.

1) Update medical/ADPKD history*
2) Update concomitant medications*
3) Assess adverse events*
4) Assess tolerability* (medical and subject-driven)
5) Perform directed physical exam as appropriate (full physical exam at 36 Month/ET visit)*
6) Assess vital signs (heart rate, blood pressure, body weight)*
7) ECG (12-lead) (36 Month/ET only)*
8) Collect blood and/or urine for:
    a) Urine pregnancy test (for WOCBP)*

b) Clinical safety (blood and urine chemistry, hematology, coagulation, urinalysis)*

c) Composite secondary efficacy (urine albumin/creatinine ratio, serum creatinine,)*

d) Blood for PK (Months 12, 24, 36/ET only, note date and time of PK draw and date and time of last dose taken)*

e) Blood for cystatin C and blood uric acid and urine for MCP-1 and blood and urine aliquots for exploratory endpoints (to be taken as close to PK draw as possible). (Months 12, 24, 36/ET only)*

9) Assess hypertension and its therapy, renal pain scale, check for severe renal pain*
10) Document PKD Outcomes in source for past 4 months
11) Register subject status in IVRS*
12) At Months 8, 20 and 32, dispense collection vessel and instructions for collecting trough urine sample for determination of osmolality at Months 12, 24 and 36, respectively.* (No ET sample will be taken)
13) Dispense and/or return investigational product and perform compliance assessment*

***Subjects who withdraw from investigational product use only will not have these tests performed past the ET visit**

3.7.1.7 Follow-up Visits

3.7.1.7.1 Follow-up Visit #1

Subjects will return to the clinic +7 (to +21) days after their Month 36/ ET visit. The following assessments will be made:

1) Update medical/ADPKD history
2) Update concomitant medications
3) Assess adverse events
4) Perform directed physical exam as appropriate
5) Assess vital signs (heart rate, blood pressure and body weight)
6) Collect blood and/or urine for:

a) Clinical safety collection (blood and urine chemistry, hematology, coagulation, urinalysis)

b) Composite secondary efficacy (urine albumin/creatinine ratio, serum creatinine)

7) Assess hypertension and its therapy, renal pain scale, check for severe renal pain
8) Document PKD Outcomes in source since last visit
9) Register subject status in IVRS
10) Dispense collection vessel and instructions for collecting fasting trough urine sample for determination of osmolality at Follow up Visit #2.

3.7.1.7.2 Follow up Visit #2

Subjects will return to the clinic +7 (to +21) days after their Follow-up #1 visit. The following assessments will be made:

1) Update medical/ADPKD history
2) Update concomitant medications
3) Assess adverse events
4) Perform directed physical exam as appropriate
5) Assess vital signs (heart rate, blood pressure and body weight)
6) Collect body height
7) Collect blood and/or urine for:
    a) Urine pregnancy test (for WOCBP)
    b) Clinical safety (blood and urine chemistry, hematology, coagulation, urinalysis)
    c) Composite secondary efficacy (urine albumin/creatinine ratio, serum creatinine,)
    d) Blood for cystatin C and blood uric acid and urine for MCP-1 and blood and urine aliquots for exploratory endpoints
    e) Fasting NPO trough urine sample for determination of osmolality
8) Assess hypertension and its therapy, renal pain scale, check for severe renal pain
9) Document PKD Outcomes in source since last visit
10) Register subject status in IVRS

For subjects completing their Month 36/ET visit prior to Amendment 2 implementation, subjects will only be contacted by the clinic for a phone Follow-up 7 (+7) days after their Month 36/ET visit.

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3.7.2 Safety Assessments

3.7.2.1 Clinical Laboratory Data

Blood and/or urine samples will be collected as indicated in the schedule of assessments, Table 3.7-1. All safety labs will be performed at Screening, Baseline (Day -31 to day -14), Titration Weeks 1, 2 and 3/or End Titration visit, Treatment Months 4, 8, 12, 16, 20, 24, 28, 32, 36/ET, Follow-up Visit #1, and Follow-up Visit #2.

Urine pregnancy testing will be performed with commercially available, high-sensitivity kits supplied to the subject by the site (acquired by the sponsor or through the central laboratory for uniformity). Female subjects who are capable of bearing children will have their urine tested in clinic prior to trial entry (Screening, Baseline and Day 1). Once placed on treatment, testing will be performed per the trial schedule. The subject should contact the clinic immediately on suspicion of pregnancy, and unscheduled urine or blood pregnancy testing will be performed.

Table 3.7.2.1-1 Clinical Laboratory Tests	
Tests for Safety	
Hematology: White Blood Cell Count (WBC) with differential Hematocrit, or Red Blood Cell Count (RBC) and Hemoglobin Mean Corpuscular Volume (MCV) Mean Corpuscular Hemoglobin Concentration (MCHC) Platelet count Prothrombin Time (PT) as INR Activated partial thromboplastin time (aPTT)	Serum Chemistry: Aspartate Transaminase (AST or SGOT) Alanine Transaminase (ALT or SGPT) Gamma Glutamyl Transferase (GGT) Lactic Dehydrogenase (LDH) Alkaline Phosphatase (ALP) Total Bilirubin Cholesterol Calcium Glucose Sodium Blood urea nitrogen Potassium Total Protein Albumin
Urinalysis: (Specific gravity, pH, color, clarity, blood, protein, glucose, microscopic analysis [including quantitation of RBC, WBC, and casts per high-power field])	Urine Pregnancy (only in women of childbearing potential)
Tests for Efficacy and PKD Biomarkers	
Tests for GFR, albuminuria and concentrating ability Serum Creatinine Urine albumin/creatinine ratio creatinine clearance (calculated for eligibility only) Urine osmolality after overnight fast (NPO)	**Pharmacodynamic Biomarkers** Serum Cystatin C Blood uric acid Urine MCP-1 Non-fasting Trough Urine osmolality Plasma (collect and process per PK sample) Urine (50 mL aliquot)

3.7.2.2 Physical Examination and Vital Sign Data

Physical examinations including body weight will be performed and documented according to the schedule of assessments at Baseline, and Month 36/ET visits**.** A complete physical exam is required at Baseline and Month 36/ET. For all other visits (Screening, Day 1, Weeks 1, 2, 3 or End of Titration, Months 4, 8, 12, 16, 20, 24, 28. 32, Follow-up visit #1 and Follow-up visit #2), a directed exam should be conducted at the investigator's discretion if deemed necessary to assess changes in medical history, AEs or other medically indicated parameters. In some regions, more frequent subject visits may be the norm; therefore vital signs and clinically significant physical findings will be documented as source and recorded on unscheduled CRF pages. Any clinically significant physical findings, changes in medication or adverse events will be recorded in the source documents and subsequently transcribed on to the CRF.

Body weight will be taken post-void. It is preferable to use the same scale for each measurement. Clinic scales should be calibrated at least yearly. The Investigator or his/her appointed designee is primarily responsible to perform the physical exam. If the appointed designee is to perform the physical exam, he/she must be permitted by local regulations and his/her name must be included on any globally and locally required documents (eg individual must be added for all sites on a US FDA Form 1572, while local regulations determine their being named in the ICF). Whenever possible, the same individual should perform all physical exams. Any undesirable condition present at the post treatment physical exam that was not present at the Baseline exam should be documented as an adverse event and followed to a satisfactory conclusion.

Vital sign data including seated blood pressure and heart rate will be taken at visits Screening, Baseline, Day 1, Weeks 1, 2, and 3 (or End of Titration), Months 4, 8, 12, 16, 20, 24, 28, 32, 36/ET, Follow-up visit #1 and Follow-up visit #2 . The subject's height is to be taken at Screening or Baseline and again at Follow-up visit #2.

3.7.2.3 ECG Data

Standard 12-lead ECG will be performed at trial Baseline, Day 1, Week 3 (or End of Titration visit) and at 36 Month/ET and at intervals dictated by individual clinical condition or regional requirements. ECG recording will include 10 seconds of full 12-lead strip (displaying 2.5-3 seconds) with a lead-2 rhythm strip. ECG should be printed in duplicate. High-quality photocopies should be made only if duplicate printing is not possible. One original reading is to be kept by the site and the other is to be sent to eRT. The ECG will be sent to eRT for central reading after monitoring by the CRA. If only one original is available, a same size photocopy will be retained at the site as "source", while the original, after monitoring, is sent unless regional differences mandate otherwise. The local investigator or a qualified designee will assess the ECG's clinical relevance, noting this on the ECG label and source documents. Any clinically relevant findings meeting AE criteria should be recorded on the appropriate CRF page.

3.7.2.4 Tolerability Question

At each visit while taking investigational product, subjects will be asked about investigational product tolerability using the following wording exactly, "Could you tolerate taking this dose of investigational product for the rest of your life, please answer only yes or no?" If during titration visits, the answer to this is "Yes" the subject will be prescribed the next available higher dose of investigational product, provided clinical assessment of tolerability is also positive. If at any visit, the answer is "No", the subject

will be returned to the next lower dose. If the subject cannot tolerate the lowest dose of investigational product, then they should be withdrawn from the trial. If during the interval of treatment, the subject is unable to tolerate the tolvaptan regimen, they should immediately contact the Investigator who will instruct the subject to either return to the next lower dose or, as appropriate, withdraw the subject from the trial. The doses to be used in this trial are outlined in Figure 3.1-1 and Section 3.2. Permanent dose changes should be recorded by the Investigator using the IVRS system.

3.7.2.5 Dietary Recommendations

Restriction of excess dietary sodium and protein may prove beneficial to subjects with a history of, or predisposition for, hypertension or kidney disease in general and should be applied to all subjects diagnosed with ADPKD, particularly if there is evidence for a propensity for rapid progression. This has become a standard recommendation for those treating PKD. Therefore, beginning at screening, and in the absence of alternate regional recommendations all subjects should be instructed to keep dietary salt < 5g/day and dietary protein <1 g/kg/day. A general recommendation to limit caffeinated drinks/foods should also be given (no more than ≤ 2 coffee equivalents per day). It is recognized that there may be some regional variability in level restrictions or ability to maintain compliance with one or more of these guidelines, therefore the CRF should capture self-reported qualitative compliance and the site specific recommendations for dietary intake.

Additionally, fluid intake is generally encouraged in subjects with PKD. Given the potential for dehydration with tolvaptan treatment, all subjects should be instructed to ingest fluids in anticipation of, or at the first sign of thirst in order to avoid excessive thirst or dehydration. Additionally, subjects should ingest 1-2 cups of water before bedtime regardless of perceived thirst and replenish fluids overnight with each episode of nocturia. An exception will be made for strictly fasting (ie, NPO) assessments. Additionally, subjects should be advised that the ingestion of grapefruit or Seville orange products might affect the study drug's actions and these should be avoided. In the event of an unintentional ingestion of such products, the investigator may ask the subject to delay or withhold a dose of study medication.

3.7.3 Efficacy Assessments

3.7.3.1 Magnetic Resonance Imaging Assessments

MRI assessments will be performed at Baseline and 12, 24, 36/ET Months. The MRI's are to be performed as close to an annual schedule as possible. Those subjects terminating early will have a MRI performed at or as near to, the clinical ET visit as is practical. For subjects who ET, a MRI will be done only if the ET visit is at least 6

months after the last MRI. Subjects with ferro-magnetic prostheses, aneurysm clips, severe claustrophobia or other contraindications or exclusions interfering with the MRI endpoint will be excluded from participation. The parameter to be measured for primary efficacy analysis (using a central reader) will be combined renal volume of both kidneys.

Depending on technical feasibility, combined renal cyst volume (total cyst volume of both kidneys) and combined renal parenchyma volume (total parenchyma volume of both kidneys may be determined at a later date for a subset of subjects.

3.7.3.2 Hypertension Assessment

Each subject will have blood pressure measured using in-clinic conventional blood pressure measurement. Hypertension will be evaluated using brachial artery blood pressure with the cuff at the level of the mid-sternum (heart) after 5 minutes of rest in a seated position. Both systolic and diastolic BP and heart rate will be noted. In clinic, measurements will be performed by a trained trial team member ideally using a manual mercury, aneroid or if validated, an oscillometric blood pressure device (in order of preference as is allowable by local regulations) with the appropriate cuff size. Documentation of which type of device is to be used and a copy of its specifications and validations should be retained in the site's study files. Two measurements will be performed and both will be recorded. In case the values vary by > 5 mmHg, two additional measurements should be performed and recorded. The average of all valid (technically correct) measures (up to 4) is to be recorded in the CRF for each scheduled or unscheduled visit. Measurements will be taken at Screening, Baseline, Day 1, Weeks 1, 2, and 3 (or End of Titration), Months 4, 8, 12, 16, 20, 24, 28, 32, 36/ET, Follow-up Visit #1 and Follow-up Visit #2. Subjects' blood pressure will be categorized according to Table 3.7.3.2-1, where the higher category of either the systolic or diastolic measure will determine the subject's category.

Table 3.7.3.2-1 Hypertension Assessment

Category	Systolic BP (mm Hg)	Diastolic (mm Hg)
Non-hypertensive	< 120	<80
Low-pre-hypertensive	120-129	80-84
High-pre-hypertensive	130-139	85-89
Hypertensive	>139[a]	>89[a]

[a]Hypertensive also includes those at any BP level who are taking anti-hypertensive medication for control of blood pressure

Changes to medications used to specifically control blood pressure should be documented in source and entered onto appropriate CRFs capturing concomitant medications and hypertension outcomes. Please refer to the case report form completion guidelines for further instructions. Anti-hypertensive therapy is to be started or adjusted as noted in the hypertension treatment guidelines in Section 3.2.2, only after measures at two consecutive visits (including unscheduled visits, which should be used if significant changes in BP are noted) meet guideline requirements. While in some subjects, self-blood pressure monitoring or ambulatory blood pressure monitoring may be clinically indicated or recommended, these values will not be used for determination of clinical endpoint data by blood pressure change, they may however, be considered in determining whether prescribed medications should be adjusted.

3.7.3.3 Renal Function

Renal function will be assessed using central serum creatinine measurements at visits Screening, Baseline, Week 3 (or End of Titration), Months 4, 8, 12, 16, 20, 24, 28, 32, 36/ET, Follow-up visit #1 and Follow-up visit #2 using standard Cockcroft-Gault and reciprocal serum creatinine formulae.

For the "Composite Secondary Efficacy Endpoint", the reciprocal serum creatinine will be the primary analysis with any consistent (defined two consecutive visits separated by 2 weeks including unscheduled assessments) 25% reduction from Baseline in the reciprocal being classified as an event occurring at the date of the first included value. 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.

Table 3.7.3.3-1 presents serum creatinine values and their reciprocals and is provided as a reference to allow Investigators to easily determine if the 25% reduction threshold has been met.

Table 3.7.3.3-1 Renal Function (Serum Creatinine)

Baseline Serum Creatinine	Baseline 1/Serum Creatinine	25% Decrease in 1/Serum Creatinine	1/Serum Creatinine Threshold for "Event"	Serum Creatinine Threshold for "Event"
0.60	1.67	0.42	1.25	0.80
0.70	1.43	0.36	1.07	0.93
0.80	1.25	0.31	0.94	1.07
0.90	1.11	0.28	0.83	1.20
1.00	1.00	0.25	0.75	1.33
1.10	0.91	0.23	0.68	1.47
1.20	0.83	0.21	0.63	1.60
1.30	0.77	0.19	0.58	1.73
1.40	0.71	0.18	0.54	1.87
1.50	0.67	0.17	0.50	2.00
1.60	0.63	0.16	0.47	2.13
1.70	0.59	0.15	0.44	2.27
1.80	0.56	0.14	0.42	2.40
1.90	0.53	0.13	0.39	2.53
2.00	0.50	0.13	0.38	2.67
2.10	0.48	0.12	0.36	2.80
2.20	0.45	0.11	0.34	2.93
2.30	0.43	0.11	0.33	3.07
2.40	0.42	0.10	0.31	3.20
2.50	0.40	0.10	0.30	3.33

On meeting the criteria for an event, the average of the two values meeting criteria will establish a new Baseline for the next event.

The reciprocal creatinine is independent of spurious changes in body weight and therefore is more likely to represent a more accurate assessment of change in renal function based on a simple blood test. Therefore, the reciprocal creatinine will be used for all endpoint assessments as it provides a measure of change in GFR. Other formulae which include assessment of gender, weight and other factors will provide a more accurate prediction actual GFR. Therefore, to determine eligibility for the trial, the Cockcroft-Gault formula will be used. The 6- or 4-component (modification of diet in renal disease [MDRD]) formula is not preferred as its accuracy around a GFR of 60 mL/min is questionable and so will be not be used to estimate GFR.[20] The formula for Cockcroft-Gault is as follows:[21]

Creatinine clearance (estimated GFR) = [(140 - age) x (weight) x (0.85 if female)]/72 x [Pcr]

Where: Pcr = serum creatinine concentration (mg/dL)
weight = body weight (kg)
age = age (years)

This formula is based on a serum creatinine assessment by Jaffe's method, and will slightly over-estimate GFR when using the preferred enzymatic method to be employed by the central laboratory.

The formula for reciprocal Serum creatinine is:

1/Pcr

Where: Pcr = serum creatinine concentration (mg/dL)

These assessments will use the most recent available variables.

Per instructions from the central laboratory, the blood volume to be collected will be sufficient volume to allow replicate analysis by the central laboratory if needed. Testing should be validated to produce accurate results over time using a single central laboratory for each region, cross calibrated and ideally using the same machine and reagents. The preferred method will be an enzymatic method (for example, Roche CREA Plus). The creatinine data are to be to the maximum number of significant digits (the highest level of precision) available to the laboratory without rounding (for example, Roche CREA Plus will be reported to a minimum of 3 significant digits). This central laboratory value will be used to determine eligibility during Screening/Baseline.

3.7.3.4 Albuminuria Assessment

Albuminuria will be assessed using central spot urine albumin/creatinine ratio measurements determined for urine samples collected at the clinic during visits at Screening, Baseline, Week 3 (or End of Titration), Months 4, 8, 12, 16, 20, 24, 28, 32, 36/ET, Follow-up visit #1 and Follow-up visit #2. This sample should be provided as a mid-stream, clean catch sample.

Albuminuria stages are denoted as "A", "B" and "C" with "A" being "Normal" (urine albumin/ creatinine of < 2.8 mg/mmol female or < 2.0 mg/mmol male), "B" being "microalbuminuria" (urine albumin/ creatinine of 2.8-28 mg/mmol female or 2.0-20 mg/mmol male) and "C" being "overt proteinuria" (urine albumin/ creatinine of >28 mg/mmol female or >20 mg/mmol male). Baseline category will be determined by the first two (or three using best 2 of 3, if first two are discordant) values. Values are considered invalid in the presence of gross hematuria or UTI.

For the "Composite Secondary Efficacy Endpoint" an event will be counted when a subject increases from one category to the next in 2 of 3 sequential observations (including unscheduled evaluations) and will be said to have occurred on the date of the first contributing laboratory value.

For example: in sequence AABBABB the subject changed from category "A" to "B" at the third visit (an event), whereas for ABABBB, the subject changed from category of "A" to category "B" at the second visit (an event), while ABAABAA remains in Baseline category "A" (no event). Note, however, that movement to a lesser category does not re-establish a new Baseline from which progression to the previous level counts as an event. So in a more complicated example: AABABABBCC where the subject has a Baseline of "A", then shifts to "B" at the third visit (first event), shifts back to "A" at the fourth visit, (no event), moves back to "B" at the 5th visit (no event) and to category "C" at the ninth visit (second event). Thus for a subject with a Baseline of "A" or normal, a maximum of two events are possible.

3.7.3.5 Renal Pain Assessment

Subjects will be asked a question at each scheduled visit (Screening, Baseline, Day 1, Weeks 3 (or End of Titration), Months 4, 8, 12, 16, 20, 24, 28, 32, 36/ET, Follow-up visit #1 and Follow-up visit #2 to assess the relative level of pain attributed to their kidneys. This question is, "On a scale of 0 to 10, with zero representing no pain at all and 10 representing the worst pain you've ever experienced, what was the worst kidney pain you've experienced in the last 4 months?" If the latest assessment was less than 4 months prior, the question will substitute "since your last visit" for "in the last 4 months". The same trained interrogator designated to this task should be used throughout the trial for each subject.

For the "Composite Secondary Efficacy Endpoint" of "severe renal pain" requires documentation of clinical signs and symptoms that the pain originates in the upper urinary tract, such as flank tenderness or evidence of cystic expansion, or hemorrhage. Upper urinary tract infection and symptomatic nephrolithiasis may be included; however other causes such as diverticulitis should be excluded.[23] The Investigator's clinical judgment as to need for medical intervention will be the final arbiter of whether the level of pain will define endpoint. Intervention to meet the endpoint should be significant such as:

- prescription of narcotic pain relievers
- prescription of tricyclic antidepressant medications for pain
- prescription of surgical or invasive radiological procedures

- prescription of a work absence (or other similar limitation of activity) due to the pain
- prescription of other "last resort" medications, over the counter or prescription analgesics (ie, medications for which an individual subject might have other relative contraindications such as gastric erosion, bleeding, renal toxicities)

Other types of events will qualify if after consultation with the Medical Monitor for the trial, they are judged to be medically significant.

Medical resource utilization (office/ER healthcare visits, hospital admissions, procedures and therapies) and productive days lost due to renal pain will be reported as part of the PKD outcomes survey.

3.7.3.6 PKD History and Outcomes

Patients will be asked about their PKD History at all visits. This information should be recorded as source data in the patient's medical records and transcribed on to the appropriate CRF page. PKD History will capture information from the subject's recollection, and documented past medical history where available. This information should be updated at each visit if new information regarding past history becomes available. PKD Outcomes will be collected at all study visits and will collect information relevant to the medical, social and economic consequences of new and ongoing PKD-related morbidities. This information should be recorded as source data in the patient's medical records and transcribed on to the appropriate CRF page. New clinically relevant information and specific questions about outcomes will be updated at visits Baseline, Day 1, Week 3 (or End of Titration), Months 4, 8, 12, 16, 20, 24, 28, 32, 36/ET, Follow-up visit #1 and Follow-up visit #2.

If a subject who has been randomized and taking investigational product discontinues from the use of investigational product, telephone contact for PKD outcomes will be performed at the normally scheduled trial visits to Month 36, Follow-up visit #1 and Follow-up visit #2. These data will not be used in the primary analysis, but may be utilized in exploratory ITT analyses.

Medical resource utilization (office/ER healthcare visits, hospital admissions, procedures and therapies) and productive days lost due to PKD outcomes will be reported for subjects as part of the PKD outcomes.

3.7.4 Pharmacodynamic Assessments

3.7.4.1 Trough Urine Osmolality, MCP-1

Fasting spot urine osmolality will be determined for the morning of Randomization, Day 1 and for Follow-up Visit #2. Non-fasting spot urine osmolality at trough will be determined immediately prior to morning dosing for Week 3 (or End of Titration) and Months 12, 24, and 36. No ET sample will be obtained. This sample should be obtained from a second urine void taken after the first morning's void and will ideally be provided as a mid-stream, clean catch sample. Date and time of the urine sample, as well as the date and time of the last preceding dose should be noted.

The urine sample for determination of MCP-1 should be obtained from the same sample used to determine the urine albumin/creatinine ratio collected at the clinic during the trial visit. All samples will be stored according to directions from the central clinical chemistry laboratory. Selected samples may be assayed at a later date for exploratory purposes.

3.7.4.2 Blood for Cystatin C and BUA

A blood sample for Cystatin C, taken following the PK blood sample, will be collected and processed according to the directions provided by the central clinical chemistry laboratory. Samples will be collected at Baseline, Week 3 (or End of Titration) and Months 12, 24, 36/ET, and Follow-up visit #2. All samples will be stored according to directions from the central clinical chemistry laboratory. Selected samples may be assayed at a later date for exploratory purposes.

A blood sample for determination of BUA, taken following the PK blood sample, will be collected and processed according to the directions provided by the central clinical chemistry laboratory. Samples will be collected at Baseline, Week 3 (or End of Titration) and Months 12, 24, 36/ET, and Follow-up visit #2. Selected samples may be assayed at a later date for exploratory purposes.

3.7.4.3 PKD Biomarkers (Exploratory)

A variety of urine and blood markers have been proposed as being potentially helpful in tracking the progression of ADPKD, or the progress of PKD therapy. Other markers, specific to the mechanism of action for tolvaptan, may provide useful insight into the compound's effects in subjects. A blood sample will be taken following the PK sample (10 mL) and processed as for PK blood sample. A spot urine sample (50 mL) will be collected (as part of the urine sample used to determine albumin/creatinine ratio) at

Baseline, Week 3 (or End of Titration), Months 12, 24 36/ET, and Follow-up visit #2. Detailed handling and shipping instructions are in Appendix 3.

3.7.5 Pharmacokinetic Assessments

3.7.5.1 Pharmacokinetic Blood Samples

Sparse samples will be taken for determination of tolvaptan and metabolite plasma concentrations. Blood samples for pharmacokinetic analysis will be collected by trial centers that have appropriate facilities; a 10 mL sample will be collected at Baseline, Week 3 (or End of Titration) and Months 12, 24, 36/ET, and Follow-up visit #2. The date and time of the PK sample and the date and time of the most recent dose taken prior to the blood sample must be recorded on the sample requisition form (except for the pre-dose sample). The exact timing of sampling relative to previous dose is not critical and can vary as much as is operationally practical.

All plasma samples will be shipped to the central clinical laboratory for storage. Detailed handling and shipping instructions are in Appendix 3.

3.7.6 Exploratory Assessments

3.7.6.1 Urine Concentrating Ability

Tolvaptan is expected to acutely influence urinary concentration ability, but may prevent worsening of the concentrating defect in ADPKD subjects. Therefore, it can only be assessed while off investigational product.

On the morning of their Day 1 trial visit and the morning of their Follow-up Visit #2, the subject will collect a fasting urine sample (ideally, with the morning's second void; first void at least 10 hours after *NPO,* second void anytime thereafter while still *NPO)*.

3.7.7 End of Trial

The End of Trial Date is defined as the last Date of Contact or the Date of Final Contact Attempt from the Post-treatment Follow-up or withdrawing from the trial.

3.7.8 Independent Data Monitoring Committee

For this trial an Independent Data Monitoring Committee (IDMC, also known as Data Safety and Monitoring Committee [DSMC]) will be established. The role of the IDMC will be delineated in a separate IDMC Charter document, but in general this group will meet on a regular basis and to ensure the safe and ethical treatment of trial subjects, ensure the scientific integrity of the trial and to ensure the trial is conducted within the bounds of ethical medical practice. This IDMC may make recommendations to the

sponsor and trial steering committee to amend or terminate the trial based on grounds of safety, futility or greater than expected efficacy as defined by the accepted statistical practices and procedures to be detailed in their Charter. A safety oversight committee for tolvaptan's nephrology programs has been established by the sponsor for the review of safety data from the tolvaptan ADPKD program. This body will provide interim safety evaluation until the IDMC for this trial is formed.

3.8 Stopping Rules, Withdrawal Criteria and Procedures

3.8.1 Entire Trial or Treatment Arm(s)

The Investigators will be notified promptly if the trial is terminated. If the sponsor decides to terminate or suspend the trial for safety or unanticipated other reasons, the sponsor will promptly notify investigators, IRB/IEC, and regulatory authorities as required by the applicable regulatory requirements.

3.8.2 Individual Center

The sponsor should be notified promptly if the trial is terminated at an individual center. If the investigator, IEC or sponsor decides to terminate or suspend the trial's conduct at a particular center for safety or unanticipated other reasons, the above and other parties, as required by the applicable regulatory requirements, will be promptly notified.

3.8.3 Individual Subject

If a subject discontinues the trial prematurely, the reason given must be fully evaluated and recorded appropriately in source documents and the CRF. If the subject is being withdrawn because of an adverse event (AE), that AE should be indicated as the reason for withdrawal. In this protocol, a "partial withdrawal from investigational product administration" will be allowed, while continuing in the trial for some assessments. Should this happen, appropriate documentation of this partial withdrawal will also be made as specified in 3.4.1.

All subjects have the right to withdraw at any time during treatment without prejudice. The investigator can discontinue a subject's participation in the trial at any time if medically necessary. In addition, subjects meeting the following criteria must be withdrawn from the trial:

- Occurrence of any AE, intercurrent illness or abnormality in laboratory assessment results which, in the opinion of the investigator, warrants the subject's permanent withdrawal from the trial;
- Treatment with a prohibited concomitant medication other than the use of appropriate medications for the treatment of AEs under direction of the investigator;

- Subject noncompliance, defined as refusal or inability to adhere to the trial schedule or procedures;
- At the request of the investigator, sponsor, or regulatory authority;
- Subject is lost to follow-up;
- Medications or procedures that would confound endpoint assessments

The sponsor should be notified promptly when a subject is withdrawn or if the trial is stopped. A subject who discontinues investigational product for reasons other than non-compliance or lost to follow-up may continue limited participation in the trial for further telephone/remote collection of PKD outcomes as described in 3.7.3.6.

3.9 Screen Failures

A screen failure subject is one from whom informed consent is obtained and is documented in writing (ie, subject signs an informed consent form), but who is not started on treatment (whether randomized or not). Subjects who have screen failed may be re-screened at any time if the condition limiting their participation has changed and is no longer limiting, however they will be assigned a new screening number.

3.10 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for primary and/or secondary objectives of the trial irrespective of whether or not the subject actually consumed all doses of investigational product. Trial completers are defined as subjects who are evaluated for the Primary Efficacy Endpoint, Composite Secondary Efficacy Endpoint and PKD Outcomes at the last scheduled visit (Month 36) during the treatment period.

3.11 Definition of Lost to Follow-up

Subjects who cannot be contacted on or before Visit Month 36 during the treatment period and who do not have a known reason for discontinuation (eg, withdrew consent or adverse event, etc) will be classified as “lost to follow-up” as the reason for discontinuation.

3.12 Subject Compliance

Subject compliance will be monitored by pill counts as drug is returned. Any subject who, without the instruction of the investigator, discontinues investigational product for 30 consecutive days or misses > 30% of the doses intended for a period between visits (whichever is greater) will be deemed non-compliant. Depending on the circumstances leading to non-compliance, the subject may be withdrawn from the trial or discontinued

from investigational product administration by the investigator and/or sponsor. A subject may proactively withdraw consent for continued investigational product administration, or be withdrawn by the investigator for reasons other non-compliance or lost to follow-up may be allowed to continue participation in the trial for the purpose of collecting PKD Outcomes.

3.13 Protocol Deviations

This trial is to be conducted as described in this protocol. In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the investigator or designee must contact the sponsor at the earliest possible time. This will allow an early joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator and the sponsor, and reviewed by the monitor.

4 Restrictions

4.1 Prohibited Medications

Medications or surgical therapies used for the purpose or potential for modifying the progression of PKD cyst growth or development will be prohibited. These include, but are not restricted to somatostatin agonists, rapamune (sirolimus), anti-sense RNA therapies, tolvaptan, and other vasopressin antagonists (eg, OPC-31260 (mozavaptan), Vaprisol (conivaptan), or agonists (eg, desmopressin [DDAVP]) and cyst decompression surgery.

Continuous or short term use of other medications, while not prohibited, may be restricted by the investigator because of their potential for interference with metabolism or efficacy endpoints. This includes the use of diuretics which can be used intermittently but not within 7 days of a urine assessment. Chronic use of diuretics (eg, for hypertension) would be prohibited due to potential endpoint interference. Patients taking such agents must first sign an ICF and then agree to be switched to an alternate form of therapy in order to be eligible for the trial. Since tolvaptan is a weak CYP3A4 substrate, potent CYP3A4 inhibitors should be avoided during the trial, with the exception of amiodarone which was found to have no effect on tolvaptan. A partial list of other CYP3A4 inhibitors can be found in Table 4.1-1.

Table 4.1-1 CYP3A Inhibitors (partial list)			
amprenavir	atorvastin	aprepitant	chloramphenicol (if used orally)
cimetidine	clarithromycin	clotrimazole (if used orally)	danazol
delavirdine	diltiazem	erythromycin,	fluconazole
fluvoxamine	indinavir	isoniazid	itraconzazole
josamycin	ketoconazole (if used orally)	nelfinavir	nefazadone
quinupristin/ dalfopristin	ritonavir	saquinavir	troleandomycin
verapamil	Seville orange products	Grapefruit products	

5 Reporting of Adverse Events

The following describes the methods and timing for assessing, recording, and analyzing safety parameters, as well as the procedures for eliciting reports of and recording and reporting AEs and intercurrent illnesses and the type and duration of the follow-up of subjects after AEs.

ADPKD is a progressive disorder involving the kidney, liver and occasionally other organ systems. A number of adverse events may be associated with this disorder and are endpoints in this trial. As such, these events are considered "expected" in this trial population and will not qualify for the purposes of regulatory expedited reporting (eg, SUSARs and IND safety reports).

These events will be evaluated on a regular basis by the DSMB/IDMC, and where necessary, provided in closed session partially or fully un-blinded data so as to appropriately assess risk/benefit in the trial population.

5.1 Definitions

An AE is defined as any untoward medical occurrence in a patient or subject enrolled in the clinical trial and which does not necessarily have to have a causal relationship with the investigational product.

A treatment-emergent AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the investigational product, whether or not considered related to have a causal relationship with the investigational product.

A serious AE (SAE) or reaction is any untoward medical occurrence that at any dose:

- results in death.

- is life-threatening, ie, the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event which hypothetically might have caused death if it were more severe
- requires in-patient hospitalization or prolonged existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

Other medically significant events that, based on appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above, eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse should also usually be considered serious.

A non-serious AE is any AE that does not meet the criteria for an SAE.

An immediately reportable event (IRE) is any SAE, or any AE that necessitates discontinuation of the investigational product. Pregnancies are also defined as IREs (although normal pregnancy is not an AE). These events must be reported to the sponsor on an IRE form (refer to Section 5.3.1). Additionally, in the EU region, events involving overdose, misuse and abuse as well as reported lack of efficacy must also be reported as IREs.

An adverse drug reaction (ADR) is any noxious and unintended response to an investigational product related to any dose, where the causal relationship between an investigational product and an AE is at least a reasonable possibility, ie, the relationship cannot be ruled out. Additionally, in the EU region, an adverse procedure-related reaction is any noxious or unintended response to a trial-related procedure.

An unexpected ADR is an adverse reaction, the nature or severity of which is not consistent with the applicable product information in the Investigator's Brochure

Changes in Clinical Laboratory Assessment Results: It is the investigator's responsibility to review the results of all laboratory tests as they become available. This review will be documented by the investigator's dated signature on the laboratory report. For each abnormal laboratory test result, the investigator needs to ascertain if this is an abnormal (ie, clinically significant) change from Baseline for that individual subject. (This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests). If this laboratory value is

determined by the investigator to be a clinically significant change from Baseline for that subject, the value is considered an AE.

Severity: AEs will be graded on a 3-point scale and reported as indicated on the CRF. The intensity of an adverse experience is defined as follows:

1 = Mild: Discomfort noticed, but no disruption to daily activity.

2 = Moderate: Discomfort sufficient to reduce or affect normal daily activity.

3 = Severe: Inability to work or perform normal daily activity.

The causal relationship of the investigational product to an AE will be assessed as related or unrelated, as follows:

Related:

Definite: There is a reasonable causal relationship between the investigational product and the AE, when the event responds to withdrawal of the investigational product (dechallenge), and recurs with rechallenge by administration of the investigational product.

Probable: There is a reasonable causal relationship between the investigational product and the AE. The event responds to dechallenge. Rechallenge is not required.

Possible: There is a reasonable causal relationship between the investigational product and the AE. Dechallenge is lacking or unclear.

Unrelated:

Not Likely: There is a temporal relationship to investigational product administration, but there is not a reasonable causal relationship between the investigational product and the event.

Not Related: There is not a temporal or causal relationship to the investigational product administration.

In the EU region, trial procedures are also to be considered when assigning causality to an AE.

5.2 Eliciting and Reporting Adverse Events

The investigator will periodically assess subjects for the occurrence of AEs and record AE information offered spontaneously by subjects. To avoid bias in eliciting AEs, subjects should be asked the following non-leading question: "How have you felt since your last visit?" Once a subject has signed the ICF, all AEs (serious and non-serious) reported by the subject must be recorded on the source documents and CRFs provided by the sponsor.

In addition, the sponsor, or its representatives must be notified immediately by telephone or fax of any immediately reportable events according to the procedure outlined below. Special attention should be paid to recording hospitalization and concomitant medications.

5.3 Immediately Reportable Events (IRE)

5.3.1 IREs Reportable Within 24 Hours

The investigator must report any SAE or confirmed pregnancy by telephone or by fax to the sponsor immediately after the investigator becomes aware of the event (refer to contact information in Appendix 1). An Immediately Reportable Event (IRE) form should be completed and sent by fax or overnight courier to the sponsor within 24 hours of knowledge of the event by the site. (Please note that the IRE form is NOT the AE CRF.)

Subjects experiencing SAEs should be followed clinically until their health has returned to Baseline status or until all parameters have returned to normal, or have otherwise been explained. It is expected that the investigator will provide or arrange appropriate supportive care for the subject.

In accordance with applicable regulations and local laws, the sponsor will identify and report within the required timeframe to regulatory authorities, investigators, and IRBs/IECs, all ADRs that are determined to be reportable on an expedited basis. ADPKD is a progressive disorder involving the kidney, liver and occasionally other organ systems. A number of adverse events may be associated with this disorder and are endpoints in this trial. As such, these events are considered “expected” in this trial population and will not qualify for the purposes of regulatory expedited reporting (eg, SUSARs and IND safety reports).

5.3.2 IREs Reportable Within 3 Working Days

Non-serious events that require discontinuation of the investigational product (including laboratory abnormalities) should be reported to the sponsor within 3 working days. The IRE form should be completed and sent to the sponsor by the fastest route possible, eg, fax or overnight courier.

5.4 Pregnancy

Women of childbearing potential (WOCBP) who are sexually active must use an effective method of birth control during the course of the trial so risk of failure is minimized. Unless the subject and his/her partner(s) are sterile (ie, women who have had

an oophorectomy and/or hysterectomy or have been postmenopausal for at least 12 consecutive months; or men who have had orchidectomy) or remain abstinent, two of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device (IUD), birth control pills, birth control implant, condom or sponge with spermicide. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy; therefore two of the above methods should be used to further reduce the likelihood of an unplanned pregnancy and a fetus' potential exposure to this investigational drug. While even two methods cannot fully guarantee pregnancy prevention, an understanding of these facts and the potential risks of non-compliance must be clearly explained to the trial subject in the ICF and consent process.

Before enrolling WOCBP in this clinical trial, investigators must review guidelines about trial participation for WOCBP. The topics should include:

- General information
- Informed consent form
- Pregnancy prevention information
- Drug interactions with hormonal contraceptives
- Contraceptives in current use
- Guidelines for the follow-up of a reported pregnancy

Prior to trial enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The subject must sign an ICF stating that the above-mentioned risk factors and the consequences were discussed.

During the trial, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual cycle).

If a subject or investigator suspects that the subject may be pregnant prior to administration of the investigational product, administration must be withheld until the results of blood serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the investigational product or be enrolled in the trial. If pregnancy is suspected while the subject is receiving treatment, the investigational product must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of a serum pregnancy test is known. If pregnancy is confirmed, the investigational product will be withheld in an appropriate manner (eg, dose tapering if necessary for subject safety) until the pregnancy and any period of breast-feeding reaches its conclusion and the investigator and study Medical

Monitor are assured of the patient's ability to safely re-enter the study. Thereafter, investigational product may be resumed as for any other interruption after confirmation of subject safety and continued eligibility. Withdrawal from the study will not be required, but remains an option as described in Protocol Section 3.8. The decision to withdraw may include considerations such as; time remaining in the study; subject compliance with birth control measures; and desire to participate in available extension studies.

Subjects should be reminded of their right to learn their study treatment assigned if such knowledge will reasonably impact their reproductive decision or management of the pregnancy. Unblinding for this purpose will not influence further study participation, although subjective data may be excluded from analysis. Procedures for unblinding are detailed in Section 5.5 of this protocol and should be followed.

The investigator must immediately notify (within 24 hours) the sponsor's Pharmacovigilance Department of any pregnancy having the gestation period beginning within 30 days after the completion of investigational product administration. Record the event on the IRE form, and forward it to the sponsor's Pharmacovigilance Department. The sponsor's Pharmacovigilance Department will forward Pregnancy Surveillance Form(s) for monitoring the outcome of the pregnancy. Pregnancy will only be documented on the AE CRF if there is an abnormality or complication to be reported.

If the subject will be discontinued, then protocol-required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator must report to the sponsor on appropriate Pregnancy Surveillance form(s), follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months.

5.5 Procedure for Breaking the Blind

The investigator should not open the treatment assignment code UNLESS knowledge of the subject's treatment is required for the subject's clinical care and safety. The investigator must contact the sponsor's medical monitor by telephone or fax with an explanation of the need for opening the treatment assignment code before or within 24 hours of opening the code. Should a decision be made to break the blind, Clinical Safety & Pharmacovigilance and Biostatistics departments should be notified immediately.

Documentation of breaking the blind should be recorded in the subject's medical record with the date and time the blind was broken, and the names of the personnel involved.

5.6 Follow-up of Adverse Events

For this trial all adverse events will be followed up until last scheduled contact (for a minimum of 14 days after the last dose of investigational product is taken).

5.6.1 Follow-up of Non-serious Adverse Events

Non-serious adverse events that are identified on the last scheduled contact must be recorded on the AE case report form (CRF) with the current status noted. All non-serious events that are ongoing at this time will be recorded as ongoing on the CRF. In such cases, the investigator should follow-up appropriately; however, resolution of such events will not be captured in the CRF.

5.6.2 Follow-up of Post Trial Serious Adverse Events

Serious adverse events that are **identified on the last scheduled contact** must be recorded on the AE CRF page and reported to the sponsor according to the reporting procedures outlined in Section 5. This may include **unresolved previously reported SAEs**, or **new SAEs.** The investigator should follow these SAEs until the events are resolved, or the subject is lost to follow-up. Resolution means the subject has returned to the Baseline state of health, or the investigator does not expect any further improvement or worsening of the subject's condition. The investigator should continue to report any significant follow-up information to the sponsor up to the point the event has been resolved.

This trial requires that subjects be actively monitored for SAEs up to Follow-up Visit #2. Any new SAEs reported by the subject to the investigator that occur **after the last scheduled contact**, and are determined by the investigator to be reasonably associated with the use of the investigational product, should be reported to the sponsor. This may include SAEs that are captured at any time point after the defined trial period (ie, up to last scheduled contact). The investigator should follow serious related AEs identified after the last scheduled contact until the events are resolved, or the subject is lost to follow-up. The investigator should continue to report any significant follow-up information to the sponsor up to the point the event has been resolved.

6 Pharmacokinetic/Pharmacodynamic Analysis

6.1 Pharmacokinetic Analysis

Sparse samples will be taken for determination of tolvaptan and metabolite (DM-4103 and DM-4107) plasma concentrations. A population PK analysis will be performed and reported separately.

6.2 Pharmacodynamic Analysis

For tolvaptan compared to placebo:

Description statistics of absolute values at each visit and change from the last pre-dose value (Baseline or Day 1) will be determined for each variable. The pre-dose fasting spot urine osmolality will be used as Baseline for the trough spot urine osmolality assessments.

7 Statistical Analysis

This is a phase 3, multi-center, double-blind, placebo-controlled trial to determine long-term safety, tolerability and efficacy of split-dose oral regimens of tolvaptan tablets in a range of 60 to 120 mg/day in subjects with ADPKD. Subjects will be titrated weekly during the first three weeks, then stay at their individually maximally tolerated doses for 36 months. During the maintenance phase, investigators may choose to up titrate subjects, with medical monitor approval, if a change in clinical status, lifestyle or concomitant treatment suggest a possibility that a higher dose may be tolerated. Up titration should occur at regularly scheduled office visits unless approved by the medical monitor. Data for all dose regimens of tolvaptan will be combined and compared to the placebo group.

7.1 Data Sets for Analysis

The intent-to-treat (ITT) dataset is defined as a dataset including data from all subjects who are randomized. A subset of the ITT dataset is a dataset of non-hypertensive subjects, which is defined as all ITT subjects with no hypertension (sBP $\leq$ 139 and dBP $\leq$ 89 mmHg, (including untreated pre-hypertensive subjects) at Baseline. Another subset of the ITT dataset is a dataset of hypertensive subjects, which is defined as all ITT subjects with hypertension at Baseline (sBP > 139 or dBP > 89 mmHg). Other subsets of the ITT dataset are also available, and will be defined when needed.

For each of the datasets mentioned above, there are Observed Cases (OC) dataset, Last Observation Carried Forward (LOCF) dataset, and time to event dataset associated with it. The OC dataset will consist of only data points obtained from those subjects who are evaluated at the Baseline visit, post-Baseline visits during the trial, and end of trial/early termination visit, so that no imputation will be made for missing data. In the LOCF dataset missing data will be filled in by the subject's preceding non-missing value based on the OC dataset, except that Baseline value will not be carried forward. The time to event dataset will consist of all randomized subjects.

If a subject who has been randomized and taking investigational product discontinues from the use of investigational product, telephone contact for PKD Outcomes (PKD outcomes survey) will be performed at the normally scheduled trial visits to Month 36, Follow-up visit #1 and Follow-up visit #2. These data will not be used in the primary analysis, but may be utilized in an exploratory ITT analyses. In addition, data collected after resuming study medications for subjects whose study medications were interrupted for at least 30 consecutive days in the study maintenance phase will be excluded from all efficacy analyses, if the collected data falls in an interval, which starts from the beginning of the interruption period, with the interval length equal to 2 times of the interruption period.

7.2 Handling of Missing Data

For longitudinal analysis (to determine slope of change), missing data will be ignored. Missing data will also be treated as no event in time to event analysis, if the event is defined by observed data. For by visit analysis, missing data will be imputed by LOCF (LOCF analysis) or censored (observed analysis) or combined with "per protocol" data for strictly exploratory purposes.

7.3 Randomization

There are three stratification factors in this trial: presence of hypertension at Baseline, as defined as systolic blood pressure (sBP) >139 and/or diastolic blood pressure (dBP) >89 mmHg or treatment for elevated blood pressure), Baseline estimated creatinine clearance <80 ml/min and Baseline combined renal volume < 1000 cc. Thus there are eight strata in this trial. Centralized randomization will be performed in this trial so that subjects will be stratified by their Baseline hypertensive, estimated GFR (using Cockroft-Gault correction for gender and race), and renal volume status. Subjects will be randomized to tolvaptan or placebo in 2:1 ratio within each of the eight strata. Although institutional balancing will not be implemented in this trial, enrollment at individual sites will be

limited by quality of data generated and compliance with regulatory requirements. Because the subjects enrolled in Japan will be formally analyzed for registration in that country, and differences in clinical care in other regions, centralized randomizations will be performed in each region independently.

7.4 Efficacy Analysis

7.4.1 Primary Efficacy Outcome Analysis

Various sensitivity analyses endpoints will be discussed in the SAP

7.4.1.1 Analysis of the Primary Efficacy Endpoint

The primary endpoint in this trial is the rate of renal volume (total, both kidneys) change (normalized as percentage) from Baseline for tolvaptan relative to placebo. In order to derive the primary endpoint, MRI will be performed to evaluate total renal volume at Baseline (31 to approximately 14 days prior to randomization), Months 12, 24, 36/ET visits. Note that subject Early Termination could happen any time, say, at 1.5 or 2.5 years after randomization. An MRI will be done at the early termination visit only if an early termination occurs at least 6 months after the subject's last MRI acquisition. Hence for the purpose of statistical modeling, time to MRI from randomization will be treated as a continuous variable, expressed as years from date of randomization to date of MRI visit (date of MRI visit – date of randomization + 1, Baseline MRI will have a time of 0), instead of a class variable with values of 0, 1, 2, or 3.

In addition, in order to reduce heterogeneity in variance and achieve linearity over time, log10 transformation will be applied to the total renal volume data.[24] This logarithmic transformation is also supported by published data.[25]

The following linear mixed effect model[26] will be fitted to the log-transformed total renal volume repeated measures data:

$$Y_{ij} = \beta_1 + \beta_2\, t_{ij} + \beta_3\, Group_i + \beta_4\, t_{ij} \times Group_i + b_{1i} + b_{2i}\, t_{ij} + e_{ij},$$

In this model, Y_{ij} is the $\log_{10}$ (total renal volume) of subject i at visit j (j = 0, 1, 2, 3), where $Group_i = 0$ for a subject in the placebo group and $Group_i = 1$ for a subject in the tolvaptan group. β_1, β_2, β_3, and β_4 are fixed effects (β_1 is the intercept of placebo, $\beta_1 + \beta_3$ is the intercept of tolvaptan, β_2 is the slope of placebo, and $\beta_2 + \beta_4$ is the slope of tolvaptan), while b_{1i} and b_{2i} are random effects assumed to be normally distributed with mean 0 and unknown variance covariance structure. The error terms in the model, e_{ij}, are assumed mutually independent and normally distributed as $N(0,\sigma^2)$; and they are also assumed to be independent of the random effects, b_{1i} and b_{2i}. Note that t_{ij} is the time

(with unit year) from date of randomization to date of the j^{th} MRI visit for subject i, and these t_{ij} may be different from subject from subject.

The fixed effects parameters in the above model will be estimated using PROC MIXED of SAS (with default REML option). Specifically the following SAS statements will be used:

```
proc mixed;
    class subject treatment;
    model log10_total_renal_volume = treatment time treatment*time/ empirical
s;
    random intercept time / type=un sub=subject g;
run;
```

This SAS code is almost identical to the one given in SAS User's Guide[27] (page 2186) except an option of empirical, which uses the "sandwich" estimate of the variance covariance matrix to provide conservative p-values in the testing of the fixed-effect parameters. In the above model β_4 represents the $\log_{10}$ of the ratio of the geometric means of the yearly rate of percent change in the total renal volume between the two treatment groups. Hence the primary null hypothesis is H_0: $\beta_4 = 0$ versus the alternative hypothesis H_1: $\beta_4 \neq 0$. The test of the primary null hypothesis will be provided by testing the contrast of the treatment time interaction in the SAS statement, using the Wald test provided by PROC MIXED. A significance level of 0.05 (two-sided) will be used to declare statistical significance at the final analysis. In addition, estimate of the contrast and its 95% CI will be obtained. Anti-log of these statistics will provide an estimate of the ratio of the geometric means of annual percent changes (expressed as a ratio of one year renal volume prediction divided by Baseline renal volume "prediction") from Baseline of the two treatment group and its 95% CI. ITT OC dataset will be used in this analysis.

In addition to the primary analysis provided above, MMRM (Mixed Model Repeated Measures) analysis will be applied to the repeated measures of change from Baseline in total renal volume (based on logarithm transformed data) as a sensitivity analysis. LS Mean difference of the two treatment groups at Year 3 under the MMRM will be used to estimate the treatment effect at Year 3. The MMRM includes stratification factors (hypertensive status, renal volume status and creatinine clearance status at Baseline and geographic regions), visit, treatment, and treatment visit interaction as class variables and Baseline renal volume as covariate. Observed cases dataset will be used in this MMRM analysis.

7.4.1.2 Rationale for the Primary Efficacy Analysis and its interpretation

Note that the primary endpoint in the analysis provided above is the rate of renal volume (total, both kidneys) change (normalized as percentage) from Baseline instead of log renal volume. The two-stage random effect formulation which leads to the linear mixed effect model described by Fitzmaurice, Laird and Ware[28] provides an insight to this. In the two-stage random effect formulation, first, slopes will be derived from each subject using the log renal volumes for each subject using the following regression model:

$$Y_{ij} = a_i + b_i\, t_{ij} + \varepsilon_{ij},$$

Here the slope, b_i for subject i, could be expressed as a ratio of one year renal volume predictor divided by the Baseline renal volume "predictor" of subject i, and could be interpreted as a log of annual percent change in renal volume.[27] Second, these derived individual-specific slopes are treated as a random variable, and then are compared between the two treatment groups. Thus, the analysis provided in the previous section is indeed an analysis of the primary endpoint of the protocol.

In addition, there is no need to add quadratic terms to the model provided in the previous section, since renal volume data have been taken a log transformation to make the over time trend straight.[24] This tendency is also found from the log renal volume data presented from the CRISP trial.[14]

For the model provided in the previous section, it is better to treat the time as a continuous variable instead of a class variable, because a subject could early terminate at any time, say, at 1.5 or 2.5 years after randomization. If the time variable is treated as class variable, say, an early termination MRI performed at 1.5 years is treated as 2 years, 25% bias (= (1/1.5 – ½)/(1/1.5)) would be introduced to the data.

As commented by Fitzmaurice, Laird and Ware[28] on the linear mixed model proposed in the previous section, "…, the random effects covariance structure does not require a balanced longitudinal design. …, in principle, each individual can have a unique sequence of measurement times." This makes linear mixed models well suited for modeling data from inherently unbalanced longitudinal designs. Thus, this proposed primary analysis will enable us to handle the unexpected withdrawal structure inherited in this trial.

7.4.2 Secondary Efficacy Outcome Analysis

Various sensitivity analyses endpoints will be discussed in the SAP.

7.4.2.1 Secondary Composite Efficacy Analysis

The secondary composite endpoint of the protocol is time to multiple ADPKD clinical progression events. This secondary composite endpoint will be tested after the primary endpoint. There are four types of events here, which are progressive hypertension, severe renal pain, worsening albuminuria, and worsening renal function.

7.4.2.1.1 Definition of the Components in the Composite Secondary Endpoint

7.4.2.1.1.1 Events of Hypertension Progress

To define an event of hypertension progress, subjects' blood pressures are grouped into four categories: normotensive (dBP < 80 and sBP < 120 mmHg and off therapy), low-pre-hypertensive (sBP ≤ 129 and dBP ≤ 84 mmHg but not normotensive and off therapy), high-pre-hypertensive (sBP ≤ 139 and dBP ≤ 89 mmHg but not normotensive/low-pre-hypertensive and off therapy) and hypertensive (sBP >139 and/or dBP > 89 mmHg or on anti-hypertensive therapy). The higher of the systolic or diastolic blood pressure will determine category. So that there are six categorical increases based on blood pressure for subjects without anti-hypertensive therapy: normotensive to low-pre-hypertensive, normotensive to high-pre-hypertensive, normotensive to hypertensive, low-pre-hypertensive to high-pre-hypertensive, low-pre-hypertensive to hypertensive and high-pre hypertensive to hypertensive. An event will occur if a subject has made one of the six possible categorical increases over two consecutive visits (including an unscheduled visit), or a subject makes one of the six categorical increase at a visit and makes another one of the six categorical increase at the next consecutive visit (including unscheduled visit). Note that, for the later case, while the beginning categories are the same for the two categorical increases, the ending categories of these two categorical increase may not be the same. In this case, the subject is considered to have an event, ie, a categorical increase (from the common category) to the less severe ending category. The timing of the hypertensive event is defined as the scheduled visit time (such as 8 Months, etc) of the first of the two consecutive visits.

While a subject may have multiple events of hypertensive category shift, only the event with the ending category higher than all the events happened before it will be included in the analysis. For example, if a subject has an event of increasing from normotensive to hypertensive at visit Month 8, and after that the subject gradually reduces the hypertensive status to low-pre-hypertensive, and then at Month 24 the subject has another event of increasing from low-pre-hypertensive to high-pre-hypertensive or hypertensive, then only the first one at Month 8 will be included in the analysis. In this way, a subject at most can have three hypertensive events due to blood pressure during the trial.

Another kind of hypertensive progressive event derives from initiation of anti-hypertensive medication, or increasing doses in anti-hypertensive medication, or introducing new prescription of anti-hypertensive medication. In this case, a subject may have multiple events based on anti-hypertensive medication. An event qualifies to be included in the analysis if there is no event with equal or higher dose of the same medication before it. For example, if a subject increases the dose of ramipril from 2.5 mg to 7.5 mg at visit Month 12, and somehow is able to reduce the dose back to 2.5 mg later, and then increase the dose to 5 or 7.5 mg again at visit Month 36, then only the first one will be included in the analysis. However, if the dose increased at visit Month 36 is 10 mg of ramipril, then both events will be included in the analysis. The timing of this kind of hypertensive event is also defined as the scheduled visit time (such as 8 Months, etc.) when the medication is prescribed. Note that anti-hypertension medication introduction and adjustments ordered by health care professionals (such as the subjects Primary Care Physician, etc.) are also included for the consideration of hypertensive progressive events.

These two types of hypertensive progression events will be combined together as ADPKD clinical progression events in time to multiple event analysis. However, if a subject has both kinds of event at the same visit, then only one of them will be used in the analysis. Because they both are timed at the scheduled visit time, it does not matter which one will be selected.

7.4.2.1.1.2 Events of Renal Pain

Event of renal pain is defined as significant interventions for relief of renal pain. This would include (in decreasing order of significance) surgical or invasive radiological procedures, introduction or increasing the dose of narcotic or tricycle antidepressant medication, prescribing medical leave or activity restrictions or using a prescription non-narcotic which carries some risk to the subject for renal pain. The first prescribed surgical or invasive radiological procedure is considered an event of renal pain. If the first procedure has been performed, then the second prescribed surgical or invasive radiological procedure will also be considered as an event of renal pain. Any second prescribed surgical or invasive radiological procedure following an un-performed first procedure will be considered as an event of renal pain. The same criterion will be applied to the third and forth prescribed surgical or invasive radiological procedures, etc. The timing of this kind of renal pain event is the date of the visit (including unscheduled visit) at which such a procedure is prescribed.

To select multiple events due to introducing/increasing dose of narcotic or tricyclic antidepressant or other prescription for activity limitation or medication in analysis, the

criterion used in events developed by introducing/increasing dose of anti-hypertensive medication will also be applied here, ie, an event which qualifies to be included in the analysis if there is no event with equal or higher dose of the same medication before it. Applying the criterion here also implies that once a subject is given narcotic or tricyclic antidepressant medication, increasing doses of non-narcotic prescription is no longer considered an event in the analysis. The timing of this kind of renal pain event is also defined as the scheduled visit time (such as 8 Months, etc.) when the medication is prescribed

7.4.2.1.1.3 Events of Worsening Albuminuria

The third classes of ADPKD, clinical, progression events are events of worsening albuminuria. Categories of albuminuria based on urine albumin/creatinine ratio include "Normal" (urine albumin/ creatinine of < 2.8 mg/mmol female or < 2.0 mg/mmol male), "microalbuminuria" (urine albumin/ creatinine of 2.8-28 mg/mmol female or 2.0-20 mg/mmol male), and "overt proteinuria" (urine albumin/ creatinine of >28 mg/mmol female or >20 mg/mmol male).

An event of albuminuria is defined as a shift from lesser to higher categories at two of three consecutive visits using spot urine albumin/creatinine ratio or a shift at a visit and confirmed by an unscheduled albumin/creatinine ratio. There are three categorical increases: normal to microalbuminuria, microalbuminuria to overt proteinuria, and normal to overt proteinuria. An event will occur if a subject has made one of the three categorical increases twice, or a subject makes a change from normal to microalbuminuria first, and then reaches overt proteinuria next, or a subject makes a change from normal to overt proteinuria first, and reduces to microalbuminuria later, at two of three consecutive visits, or at a visit followed by an unscheduled albumin/creatinine ratio. The last two cases are both considered as making an event of increasing from normal to microalbuminuria at their first visit. Similar to the events of hypertensive categorical shift, while a subject may have multiple events of albuminuria category shift, only the event with the ending category higher than all the events happened before it will be included in the analysis. The timing of the albuminuria event is defined as the scheduled visit time of the first of the three consecutive visits.

7.4.2.1.1.4 Events of Worsening Renal Function

The fourth class of ADPKD clinical progression events is events of worsening renal function. These events are defined as a reduction of renal function equivalent to a 25% change in the reciprocal serum creatinine from Baseline defined as the value obtained at Week 3/End of Titration visit (see Section 3.7.3.3) and each subsequent further 25%

reduction based on the reciprocal serum creatinine observed at the previous event (see Table 3.7.3.3-1). A subject may have multiple events of worsening renal function, e.g., a subject having a serum creatinine of 0.9 mg/dL would need to reach a creatinine of 1.20 to have his first event, 1.60 the second, 2.13 the third and 2.84 the fourth, and so on. In this way, a subject may have multiple events of worsening renal function in the analysis with a doubling of the original serum creatinine occurring between the second and third/forth event. The timing of an event is defined as the visit time when the threshold was reached.

These four types of events will be pooled together as events of ADPKD clinical progression. If a subject has more than one event (an event of worsening renal function and an event of hypertension) occur at a visit, only one of them will be retained in the analysis. Worsening in blood pressure, albuminuria, and reciprocal serum creatinine at the end of treatment visit (Early Term or Month 36 visit) may be confirmed to be a clinical ADPKD progression event by using the data collected at the visit of post-treatment Follow-up #1 (+7 to + 21 days after the end of treatment visit). The timing of all these events is related to their visit. If a visit is one of the scheduled visits, the scheduled visit time (such as 8 Months, etc.) is the event time. If a visit is an unscheduled visit, the event time is the actual time (= (time of the unscheduled visit – time of randomization + 1)/30.5).

7.4.2.1.2 Analysis of Secondary Composite Endpoint

Two analyses of this secondary composite endpoint will be conducted. The first one includes all the events observed during the double blind treatment period starting from the date of first dose of study medication (for hypertension, proteinuria and kidney pain), and this analysis will be the primary analysis of this composite secondary endpoint. The second one includes all the events observed during the double blind treatment period from Week 3/End of Titration to the end of double blind treatment period, using Week 3/End of Titration as new Baseline. This analysis will be a sensitivity analysis of this endpoint. The proposal of this sensitivity analysis is due to possible un-stability during the switch of concurrent hypertensive medication per protocol in the titration period. In addition, an adjudication committee will be set up to adjudicate the events in the composite secondary endpoint. The adjudicated data will provide a sensitivity analysis to the endpoint with the analysis on all events and analysis on events starting from Week 3/End of Titration.

Analysis of time to multiple events using extended Cox model will be used for the analysis of the secondary composite endpoint. Specifically, the Andersen-Gill approach will be applied to the analysis of the ADPKD clinical progression events. Point estimate

of the hazard ratio will be provided, and the p-value will be provided by the robust Wald test. Details of the robust Wald test can be found in Therneau and Grambsch[29] and the SAS Institute publication SAS/STAT Software: Changes and Enhancements.[30]

All events of a subject will be ordered by their event time. The data of the composite secondary endpoint will have a counting process style of input: the first event will have a start time of randomization (time 0) and a stop time of the first event time, the second event will have a start time of the first event time and a stop time of the second event, etc. After the last event, a subject will still have an observation with a start time of the last event time and a stop time of trial completion/ early termination with a status of censored, if the last event occurs before trial completion/early termination. For a subject without an event during the trial, the subject will have only one observation with start time randomization and stop time trial completion/early termination with a censored status. As an example, suppose a subject 0001 treated by tolvaptan has a hypertensive event at Month 24, and a renal pain event at Month 32, and then completes the trial at Month 36 without any further events; and another subject 0002 treated by placebo has two hypertensive events at Months 8 and 28, two renal pain events at Months 16 and 28, and then has an albuminuria event and discontinues the trial at Month 29. The dataset will have the following form:

Table 7.4.2.1.2-1 Dataset Design

Subject ID	Start Time	Stop Time	Status	Treatment
0001	0	24	1	1
0001	24	32	1	1
0001	32	36	0	1
0002	0	8	1	0
0002	8	16	1	0
0002	16	28	1	0
0002	28	29	1	0

The SAS procedure of the analysis will use:

```
proc phreg covsandwich;
        model (start_time, stop_time)*status(0)= treatment/ ties=exact;
        id subject_id;
run;
```

Note that if the option of ties = exact turns out to be too cumbersome to run, the option may be changed to ties = Efron. The final option of ties will be stated in the Statistical Analysis Plan (SAP) before unblinding of the trial. This SAS procedure will provide the

parameter estimate and hazard ratio of the secondary composite endpoint, and use a robust sandwich estimate of the covariance matrix in the Wald test[30] to provide a robust p-value for the key secondary analysis. The covsandwich option of this procedure replaces a previous SAS macro %phlev which uses a SAS output dataset called dfbeta to derive the robust sandwich estimate of the covariance matrix used in the Wald tests, and the macro was used in the book of Therneau and Grambsch.[29] A significance level of 0.05 (two-sided) will be used to declare statistical significance at the final analysis.

As a supportive analysis, the same analysis will be applied to each kind of ADPKD clinical progression events. In addition, a time-to-first-event analysis will be provided where the event will be determined the first occurrence of any one of the four component events. This analysis will be done by the same method as described above.

7.4.2.2 Non-Composite Secondary Efficacy Endpoints

For tolvaptan compared to placebo:

1) Rate of GFR change from post-dose Baseline (End of Titration) to last on-drug trial visit (using 1/serum creatinine as primary measure while Cockcroft-Gault results will be exploratory)
2) For subjects who are non-hypertensive at Baseline, change from Baseline for resting mean arterial pressure (MAP) at scheduled clinic visits up to point of exposure to anti-hypertensive therapy for any reason
3) Change from Baseline in kidney pain as assessed by 1-10 pain scale as average AUC between Baseline and last trial visit or last visit prior to initiating medical (narcotic or tricyclic) or surgical therapy for pain
4) For subjects who are non-hypertensive at Baseline, time to progress to a) high-pre-hypertension (sBP > 129 and/or dBP > 84) or b) hypertension (sBP >139 and/or dBP >89 mm Hg) or c) requiring anti-hypertensive therapy
5) For subjects who are taking anti-hypertensive therapy at Baseline, percentage with clinically sustained decreases of BP leading to a sustained reduction in anti-hypertensive therapy compared to Baseline (while taking investigational product) at visit Months 12, 24 and 36 for hypertensive subjects

The other non-composite secondary efficacy endpoints will be tested after the key composite secondary efficacy endpoints using a two-sided alpha level of 0.05. These will be tested in the sequence indicated above, without adjustment for multiplicity

The analysis on non-composite secondary efficacy variable 1 (Rate of GFR from post-dose Baseline to last-dose value) will be similar to the analysis of the primary endpoint, except that the GFR value, instead of $\log_{10}$ scale of the GFR value, will be used in the analysis. This analysis will be applied to the ITT OC datasets. The primary GFR estimate used in the analysis will be one divided by serum creatinine value. In addition,

GFR estimated by Cockcroft-Gault formula will also be analyzed similarly. The formula of Cockcroft-Gault has been provided in 3.7.3.3 of the protocol. Again the ITT OC datasets will be used.

The analysis on non-composite secondary efficacy variable 2 (change from Baseline in resting mean arterial pressure (MAP) at scheduled clinic visits monitoring) will also be similar to the analysis of the primary endpoint, except that the MAP value, instead of its $\log_{10}$ scale, will be used in the analysis. This analysis will be applied to all the subjects with non-hypertensive status at Baseline. All the observations, from Baseline up to the ones observed just prior to the start of anti-hypertensive therapy for the subjects who start anti-hypertensive therapy during the trial, and from Baseline up to the last visit/early termination for the subjects who do not need anti-hypertensive therapy during the trial, will be used in the analysis.

For non-composite secondary efficacy variable 3 (change from Baseline in kidney pain as assessed by 1-10 pain scale as time average AUC between Baseline and last visit or last visit prior to initiating medical or surgical therapy) will be analyzed by ANCOVA with factors of treatment and Baseline stratification factors and covariate Baseline pain scale, using ITT OC dataset up to last trial visit for subjects without such a medical intervention during the trial or up to the last visit prior such a surgical intervention. Trapezoidal rule will be used to calculate the AUC, so that missing data between two records of pain scale reading will be ignored. The number of days used to divide the AUC to get its time average is equal to the date of the last visit defined above minus the date of randomization visit plus one.

The stratified log-rank test will be applied to non-composite secondary efficacy variable 4 (time to progressing to high-pre-hypertension, or hypertension, or requiring anti-hypertensive therapy for non-hypertensive subject) for tolvaptan to placebo comparison using non-hypertensive subject time to event dataset of the whole trial. The severity of these hypertensive events is defined from less severe to highly severe in the order from high-pre-hypertension, hypertension, to requiring antihypertensive therapy. An event will be included in the analysis of time to multiple events if there is no event with equal or high severity before it during the double blind trial period, so that a subject could have at most three events. The timing of an event is defined as the time of the scheduled visit time if the event is found at a protocol scheduled visit or equal to date of the unscheduled visit if the event is first documented at an unscheduled visit. Again, the data of the endpoint will have a counting process style of input (see Section 7.4.2.1.2). Non-hypertensive subjects who remain non-hypertensive or low-pre-hypertensive during the

trial will be considered censored, with time to censor = date of visit Month 36 (or Early Termination visit) - date of randomization + 1.

Non-composite secondary efficacy variable 5 (percentage of Baseline hypertensive subjects with clinically sustained decreases of BP leading to a sustained reduction in anti-hypertensive therapy compared to Baseline) will be analyzed by Cochran-Mantel-Haenszel statistic stratified by Baseline stratification factors at visit Months 12, 24 and 36 respectively. All subjects who are hypertensive and take anti-hypertensive therapy before randomization will be included in the trial. Subjects with clinically sustained decreases of BP leading to a sustained reduction in anti-hypertensive therapy compared to Baseline is defined as a subject whose blood pressure is lower than his/her blood pressure at Week 3/EOT (when subjects finish their dose titration) and whose dose of anti-hypertensive therapy is also lower than his/her visit Week 3 dose of anti-hypertensive therapy at visit Months 12, 24, and 36 respectively. LOCF dataset will be used for this analysis.

7.4.2.3 Safety Variables

Safety variables to be analyzed will include a descriptive summary of:

1) Reported Adverse Events
2) Vital signs
3) Clinical laboratory tests
4) ECG

Safety analysis is further described in Section 7.8.

7.4.2.4 Exploratory Variables

7.4.2.4.1 Urine Concentrating Ability

For tolvaptan-treated vs. placebo, change from Baseline values on Day 1 to Follow-up Visit #1 and Follow-up Visit #2 will be compared between treatment groups using ANCOVA with treatment and center as factors and baseline as covariate.

7.4.2.4.2 PKD Outcomes

Exploratory analysis will be conducted to the data of ADPKD outcomes and medical resource utilization collected in the PKD Outcome CRF page. Detailed analysis on these exploratory endpoints may be written in a statistical analysis plan specific for this exploratory analysis before unblinding the database.

7.5 Subgroup Analysis

Subgroup analysis of the primary, composite secondary and non-composite secondary endpoints will be conducted for age, gender and race subgroups. In addition, subgroup analysis will also be provided by geography regions.

7.6 Sample Size and Its Re-estimation

7.6.1 Sample Size Estimation

Sample size has been determined to statistically compare the combined tolvaptan dose groups to placebo, randomized in a 2:1 ratio, with an overall alpha 0.05 for the primary endpoint. However, since two interim analyses are planned, an alpha of 0.001 will be reserved for the first interim analysis, and an alpha of 0.004 for the second interim analysis (of the primary endpoint). Hence, the alpha level assigned for the final analysis of the primary endpoint is 0.050. The target power is 85%.

The most recent NIH-CRISP trial data indicated an average progression of renal volume to be about 6% per year. If an average untreated rate of progression of 7% is observed, and if we assume an average 20% rate reduction as clinically significant (although a lesser effect may also be very relevant to subjects and as a pharmacoeconomic benefit), and desire 85% power to detect this difference with a two-sided alpha of 0.050, then approximately 504 subjects (split 2 tolvaptan:1 placebo) are needed. This sample size calculation uses the sample size formula for longitudinal trial provided by J. Lefante and assumes (in log10 scale) the total noise standard deviation and the standard deviation of the slope across subjects are respectively about 0.017 and 0.0184, which were provided (0.017) or derived (0.0184) from the information provided by the HALT PKD web site.[25] [31] After an assumption of 20% withdrawal rate for the trial, about 600 subjects will be enrolled to the trial. By doubling this number, we effectively attain a power equivalent to two independent trials, while optimizing the operational management and enhancing the ability to evaluate the secondary composite endpoint which would require a higher number of subjects to achieve reasonable power.

The clinical significance of these changes can be better understood with the following illustration: Assume a subject at age 20 who progresses at 7%/year will have 3 doublings, i.e., renal volume increased to 8 times of the original size, by age 51 (31 years). If treatment leading to an effective reduction of 20% in the rate of volume increase begins at age 20, the same size, and all its consequent complications, won't be achieved until age 59 (39 years, a delay of 8 years). With a 30% rate reduction the same size is achieved at age 64 years (44 years, a delay of 13 years). Lesser degrees of reduction lead to shorter

delay in growth and manifestation of disease, however the impact of even 1 year's delay can be judged clinically relevant.

The sample size needed for the secondary composite endpoint is unknown at this planning stage since we do not have reliable information on the event rate of the secondary composite endpoint. This leads to the need for sample size re-calculation in this trial.

7.6.2 Blinded Sample Size Re-calculation

The blinded sample size re-calculation will be conducted after 1000 subjects have been enrolled or at least 200 subjects complete their 12 month visit, whichever comes first. In addition to the data for the secondary composite endpoint collected for these subjects, data for the frequency of the secondary endpoint observed during the screening period for all other subjects enrolled in the trial will also be utilized in order to maximize the amount of data available for this re-calculation. This will also allow us to have an opportunity to evaluate the event rate of the secondary composite endpoint. The sample size needed for first event analysis will be calculated using an assumption of 20% reduction in the event hazard by tolvaptan, ie, assuming a hazard ratio of 0.8. In addition, recurrent event (events after the first one) rate of the ADPKD clinical progression events will also be evaluated. Then the number of the subjects needed for the secondary composite analysis could be adjusted downward by comparing the standard errors of the parameter estimates provided by time to first event analysis. Detailed sample size calculation will be provided in the SAP.

Blinded sample size re-calculation is also needed for the primary endpoint, because the sample size estimated so far depends totally on the statistics provided by the web site of the HALT PKD trial, and on the assumption that a subject population with an average of 7% annual renal size growth rate would be enrolled to the trial.[25] Variance components and the average Baseline annual renal size percent growth rate will be derived in the blinded sample size re-calculation. If either the variance components turns out to be substantially larger than expected, or the average annual renal size growth rate turns out to be much lower than 7%, the sample size may be increased and/or the inclusion exclusion criteria may be amended to further enrich this trial with "rapid progressors". No penalty in significance level will be incurred in this sample size re-estimation.

At last, frequencies and variations of other secondary endpoints will be assessed during this blinded sample size re-calculation. After that, with combination of clinical consideration, a formal order of these other secondary endpoints will be developed for ordered statistical testing.

7.6.3 Projected Power of the Composite Secondary Endpoint

The blinded sample size re-calculation was conducted on Oct. 20, 2008 based on the available un-cleaned data, when more than 1000 subjects had been enrolled. This sample size re-calculation suggested that a total sample size of 1400 would be an appropriate size for this study, mostly driven by the consideration on the power of the composite secondary endpoint. It turns out that this sample size also falls into the sample size range of 1200 - 1500 originally specified in the protocol.

Based on the mostly recent data transfer in this study available before this Amendment 2, it was projected that there will be 975 first events and 2074 multiple events in this study using Day 1 Pre-dose as Baseline, and 872 first events and 1920 multiple events in this study using Week 3/End of Titration as Baseline. With an alpha of 0.05, it is projected that there will be at least 90% power to test 20% reduction in the composite secondary endpoint. However, since the real power of the study depends on the real number of events occurring at the conclusion of the study, this power projection only reflects the power we expect if everything falls into the assumption we made when we performed the power projection.

7.7 Analysis of Demographic and Baseline Characteristics

In general, Baseline measurements of safety and efficacy variables are defined as their last measurements prior to the first dosing on investigational product. The exception to this will be specified for each relevant variable.

Demographic characteristics and PKD medical history at Screening/Baseline will be summarized by descriptive statistics, eg proportion, mean, median, standard deviation, minimum and maximum values. Regardless of when reported, medical condition extant at time of trial entry will be considered “Baseline” for purposes of comparison to events occurring or recurring after initiation of enrollment.

7.8 Safety Analyses

Safety analysis will be conducted based on the safety dataset, which is defined as all subjects who consume at least one dose of investigational product. Safety variables to be analyzed include clinical laboratory tests, vital signs, electrocardiograms, and adverse events. Outcomes captured in the PKD Outcomes survey which qualify as new or worsened symptoms will be analyzed as a special class of AEs and will be presented in a separate summary table.

7.8.1 Adverse Events

All AEs will be coded by system organ class and Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. The incidence of the following events will be summarized by treatment groups:

- Treatment-emergent AEs (TEAEs) by severity
- TEAEs potentially causally related to the investigational product
- TEAEs with an outcome of death
- Serious TEAEs
- Discontinuations due to TEAEs

7.8.2 Clinical Laboratory Data

Summary statistics for changes from Baseline in the clinical laboratory measurements will be provided. Potentially clinically significant results in laboratory tests will also be summarized. Shift tables will be produced for assessing changes from Baseline in clinical laboratory measurements in low-normal-high scale.

7.8.3 Physical Examination and Vital Signs Data

By subject listing will be provided for physical examinations. Summary statistics for changes from Baseline in vital signs will be provided. Potentially clinically significant results in vital signs will also be summarized.

7.8.4 ECG Data

Summary statistics for changes from Baseline in electrocardiogram intervals will be provided. Incidence of categorical changes from Baseline in electrocardiogram results will also be summarized.

7.9 Interim analysis

No interim analysis will be performed for this study. The IDMC will monitor the study safety as well as efficacy.

8 Investigational Product Management

8.1 Packaging and Labeling

The investigational product will be provided to the investigators or permitted designees (eg, investigational product manager, pharmacist, nurse, depending on regional

regulations) by the sponsor (or contractor). Investigational product will be supplied as tablets of 15 or 30 mg tolvaptan (OPC-41061) or matching placebo. Each package used will be labeled to clearly disclose the subject ID, compound ID, trial number, the sponsor's name and address, instructions for storage and use, route of administration, and appropriate precautionary statements and required information by region. Any region-specific requirements will appear in the official language of the country in which the investigational product is to be used.

8.2 Storage

Investigational products will be stored in a securely locked cabinet or enclosure at the investigational site. Access should be strictly limited to the investigators or permitted designees (eg, investigational product managers, pharmacists, nurses, depending on regional regulations). The investigators, their permitted designees, and subjects are prohibited from providing investigational product to any person not participating in this protocol.

Investigational product should be stored according to the conditions specified in the investigational product label. The clinical site staff will maintain a temperature log in the drug storage area recording the temperature at least once each working day.

8.3 Accountability

The investigator, or designee, must maintain an inventory record of the investigational product (including investigational, active control, or placebo) received, dispensed, administered, and returned to assure regulatory authorities and the sponsor that the investigational product will not be dispensed to any person who is not a subject under the terms and conditions set forth in this protocol.

8.4 Returns and Destruction

Upon completion or termination of the trial, all unused and/or partially used investigational product must be returned to the sponsor or a designated agent.

All investigational product returned to the sponsor must be accompanied by the appropriate documentation and be clearly identified by protocol number and trial site number on the outermost shipping container. Returned supplies should be in the original containers (eg, subject kits). The assigned trial monitor should facilitate the return of unused and/or partially used investigational product.

9 Records Management

9.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include, but are not limited to, progress notes, electronic data, screening logs, and recorded data from automated instruments. All source documents pertaining to this trial will be maintained by the investigators and made available for direct inspection by authorized persons as defined in the ICF.

9.2 Data Collection

During each subject's visit to the clinic, a clinician participating in the trial will record progress notes to document all significant observations. At a minimum, these notes will contain:

- Documentation of the informed consent process, including any revised consents;
- List trial title and subject identifier upon trial start (in EU region);
- The date of the visit and the corresponding Visit or Day in the trial schedule;
- Documentation for the minimum number of kidney cysts as evidence of meeting Inclusion Criteria #2;
- General subject status remarks, including any significant medical findings. The severity, frequency, and duration of any adverse experiences and the investigator's assessment of relationship to investigational product must also be recorded;
- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed;
- The signature (or initials) and date of all clinicians who made an entry in the progress notes.

In addition, any contact with the subject via telephone or other means that provided significant clinical information will also be documented in the progress notes as described above. Any changes to information in the trial progress notes, other source documents, and case report forms will be initialed and dated on the day the change is made by a site trial staff member authorized to make the change. Changes will be made by striking a single line through erroneous data, and clearly entering the correct data (eg, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the clinician.

Information from the trial progress notes and other source documents will be promptly and LEGIBLY transcribed to CRFs for transmission to the sponsor. Changes will be made using the same process described above.

9.3 File Management at the Trial Site

It is the responsibility of the investigator to ensure that the trial center file is maintained in accordance with Section 8 of the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) and as required by applicable local regulations. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

9.4 Records Retention at the Trial Site

Regulatory requirements for the archival of records for this trial necessitate that participating investigators maintain detailed clinical data for the longest of the following three periods:

- A period of at least 2 years following the date on which approval to market the drug is obtained (or, if development of the investigational product is discontinued, the date on which development is discontinued); OR
- A period of at least 2 years after the date on which the trial is completed or terminated.

In addition, longer, region-specific storage requirements may apply. The investigator must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) providing an opportunity for the sponsor to collect such records. The investigator shall take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial. Such documentation is subject to inspection by the sponsor and relevant regulatory authorities. If the investigator withdraws from the trial (eg, relocation, retirement), all trial-related records should be transferred to a mutually agreed-upon designee within a sponsor-specified timeframe. Notice of such transfer will be given to the sponsor in writing.

10 Quality Control and Quality Assurance

10.1 Monitoring

The sponsor has ethical, legal and scientific obligations to carefully follow this trial in a detailed and orderly manner in accordance with established research principles, each region’s regulations and the ICH GCP Guideline. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the trial), the sponsor's monitors or designees will visit the center during the trial in addition to maintaining frequent telephone and written communication.

10.2 Auditing

The sponsor's Quality Management Unit (or representative) may conduct audits at the trial site(s). Audits will include, but are not be limited to, drug supply, presence of required documents, the informed consent process, and comparison of case report forms with source documents. The investigator agrees to participate with audits conducted at a reasonable time in a reasonable manner.

Regulatory authorities worldwide may also audit the investigator during or after the trial. The investigator should contact the sponsor immediately if this occurs, and must fully cooperate with the audits conducted at a reasonable time in a reasonable manner.

11 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, the ICH GCP Guidelines, and all other applicable regional regulatory requirements.[33] Each trial site will seek approval by an institutional review board or ethics committee according to regional requirements. The IRB/IEC will evaluate the ethical, scientific and medical appropriateness of the trial. Further, in preparing and handling CRFs, the investigator, sub-investigator and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject number and subject identification code will be used to identify each subject.

12 Confidentiality

All information generated in this trial must be considered highly confidential and must not be disclosed to any persons not directly concerned with the trial without written prior permission from the sponsor. However, authorized regulatory officials and sponsor personnel (or their representatives) will be allowed full access to inspect and copy the records. All investigational product, subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

Subjects will be identified only by initials and unique subject numbers in case report forms. Their full names may, however, be made known to a regulatory agency or other authorized officials if necessary.

13 Amendment Policy

The investigator will not make any changes to this protocol without prior written consent from the sponsor and subsequent approval by the IRB/IEC. Any permanent change to the protocol, whether it is an overall change or a change for specific trial site(s), must be handled as a protocol amendment. Any amendment to the protocol that appears indicated as the trial progresses will be fully discussed by the investigator(s) and the sponsor. If agreement is reached regarding the need for an amendment, it will be written by the sponsor. The written amendment must be submitted to the chairman of the IRB/IEC identified with this responsibility. Except for "administrative" or "non-substantial" amendments, investigators must await IRB/IEC approval of protocol amendments before implementing the change(s). Administrative amendments are defined to have no effect on the safety of the research subjects, scope of the investigation, conduct or management of the trial, quality, the scientific value of the trial, or the quality or safety of the investigational product(s) used in the trial. A protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately, and the IRB/IEC notified within 5 working days. The sponsor will ensure protocol amendments are submitted to the applicable regulatory agencies.

When, in the judgment of the chairman of the IRB/IEC, the investigators and/or the sponsor, the amendment to the protocol substantially alters the trial design and/or increases the potential risk to the subject, the currently approved written ICF will require similar modification. In such cases, repeat informed consent will be obtained from subjects enrolled in the trial before expecting continued participation.

14 References

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Appendix 1 Names of Otsuka Personnel

Clinical Director/Medical Directors:

Project Leader, Americas	Frank Czerwiec, M.D., Ph.D. Sr. Director, Global Clinical Development Otsuka Pharmaceutical Development & Commercialization, Inc 2440 Research Boulevard Rockville, MD 20850, USA Phone +01 (240) 683-3523 Fax +01 (301) 721-7523
Project Leader, Japan	Osamu Sato Clinical Director, Japan Otsuka Pharmaceutical Co., Ltd., Japan 3-2-27, Otedori, Chuo-ku Osaka 540-0021, Japan Tel: +81-6-6943-7722 Fax: +81-6-6920-2346
Project Leader, Region Europe, ROW	Dr. med. Burkhard Timmler European Project Leader Otsuka Frankfurt Research Institute GmbH Grüneburgweg 102 60323 Frankfurt am Main, Germany Phone +49 69 95 50 44 339 Fax: +49 69 95 50 44 50
Manager, Clinical Development	Suzanne Watkin Sr. Manager, Global Clinical Development, Otsuka Pharmaceutical Development & Commercialization, Inc 2440 Research Boulevard Rockville, MD 20850, USA Phone +01 (240) 683-3299 Fax +01 (301) 721-7299

Immediately Reportable Adverse Event	Clinical Safety and Pharmacovigilance Otsuka Pharmaceutical Development & Commercialization, Inc 2440 Research Boulevard Rockville, MD 20850 Phone (800) 438-9927 in USA or +01 (301) 212-5941 Fax: (800) 438-6030 in USA or +01 (301) 212-8633

Appendix 2 Institutions Concerned with the Trial

Lead Principal (Communicating) Investigator/ Steering Committee Chairman:

Vicente E. Torres, M.D., Ph.D.
Chair, Division of Nephrology
Mayo Clinic
200 First St. S.W.
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MRI Central Imaging:

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Project Management/Monitoring:

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900 Chelmsford Street
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IVR Systems:

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Central ECG Reading:

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8211 SciCor Dr.
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Sagamihara-shi,
Kanagawa, 229-1125, Japan

Prevalere Life Sciences
8282 Halsey Rd.
Whitesboro, NY 13492

Subject Recruitment/Retention:

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900 Chelmsford Street
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Investigational Materials:

Almac Clinical Services
2661 Audubon Road
Audubon, PA 19403

Appendix 3 Handling and Shipping of Bioanalytical Samples

Handling of Plasma Samples:

Sample Collection

All tubes must be labeled using the central lab's bar code labels provided with the sample collection kits. The central lab's requisition form must be completely filled out in regards to the pharmacokinetic (PK)/pharmacodynamic (PD) sample information. In addition, the subject number (NOT screening number) and date of collection must be hand-written on the sample tube. On the requisition form, it is important to note the exact time of the blood collection and the time that the most recent dose was taken.

Plasma Samples

Shipment of Plasma

Each frozen specimen must be sealed in a vial and labeled with a waterproof pen. The label containing the subject number and date of collection, must correspond to the requisition form, and must be firmly attached with transparent tape. The requisition form must contain the name, address and telephone number of the contact person from the trial site.

Twenty mL of blood (10mL for PK and 10 mL for Biomarkers) will be collected into sodium heparin tubes and should be gently inverted three to four times and then centrifuged at 2500 rpm for at least 10 minutes at 4 °C. The separated plasma from each tube should then be divided equally between the two bar-code labeled polypropylene tubes. The PK sample must be stored at -20 °C or below, the PD sample must be stored at -70 °C or below. The laboratory manual should be referenced for detailed instructions. One PK and one PD tube (primary sample) will be shipped on dry ice to the central lab. Following confirmation that the first tube arrived safely, the second tubes (backup samples) can also be shipped to the central lab.

PD Urine Sample

Each frozen specimen must be sealed in a vial and labeled with a waterproof pen. The label containing the subject number and date of collection, must correspond to the requisition form, and must be firmly attached with transparent tape. The requisition form must contain the name, address and telephone number of the contact person from the trial site.

For each of the spot urine collections specified, fifty mL of urine (for Biomarkers) will be collected and divided equally between the two bar-code labeled polypropylene tubes. The

PD samples must be stored at -70 °C or below. One PD tube (primary sample) will be shipped on dry ice to the central lab. Following confirmation that the first tube arrived safely, the second tube (backup sample) can also be shipped to the central lab.

Plasma and urine samples must be neatly packed in the kits provided by the central lab and restrained in a styrofoam container (place styrofoam container supplied within a cardboard box) with at least 15 to 20 pounds of dry ice. Boxes should be completely filled with dry ice to avoid air spaces that allow evaporation of the dry ice. The styrofoam container should be sealed with tape and placed in a cardboard box. The central lab must be alerted of sample shipment. Packages must not be shipped on Thursdays, Fridays, Saturdays, or any day prior to a holiday without the expressed consent of OPDC. Shipments from clinical sites will be via an overnight carrier to the central laboratory.

Appendix 4 Protocol Amendment/Administrative Changes

Amendment Number:
Issue Date: 28Mar2007
PURPOSE:
This amendment and administrative change will not affect the safety of subjects, the scope of the investigation or the scientific quality of the study. The amendment will delete the use of gadolinium contrast with MRI and clarify the evaluations of MRI. In addition, the screening period has been made optional and may occur up to 6 months prior to the Baseline visit. Some sections have been re-worded/re-phrased to provide clarity to the protocol. Typographical errors that were noticed after protocol approval have been corrected. The company name has been changed from Otsuka Maryland Research Institute, Inc. to Otsuka Pharmaceutical Development & Commercialization, Inc., a change occurring on January 1, 2007. Feedback obtained from various IEC, Regulatory Agencies and Investigators has been incorporated.

BACKGROUND:

Due to FDA Alert to Physicians issued in January 2007 expressing concerns with the use of gadolinium in subject with kidney disorders, the use of gadolinium was discontinued for this study. Numerous typographical errors and sections needing clarification were discovered and the sponsor company name was updated to reflect the new company name.

MODIFICATIONS TO PROTOCOL:

- **Bold and underlined text:** Changed Text
- ~~**Bold and strike through text:**~~ Deleted Text
- ***Bold and italicized text:*** Added Text

Cover Page and Protocol Synopsis

Add:

EudraCT # 2006-02768-24

Entire Document, updated with current name of company

Otsuka Maryland Research Institute, Inc.

Change to:

<u>Otsuka Pharmaceutical Development & Commercialization, Inc.</u>

Cover Page, updated address of Otsuka Pharmaceutical Co., Ltd., Japan

Otsuka Pharmaceutical Co., Ltd., Japan
3-2-27, Otedori, Chuo-ku
Osaka 540-0021, Japan

Change to:

Otsuka Pharmaceutical Co., Ltd., Japan
<u>2-9, Kandatsukasa-machi, Chiyoda-ku</u>
<u>Tokyo 101-8535, Japan</u>

Sponsor Trial Representatives, Region Europe, updated with new Project Leader for Region Europe

Change to:

Project Leader
Region Europe: Jolanta M. Wichary, M.D.
Head of Clinical Operations PKD
Otsuka Frankfurt Research Institute GmbH
Grüneburgweg 10260323 Frankfurt am Main, Germany
Tel: +49 69 95 50 44 378
Fax: +49 69 95 50 44 50

Non-sponsor Trial Representative, Independent Data Monitoring Committee Chair, updated with chair name and contact info

Add:

Interim Chair
Robert Schrier, M.D.
University of Colorado Health Science Center
Renal Diseases & Hypertension
Research Bridge 6403,
4200 E. Ninth Ave.
Denver, CO 80262
Phone: +01 (303) 315-8059

Protocol Synopsis, Criteria for Evaluation, Updated to include Exploratory endpoints

Add:

Exploratory Endpoints
Analysis of PKD outcomes and medical resource utilization

Protocol Synopsis, Inclusion/Exclusion, first bullet, removed typographical error

Delete:

~~**/1.73 m2**~~

Protocol Synopsis, Trial Assessments, first bullet, removed Sonogram as this is not a required trial assessment

Delete:

~~**renal sonography (if recent estimate of renal size is unavailable).**~~

Protocol Synopsis, Trial Assessments, second bullet, removed gadolinium contrast in MRI assessments in follow-up to FDA Alert to Physicians issued in January 2007

Delete:

MRI ~~**with gadolinium contrast**~~, blood pressure, ...

List of Abbreviations and terms is updated

Add:

AUC_t area under the concentration time-curve calculated to the time of the last observable concentration

OPDC Otsuka Pharmaceutical Development & Commercialization, Inc. (current name of the sponsor)

SUSAR- Suspected unexpected serious adverse reactions

Change:

OMRI-Otsuka Maryland Research Institute, Inc.***(former name of sponsor)***

Delete:

~~**Uosm urine osmolality**~~

Section 1.1 Nonclinical Data, Paragraph 1, sentence 3, updated to include metabolite affinity to V_2 receptors in addition to V_{1a}

Add:

Several tolvaptan metabolites (DM-4110, DM-4111 and MOP-21826) have affinity, but to a much lesser degree, for the human, rat and canine kidney V_2 receptors as compared to tolvaptan. None of the metabolites appear to have affinity for ***V_2 and*** V_{1a} receptors.

Section 1.1, Nonclinical Data, word trials replaced with word studies

Section 1.1, Nonclinical Data, Paragraph 4, Sentence 4, updated to provide most recent data from studies in nontoxic dose exposure in animals

Change to:

4.0- to 13.1-times higher than that in humans following administration of the compound at a dose of 60 mg/day. ~~**In-vitro trials have shown that tolvaptan or one of its metabolites may be phototoxic. Trials to further investigate these laboratory data are ongoing.**~~

Section 1.1, Nonclinical Data, Paragraph 5, updated to include data from in vitro studies

Add:

No phototoxicity was shown in the studies in guinea pigs and rabbits, though in vitro studies have suggested phototoxic potential of tolvaptan and one of its metabolites.

Section 1.1, Nonclinical Data, Paragraph 6, removed to reflect current data

Delete:

No male-factor effects were seen; however, appropriate precautions should be implemented for the inclusion of women of childbearing potential in clinical trials ~~**and caution should be used in areas of increased sun exposure**~~.

Section 1.2, Clinical Data, Paragraph 5, sentence 1, typographical error in protocol number corrected

Change to:

Two United States of America (US) phase 2 trials (156-04-248 and 156-04-249) and 1 Japanese trial (156-**0**4-001) were conducted to evaluate the safety, pharmacokinetics, and pharmacodynamics of tolvaptan in adults with ADPKD.

Section 1.2 Clinical Data, Paragraph 1, sentence 1, updated with most recent information on tolvaptan trials

Change to:

Tolvaptan **has completed** two Phase III trials for the treatment of hyponatremia associated with euvolemic and **hypervolemic** states and ***one Phase III trial in heart failure. It has also been studied in phase II*** as an adjunct to diuretic therapy to treat volume overload in patients with decompensated heart failure.

Section 1.4, Known and Potential Risks and Benefits, paragraph 1, updated with most recent IB information

Change to:

As of **04 August 2006, 531** healthy (non-ADPKD) volunteers have been exposed to tolvaptan in completed single (30 to 480 mg) and multiple dose (30 to 300 mg) Phase 1 trials in the United States, ***United Kingdom, Europe and Argentina***. In addition, **112** healthy volunteers have been

exposed to tolvaptan (1 to 120 mg) in trials conducted in Japan. ~~**and 78 healthy volunteers have been exposed to tolvaptan (5 to 60 mg) in trials in the UK.**~~ Safety data indicate that tolvaptan is well tolerated in healthy subjects. The most commonly reported adverse events (>10%) in healthy subjects treated with tolvaptan were thirst, dry mouth, frequent urination and non-specific headache.[10] ~~**Thirst was the most frequently reported adverse event (AE) in healthy volunteers and the only AE to show dose dependence; the incidence of thirst increased from 16.7% to 33.3%, 33.3% and 71.4% for the 30, 60, 90 and 120 mg dose groups, respectively.**[1, 10]~~

Section 1.4, Known and Potential Risks and Benefits, paragraph 4, sentence 1 added text based on most recent IB information

Add:

No subjects in any of the Phase 2, ***randomized, double-blind*** ADPKD trials experienced serious adverse events (SAEs) or withdrew because of adverse events.

Section 1.4, Known and Potential Risks and Benefits, paragraph 7, updated based on most recent IB information

Change to:

Tolvaptan has been shown to be primarily metabolized by CYP3A4. Peak tolvaptan concentrations are increased approximately 350% and total body clearance is decreased approximately 87% when tolvaptan is co-administered with ketoconazole. Therefore, subjects taking CYP3A4 inhibitors ***or ingesting grapefruit or Seville orange products*** would be expected to have higher concentrations of tolvaptan. ***While not specifically contraindicated, these agents should be avoided (see Section 4.1).*** ~~A dose reduction, or temporary lapse in tolvaptan therapy might therefore be recommended i~~**I**f a subject **must be** ~~is~~ prescribed a potent CYP3A4 inhibitor~~,~~ or ~~if~~ the subject experiences difficulty with polyuria, nocturia or excessive thirst while taking such drugs with tolvaptan***, the investigator must contact the medical monitor to discuss options***

including: a dose reduction, temporary or permanent withdrawal from tolvaptan therapy.[9,10]

Section 2.1 Trial Rationale, Paragraph 3, sentence 1, typographical error corrected

Delete:

For these reasons, this trial will evaluate efficacy and safety in subjects with preservation of at least 50% of residual renal function (estimated GFR ≥ 60 mL/min~~/1.73m^2~~) and where recent kidney size is consistent with rapid cystic growth.

Section 2.2, Dosing Rationale, Paragraph 1, changed to clarify twice daily dosing regimen

Add:

The twice-daily (q9h) regimen is designed to produce a maximal inhibition on waking with a gradual fall-off of effect during **sleep**. To this end, a higher dose is used **on awakening**, with a lower dose **approximately 9 hours later**. ***The ideal interval between doses is 9 hours in order to prevent increased urine production during the sleep period.***

Section 2.2 Dosing Rationale, Paragraph 6, changed text to clarify time of first dose and titration

Change to:

Therefore, this trial will implement a titration strategy. ~~On Day 1, all subjects will receive a single 15 mg dose of tolvaptan during the clinic visit, to minimize the first day effect and uniformly document date and time of first dose. On Day 2, subjects will begin the full daily dose regimen, starting at the relatively low daily dose of 45/15 and progressing to the highest tolerated dose. All subjects will be encouraged to progress to the highest dose as this is likely to be the most effective. Throughout the trial, subjects will have an option to down and up titrate, as circumstances warrant.~~ ***On Day 1, if subjects cannot begin their first dose (on awakening) by 11 am, they will begin with the afternoon dose. On Day 2, all subjects will begin the full daily dose regimen, starting at the***

relatively low daily dose of 45/15 and progressing to the highest tolerated dose. The day following their next weekly titration visit, subjects will begin the new titration regimen, provided tolerance at the previous dose was established. All subjects will be encouraged to progress to the highest dose as this is likely to be the most effective. Throughout the trial, subjects will have an option to down titrate, as circumstances warrant. During the maintenance phase, Investigator's may choose to up titrate subjects, with medical monitor approval, if a change in clinical status, lifestyle or concomitant treatment suggest a possibility that a higher dose may be tolerated. Up titration should occur at regularly scheduled office visits unless approved by the medical monitor.

Table 2.2-1, Tolvaptan/Placebo Dosing Schedule Example, changed to reflect nominal dose times 9 hours apart.

Change to:

Nominal Time
8 **AM** & **5 PM**

Table 2.2-1, Tolvaptan/Placebo Dosing Schedule, changed to remove ability to up/down titrate

Delete:

Week 3 to Month 36 [a]	8 AM & **5** PM	Highest tolerated regimen **~~(up and/or down titration allowed)~~**

Table 2.2-1, Tolvaptan/Placebo Dosing Schedule, Footnote 'a'

Change to:

[a]Actual time may vary depending on sleep cycle

Section 3.1, Type/Design of Trial, Paragraph 3, sentence 4, updated to reflect actual number randomized subjects and to clarify optional screening period

Change to:

It is anticipated that approximately 2000 subjects will need to be formally screened in order to obtain 1200**-1500** randomized subjects. Critical pre-screening parameters include serum creatinine and estimation of renal volume (by sonography) unless adequate historical radiographic data are

available. Sonography is preferable to MRI for pre-screening volume assessment because of wider availability. Informed consent must be obtained from each subject prior to conducting screening assessments. Eligibility will be determined prior to randomization, however, subjects ***signing Informed Consent*** may enroll in *an optional* non-treatment ~~**observation**~~ period (up to 6 months) to document the ~~**Baseline incidence of secondary composite parameters**~~ ***at the Investigator's discretion.***

Section 3.1, Type/Design of Trial, Paragraph 5, sentence 4, updated to reflect actual centralized analysis by region

Delete:

Centralized randomization will be performed in this trial so that subjects will be stratified by their Baseline hypertensive status, renal function and renal volume. ~~**Because the subjects enrolled in Japan will be formally analyzed for registration in that country, centralized randomizations will be performed independently in each of the major regions: the Americas, Japan and Europe plus the rest of the world (ROW).**~~

Section 3.1, Type/Design of Trial, Paragraph 6, sentence 2, updated to clarify when up titration dose should be administered

Add:

Subjects will begin treatment with the lowest dose and after each 1-week safety assessment, titrate to the next higher dose treatment group***, on the subsequent day,*** until a level of intolerability is reached.

Section 3.1, Type/Design of Trial, Delete Paragraph 7

Delete:

~~**A separate open-label extension safety trial is planned. Subjects completing the treatment phase of this trial will be eligible for that trial, if it is approved and available in their region**~~.

Section 3.1, Type/Design of Trial, Study Schematic, updated to reflect optional screening and remove reference to open label trial

Section 3.2.1, Investigational Product, changed to reflect length of study, clarify dosing times and clarify requirements for dose titration

Change to:

Tolvaptan or placebo tablets (as multiples of 15 or 30 mg) will be given orally twice daily ***for three years***. ***Dosing should occur*** ~~(~~on waking and approximately 9 hours later~~)~~, irrespective of meals. Exact timing of dosing may be adjusted based on wake/sleep habits (eg, standard 8 AM and 5 PM may be switched to 10 PM and 7 AM if working a night shift). However, dosing times should be consistent for each individual's daily dose to avoid breakthrough. Doses will initially be titrated weekly beginning with a 45/15 mg regimen and progressing to 60/30 mg and 90/30 mg, if tolerated. Subjects may ~~**up- or**~~ down-titrate at any time, depending on their current dose. **During the maintenance phase, Investigators may choose to up titrate subjects, with medical monitor approval, if a change in clinical status, lifestyle or concomitant treatment suggest a possibility that a higher dose may be tolerated. Up titration should occur at regularly scheduled office visits unless approved by the medical monitor.** ~~Doses will be given for up to 3 years. Doses will be given for up to 3 years. The Investigator may dechallenge (ie,interrupt use of investigational product) and rechallenge investigational product as needed to aid in assessment of adverse event causality. Subjects unable to tolerate the 45/15 mg dose will be discontinued from investigational product use yet continue with PKD outcomes assessments in the trial, see Section 3.7.3.6.~~

Section 3.2.2, Treatment of Hypertension, Paragraph 1, changed to further clarify use of diuretics during the trial and sodium changed to salt and statement added to clarify variance in regional medical practices

Change to:

...Use of diuretics are not preferred as they may impact certain assessments (eg, urine sodium or osmolality). ***Therefore, chronic use of diuretics to control hypertension will not be allowed. Subjects using diuretics for this purpose must sign a informed consent and agree to a change in this therapy before being deemed eligible.*** Blood pressures determined at two consecutive visits will be used to determine blood pressure status.The recommendations for treatment agents have not yet

met clinical equipoise in all regions for high-normal blood pressure (pre-hypertensive [sBP 120-139 and/or dBP 80-89 mm Hg), however since ADPKD subjects are at greater risk for developing renal dysfunction, treatment with prescribed medications will be required (unless otherwise contraindicated) in subjects at the higher limit of this range (sBP 130-139 and/or dBP 85-89 mm Hg) and recommended, but optional, at the lower end of this range (sBP 120-129 and/or dBP 80-84 mm Hg.In addition, standard region- specific recommendations for dietary restrictions (eg, **salt**[< 5g/day], protein [<1 g/kg/day], and caffeine ≤ 2 coffee equivalents/day, ***please note these are only examples and may not reflect regional medical practice***) and adequate fluid intake (see below) will be reiterated at all visits during the trial (with consideration for cultural differences). Subject compliance will be **noted as stated by subject.** If significant...

Section 3.2.3, Fluid Intake, Sentence 4, text added to clarify percentage of change in body weight which should be reported

Change to:

Acute changes of greater than 3% of body weight ***(increase or decrease)*** over any 7-day period should be noted. ***Subjects should be instructed to report acute changes in body weight to the trial physician for further evaluation and recommendations.***

Section 3.3.3, Sentence 1, typographical error removed

Delete:

Subjects will have a GFR ≥60 mL/min ~~/1.73m^2~~ (by using Cockcroft-Gault with correction for gender and ethnicity). A GFR of 60 mL/min ~~/1.73m^2~~ represents Stage 2 kidney disease according to the US National Kidney Foundation

Section 3.4.1, Informed Consent, Paragraph 1, sentence 5, removal of information regarding ICF translations from the protocol

Delete:

~~**Translations of the ICF into the subject populations' native language should be certified and have been back translated with sponsor approval of the back translation.**~~

Section 3.4.1, Informed Consent, Paragraph 6 deleted

Delete:

~~**A separate open-label extension safety trial is planned. Subjects completing the treatment-phase of this trial will be eligible for that trial, if it is approved and available in their region.**~~

Table 3.4.2-1, Change Inclusions 4 & 5

Change to:

4. Estimated GFR ≥ 60 mL/min~~**/1.73m^2**~~ within -31 days of randomization.
5. Rapid estimated rate of renal volume increase based on total renal size ≥750 cc by MRI at randomization. [Excluding, ~~**as possible**~~, those ~~**clearly**~~ meeting criteria solely due to six or fewer predominant cysts.]

Table 3.4.3-1, Change Exclusions 1, 2 4 & 5

Change to:

1. Subjects who have clinically significant allergic reactions to tolvaptan or chemically related structures such as benzazepines (benzazepril, ***conivaptan, fenoldopam mesylate*** or mirtazapine), those with critical electrolyte imbalances, ***or low blood volume***, those with clinically significant anemia, pregnant or breast-feeding women.]
2. Subjects who are unlikely to adequately comply with the trial's procedures. [For example: Subjects having medical conditions likely to require an extended interruption or discontinuation during the first year

of trial, with ~~recurrent recent~~ ***a history of*** substance abuse (~~illicit drugs or alcohol~~ ***within the last 3 years***) with a history of persistent non-compliance with anti-hypertensive or other important medical therapy.]

4. Subjects ***taking medications or*** having concomitant illnesses likely to confound endpoint assessments [For example: ~~advanced diabetes (ie, fasting glucose >126 and glycosuria by dipstick)~~***chronic use of diuretics, advanced diabetes (ie, those with pure glycemic control evidenced by a history of severely elevated hemoglobin A1C, or with evidence of advanced retinopathy, nephropathy or peripheral vascular disease due to micro-or-macro vascular disease),*** evidence of significant renal disease (ie, currently active glomerular nephritidies), renal cancer, single kidney, recent (within last 3 years) renal surgery etc.]

5. Subjects taking other experimental ***(ie, non marketed)*** therapies, or taking approved therapies for the purpose of affecting PKD cysts, or those taking or have a history of taking tolvaptan. [For example: tolvaptan, anti-sense RNA therapies, rapamycin, ***sirolimus, everolimus***, somatostatin analogs (ie, ***octreotide,sandostatin***), recent (within 3 years) or anticipated cyst decompression, etc.]

Section 3.5.2.2 non-composite Secondary Efficacy Endpoints, changed order of text

Change to:

1) For subjects who are non-hypertensive at Baseline, change from Baseline for resting mean arterial pressure (MAP) at scheduled clinic visits up to point of exposure to anti-hypertensive therapy for any reason.
2) For subjects who are non-hypertensive at Baseline, time to progress to a) high-pre-hypertension (sBP > 129 and/or dBP > 84) or b) hypertension (sBP >139 and/or dBP >89 mm Hg) or c) requiring anti-hypertensive therapy.
3) For subjects who are taking anti-hypertensive therapy at Baseline, percentage with clinically sustained decreases of BP leading to a sustained reduction in anti-hypertensive therapy compared to Baseline (while taking investigational product) at visit Months 12, 24 and 36 for hypertensive subjects.

4) Rate of GFR change from postdose Baseline (End of Titration) to last on-drug trial visit (using 1/serum creatinine as primary measure while Cockcroft-Gault results will be exploratory).
5) Change from Baseline in kidney pain as assessed by 1-10 pain scale as average AUC between Baseline and last trial visit or last visit prior to initiating medical (narcotic or tricyclic) or surgical therapy for pain.

Section 3.5.2.6 Exploratory Variables, Clarification of required time point for collection

Add:

Fasting urine osmolality ***(at randomization visit only)***

Section 3.6, Measures to Minimize/Avoid Bias, Paragraph 2, re-phrased for clarification

Change to:

All blood and urine chemistry, ***ECG*** and MRI endpoint data will be analyzed and read centrally. Local ~~laboratories~~ **laboratory** ***and local ECG data collected*** for safety purposes, will not be included in the clinical database (other than in comments ***or with findings captured on the CRF as AEs*** as appropriate). The imaging charter will define measures to be used to limit central reader bias. ~~**For example temporal bias may be minimized by using multiple readers and employing pooled, non-sequential reading with blinding of scan dates and subject or visit identifiers.**~~

Section 3.7.1, Schedule of Assessments, Updated to reflect current requirements of the protocol as indicated in revised text.

Section 3.7.1.1, Screening , Paragraph 1, Changed text to make screening optional

Change to:

3.7.1.1. ***Optional*** Screening ~~**(Up to Month -6 to Day -32)**~~ (***Up to 6 Months prior to Baseline Visit***)

At any time, subjects may be pre-screened with review of medical history (per local regulations) but must be consented prior to undergoing any screening assessments. Investigators may pre-screen using existing and recent laboratory or imaging data ***including sonogram***. Subjects' preliminary eligibility will be evaluated formally once obtaining an informed consent, with a complete PKD history and optional screening examination, ~~**sonogram (if needed)**~~. Subjects may be asked to participate in a screening period for up to 6 months, ~~**in order to gather data on the Composite Secondary Efficacy Endpoint in the screened population**~~ ***at the Investigator's discretion.*** ~~**This will provide a Baseline (non-treatment) estimate of event rates for secondary composite endpoints and exploratory endpoints critical for evaluating power and statistical management of those endpoints.**~~

Section 3.7.1.1, Screening , Paragraph 4, added assessments to be completed at screening, regroup/renumber assessments

Add:

1) Present, discuss and sign informed consent
8b) Baseline clinical safety collection (blood and urine chemistry, hematology, coagulation, urinalysis)

Section 3.7.1.2, Baseline (Day -31 to day -14), sentence 1, deleted sentence as no longer applies since screening period is optional

Change to:

~~**After the first three months of trial initiation, new subjects may enter directly into Baseline assessment without having a Screening visit.**~~

Section 3.7.1.2, Baseline (Day -31 to day -14), Bullet 1, removed reference to other section of the protocol

Delete:

1) Present, discuss and sign informed consent if not already obtained ~~**(as described in Section 3.4.1)**~~

Section 3.7.1.3, Randomization (Day 1), Item 1, updated terminology to reflect appropriate abbreviation

Change to:

1) Update medical/**ADPKD** history

Section 3.7.1.3, Randomization (Day 1),Item 7, updated to specify pregnancy test obtained for WOCBP and requirements for blood/urine collection

Add:

Collect blood and/or urine for:
a) Urine pregnancy test ***for WOCBP***
b) Clinical safety collection (blood and urine chemistry, hematology, coagulation, urinalysis)

Section 3.7.1.3, Randomization (Day 1), Item 8, updated to specify requirement that subject should be NPO

Add:

Collect fasted ***(NPO)*** urine osmolality sample from subject. Dispense collection vessel and instructions for collecting non-fasting trough urine sample for determination of osmolality at Week 3 (or End of Titration).

Section 3.7.1.3, Randomization (Day 1), Item 10, changed text for clarification

Add:

~~**Complete**~~ ***Assess*** Baseline PKD Outcomes ***and document in source***

Section 3.7.1.3, Randomization (Day 1), Item 12, added text for further clarification of time of first dose

Add:

If the subject can not begin their first dose ***(on awakening)*** by 11 AM, they will begin with the afternoon dose.

Section 3.7.1.3, Randomization (Day 1), Item 14, clarification of amount of medication dispensed

Add:

14) Dispense trial medication (sufficient for 1 ***Week*** **<u>of dosing</u>**). Arrange for next visit

Section 3.7.1.4, Title, added text for clarification

Add:

3.7.1.4 Dose Titration ***Visits*** (Week 1, 2 and 3 / End of Titration [ie, days 7, 14 , 21 ± 2 days])

Section 3.7.1.4, Dose Titration, Paragraph 1, Sentence 2, added text for clarifications of changes in body weight which should be assessed

Add:

An interim unscheduled visit or telephone contact may occur to assess wide fluctuations in body weight (ie, >3%/week, ***increase or decrease***) or to evaluate AEs.

Section 3.7.1.4, Dose Titration, Paragraph 2, Sentence 2, added text for clarification of up titration parameters

Add:

If the answer to this is "Yes" the subject will be prescribed the next available higher dose of tolvaptan for the next visit, ***provided clinical assessment of tolerability is also positive.***

Section 3.7.1.4, Dose Titration, Item 1, updated terminology to reflect appropriate abbreviation

Change to:

Update medical/**<u>ADPKD</u>** history

Section 3.7.1.4, Dose Titration, Item 4, Added text for clarification of tolerability assessment

Add:

Assess tolerability (***medical and subject-driven***)

Section 3.7.1.4, Dose Titration, Item 8a, updated to specify pregnancy test obtained for WOCBP

Change to:

Urine pregnancy test ~~**(Week 3 or End of Titration visit only)**~~ ***for WOCBP***

Section 3.7.1.4, Dose Titration, Item 11, re-worded for clarification

Change to:

~~**Complete**~~ ***Document*** PKD Outcomes ~~**Survey**~~ ***in source*** (Week 3 or End of Titration visit only)

Section 3.7.1.6, Safety and Efficacy Clinical Visits, added text for clarification

Add:

Safety & Efficacy Clinical ***Maintenance*** Visits (Months 4, 8, 12, 16, 20, 24, 28, 32, & 36 [± 2 weeks]/Early Termination [+2 weeks])

Section 3.7.1.6, Safety & Efficacy Clinical Visits, Item 1, updated terminology to reflect appropriate abbreviation

Change to:

Update medical/**ADPKD** history*

Section 3.7.1.6, Safety & Efficacy Clinical Visits, Item 4, Added text for clarification of tolerability assessment

Add:

Assess tolerability (***medical and subject-driven***)

Section 3.7.1.6, Safety & Efficacy Clinical Visits, Item 10, re-worded for clarification

Change to:

~~**Complete**~~ ***Document*** PKD Outcomes ~~**Survey**~~ ***in source*** for past 4 months

Section 3.7.1.6, Safety & Efficacy Clinical Visits, Last Paragraph

Change to:

Subjects who withdraw from Investigational product use only will not have these tests performed past* the ~~Not done past**~~ ET visit ~~**if subject withdraws from Investigational product administration as described in** Sections 3.8.3 and 3.7.3.6.~~

Section 3.7.1.7, Follow-up Telephone Contact (7 [+7] days), Item 4, re-worded for clarification

Change to:

~~**Complete**~~ ***Document*** PKD Outcomes ~~**Survey**~~ ***in source***

Section 3.7.2.1, Clinical Laboratory Data, Paragraph 2, Sentence 2, added text for clarification

Add:

Female subjects who are capable of bearing children will **have** ~~test~~ their urine ***tested*** in clinic prior to trial entry (Screening, Baseline and Day 1).

Table 3.7.2.1-1, Clinical Laboratory Tests, Tests for Efficacy and PKD Biomarkers, Tests for GFR, albumiuria and concentrating ability, added required laboratory test

Add:

Creatinine clearance ***(calculated for eligibility only)***

Section 3.7.2.2, Physical Examination and Vital Sign Data, Paragraph 1, Correct typo, add clarifications

Change to:

Directed physical exams (examinations focused only on new or ongoing complaints or symptoms and to collect protocol specified measures) may be performed at Screening, Day 1, Weeks 1, 2, 3 (or End of Titration), Months 4, 8, 12, 16, 20, 24, 28, 32, 3***6/ET*** and as directed at the 7-day Follow-up. In some regions, more frequent subject visits may be the norm; ~~however vital signs and clinically significant physical findings will only be recorded as source and recorded in the next visit's CRF as applicable. Any changes in medication or adverse events will be recorded in the CRF~~. **therefore, vital signs and clinically significant physical findings will be documented as source and recorded on unscheduled CRF pages**. Any ***clinically significant physical findings,*** changes in medication or adverse events will be recorded in ***the source documents and subsequently transcribed on to*** the CRF.

Section 3.7.2.2, Physical Examination and Vital Sign Data, Paragraph 2, Sentence 5, deleted words to correct grammar

Delete:

If the appointed designee is to perform the physical exam, he/she must be permitted by local regulations and his/her name must be included on ~~**the and**~~ any globally and locally required documents (eg, individual must be added for all sites on a US FDA Form 1572, while local regulations determine their being named in the ICF).

Section 3.7.2.3, ECG Data, reworded paragraph for clarification

Change to:

Standard 12-lead ECGs will be performed at trial Baseline, Day 1, Week 3 (or End of Titration visit) and at 36 Month/ET ***and at intervals dictated by individual clinical condition or regional requirements.*** ECG recording will include 10 seconds of full 12-lead strip (displaying 2.5-3 seconds) with a lead-2 rhythm strip. ~~**At a minimum**~~, ECGs should be printed in duplicate. ***High-quality photocopies should be made only if duplicate printing is not possible.*** ~~**with o**~~***O***ne original ***reading is*** to be kept by the

site and the other to be ***sent to eRT for*** ~~**collected by the sponsor if later**~~ central reading ***after monitoring by the CRA.*** ~~**or evaluation is required.**~~ If only one ***original*** is available, a same size photocopy will be retained at the site as "source", while the original***, after monitoring,*** is **sent** ~~collected~~ unless regional differences mandate otherwise. The local investigator or a qualified designee will assess the ECG's clinical relevance, noting this on the ECG ~~**and CRF**~~**label and source documents. Any clinically relevant findings meeting AE criteria should be recorded on the appropriate CRF page.**

Section 3.7.2.4 Tolerability Question, Sentence 2, added text to provide clarification of titration parameters

Change to:

If the answer to this is "Yes" the subject will be prescribed the next available higher dose of investigational product, ~~**until the next titration visit**~~ ***provided clinical assessment of tolerability is also positive.***

Section 3.7.2.4 Tolerability Question, Sentence 6, deleted typographical error

Change to:

~~**This**~~ **Any dose** change should be recorded by the Investigator using the IVRS system.

Section 3.7.2.5 Dietary Recommendations, Paragraph 1, Sentence 3, added text for clarification

Change to:

Therefore, beginning at screening, ***and in the absence of alternate regional recommendations*** all subjects should be instructed to keep dietary **salt** < 5g/day and dietary protein <1 g/kg/day.

Section 3.7.2.5 Dietary Recommendations, Paragraph 1, Sentence 5, added/removed text for clarification

Change to:

It is recognized that there may be some regional variability in level ~~**of**~~ ***restrictions or ability to maintain*** compliance with one or more of these guidelines, therefore the CRF should capture ***self-reported qualitative*** compliance ~~**and the strictness of the prescription (eg if sodium is held only to <10 g/day**~~ ***and the site specific recommendations for dietary intake.***

Section 3.7.2.5 Dietary Recommendations, Paragraph 2, Sentence 4, added text regarding interaction between Seville orange products and study drug action

Add:

Additionally, subjects should be advised that the ingestion of grapefruit or Seville orange products might affect the study drug's actions and these should be avoided. In the event of an unintentional ingestion of such products, the investigator may ask the subject to delay or withhold a dose of study medication.

Section 3.7.3.1, Magnetic Resonance Imaging Assessments, Paragraph 1, Sentence 4, removal of requirement to obtain MRIs with gadolinium contrast in follow-up to FDA Alert to Physicians issued in January 2007

Delete:

~~**All MRI scans will be obtained with contrast.**~~

Section 3.7.3.1, Magnetic Resonance Imaging Assessments, Paragraph 1, Sentence 5, Gadolinium contrast will not be used therefore, gadolinium reactions will not be relevant exclusionary criteria

Delete:

Subjects with ferro-magnetic prostheses, aneurysm clips, severe claustrophobia, ~~**or severe gadolinium reactions**~~ or other contraindications or exclusions interfering with the MRI endpoint will be excluded from participation.

Section 3.7.3.2 Hypertension Assessment, Paragraph 1, Sentence 4, changed text for clarification

Change to :

In clinic, measurements will be performed by a trained trial team member ideally using a manual mercury, aneroid ***or if validated, an oscillometric blood pressure device*** (in order of preference as is allowable by local regulations) with the appropriate cuff size. ~~**Aneroid devices should be calibrated at least yearly.**~~

Section 3.7.3.2 Hypertension Assessment, Paragraph 1, Sentence 4, added text for clarification

Add :

Measurements will be repeated at least twice (two additional measures will be performed if either replicate of sBP or dBP vary by > 5 mmHg), each replicate separated ~~**by at least 1 minute of rest.**~~ ***by an appropriate (for that device or technique) interval of rest.***

Section 3.7.3.2 Hypertension Assessment, Paragraph 1, Sentence 8, typo corrected and text added for clarification

Add :

Subjects blood pressure will be categorized according to Table

3.7.3.2-1, ***where the higher category of either the systolic or diastolic measure will determine the subject's category.***

Section 3.7.3.2, Hypertension Assessment, Paragraph 2, re-phrased for clarification

Change to:

Changes to medications used to control blood pressure should be documented in source and entered onto appropriate CRFs capturing concomittant medications and hypertension outcomes. Please refer to the case report form completion guidelines for further instructions. ~~**An assessment of whether prescribed medications to control blood pressure were adjusted**~~ Anti-hypertensive therapy is to be started or

adjusted as noted in the hypertension treatment guidelines in ***Section*** 3.2.2, only after measures at two consecutive visits (including unscheduled visits, which should be used if significant changes in BP are noted) meet guideline requirements. While in some subjects, self-blood pressure monitoring or ambulatory blood pressure monitoring may be clinically indicated or recommended, these values will not be used for determination of clinical endpoint data, they may however, be considered in determining whether prescribed medications should be adjusted.

Section 3.7.3.3, Renal Function, Paragraph 2, grammatical corrections, remove reference to open label study and reword for clarification

Change:

For the "Composite Secondary Efficacy Endpoint", the reciprocal serum creatinine will be **the** primary analysis with any consistent (defined two consecutive visits separated by 2 weeks including unscheduled assessments) 25% reduction from Baseline in the reciprocal ***being*** ~~**a will be**~~ classified as an event occurring at the date of the first included value.

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 reciprocal serum creatinine value at the Baseline visit may also be used to determine rate of GFR change for those subjects participating in the open-label extension trial (predose visit).**~~

Section 3.7.3.3, Renal Function, Paragraph 5, re-phrased for clarification

Change:

The reciprocal creatinine ~~**measure**~~ i***s independent of spurious changes in body weight and therefore is more likely to represent a more accurate assessment of change in renal function based on a simple blood test. Therefore, the reciprocal creatinine*** will be used for all endpoint assessments as it provides a measure of change in GFR***. Other formulae which include assessment of gender, weight and other factors will provide a more accurate prediction of actual GFR.*** ~~**which least**~~

~~influenced by changes in anthropomorphic measures and shifts in weight which may not contribute to creatinine (such as obesity and fluid shifts), it does not provide an estimate of GFR.~~ Therefore, to determine eligibility for the trial, the Cockcroft-Gault formula will be used. The 6- or 4-component (modification of diet in renal disease [MDRD] formula is not preferred as its accuracy around a GFR of 60 mL/min**~~/1.73m^2~~** is questionable and ***so*** will be not be used to estimate GFR. [20] ...

Section 3.7.3.3, Renal Function, Paragraph 6, Sentence 1, changed to reflect the correct laboratory specimen

Change:

Per instructions from the central laboratory, the **blood** **~~urine~~** volume to be collected will be sufficient volume to allow replicate analysis by the central laboratory if needed.

Section 3.7.3.5, Renal Pain Assessment, Paragraph 2, Bullet 5, re-phrased for clarification

Change:

- prescription of other "last resort" ***medications, over the counter*** or prescription analgesics (ie, medications ***for*** which **~~for~~** an individual subject might have other relative contraindications such as gastric erosion, bleeding, renal toxicities**~~, but not use of generally accepted as safe over the counter medicines or herbs which carry little risk to the subject~~**)

Section 3.7.3.6, PKD History and Outcomes, Header, removal of word survey to be consistent with wording used in CRF

Delete:

PKD History and Outcomes **~~Surveys~~**

Section 3.7.3.6, PKD History and Outcomes, Paragraph 1, re-worded for clarification

Change:

~~**A short PKD History Survey will capture information from the subject's recollection, and documented past medical history where available**~~. ***Patients will be asked about their PKD History at all visits. This information should be recorded as source data in the patient's medical records and transcribed on to the appropriate CRF page. PKD History will capture information from the subject's recollection, and documented past medical history where available.*** This ***information*** should be updated at each visit if new information regarding past history becomes available. ~~**The**~~ PKD Outcomes ~~**survey**~~ will ***be*** collect***ed at all study visits and will collect*** information relevant to the medical, social and economic consequences of new and ongoing PKD-related morbidities. ***This information should be recorded as source data in the patient's medical records and transcribed on the appropriate CRF page.*** New clinically relevant information and specific questions about outcomes will be updated at visits Screening, Day 1, Week 3 (or End of Titration), Months 4, 8, 12, 16, 20, 24, 28, 32, 36/ET and 7-day Follow-up Telephone Contact. ~~**The subject will complete a PKD history survey, if possible with the assistance of their personal physician, once during screening**~~.

Section 3.7.3.6, PKD History, Paragraph 3, Sentence 1, delete the word survey to be consistent with wording in the CRF

Delete:

Medical resource utilization (office/ER healthcare visits, hospital admissions, procedures and therapies) and productive days lost due to PKD outcomes will be reported for subjects as part of the PKD outcomes ~~**survey**~~.

Section 3.7.4.1, Trough Urine Osmolality, MCP-1, Paragraph 2, Sentence 6, deleted additional text to allow for exploratory analysis of selected samples

Change:

Selected samples ~~**will**~~ ***may*** be assayed ~~**for those subjects that show increases in serum creatinine based on the criteria described in Section 3.7.3.3. For analysis, the urine MCP-1/urine creatinine ratio will be reported.**~~ ***at a later date for exploratory purposes.***

Section 3.7.4.2, Blood for Cystatin C and BUA, Paragraph 1, Sentence 4, deleted additional text to allow for exploratory analysis of selected samples

Change:

Selected samples ~~**will**~~ ***may*** be assayed ~~**for those subjects that show increases in serum creatinine based on the criteria described in Section 3.7.3.3.**~~ ***at a later date for exploratory purposes.***

Section 3.7.4.2, Blood for Cystatin C and BUA, Paragraph 2, Sentence 3, added text to permit exploratory analysis of selected samples

Add:

Selected samples may be assayed at a later date for exploratory purposes.

Section 3.7.6.1, Urine Concentrating Ability, Paragraph 2, Sentence 2, removed reference to open label extension study

Delete:

~~**The fasting urine osmolality value at the Day 1 visit may also be used to determine the change in urine concentrating ability for those subjects participating in the open-label extension trial (predose visit).**~~

Section 3.7.8, Independent Data Monitoring Committee, Paragraph 1, added text regarding safety review of data until IDMC is formed

Add:

A safety oversight committee for tolvaptan's nephrology programs has been established by the sponsor for the review of safety data from the tolvaptan ADPKD program. This body will provide interim safety evaluation until the IDMC for this trial is formed.

Section 4.1, Prohibited Medications, added prohibited medications and clarification to other medication which may be exclusionary

Add:

Medications or surgical therapies used for the purpose or potential for modifying the progression of PKD cyst growth or development will be prohibited. These include, but are not restricted to somatostatin agonists, anti-sense RNA therapies, tolvaptan, and other vasopressin antagonists (eg, OPC-31260 ***(mozavaptan)***, Vaprisol (conivaptan), lixivaptan) or agonists (eg, desmopressin [DDAVP]) and cyst decompression surgery.

Continuous or short term use of other medications, while not prohibited, may be restricted by the investigator because of the potential for interference with metabolism or efficacy endpoints. This includes the use of diuretics which can be used intermittently but not within 7 days of a urine assessment. Chronic use of diuretics (eg, for hypertension) would be prohibited due to potential endpoint interference. Patients taking such agents must first sign an ICF and then agree to be switched to an alternate form of therapy in order to be eligible for the trial. Since tolvaptan is a weak CYP3A4 substrate, potent CYP3A4 inhibitors should be avoided during the trial, with the exception of amiodarone which was found to have no effect on tolvaptan. A partial of list CYP3A4 inhibitors can be found in Table 4.1-1.

Table 4.1-1 CYP3A4 inhibitors (partial list)			
amprenavir	***atorvastin***	***aprepitant***	***chloramphenicol (if used orally)***
cimetidine	***clarithromycin***	***clotrimazole (if used orally)***	***danazol***
delavirdine	***diltiazem***	***erythromycin***	***fluconazole***
fluvoxamine	***indinavir***	***isoniazid***	***itraconzazole***
josamycin	***ketoconazole (if used orally)***	***nelfinavir***	***nefazadone***
quinupristin/ dalfopristin	***ritonavir***	***saquinavir***	***troleandomycin***

Table 4.1-1 CYP3A4 inhibitors (partial list)			
amprenavir	***atorvastin***	***aprepitant***	***chloramphenicol (if used orally)***
verapamil	***Seville orangeproducts***	***Grapefruit products***	

Section 5.1, Definitions, Paragraph 2, Bullet 3, added text for clarification

Add:

requires in-patient hospitalization or prolonged ***existing*** hospitalization

Section 5.5, Procedure for Breaking the Blind, Sentence 3,

Delete:

Should a decision be made to break the blind, ~~**Otsuka's**~~ Clinical Safety & Pharmacovigilance and Biostatistics departments should be notified immediately.

Section 7, Statistical Analysis, Paragraph 1, delete phrase regarding titration at any point in trial since titration should occur at regularly scheduled office visits unless approved by the medical monitor.

Change:

This is a phase 3, multi-center, double-blind, placebo-controlled trial to determine long-term safety, tolerability and efficacy of split-dose oral regimens of tolvaptan tablets in a range of 60 to 120 mg/day in subjects with ADPKD. Subjects will be titrated weekly during the first three weeks, then stay at their individually maximally tolerated doses for 36 months. ~~**Titration during any subsequent point in the trial is possible. Data for all dose regimens of tolvaptan will be combined and compared to the placebo group.**~~

During the maintenance phase, Investigator's may choose to up titrate subjects, with medical monitor approval, if a change in clinical status, lifestyle or concomitant treatment suggest a possibility that a higher dose may be tolerated. Up titration should occur at regularly scheduled office visits unless approved by the medical monitor. Data for all dose

regimens of tolvaptan will be combined and compared to the placebo group.

Section 7.3, Randomization, Sentence 1, delete typographical error

Delete:

There are three stratification factors in this trial: presence of hypertension at Baseline, as defined as systolic blood pressure (sBP) >139 and/or diastolic blood pressure (dBP) >89 mmHg or treatment for elevated blood pressure), Baseline estimated creatinine clearance <80 ml/min~~/1.73m^2~~ and Baseline combined renal volume < 1000 cc.

Section 7.3, Randomization, Paragraph 1, added text for clarification

Add:

Subjects will be randomized to tolvaptan or placebo in 2:1 ratio within each of the eight strata. ***Although institutional balancing will not be implemented in this trial, enrollment at individual sites will be limited by quality of data generated and compliance with regulatory requirements.*** Because the subjects enrolled in Japan will be formally analyzed for registration in that country, and differences in clinical care in other regions, centralized randomizations will be performed in each region independently:

Section 7.4.1.1, Analysis of Primary Efficacy Endpoint, Paragraph 1, Sentence 1, added text for clarification

Add:

The primary endpoint in this trial is the rate of renal volume (total, both kidneys) change (normalized as percentage) from Baseline ***for tolvaptan relative to placebo***.

Section 7.4.1.1, Analysis of the Primary Efficacy Endpoint, Paragraph 6, Sentence 1, correct spelling error

Change to:

This SAS code is almost identical to the one given in SAS User's Guide[29] (page 2186) except an option of **empirical,** which uses the "sandwich" estimate of the variance covariance matrix to provide conservative p-values in the testing of the fixed-effect parameters.

Section 7.4.1.2, Argument and Interpretation of the Primary Efficacy, Header, title changed to more accurately reflect the information in this section

Change to:

Rationale for the Primary Efficacy Analysis and its interpretation

Section 7.4.2.1.1, Events of Hypertension Progress, Paragraph 1, Sentence 2

Add:

The higher of the systolic or diastolic blood pressure will determine category.

Section 7.4.2.1.1, Events of Hypertension Progress, Paragraph 3, Sentence 7, added text for clarification

Add:

The timing of this kind ***of*** hypertensive event is also defined as the scheduled visit time (such as 8 Months, etc.) when the medication ***is*** prescribed. ***Note that anti-hypertension medication introduction and adjustments ordered by health care professionals (such as the subjects Primary Care Physician, etc.) are also included for the consideration of hypertensive progressive events.***

Section 7.4.2.1.1.4, Events of Worsening Renal Failure, Paragraph 1, Sentence 1, typographical error corrected

Change to:

The **fourth** class of ADPKD clinical progression events is events of worsening renal function.

Section 7.4.2.1.1, Events of Hypertension Progress, Paragraph 2, Sentence 1, grammatical error corrected

Add:

These four types of events will ***be*** pooled together as events of ADPKD clinical progression.

Section 7.4.2.1.1, Events of Hypertension Progress, Paragraph 2, Sentence 2, typographical error corrected

Delete:

If a subject has more than one event (an event of worsening renal function and an event of hypertension) occurr~~ed~~ at a visit, only one of them will be retained in the analysis.

Section 7.4.2.2, Non-Composite Secondary Efficacy Endpoints, order of items listed changed

Change:

1) For subjects who are non-hypertensive at Baseline, change from Baseline for resting mean arterial pressure (MAP) at scheduled clinic visits up to point of exposure to anti-hypertensive therapy for any reason.
2) For subjects who are non-hypertensive at Baseline, time to progress to a) high-pre-hypertension (sBP > 129 and/or dBP > 84) or b) hypertension (sBP >139 and/or dBP >89 mm Hg) or c) requiring anti-hypertensive therapy.
3) For subjects who are taking anti-hypertensive therapy at Baseline, percentage with clinically sustained decreases of BP leading to a sustained reduction in anti-hypertensive therapy compared to Baseline (while taking investigational product) at visit Months 12, 24 and 36 for hypertensive subjects.

4) Rate of GFR change from postdose Baseline (End of Titration) to last on-drug trial visit (using 1/serum creatinine as primary measure while Cockcroft-Gault results will be exploratory).

5) Change from Baseline in kidney pain as assessed by 1-10 pain scale as average AUC between Baseline and last trial visit or last visit prior to initiating medical (narcotic or tricyclic) or surgical therapy for pain.

Section 7.4.2.2, Non-Composite Secondary Efficacy Endpoints, Paragraph 5, Sentence 1, typographical error corrected to Month 24

Change:

Non-composite secondary efficacy variable 3 (percentage of Baseline hypertensive subjects with clinically sustained decreases of BP leading to a sustained reduction in anti-hypertensive therapy compared to Baseline) will be analyzed by Cochran-Mantel-Haenszel statistic stratified by Baseline stratification factors at visit Months 12, ***24~~3~~*** and 36 respectively.

Section 7.4.2.2, Non-Composite Secondary Efficacy Endpoints, Paragraph 5, Sentence 3, text added to clarify Week 3 or EOT

Add:

Subject***s*** with clinically sustained decreases of BP leading to a sustained reduction in anti-hypertensive therapy compared to Baseline is defined as a subject whose blood pressure~~s~~ is lower than his/her blood pressure at Week 3***/EOT*** (when subjects finish their dose titration) and whose dose of anti-hypertensive therapy is also lower than his/her visit Week 3 dose of anti-hypertensive therapy at visit Months 12, 24, and 36 respectively.

Section 7.4.2.4.1, Urine Concentrating Ability, added text regarding exploratory analysis of PKD Outcomes obtained

Add:

An exploratory analysis of the PKD Outcomes including medical resource utilization will be performed.

Section 9.3, Source Documents, Paragraph deleted as this information is redundant with information in section 9.1

Delete:

~~**Source documents are defined as first documented results of original observations and activities of a clinical investigation. Source documents will include, but are not limited to, progress notes, electronic data, screening logs, and recorded data from automated instruments. All source documents pertaining to this trial will be maintained by the investigators and made available for direct inspection by authorized persons. In Japan, it is anticipated that the CRF will be utilized as "source" for certain information not usually recorded in a subject chart. This will include reason for discontinuation, assessment of investigational product relationship, and comments on ECGs.**~~

Appendix 1, Updated to include the most current Otsuka Personnel

Appendix 2, Updated to include the institutions concerned with the trial

ADDITIONAL RISK TO THE SUBJECT:

The FDA alert concerning the use of gadolinium contrast in subjects with abnormal renal function has been added to this protocol. The use of gadolinium contrast for MRI has been removed.

Amendment Number:

Issue Date: 10 Sep 2009

PURPOSE:

This amendment and administrative change is intended to clarify the endpoints of the trial, allow for administrative changes and will not affect the safety of subjects or the scientific quality of the study.

The amendment will remove the 7 day follow visit and add two off study drug follow up visits. The statistical section has been clarified for the composite secondary endpoint and addition of an independent adjudication committee. The interim analysis has been removed. Provisions have been made for Subjects who become unintentionally pregnant during their trial participation. In addition, some sections have been re-worded/re-phrased to provide clarity to the protocol. Typographical errors/inconsistency across sections within the protocol that were noticed after protocol approval, have been corrected. **BACKGROUND:**

This amendment will provide confirmation and clarification of the primary, key secondary and other secondary endpoints. The two additional off study drug visits have been added to assess persistence of effects on hypertension, renal function, pain and albuminuria as well as safety of the Subjects upon study treatment withdrawal. An independent adjudication committee has been added to assess/confirm events of the composite secondary endpoints. The interim analysis requires secondary composite endpoints at predicted event rates. Any decision related to the endpoints would not be possible prior to the minimum events being reported which would be unlikely prior to 2 years/termination of the trial. For this reason the interim analysis has been removed. Numerous typographical/administrative errors and sections needing clarification were discovered.

MODIFICATIONS TO PROTOCOL:

- **<u>Bold and underlined text:</u>** Changed Text
- ~~**Bold and strike through text:**~~ Deleted Text
- ***Bold and italicized text:*** Added Text

COVER PAGE

Change to:

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Immediately Reportable Adverse Event	Clinical Safety and Pharmacovigilance Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Boulevard Rockville, MD 20850 Phone (800) 438-9927 in USA or +01 (301) 212-5941 Fax: (800) 438-60**30** in USA or +01 (301) 212-**8633**

Non-sponsor Trial Representatives:

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Independent Data Monitoring Committee Chair ~~**(Interim)**~~	**Sidney Goldstein, MD** **Henry Ford Hospital** **2799 West Grand Blvd** **Detroit, MI 48202, USA** **Phone: +01 (313) 303-5728**

Synopsis

Change to (Evaluation Section):

Non-composite Secondary Efficacy Endpoints:

For tolvaptan compared to placebo:

1) ~~**For subjects who are non-hypertensive at Baseline, change from Baseline for resting mean arterial pressure (MAP) at scheduled clinic visits up to point of exposure to anti-hypertensive therapy for any reason**~~ **Rate of GFR change from post-dose Baseline (End of Titration) to last on-drug trial visit (using 1/serum creatinine as primary measure while Cockcroft-Gault results will be exploratory)**

2) ~~**For subjects who are non-hypertensive at Baseline, time to progress to a) high-pre-hypertension (sBP > 129 and/or dBP > 84) or b) hypertension (sBP >139 and/or dBP >89 mm Hg) or c) requiring anti-hypertensive therapy**~~ **For subjects who are non-hypertensive at Baseline, change from Baseline for resting mean arterial pressure (MAP) at scheduled clinic visits up to point of exposure to anti-hypertensive therapy for any reason.**

3) ~~**For subjects who are taking anti-hypertensive therapy at Baseline, percentage with clinically sustained decreases of BP leading to a sustained reduction in anti-hypertensive therapy compared to Baseline (while taking investigational product) at visit Months 12, 24 and 36 for hypertensive subjects.**~~ **Change from Baseline in kidney pain as assessed by 1-10 pain scale as average area under the concentration -time curve (AUC) between Baseline and last trial visit or last visit prior to initiating medical (eg, narcotic or tricyclic) or surgical therapy for pain**

4) ~~**Rate of GFR change from post-dose Baseline (End of Titration) to last on-drug trial visit (using 1/serum creatinine as primary measure while Cockcroft-Gault results will be exploratory)**~~ **For subjects who are non-hypertensive at Baseline, time to progress to a) high-pre-hypertension (sBP > 129 and/or dBP > 84) or b) hypertension (sBP >139 and/or dBP >89 mm Hg) or c) requiring anti-hypertensive therapy**

5) ~~**Change from Baseline in kidney pain as assessed by 1-10 pain scale as average area under the concentration -time curve (AUC) between Baseline and last trial visit or last visit prior to initiating medical (eg, narcotic or tricyclic) or surgical therapy for pain**~~ **For subjects who are taking anti-hypertensive therapy at Baseline, percentage with clinically sustained decreases of BP leading to a sustained reduction in anti-hypertensive therapy compared to Baseline (while taking investigational product) at visit Months 12, 24 and 36 for hypertensive subjects**

Exploratory Endpoint

1~~) Analysis of PKD outcomes and medical resource utilization~~ **Fasting urine osmolality (at randomization and Follow-up visit #2 only)**

2) ADPKD outcomes and medical resource utilization. Analysis of additional events attributed to ADPKD for tolvaptan-treated subjects as compared to placebo, including their health-economic outcomes

Trial Duration

Up to 6 Months initial screening and secondary endpoint frequency observation, 3 years treatment, ***2-6 weeks follow up,*** 5 years total to last subject complete (estimated completion date 201~~1~~**2**)

List of Abbreviations and Definitions of Terms

Add:

EOT	***end of titration***
MMRM	***mixed model repeated measures***

1 Introduction

Change to:

(Paragraph 1, sentence 9)

Human autosomal dominant polycystic ***kidney*** disease (ADPKD) subjects have elevated plasma AVP concentrations or exaggerated response of AVP to sodium challenge and their cyst fluid cAMP levels are elevated by AVP suggesting similar mechanisms may be responsible for disease progression across species and causative mutations

Section 3.1 Type/Design of Trial

Change to:

(Paragraph 3, sentence 1)

The trial will enroll (randomize) approximately 1200-1500 ADPKD subjects naive to tolvaptan to obtain long-term data on approximately 1000 ***- 1200*** (20% withdrawal).

(Paragraph 5, sentence 1)

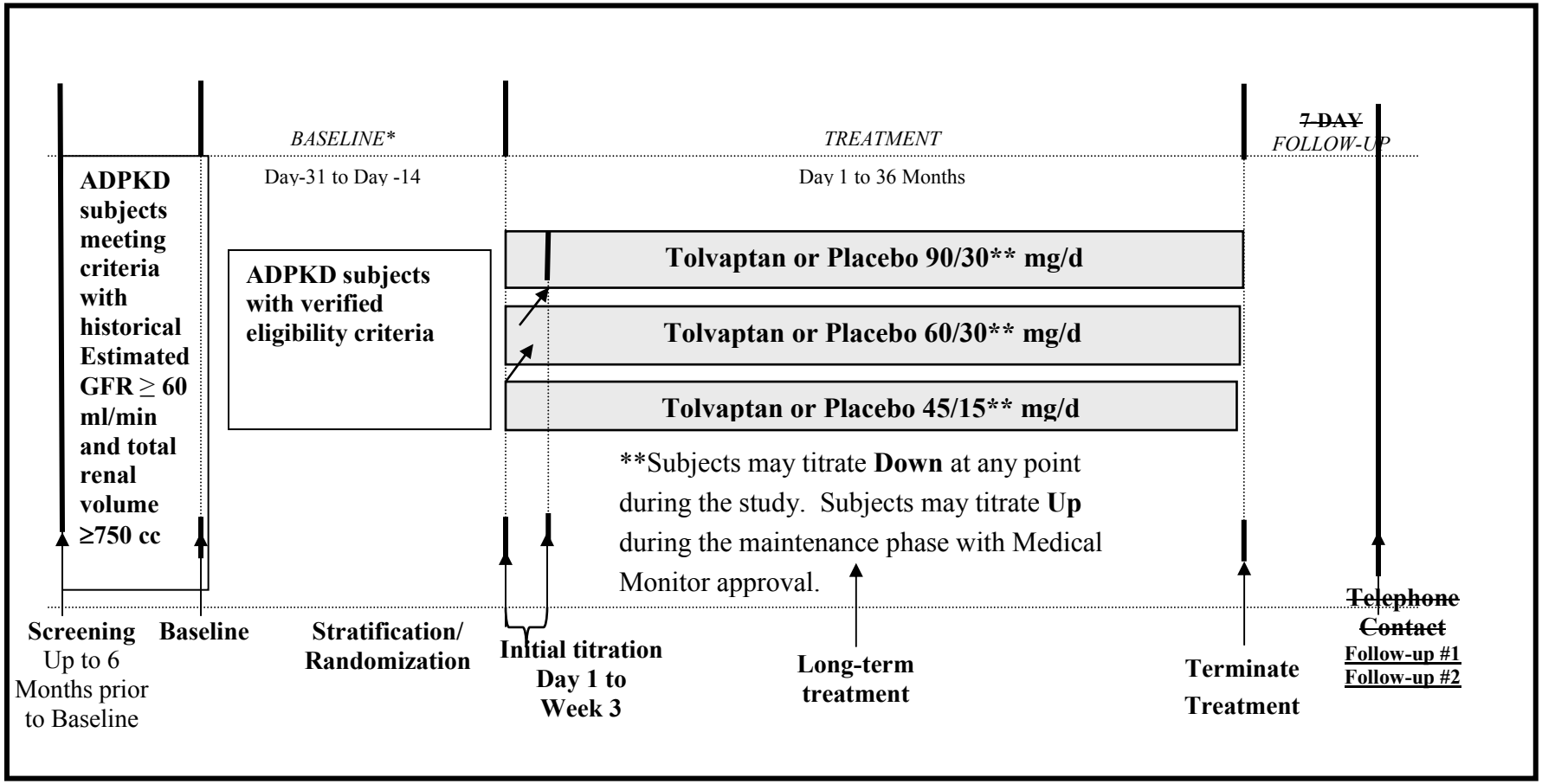
At randomization, Baseline assessments will be established and subjects will be randomly assigned to one of the two treatment groups (2:1 ratio, tolvaptan:placebo) stratified on presence of hypertension at Baseline (systolic blood pressure [sBP] > 139 and/or diastolic blood pressure [dBP] > 89 mmHg or anti-hypertensive treatment), Baseline estimated creatinine clearance (<80 ml/min~~**/1.73m^2**~~) and Baseline combined renal volume (<1000 cc). Thus there are eight strata in this trial.

(Paragraph 5, sentence 7)

Subjects withdrawing from this trial ~~**will not be eligible for participation in other open-label tolvaptan trials, but**~~ will be offered continued follow-up for outcomes on a telephone contact basis to Month 36 ***and the additional follow-up period.*** The treatment phase of this trial is planned to continue for 3 years, unless terminated by the DSMB/IDMC for safety, futility or significant evidence of clinically relevant efficacy. ***Subjects will be followed in-person for an additional period after treatment discontinuation to further assess safety and persistence of tolvaptan effects. The IDMC will define appropriate rules for making such recommendations in their charter.***

Figure 3.1-1 Trial Design Schematic

Change to:



Section 3.5.2.1 Composite Secondary Efficacy Endpoints

Change to:

Time to multiple ***Investigator- reported*** ADPKD clinical progression events, ie, progressing hypertension [blood pressure measurement, need for treatment], severe renal pain [requiring medical intervention], worsening albuminuria [by category], worsening renal function [25% change in reciprocal serum creatinine as a measure of glomerular filtration rate from steady-state post-dose Baseline] for subjects taking tolvaptan (combining all doses) relative to subjects on placebo. ***These events will be evaluated by an independent adjudication committee for sensitivity analysis.***

Section 3.5.2.2 Non-composite Secondary Efficacy Endpoints

Change to:

For tolvaptan compared to placebo:

1) ~~**For subjects who are non-hypertensive at Baseline, change from Baseline for resting mean arterial pressure (MAP) at scheduled clinic visits up to point of exposure to anti-hypertensive therapy for any reason**~~ **Rate of GFR change from post-dose Baseline (End of Titration) to last on-drug trial visit (using 1/serum creatinine as primary measure while Cockcroft-Gault results will be exploratory)**

2) ~~**For subjects who are non-hypertensive at Baseline, time to progress to a) high-pre-hypertension (sBP > 129 and/or dBP > 84) or b) hypertension (sBP >139 and/or dBP >89 mm Hg) or c) requiring anti-hypertensive therapy**~~

For subjects who are non-hypertensive at Baseline, change from Baseline for resting mean arterial pressure (MAP) at scheduled clinic visits up to point of exposure to anti-hypertensive therapy for any reason

3) ~~**For subjects who are taking anti-hypertensive therapy at Baseline, percentage with clinically sustained decreases of BP leading to a sustained reduction in anti-hypertensive therapy compared to Baseline (while taking investigational product) at visit Months 12, 24 and 36 for hypertensive subjects**~~ **Change from Baseline in kidney pain as assessed by 1-10 pain scale as average area under the concentration -time curve (AUC) between Baseline and last trial visit or last visit prior to initiating medical (eg, narcotic or tricyclic) or surgical therapy for pain**

4) ~~**Rate of GFR change from post-dose Baseline (End of Titration) to last on-drug trial visit (using 1/serum creatinine as primary measure while Cockcroft-Gault results will be exploratory)**~~ **For subjects who are non-hypertensive at Baseline, time to progress to a) high-pre-hypertension (sBP > 129 and/or dBP > 84) or b) hypertension (sBP >139 and/or dBP >89 mm Hg) or c) requiring anti-hypertensive therapy**

5) ~~**Change from Baseline in kidney pain as assessed by 1-10 pain scale as average area under the concentration -time curve (AUC) between Baseline and last trial visit or last visit prior to initiating medical (eg, narcotic or tricyclic) or surgical therapy for pain**~~ **For subjects who are taking anti-hypertensive therapy at Baseline, percentage with clinically sustained decreases of BP leading to a sustained reduction in anti-hypertensive therapy compared to Baseline (while taking investigational product) at visit Months 12, 24 and 36 for hypertensive subjects**

Section 3.5.2.76 Exploratory Variables

Change to:

For tolvaptan compared to placebo:

1) Fasting urine osmolality (at randomization visit ***and post treatment Follow-up visit #2*** only)

2) ADPKD outcomes and medical resource utilization. Analysis of additional events attributed to ADPKD for tolvaptan-treated subjects as compared to placebo, including their health-related economic outcomes.

Table 3.7-1 Schedule of Assessments

Change to:

Table 3.7-1 Schedule of Assessments

Assessment	Optional Screening Up to 6 Months prior to Baseline visit[a]	Baseline Day -31 to Day -14	Randomiz-ation Day 1	Titration Wk 1, 2	Wk 3/End of Titration	Mo 4, 8, 16, 20, 28, 32	Mo 12, 24	Mo 36/ET (Early Term)[b]	Follow-up ~~Telephone Contact 7 Days~~ Visit #1 +7 to 21 days post Mo 36/ET	*Follow-up Visit #2 +7 to 21 days post Follow-up visit #1*
Informed Consent	X	X								
Inclusion/Exclusion	X	X	X							
Medical/ADPKD History	X	X	X	X	X	X	X	X	X	***X***
Concomitant meds	X	X	X	X	X	X	X	X	X	***X***
Adverse Events	X	X	X	X	X	X	X	X	X	***X***
Tolerability				X	X	X	X	X		
Physical Exam[c]	D	X	D	D	D	D	D	X	D	***D***
VS/weight	X	X	X	X	X	X	X	X	***X***	***X***
ECG		X	X		X			X		
Blood: PK		X			X		X	X		
Blood/urine: PD		X			X		X	X		***X***
Blood/urine: Safety	X	X	X	X	X	X	X	X	***X***	***X***
Urine Pregnancy	X	X	X	X	X	X	X	X		***X***
1° Endpoint MRI		X					X	Xd		
Composite 2° Efficacy Endpoints Labs/Pain/BPe	X	X			X	X	X	X	X	***X***

Table 3.7-1 Schedule of Assessments

Assessment	Optional Screening Up to 6 Months prior to Baseline visit[a]	Baseline Day -31 to Day -14	Randomiz-ation Day 1	Titration Wk 1, 2	Wk 3/End of Titration	Mo 4, 8, 16, 20, 28, 32	Mo 12, 24	Mo 36/ET (Early Term)[b]	Follow-up ~~Telephone Contact 7 Days~~ Visit #1 +7 to 21 days post Mo 36/ET	*Follow-up Visit #2 +7 to 21 days post Follow-up visit #1*
PKD Outcomes	X	X	X		X	X	X	X	X	***X***
~~**Telephone Contact**~~									~~X~~[f]	
Non-fasting spot urine osmolality					***X***		***X***	***X***[f]		
Fasting spot urine osmolality			**X**							***X***
IVRS entry	X	X	X	X	X	X	X	X	X	***X***
Stratify/Randomize			X							
Receive/return drug			X	X	X	X	X	X		
Height	X	X								***X***

[a] If subject screening period exceeds 6 months, they must be re-screened before moving on to the Baseline visit.

[b] Telephone contact (for outcomes only) will occur through **Follow-up Visit #2** for all randomized subjects who ***permanently*** discontinue from investigational product administration.

[c] A complete exam is required at Baseline and Month 36/ET. For all other visits, a directed exam should be conducted at the investigators discretion if deemed necessary to assess changes in Medical History, AEs or other medically indicated parameters (D=directed)

[d] MRI will be performed at, or as near to, a clinical ET visit as is practical, MRI will be done only if >6 months has elapsed since last MRI and will not be repeated beyond the ET visit

[e] Blood required for renal function includes serum creatinine, urine for renal function includes spot albumin/creatinine ratio, clinic exam for BP, standardized renal pain score to be assessed in conjunction with confirmation of renal origin of pain by exam and/or history.

[f] ~~**At the investigators discretion, a clinic visit may be performed if deemed necessary to assess changes in Medical History, AEs or to assess other medically indicated parameters (eg hypertension)**~~ ***Non-fasting spot urine osmolality not done at Early Termination visit***

3.7.1.1 Optional Screening (Up to 6 Months prior to Baseline Visit)

Change to:

11) Assess PKD Outcomes and document in source

3.7.1.2 Baseline (Day -31 to day -14)

Change to:

14) Assess PKD Outcomes and document in source

Section 3.7.1.4 Dose Titration Visits (Weeks 1, 2, and 3/ End of Titration [ie, days 7, 14, 21 ± 2 days])

Change to:

(Paragraph 2, Sentence 1)

At each week's visit, subjects will be asked about tolvaptan tolerability using the following wording exactly, "Could you tolerate taking this dose of **~~tolvaptan~~ investigational product** for the rest of your life, please answer only yes or no?"

Section 3.7.1.7 Follow-up Telephone Contact (7 [+7] days)

Change to:

Section 3.7.1.7 Follow-up Visits

3.7.1.7.1 Follow up Visit #1

Subjects will return to the clinic +7 (to +21) days after their Month 36/ ET visit. The following assessments will be made:

1) **Update medical/ADPKD history**
2) **Update concomitant medications**
3) **Assess adverse events**
4) **Perform directed physical exam as appropriate**
5) **Assess vital signs (heart rate, blood pressure and body weight)**
6) **Collect blood and/or urine for:**
   a) **Clinical safety collection (blood and urine chemistry, hematology, coagulation, urinalysis)**

b) **Composite secondary efficacy (urine albumin/creatinine ratio, serum creatinine)**

7) **Assess hypertension and its therapy, renal pain scale, check for severe renal pain**
8) **Document PKD Outcomes in source since last visit**
9) **Register subject status in IVRS**
10) **Dispense collection vessel and instructions for collecting fasting trough urine sample for determination of osmolality at Follow up Visit #2.**

3.7.1.7.2 Follow up Visit #2

Subjects will return to the clinic +7 (to +21) days after their Follow-up #1 visit. The following assessments will be made:

1) **Update medical/ADPKD history**
2) **Update concomitant medications**
3) **Assess adverse events**
4) **Perform directed physical exam as appropriate**
5) **Assess vital signs (heart rate, blood pressure and body weight)**
6) **Collect body height**
7) **Collect blood and/or urine for:**
   a) **Urine pregnancy test (for WOCBP)**
   b) **Clinical safety (blood and urine chemistry, hematology, coagulation, urinalysis)**
   c) **Composite secondary efficacy (urine albumin/creatinine ratio, serum creatinine,)**
   d) **Blood for cystatin C and blood uric acid and urine for MCP-1 and blood and urine aliquots for exploratory endpoints**
   e) **Fasting NPO trough urine sample for determination of osmolality**
8) **Assess hypertension and its therapy, renal pain scale, check for severe renal pain**
9) **Document PKD Outcomes in source since last visit**
10) **Register subject status in IVRS**

For subjects completing their Month 36/ET visit prior to Amendment 2 implementation, subjects will only be contacted by the clinic for a phone follow-up 7 (+7) days after their Month 36/ET visit.

Section 3.7.2.1 Clinical Laboratory Data

Change to:

(Paragraph 1)

Blood and/or urine samples will be collected as indicated in the schedule of assessments, Table 3.7-1. All safety labs will be performed at Screening, Baseline (Day -31 to day -14), Titration Weeks 1, 2 and 3/or End Titration visit, Treatment Months 4, 8, 12, 16, 20, 24, 28, 32, 36/ET, ***Follow-up Visit #1, and Follow-up Visit #2.***

Section 3.7.2.2 Physical Examination and Vital Sign Data

Change to:

Physical examinations including body weight will be performed and documented according to the schedule of assessments at Baseline, and Month 36/ET visits**. ~~Directed physical exams (examinations focused only on new or ongoing complaints or symptoms and to collect protocol specified measures) may be performed at Screening, Day 1, Weeks 1, 2, 3 (or End of Titration), Months 4, 8, 12, 16, 20, 24, 28, 32, 36/ET and as directed at the 7-day Follow-up~~.** ***A complete physical exam is required at Baseline and Month 36/ET. For all other visits (Screening, Day 1, Weeks 1, 2, 3 or End of Titration, Months 4, 8, 12, 16, 20, 24, 28. 32, Follow-up visit #1 and Follow-up visit #2), a directed exam should be conducted at the investigator's discretion if deemed necessary to assess changes in medical history, AEs or other medically indicated parameters.*** In some regions, more frequent subject visits may be the norm; therefore vital signs and clinically significant physical findings will be documented as source and recorded on unscheduled CRF pages. Any clinically significant physical findings, changes in medication or adverse events will be recorded in the source documents and subsequently transcribed on to the CRF.

Body weight will be taken post-void. It is preferable to use the same scale for each measurement. Clinic scales should be calibrated at least yearly. The Investigator or his/her appointed designee is primarily responsible to perform the physical exam. If the appointed designee is to perform the physical exam, he/she must be permitted by local regulations and his/her name must be included on any globally and locally required documents (eg individual must be added for all sites on a US FDA Form 1572, while local regulations determine their being named in the ICF). Whenever possible, the same individual should perform all physical exams. Any undesirable condition present at the post treatment physical exam that was not present at the Baseline exam should be documented as an adverse event and followed to a satisfactory conclusion.

Vital sign data including seated blood pressure and heart rate will be taken at visits Screening, Baseline, Day 1, Weeks 1, 2, and 3 (or End of Titration), Months 4, 8, 12, 16, 20, 24, 28, 32, 36/ET, ***Follow-up visit #1 and Follow-up visit #2 . The subject's height is to be taken at Screening or Baseline and again at Follow-up visit #2***.

Section 3.7.2.4 Tolerability Question

Change to:

(Last sentence of section)

~~**Any**~~ **Permanent** dose change**s** should be recorded by the Investigator using the IVRS system.

Section 3.7.3.2 Hypertension Assessment

Change to:

(Sentence 5)

Documentation of which type of device is to be used and a copy of its specifications and validations should be retained in the site's study files. ***Two measurements will be performed and both will be recorded. In case the values vary by > 5 mmHg, two additional measurements should be performed and recorded.*** ~~**Measurements will be repeated at least twice (two additional measures will be performed if either replicate of sBP or dBP vary by > 5 mmHg), each replicate separated by an appropriate (for that device or technique) interval of rest.**~~ The average of all valid (technically correct) measures (up to 4) is to be recorded in the CRF for each scheduled or unscheduled visit.

(Sentence 8)

Measurements will be taken at Screening, Baseline, Day 1, Weeks 1, 2, and 3 (or End of Titration), Months 4, 8, 12, 16, 20, 24, 28, 32, ~~**and**~~ 36/ET, ***Follow-up Visit #1 and Follow-up Visit #2***).

(Paragraph 2)

Changes to medications used to ***specifically*** control blood pressure should be documented in source and entered onto appropriate CRFs capturing concomitant medications and hypertension outcomes. Please refer to the case report form completion guidelines for further instructions. Anti-hypertensive therapy is to be started or adjusted as noted in the hypertension treatment guidelines in Section 3.2.2, only after measures at two consecutive visits (including unscheduled visits, which should be used if significant changes in BP are noted) meet guideline requirements. While in some subjects, self-blood pressure monitoring or ambulatory blood pressure monitoring may be clinically indicated or recommended, these values will not be used for determination of clinical endpoint data ***by blood pressure change***, they may however, be considered in determining whether prescribed medications should be adjusted

Section 3.7.3.3 Renal Function

Change to:

(Paragraph 1)

Renal function will be assessed using central serum creatinine measurements at visits Screening, Baseline, Week 3 (or End of Titration), Months 4, 8, 12, 16, 20, 24, 28, 32, 36/ET, ~~**and 7-day Follow-up**~~ ***Follow-up visit #1 and Follow-up visit #2*** using standard Cockcroft-Gault and reciprocal serum creatinine formulae.

Table 3.7.3.3-1 Renal Function (Serum Creatinine)

Change to:

Baseline Serum Creatinine	Baseline 1/Serum Creatinine	25% Decrease in 1/Serum Creatinine	1/Serum Creatinine Threshold for "Event"	Serum Creatinine Threshold for "Event"
0.60	1.67	0.42	1.25	0.80
0.70	1.43	0.36	1.07	0.93
0.80	1.25	0.31	0.94	1.07
0.90	1.11	0.28	0.83	1.20
1.00	1.00	0.25	0.75	1.33
1.10	0.91	0.23	0.68	1.47
1.20	0.83	0.21	0.63	1.60
1.30	0.77	0.19	0.58	1.73
1.40	0.71	0.18	0.54	1.87
1.50	0.67	0.17	0.50	2.00
1.60	0.63	0.16	0.47	2.13
1.70	0.59	0.15	0.44	2.27
1.80	0.56	0.14	0.42	2.40
1.90	0.53	0.13	0.39	2.53
2.00	0.50	0.13	0.38	2.67
2.10	0.48	0.12	0.36	2.80
2.20	0.45	0.11	0.34	2.93
2.30	0.43	0.11	0.33	3.07
2.40	0.42	0.10	0.31	3.20
2.50	***0.40***	***0.10***	***0.30***	***3.33***

Section 3.7.3.4 Albuminuria Assessment

Change to:

(Paragraph 1)

Albuminuria will be assessed using central spot urine albumin/creatinine ratio measurements determined for urine samples collected at the clinic during visits at Screening, Baseline, Week 3 (or End of Titration), Months 4, 8, 12, 16, 20, 24, 28, 32, ~~and~~ 36/ET, ***Follow-up visit #1 and Follow-up visit #2***. This sample should be provided as a mid-stream, clean catch sample

Section 3.7.3.5 Renal Pain Assessment

Change to:

Subjects will be asked a question at each scheduled visit (Screening, Baseline, Day 1, Weeks 3 (or End of Titration), Months 4, 8, 12, 16, 20, 24, 28, 32, ~~and~~ 36/ET, ***Follow-up visit #1 and Follow-up visit #2*** to assess the relative level of pain attributed to their kidneys.

Section 3.7.3.6 PKD History and Outcomes

Change to:

Patients will be asked about their PKD History at all visits. This information should be recorded as source data in the patient's medical records and transcribed on to the appropriate CRF page. PKD History will capture information from the subject's recollection, and documented past medical history where available. This information should be updated at each visit if new information regarding past history becomes available. PKD Outcomes will be collected at all study visits and will collect information relevant to the medical, social and economic consequences of new and ongoing PKD-related morbidities. This information should be recorded as source data in the patient's medical records and transcribed on to the appropriate CRF page. New clinically relevant information and specific questions about outcomes will be updated at visits Baseline, Day 1, Week 3 (or End of Titration), Months 4, 8, 12, 16, 20, 24, 28, 32, 36/ET ~~**and 7-day Follow-up Telephone Contact.**~~ ***Follow-up visit #1 and Follow-up visit #2***.

If a subject who has been randomized and taking investigational product discontinues from the use of investigational product, telephone contact for PKD outcomes will be performed at the normally scheduled trial visits to Month 36, ***Follow-up visit #1 and Follow-up visit #2*** ~~**and 7-day Follow-up**~~. These data will not be used in the primary analysis, but may be utilized in exploratory ITT analyses.

Section 3.7.4.1 Trough Urine Osmolality, MCP-1

Change to:

Fasting spot urine osmolality will be determined for the morning of Randomization, Day 1 and for Follow-up Visit #2. Non-fasting spot urine osmolality at trough will be determined immediately prior to morning dosing for Week 3 (or End of Titration) ***and*** Months 12, 24, and 36. No ET sample will be obtained. This sample should be obtained from a second urine void taken after the first morning's void and will ideally be provided as a mid-stream, clean catch sample. Date and time of the urine sample, as well as the date and time of the last preceding dose should be noted.

Section 3.7.4.2 Blood for Cystatin C and BUA

Change to:

A blood sample for Cystatin C, taken following the PK blood sample, will be collected and processed according to the directions provided by the central clinical chemistry laboratory. Samples will be collected at Baseline, Week 3 (or End of Titration) and Months 12, 24, ~~**and**~~ 36/ET, ***and Follow-up visit #2***. All samples will be stored according to directions from the central clinical chemistry laboratory. Selected samples may be assayed at a later date for exploratory purposes.

A blood sample for determination of BUA, taken following the PK blood sample, will be collected and processed according to the directions provided by the central clinical chemistry laboratory. Samples will be collected at Baseline, Week 3 (or End of Titration) and Months 12, 24, ~~**and**~~ 36/ET, ***and Follow-up visit #2***. Selected samples may be assayed at a later date for exploratory purposes.

Section 3.7.4.3 PKD Biomarkers (Exploratory)

Change to:

A variety of urine and blood markers have been proposed as being potentially helpful in tracking the progression of ADPKD, or the progress of PKD therapy. Other markers, specific to the mechanism of action for tolvaptan, may provide useful insight into the compound's effects in subjects. A blood sample will be taken following the PK sample (10 mL) and processed as for PK blood sample. A spot urine sample (50 mL) will be collected (as part of the urine sample used to determine albumin/creatinine ratio) at Baseline, Week 3 (or End of Titration), Months 12, 24 ~~**and**~~ 36/ET, ***and Follow-up visit #2.*** Detailed handling and shipping instructions are in Appendix 3.

Section 3.7.5.1 Pharmacokinetic Blood Samples

Change to:

Sparse samples will be taken for determination of tolvaptan and metabolite plasma concentrations. Blood samples for pharmacokinetic analysis will be collected by trial centers that have appropriate facilities; a 10 mL sample will be collected at Baseline, Week 3 (or End of Titration) and Months 12, 24, ~~**and**~~ 36/ET, ***and Follow-up visit #2***.

Section 3.7.6.1 Urine Concentrating Ability

Change to:

(Paragraph 2)

On the morning of their Day 1 trial visit ***and the morning of their Follow-up Visit #2***, the subject will collect a fasting urine sample (ideally, with the morning's second void; first void t least 10 hours after *NPO*, second void anytime thereafter while still *NPO*).

Section 3.8.3 Individual Subject

Change to:

(Paragraph 2 and 3)

All subjects have the right to withdraw at any time during treatment without prejudice. The investigator can discontinue a subject's participation in the trial at any time if medically necessary. In addition, subjects meeting the following criteria must be withdrawn from the trial:

- Occurrence of any AE, intercurrent illness or abnormality in laboratory assessment results which, in the opinion of the investigator, warrants the subject's permanent withdrawal from the trial;
- Treatment with a prohibited concomitant medication other than the use of appropriate medications for the treatment of AEs under direction of the investigator;
- Subject noncompliance, defined as refusal or inability to adhere to the trial schedule or procedures;
- At the request of the investigator, sponsor, or regulatory authority;
- ~~**Subject becomes pregnant**~~
- Subject is lost to follow-up
- ***Medications or procedures that would confound endpoint assessments***

~~**The sponsor should be notified promptly when a subject is withdrawn.**~~ The sponsor should be notified promptly when a subject is withdrawn or if the trial is stopped. A subject who discontinues investigational product for reasons other than non-compliance

or lost to follow-up may continue limited participation in the trial for further telephone/remote collection of PKD outcomes as described in

Section 3.12 Subject Compliance

Change to:

(Sentence 2)

Any subject who, without the instruction of the investigator, discontinues investigational product for 30 consecutive days or misses >30% of the doses intended for a period ***between visits*** (whichever is greater) will be deemed non-compliant.

Section 4.1 Prohibited Medications

Change to:

(Sentence 2)

These include, but are not restricted to somatostatin agonists, ~~**rapamunw**~~ **rapamune** (sirolimus), anti-sense RNA therapies, tolvaptan, and other vasopressin antagonists (eg, OPC-31260 (mozavaptan), Vaprisol (conivaptan), or agonists (eg, desmopressin [DDAVP]) and cyst decompression surgery.

Section 5.1 Definitions

Change to:

(Paragraph 5)

An immediately reportable event (IRE) is any SAE, or any AE that necessitates discontinuation of the investigational product. Pregnancies are also defined as IREs (although normal pregnancy is not an AE~~**, it will mandate drug discontinuation**~~).

Section 5.4 Pregnancy

Change to:

Women of childbearing potential (WOCBP) who are sexually active must use an effective method of birth control during the course of the trial so risk of failure is

minimized. Unless the subject and his/her partner(s) are sterile (ie, women who have had an oophorectomy and/or hysterectomy or have been postmenopausal for at least 12 consecutive months; or men who have had orchidectomy) or remain abstinent, two of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device (IUD), birth control pills, birth control implant, condom or sponge with spermicide. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy; therefore two of the above methods should be used to further reduce the likelihood of an unplanned pregnancy and a fetus' potential exposure to this investigational drug. While even two methods cannot fully guarantee pregnancy prevention, an understanding of these facts and the potential risks of non-compliance must be clearly explained to the trial subject in the ICF and consent process.

Before enrolling WOCBP in this clinical trial, investigators must review guidelines about trial participation for WOCBP. The topics should include:

- General information
- Informed consent form
- Pregnancy prevention information
- Drug interactions with hormonal contraceptives
- Contraceptives in current use
- Guidelines for the follow-up of a reported pregnancy

Prior to trial enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The subject must sign an ICF stating that the above-mentioned risk factors and the consequences were discussed.

During the trial, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual cycle).

If a subject or investigator suspects that the subject may be pregnant prior to administration of the investigational product, administration must be withheld until the results of blood serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the investigational product or be enrolled in the trial. If pregnancy is suspected while the subject is receiving treatment, the investigational product must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of a serum pregnancy test is known. If pregnancy is confirmed, the investigational product will be ~~**permanently discontinued**~~ ***withheld*** in an appropriate manner (eg, dose tapering if necessary for subject safety) ~~**and**~~

~~**the subject withdrawn from the trial**~~ ***until the pregnancy and any period of breast-feeding reaches its conclusion and the investigator and study Medical Monitor are assured of the patient's ability to safely re-enter the study. Thereafter, investigational product may be resumed as for any other interruption after confirmation of subject safety and continued eligibility. Withdrawal from the study will not be required, but remains an option as described in Protocol Section 3.8. The decision to withdraw may include considerations such as; time remaining in the study; subject compliance with birth control measures; and desire to participate in available extension studies.***

Subjects should be reminded of their right to learn their study treatment assigned if such knowledge will reasonably impact their reproductive decision or management of the pregnancy. Unblinding for this purpose will not influence further study participation, although subjective data may be excluded from analysis. Procedures for unblinding are detailed in Section 5.5 of this protocol and should be followed.

The investigator must immediately notify (within 24 hours) the sponsor's Pharmacovigilance Department of any pregnancy having the gestation period beginning within 30 days ***after the completion*** of investigational product administration. Record the event on the IRE form, and forward it to the sponsor's Pharmacovigilance Department. The sponsor's Pharmacovigilance Department will forward Pregnancy Surveillance Form(s) for monitoring the outcome of the pregnancy. Pregnancy will only be documented on the AE CRF if there is an abnormality or complication to be reported.

If the subject will be discontinued, then protocol-required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator must report to the sponsor on appropriate Pregnancy Surveillance form(s), follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months.

Section 5.6 Follow-up of Adverse Events

Change to:

For this trial all adverse events will be followed up ***until last scheduled contact (***for a minimum of **14** days after the last dose of investigational product is taken***)***~~**, in accord with the active component's half-life**~~.

Section 5.6.2 Follow-up of Post Trial Serious Adverse Events

Change to:

(Paragraph 2)

This trial requires that subjects be actively monitored for SAEs up to **Follow-up Visit #2** ~~**after discharge from the trial**~~. Any new SAEs reported by the subject to the investigator that occur **after the last scheduled contact**, and are determined by the investigator to be reasonably associated with the use of the investigational product, should be reported to the sponsor. This may include SAEs that are captured ~~**on follow-up telephone contact or**~~ at any ~~**other**~~ time point after the defined trial period (ie, up to last scheduled contact). The investigator should follow serious related AEs identified after the last scheduled contact until the events are resolved, or the subject is lost to follow-up. The investigator should continue to report any significant follow-up information to the sponsor up to the point the event has been resolved.

Section 7.1 Data Sets for Analysis

Change to:

(Paragraph 3)

If a subject who has been randomized and taking investigational product discontinues from the use ~~**if**~~ **of** investigational product, telephone contact for PKD Outcomes (PKD outcomes survey) will be performed at the normally scheduled trial visits to Month 36, ***Follow-up visit #1 and Follow-up visit #2*** ~~**and 7-day Follow-up**~~. These data will not be used in the primary analysis, but may be utilized in an exploratory ITT analyses. ***In addition, data collected after resuming study medications for subjects whose study medications were interrupted for at least 30 consecutive days in the study maintenance phase will be excluded from all efficacy analyses, if the collected data falls in an interval, which starts from the beginning of the interruption period, with the interval length equal to 2 times of the interruption period.***

Section 7.4.1 Primary Efficacy Outcome Analysis

Change to:

Various sensitivity analyses endpoints will be discussed in the SAP.

Section 7.4.1.1 Analysis of the Primary Efficacy Endpoint

Change to:

(Paragraph 5, Sentences 5-7)

A significance level of 0.05~~0~~ (two-sided) will be used to declare statistical significance at the final analysis. In addition, estimate of the contrast and its 95~~.~~**.5**% CI will be obtained. Anti-log of these statistics will provide an estimate of the ratio of the geometric means of annual percent changes (expressed as a ratio of one year renal volume prediction divided by Baseline renal volume "prediction") from Baseline of the two treatment group and its 95~~.~~**.5**% CI.

(New last paragraph)

In addition to the primary analysis provided above, MMRM (Mixed Model Repeated Measures) analysis will be applied to the repeated measures of change from Baseline in total renal volume (based on logarithm transformed data) as a sensitivity analysis. LS Mean difference of the two treatment groups at Year 3 under the MMRM will be used to estimate the treatment effect at Year 3. The MMRM includes stratification factors (hypertensive status, renal volume status and creatinine clearance status at Baseline and geographic regions), visit, treatment, and treatment visit interaction as class variables and Baseline renal volume as covariate. Observed cases dataset will be used in this MMRM analysis.

Section 7.4.1.2 Rationale for the Primary Efficacy Analysis and its Interpretation

Change to:

(Sentence 2)

The two-stage random effect formulation which leads to the linear mixed effect model described by Fitzmaurice, Laird and Ware ~~**(page 196)**~~ provides an insight to this.

Section 7.4.2 Secondary Efficacy Outcome Analysis

Change to:

Various sensitivity analyses endpoints will be discussed in the SAP.

Section 7.4.2.1.1.2 Events of Renal Pain

Change to:

Event of renal pain is defined as significant interventions for relief of renal pain. This would include (in decreasing order of significance) surgical or invasive radiological procedures, introduction or increasing the dose of narcotic or tricycle antidepressant medication, prescribing medical leave or activity restrictions or using a prescription non-narcotic which carries some risk to the subject for renal pain. ~~**Each performed surgical or invasive radiological procedure will be defined as an event, so that if a subject has two procedures performed at two different visits, the subject will simply have two events. The timing of an event of performed surgical or invasive radiological procedure is defined as the scheduled visit time when such a procedure is decided to be performed.**~~ ***The first prescribed surgical or invasive radiological procedure is considered an event of renal pain. If the first procedure has been performed, then the second prescribed surgical or invasive radiological procedure will also be considered as an event of renal pain. Any second prescribed surgical or invasive radiological procedure following an un-performed first procedure will be considered as an event of renal pain. The same criterion will be applied to the third and forth prescribed surgical or invasive radiological procedures, etc. The timing of this kind of renal pain event is the date of the visit (including unscheduled visit) at which such a procedure is prescribed.***

To select multiple events due to introducing/increasing dose of narcotic or ~~**tricycle**~~ **tricyclic** antidepressant or other prescription for activity limitation or medication in analysis, the criterion used in events developed by introducing/increasing dose of anti-hypertensive medication will also be applied here, ie, an event which qualifies to be included in the analysis if there is no event with equal or higher dose of the same medication before it. Applying the criterion here also implies that once a subject is given narcotic or tricyclic antidepressant medication, increasing doses of non-narcotic prescription is no longer considered an event in the analysis. The timing of this kind of renal pain event is also defined as the scheduled visit time (such as 8 Months, etc.) when the medication is prescribed.

Section 7.4.2.1.1.4 Events of Worsening Renal Function

Change to:

(Paragraph 2)

These four types of events will be pooled together as events of ADPKD clinical progression. If a subject has more than one event (an event of worsening renal function and an event of hypertension) occur at a visit, only one of them will be retained in the analysis. ***Worsening in blood pressure, albuminuria, and reciprocal serum creatinine at the end of treatment visit (Early Term or Month 36 visit) may be confirmed to be a clinical ADPKD progression event by using the data collected at the visit of post-treatment Follow-up #1 (+7 to + 21 days after the end of treatment visit).*** The timing of all these events is related to their visit. If a visit is one of the scheduled visits, the scheduled visit time (such as 8 Months, etc.) is the event time. If a visit is an unscheduled visit, the event time is the actual time (= (time of the unscheduled visit – time of randomization + 1)/30.5).

Section 7.4.2.1.2. Analysis of Secondary Composite Endpoints

Change to:

Two analyses of this secondary composite endpoint will be conducted. The first one includes all the events observed during the double blind treatment period starting from the date of first dose of study medication (for hypertension, proteinuria and kidney pain), and this analysis will be the primary analysis of this composite secondary endpoint. The second one includes all the events observed during the double blind treatment period from Week 3/End of Titration to the end of double blind treatment period, using Week 3/End of Titration as new Baseline. This analysis will be a sensitivity analysis of this endpoint. The proposal of this sensitivity analysis is due to possible un-stability during the switch of concurrent hypertensive medication per protocol in the titration period. In addition, an adjudication committee will be set up to adjudicate the events in the composite secondary endpoint. The adjudicated data will provide a sensitivity analysis to the endpoint with the analysis on all events and analysis on events starting from Week 3/End of Titration.

~~**For the analysis of secondary composite endpoint, all the clinical ADPKD progression events (selected by the way given in the previous section) occurring from the date of randomization to the date of trial completion/early termination will be included in the analysis, for all ITT subjects.**~~

Analysis of time to multiple events using extended Cox model will be used for the analysis of the secondary composite endpoint. Specifically, the Andersen-Gill approach will be applied to the analysis of the ADPKD clinical progression events. Point estimate of the hazard ratio will be provided, and the p-value will be provided by the robust Wald test. Details of the robust Wald test can be found in Therneau and Grambsch[29] and the SAS Institute publication SAS/STAT Software: Changes and Enhancements.[30]

All events of a subject will be ordered by their event time. The data of the composite secondary endpoint will have a counting process style of input: the first event will have a start time of randomization (time 0) and a stop time of the first event time, the second event will have a start time of the first event time and a stop time of the second event, etc. After the last event, a subject will still have an observation with a start time of the last event time and a stop time of trial completion/ early termination with a status of censored, if the last event occurs before trial completion/early termination. For a subject without an event during the trial, the subject will have only one observation with start time randomization and stop time trial completion/early termination with a censored status. As an example, suppose a subject 0001 treated by tolvaptan has a hypertensive event at Month 24, and a renal pain event at Month 32, and then completes the trial at Month ~~**40**~~ **36** without any further events; and another subject 0002 treated by placebo has two hypertensive events at Months 8 and 28, two renal pain events at Months 16 and 28, and then has an albuminuria event and discontinues the trial at Month 29. The dataset will have the following form:

Table 7.4.2.1.2-1 Dataset Design

Subject ID	Start Time	Stop Time	Status	Treatment
0001	0	24	1	1
0001	24	32	1	1
0001	32	~~**40**~~ **36**	0	1
0002	0	8	1	0
0002	8	16	1	0
0002	16	28	1	0
0002	28	29	1	0

The SAS procedure of the analysis will use:

```
proc phreg covsandwich;
        model (start_time, stop_time)*status(0)= treatment/ ties=exact;
         id subject_id;
run;
```

Note that if the option of ties = exact turns out to be too cumbersome to run, the option may be changed to ties = Efron. The final option of ties will be stated in the Statistical Analysis Plan (SAP) before unblinding of the trial. This SAS procedure will provide the parameter estimate and hazard ratio of the secondary composite endpoint, and use a robust sandwich estimate of the covariance matrix in the Wald test[30] to provide a robust p-value for the key secondary analysis. The covsandwich option of this procedure replaces a previous SAS macro %phlev which uses a SAS output dataset called dfbeta to derive the robust sandwich estimate of the covariance matrix used in the Wald tests, and the macro was used in the book of Therneau and Grambsch.[29] A significance level of 0.05 (two-sided) will be used to declare statistical significance at the final analysis.

As a supportive analysis, the same analysis will be applied to each kind of ADPKD clinical progression events. In addition, a time-to-first-event analysis will be provided where the event will be determined the first occurrence of any one of the four component events. This analysis will be done by the same method as described above.

Section 7.4.2.2 Non-Composite Secondary Efficacy Endpoints

Change to:

1) ~~**For subjects who are non-hypertensive at Baseline, change from Baseline for resting mean arterial pressure (MAP) at scheduled clinic visits up to point of exposure to anti-hypertensive therapy for any reason**~~ **Rate of GFR change from post-dose Baseline (End of Titration) to last on-drug trial visit (using 1/serum creatinine as primary measure while Cockcroft-Gault results will be exploratory)**

2) ~~**For subjects who are non-hypertensive at Baseline, time to progress to a) high-pre-hypertension (sBP > 129 and/or dBP > 84) or b) hypertension (sBP >139 and/or dBP >89 mm Hg) or c) requiring anti-hypertensive therapy**~~

For subjects who are non-hypertensive at Baseline, change from Baseline for resting mean arterial pressure (MAP) at scheduled clinic visits up to point of exposure to anti-hypertensive therapy for any reason

3) ~~**For subjects who are taking anti-hypertensive therapy at Baseline, percentage with clinically sustained decreases of BP leading to a sustained reduction in anti-hypertensive therapy compared to Baseline (while taking investigational product) at visit Months 12, 24 and 36 for hypertensive subjects**~~ **Change from Baseline in kidney pain as assessed by 1-10 pain scale as average area under the concentration -time curve (AUC) between Baseline and last trial visit or last visit prior to initiating medical (eg, narcotic or tricyclic) or surgical therapy for pain**

4) ~~Rate of GFR change from post-dose Baseline (End of Titration) to last on-drug trial visit (using 1/serum creatinine as primary measure while Cockcroft-Gault results will be exploratory)~~ **For subjects who are non-hypertensive at Baseline, time to progress to a) high-pre-hypertension (sBP > 129 and/or dBP > 84) or b) hypertension (sBP >139 and/or dBP >89 mm Hg) or c) requiring anti-hypertensive therapy**

5) ~~Change from Baseline in kidney pain as assessed by 1-10 pain scale as average area under the concentration -time curve (AUC) between Baseline and last trial visit or last visit prior to initiating medical (eg, narcotic or tricyclic) or surgical therapy for pain~~ **For subjects who are taking anti-hypertensive therapy at Baseline, percentage with clinically sustained decreases of BP leading to a sustained reduction in anti-hypertensive therapy compared to Baseline (while taking investigational product) at visit Months 12, 24 and 36 for hypertensive subjects**

~~All the tests on the non-composite secondary efficacy endpoints will be conducted with a two-sided alpha level of 0.05, and will be tested in the order in which they are listed.~~ **The other non-composite secondary efficacy endpoints will be tested after the key composite secondary efficacy endpoints using a two-sided alpha level of 0.05. These will be tested in the sequence indicated above, without adjustment for multiplicity.**

~~The analysis on non-composite secondary efficacy variable 1 (change from Baseline in resting mean arterial pressure (MAP) at scheduled clinic visits monitoring) will also be similar to the analysis of the primary endpoint, except that the MAP value, instead of its $\log_{10}$ scale, will be used in the analysis. This analysis will be applied to all the subjects with non-hypertensive status at Baseline. All the observations, from Baseline up to the ones observed just prior to the start of anti-hypertensive therapy for the subjects who start anti-hypertensive therapy during the trial, and from Baseline up to the last visit/early termination for the subjects who do not need anti-hypertensive therapy during the trial, will be used in the analysis.~~ **The analysis on non-composite secondary efficacy variable 1 (Rate of GFR from post-dose Baseline to last-dose value) will be similar to the analysis of the primary endpoint, except that the GFR value, instead of $\log_{10}$ scale of the GFR value, will be used in the analysis. This analysis will be applied to the ITT OC datasets. The primary GFR estimate used in the analysis will be one divided by serum creatinine value. In addition, GFR estimated by Cockcroft-Gault formula will also be analyzed similarly. The formula of Cockcroft-Gault has been provided in 3.7.3.3 of the protocol. Again the ITT OC datasets will be used.**

~~**The stratified log-rank test will be applied to non-composite secondary efficacy variable 2 (time to progressing to high-pre-hypertension, or hypertension, or requiring anti-hypertensive therapy for non-hypertensive subject) for tolvaptan to placebo comparison using non-hypertensive subject time to event dataset of the whole trial. The severity of these hypertensive events is defined from less severe to highly severe in the order from high-pre-hypertension, hypertension, to requiring antihypertensive therapy. An event will be included in the analysis of time to multiple events if there is no event with equal or high severity before it during the double blind trial period, so that a subject could have at most three events. The timing of an event is defined as the time of the scheduled visit time if the event is found at a protocol scheduled visit or equal to date of the unscheduled visit if the event is first documented at an unscheduled visit. Again, the data of the endpoint will have a counting process style of input (see Section 7.4.2.1.2). Non-hypertensive subjects who remain non-hypertensive or low-pre-hypertensive during the trial will be considered censored, with time to censor = date of visit Month 36 (or Early Termination visit) - date of randomization + 1.**~~ **The analysis on non-composite secondary efficacy variable 2 (change from Baseline in resting mean arterial pressure (MAP) at scheduled clinic visits monitoring) will also be similar to the analysis of the primary endpoint, except that the MAP value, instead of its $\log_{10}$ scale, will be used in the analysis. This analysis will be applied to all the subjects with non-hypertensive status at Baseline. All the observations, from Baseline up to the ones observed just prior to the start of anti-hypertensive therapy for the subjects who start anti-hypertensive therapy during the trial, and from Baseline up to the last visit/early termination for the subjects who do not need anti-hypertensive therapy during the trial, will be used in the analysis.**

~~**Non-composite secondary efficacy variable 3 (percentage of Baseline hypertensive subjects with clinically sustained decreases of BP leading to a sustained reduction in anti-hypertensive therapy compared to Baseline) will be analyzed by Cochran-Mantel-Haenszel statistic stratified by Baseline stratification factors at visit Months 12, 24 and 36 respectively. All subjects who are hypertensive and take anti-hypertensive therapy before randomization will be included in the trial. Subjects with clinically sustained decreases of BP leading to a sustained reduction in anti-hypertensive therapy compared to Baseline is defined as a subject whose blood pressure is lower than his/her blood pressure at Week 3/EOT (when subjects finish their dose titration) and whose dose of anti-hypertensive therapy is also lower than**~~

~~his/her visit Week 3 dose of anti-hypertensive therapy at visit Months 12, 24, and 36 respectively. LOCF dataset will be used for this analysis.~~ **For non-composite secondary efficacy variable 3 (change from Baseline in kidney pain as assessed by 1-10 pain scale as time average AUC between Baseline and last visit or last visit prior to initiating medical or surgical therapy) will be analyzed by ANCOVA with factors of treatment and Baseline stratification factors and covariate Baseline pain scale, using ITT OC dataset up to last trial visit for subjects without such a medical intervention during the trial or up to the last visit prior such a surgical intervention. Trapezoidal rule will be used to calculate the AUC, so that missing data between two records of pain scale reading will be ignored. The number of days used to divide the AUC to get its time average is equal to the date of the last visit defined above minus the date of randomization visit plus one.**

~~The analysis on non-composite secondary efficacy variable 4 (Rate of GFR from post-dose Baseline to last-dose value) will be similar to the analysis of the primary endpoint, except that the GFR value, instead of $\log_{10}$ scale of the GFR value, will be used in the analysis. This analysis will be applied to the ITT OC datasets. The primary GFR estimate used in the analysis will be one divided by serum creatinine value. In addition, GFR estimated by Cockcroft-Gault formula will also be analyzed similarly. The formula of Cockcroft-Gault has been provided in 3.7.3.3 of the protocol. Again the ITT OC datasets will be used.~~ **The stratified log-rank test will be applied to non-composite secondary efficacy variable 4 (time to progressing to high-pre-hypertension, or hypertension, or requiring anti-hypertensive therapy for non-hypertensive subject) for tolvaptan to placebo comparison using non-hypertensive subject time to event dataset of the whole trial. The severity of these hypertensive events is defined from less severe to highly severe in the order from high-pre-hypertension, hypertension, to requiring antihypertensive therapy. An event will be included in the analysis of time to multiple events if there is no event with equal or high severity before it during the double blind trial period, so that a subject could have at most three events. The timing of an event is defined as the time of the scheduled visit time if the event is found at a protocol scheduled visit or equal to date of the unscheduled visit if the event is first documented at an unscheduled visit. Again, the data of the endpoint will have a counting process style of input (see Section 7.4.2.1.2). Non-hypertensive subjects who remain non-hypertensive or low-pre-hypertensive during the trial will be considered censored,**

with time to censor = date of visit Month 36 (or Early Termination visit) - date of randomization + 1.

~~**For non-composite secondary efficacy variable 5 (change from Baseline in kidney pain as assessed by 1-10 pain scale as time average AUC between Baseline and last visit or last visit prior to initiating medical or surgical therapy) will be analyzed by ANCOVA with factors of treatment and Baseline stratification factors and covariate Baseline pain scale, using ITT OC dataset up to last trial visit for subjects without such a medical intervention during the trial or up to the last visit prior such a surgical intervention. Trapezoidal rule will be used to calculate the AUC, so that missing data between two records of pain scale reading will be ignored. The number of days used to divide the AUC to get its time average is equal to the date of the last visit defined above minus the date of randomization visit plus one.**~~ **Non-composite secondary efficacy variable 5 (percentage of Baseline hypertensive subjects with clinically sustained decreases of BP leading to a sustained reduction in anti-hypertensive therapy compared to Baseline) will be analyzed by Cochran-Mantel-Haenszel statistic stratified by Baseline stratification factors at visit Months 12, 24 and 36 respectively. All subjects who are hypertensive and take anti-hypertensive therapy before randomization will be included in the trial. Subjects with clinically sustained decreases of BP leading to a sustained reduction in anti-hypertensive therapy compared to Baseline is defined as a subject whose blood pressure is lower than his/her blood pressure at Week 3/EOT (when subjects finish their dose titration) and whose dose of anti-hypertensive therapy is also lower than his/her visit Week 3 dose of anti-hypertensive therapy at visit Months 12, 24, and 36 respectively. LOCF dataset will be used for this analysis.**

Section 7.4.2.4.1 Urine Concentrating Ability

Change to:

~~**For tolvaptan-treated vs. placebo, descriptive statistics for values on Day 1 will be determined.**~~ **For tolvaptan-treated vs. placebo, change from Baseline values on Day 1 to Follow-up Visit #1 and Follow-up Visit #2 will be compared between treatment groups using ANCOVA with treatment and center as factors and baseline covariate.**

Section 7.4.2.4.2 PKD Outcomes

Change to:

~~**An exploratory analysis of the PKD Outcomes including medical resource utilization will be performed.**~~ ***Exploratory analysis will be conducted to the data of ADPKD outcomes and medical resource utilization collected in the PKD Outcome CRF page. Detailed analysis on these exploratory endpoints may be written in a statistical analysis plan specific for this exploratory analysis before unblinding the database.***

Section 7.6.3 Projected Power of the Composite Secondary Endpoint

Change to (add section):

The blinded sample size re-calculation was conducted on Oct. 20, 2008 based on the available un-cleaned data, when more than 1000 subjects had been enrolled. This sample size re-calculation suggested that a total sample size of 1400 would be an appropriate size for this study, mostly driven by the consideration on the power of the composite secondary endpoint. It turns out that this sample size also falls into the sample size range of 1200 - 1500 originally specified in the protocol.

Based on the mostly recent data transfer in this study available before this Amendment 2, it was projected that there will be 975 first events and 2074 multiple events in this study using Day 1 Pre-dose as Baseline, and 872 first events and 1920 multiple events in this study using Week 3/End of Titration as Baseline. With an alpha of 0.05, it is projected that there will be at least 90% power to test 20% reduction in the composite secondary endpoint. However, since the real power of the study depends on the real number of events occurring at the conclusion of the study, this power projection only reflects the power we expect if everything falls into the assumption we made when we performed the power projection.

Section 7.9 Interim Analysis

Change to:

~~**Two interim analyses will be conducted to evaluate the effect of tolvaptan on the primary endpoint. An Independent Data Monitoring Committee (IDMC) will handle the interim analyses. This IDMC's charter will review the results of the interim analyses of the efficacy and safety endpoints at one-year and two-year time points, respectively, when all subjects (excluding subjects early withdrawn)**~~

~~**complete one year and two years of the trial. An alpha of 0.001 and an alpha of 0.004, both are two-sided, will be allocated to the first and the second interim analyses. Since no formal group sequential decision boundaries are assigned in these analyses, the IDMC will also develop criteria for making decisions on stopping the trial based on safety, futility or clear efficacy considerations. Both the Primary and Composite Secondary endpoints may be considered in establishing these criteria. The IDMC would make a recommendation to the sponsor when criteria of the interim analysis are met during the interim analyses. Their recommendations will be reviewed by the trial's steering committee and relevant regulatory authorities prior to making a decision on trial suspension or early termination**~~

No interim analysis will be performed in this study. The IDMC will monitor the study safety as well as efficacy.

Section 9.2 Data Collection

Change to:

(Add bullet 4)

- ***Documentation for the minimum number of kidney cysts as evidence of meeting Inclusion Criteria #2***

Appendix 1 Names of Otsuka Personnel

Change to:

Project Leader, Americas	Frank Czerwiec, MD, PhD Sr. Director, Global Clinical Development Otsuka Pharmaceutical Development & Commercialization, Inc 2440 Research Boulevard Rockville, MD 20850***, USA*** Phone +01 (240) 683-3523 Fax +01 (301) 721-7523
Project Leader, Japan	Osamu Sato Clinical Director**, Japan** Otsuka Pharmaceutical Co., Ltd., Japan 3-2-27, Otedori, Chuo-ku Osaka 540-0021, Japan Tel: +81-6-6943-7722 Fax: +81-6-6920-2346

Project Leader, Region Europe, ***ROW***	**Dr. med. Burkhard Timmler** **European Project Leader** Otsuka Frankfurt Research Institute GmbH ~~**Hochhaus am Park,**~~ Grüneburgweg 102 60323 Frankfurt am Main, Germany Phone +49 69 95 50 44 **339** Fax: +49 69 95 50 44 50
Manager, Clinical Development	**Suzanne Watkin** **Sr.** Manager, Global Clinical Development, Otsuka Pharmaceutical Development & Commercialization, Inc 2440 Research Boulevard Rockville, MD 20850***, USA*** Phone +01 (240) 683-32**99** Fax +01 (301) 721-72**99**
Immediately Reportable Adverse Event	Clinical Safety and Pharmacovigilance Otsuka Pharmaceutical Development & Commercialization, Inc 2440 Research Boulevard Rockville, MD 20850 Phone (800) 438-9927 ***in USA*** or +01 (301) 212-5941 Fax: (800) 438-**6030** ***in USA*** or +01 (301) 212-**8633**

Appendix 2 Institutions Concerned with the Trial

Change to:

Lead Principal (Communicating) Investigator/ *Steering Committee Chairman*:

Vicente E. Torres, M.D., Ph.D.
Chair, Division of Nephrology
Mayo Clinic
200 First St. S.W.
Rochester, MN 55905
+ 01-501-266-7093

MRI Central Imaging:

Perceptive Informatics, Inc.
2 Federal Street
Billerica, MA 01821
+01-978-313-3900

Project Management/Monitoring:

PAREXEL International
900 Chelmsford Street
Lowell, MA 01851
+01-978-275-0062

IVR Systems:

Perceptive Informatics, Inc.
2 Federal Street
Billerica, MA 01821
+01-978-313-3900

~~**Sonic Clinical Laboratories**~~
~~**95 Epping Road, North Ride**~~
~~**New South Wales 2113**~~
~~**Australia**~~

Subject Recruitment/Retention:

PAREXEL International
900 Chelmsford Street
Lowell, MA 01851
+01-978-275-0062

Appendix 3 Handling and Shipping of Bioanalytical Samples

Change to:

(Paragraph 3)
Twenty mL of blood (10mL for PK and 10 mL for Biomarkers) will be collected into sodium heparin tubes and should be gently inverted three to four times and then centrifuged at 2500 rpm for at least 10 minutes at 4 °C. The separated plasma from each tube should then be divided equally between the two bar-code labeled polypropylene tubes. The PK sample must be stored at -20 °C or below, the PD sample must be stored at -70 °C or below. ***The laboratory manual should be referenced for detailed instructions***.

One PK and one PD tube (primary sample) will be shipped on dry ice to the central lab. Following confirmation that the first tube arrived safely, the second tubes (backup samples) can also be shipped to the central lab.

ADDITIONAL RISK TO THE SUBJECT:

No additional risk to the subject

Otsuka Pharmaceutical Development & Commercialization, Inc.

OPC-41061
SIGNATURE PAGE

Short Title: Protocol_156-04-251_Amend 2_10SEP2009

Object ID: 0900854880a01fc4 **Document Version:** 3.0,Approved,CURRENT

Approval Name	Approval Capacity	Approval Date Local
Czerwiec_Frank	Clinical Research	10-Sep-2009 17:07:19
Mallikaarjun_Suresh	Clinical Pharmacology	10-Sep-2009 17:28:37
Ali_Mirza	Biostatistics	11-Sep-2009 09:31:00

Agreement

I, the undersigned principal investigator, have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal and scientific information necessary to conduct this trial in accordance with the principles of Good Clinical Practices and as described herein and in the sponsor's (or designee's) Clinical Research Agreement.

I will provide copies of the protocol to all physicians, nurses and other professional personnel to whom I delegate trial responsibilities. I will discuss the protocol with them to ensure that they are sufficiently informed regarding the investigational new drug, **OPC-41061** , the concurrent medications, the efficacy and safety parameters and the conduct of the trial in general. I am aware that this protocol must be approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) responsible for such matters in the clinical trial facility where **OPC-41061** will be tested prior to commencement of this trial. I agree to adhere strictly to the attached protocol (unless amended in the manner set forth in Paragraph I of the sponsor's Clinical Research Agreement, at which time I agree to adhere strictly to the protocol as amended).

I understand that this IRB- or IEC-approved protocol will be submitted to the appropriate regulatory authority/ies by the sponsor. I agree that clinical data entered on case report forms by me and my staff will be utilized by the sponsor in various ways such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow sponsor monitors and auditors full access to all medical records at the research facility for subjects screened or enrolled in the trial.
I agree to await IRB/IEC approval before implementation of any protocol amendments to this protocol. If, however, there is an immediate hazard to subjects, I will implement the amendment immediately, and provide the information to the IRB/IEC within 5 working days. Administrative changes to the protocol will be transmitted to the IRB/IEC for informational purposes only.

I agree to provide all subjects with informed consent forms, as required by the applicable regulations and by ICH guidelines. I agree to report to the sponsor any adverse experiences in accordance with the terms of the sponsor's Clinical Research Agreement and the relevant regional regulation(s) and guideline(s). I further agree to provide all required information regarding financial certification or disclosure to the sponsor for all investigators and subinvestigators in accordance with the terms of the relevant regional regulation(s). I understand that participation in the protocol involves a commitment to publish the data from this study or trial in a cooperative publication prior to publication of efficacy and safety results on an individual basis.

_____
Principal or Coordinating Investigator Signature and Date

_____
Sponsor Representative Signature and Date