

# 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 later-stage autosomal dominant polycystic kidney disease. *N Engl J Med* 2017;377:1930-42. DOI: 10.1056/NEJMoa1710030

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes.

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Otsuka Pharmaceutical  
Development & Commercialization, Inc.

Investigational Medicinal Product

Tolvaptan (OPC-41061)

**CLINICAL PROTOCOL**

A Phase 3b, Multi-center, Randomized-withdrawal, Placebo-controlled, Double-blind, Parallel-group Trial to Compare the Efficacy and Safety of Tolvaptan (45 to 120 mg/day, Split-dose) in Subjects with Chronic Kidney Disease Between Late Stage 2 to Early Stage 4 Due to Autosomal Dominant Polycystic Kidney Disease

Protocol No. 156-13-210

IND No. 72,975

EudraCT No. 2014-000226-38

**CONFIDENTIAL – PROPRIETARY INFORMATION**

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## Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc.	Protocol # 156-13-210 IND# 72,975
Name of Investigational Medicinal Product: Tolvaptan (OPC-41061)	EudraCT# 2014-000226-38
Protocol Title:	A Phase 3b, Multi-center, Randomized-withdrawal, Placebo-controlled, Double-blind, Parallel-group Trial to Compare the Efficacy and Safety of Tolvaptan (45 to 120 mg/day, Split-dose) in Subjects with Chronic Kidney Disease Between Late Stage 2 to Early Stage 4 Due to Autosomal Dominant Polycystic Kidney Disease
Clinical Phase/Trial Type:	Phase 3b/Therapeutic use
Treatment Indication:	Autosomal Dominant Polycystic Kidney Disease (ADPKD)
Objective(s):	<p>Primary: To compare the efficacy of tolvaptan treatment in reducing the change in estimated glomerular filtration rate (eGFR) from pre-treatment baseline to post-treatment follow-up, as compared with placebo, in subjects with late-stage chronic kidney disease (CKD) due to ADPKD who tolerate tolvaptan during an initial run-in period.</p> <p>Secondary: To compare the efficacy of tolvaptan treatment in reducing the decline of annualized eGFR slope, as compared with placebo, in subjects with late-stage CKD due to ADPKD who tolerate tolvaptan during an initial run-in period.</p> <p>To compare overall and hepatic safety of tolvaptan with placebo and to compare incidence of ADPKD complications (outcomes) during the trial.</p>

Trial Design:	Multi-center, randomized-withdrawal, placebo-controlled, double-blind, parallel-group trial:  <u>Screening period (2 weeks):</u> Screening period may be extended up to an additional 8 weeks for subjects who require modification of medical care specifically for this trial. This may include, for example, stabilizing anti-hypertensive regimens for subjects discontinuing diuretics or “wash-out” of tolvaptan or other investigational agents for candidates who participated in previous trials. Preliminary eligibility for the trial will be initially assessed using the subjects’ historical laboratory or imaging data. Eligibility will be confirmed by the mean of eGFR calculated from the subjects’ first 2 pre-treatment, central-lab serum creatinine assessments. The eGFR values will be estimated based on the Chronic Kidney Disease-Epidemiology (CKD-EPI) formula (eGFR <sub>CKD-EPI</sub> , hereafter referred to as eGFR). Confirmation of ADPKD diagnosis (using the modified Pei-Ravine criteria) may require confirmatory imaging.  <u>Placebo run-in period (1 week):</u> Subjects will be given placebo in a daily split dose of a single 0 mg tablet upon awakening and another 0 mg tablet approximately 8 to 9 hours later (abbreviated 0/0 mg), in a form identical to tolvaptan tablets. Blood will be drawn 2 times on separate days (at least 24 hours apart), including the last day of the run-in period, for efficacy and safety measures. Subjects unable to tolerate the placebo dose regimen will be considered “Run-in failures”, they will complete an end of treatment (EoTx) visit and be followed up after 7 days by phone call to assess any ongoing adverse events (AEs).  <u>Tolvaptan titration period (2 weeks):</u> Subjects will be given a split dose of 30/15 mg tolvaptan with upward titration every 3 to 4 days to 45/15 mg, 60/30 mg, up to a maximum dose of 90/30 mg per day over 2 weeks. Subjects who are unable to tolerate at least 60/30 mg of daily tolvaptan will be considered “Run-in failures” and will complete an EoTx visit and be followed up after 7 days by phone call to assess any ongoing AEs. Subjects will have blood drawn on the last day of this period for efficacy and safety measures.
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Trial Design, cont.:	<p><u>Tolvaptan run-in period (3 weeks):</u> Subjects who tolerate the tolvaptan 60/30 mg or 90/30 mg daily dose regimen will enter the tolvaptan run-in period at the tolerated dose for 3 additional weeks. Except for management of AEs, no dose adjustment will be permitted. Subjects unable to tolerate at least 3 weeks of daily tolvaptan treatment at 60/30 mg or higher will be considered “Run-in failures” and will complete an EoTx visit and be followed up after 7 days by phone call to assess any ongoing AEs. During the last 2 weeks of this period, blood will be drawn 2 times on separate days (at least 24 hours apart), including the last day of the run-in period, for efficacy and safety measures.</p> <p><u>Double-blind, randomized treatment period (12 months):</u> Only subjects who reach the end of the tolvaptan run-in period and are able to tolerate tolvaptan 60/30 mg or 90/30 mg daily “for the rest of their lives” are eligible to enter this period. Randomization will be 1:1, tolvaptan to placebo. Subjects will be stratified by their baseline eGFR, at a threshold of <math>\leq 45</math> or <math>&gt; 45 \text{ mL/min}/1.73\text{m}^2</math>, and by age (<math>\leq 55</math> or <math>&gt; 55</math> years old). Subjects will also be stratified by total kidney volume (TKV; <math>\leq 2000 \text{ mL}</math> or <math>&gt; 2000 \text{ mL}</math>), if known. Post-randomization, the maximally-tolerated dose of tolvaptan established during the run-in period, or the equivalent as matching placebo tablets, will be dispensed according to the subject’s randomization outcome. If continued tolerability becomes an issue, subjects may titrate downward to 45/15 mg (or 30/15 mg, with medical monitor approval) or temporarily interrupt treatment as needed. Return to higher doses is also allowed.</p> <p><u>Follow-up period (3 weeks):</u> For randomized subjects, after Month 12 (or the EoTx visit, if a subject discontinues IMP prematurely) each subject will enter a 3-week follow-up period. No assessments will be taken for the first week of this period; however, 5 visits will be scheduled for the last 2 weeks of follow-up for post-treatment efficacy and safety measures.</p>
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Subject Population:	This trial will randomize approximately 800 subjects with ADPKD, with a minimum of 700 and a maximum of 1000 subjects planned to be enrolled. Male and female adults will be enrolled, from 18-55 years of age with eGFR between 25 and 65 mL/min/1.73m <sup>2</sup> or 56 to < 66 years of age with eGFR between 25 and 44 mL/min/1.73m <sup>2</sup> (with medical monitor approval). Only subjects tolerating a single-blind run-in period of tolvaptan (60/30 mg per day or 90/30 mg per day) will be randomized, to limit subsequent withdrawal due to lack of tolerability.
Inclusion/Exclusion Criteria:	<p>Main inclusion criteria:</p> <ul style="list-style-type: none"> <li>• eGFR between 25 and 65 mL/min/1.73m<sup>2</sup> (18 to 55 years) or eGFR between 25 and 44 mL/min/1.73m<sup>2</sup> (56 to &lt; 66 years, by medical monitor discretion only).</li> <li>• Diagnosis of ADPKD by modified Pei-Ravine criteria <ul style="list-style-type: none"> <li>• With family history: several cysts per kidney (3 if by sonography, 5 if by computed tomography or magnetic resonance imaging).</li> <li>• Without family history: 10 cysts per kidney (by any radiologic method above) and exclusion of other cystic kidney diseases. 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.</li> </ul> </li> <li>• Distribution and number of cysts consistent with the observed level of renal function deficit.</li> </ul> <p>Main exclusion criteria:</p> <ul style="list-style-type: none"> <li>• Need for chronic diuretic use.</li> <li>• Hepatic impairment or liver function abnormalities other than that expected for ADPKD with typical cystic liver disease during the pre-randomization period.</li> <li>• Subjects with advanced diabetes (eg, glycosylated hemoglobin [HgbA1c] &gt; 7.5 and/or glycosuria by dipstick), evidence of additional significant renal disease(s) (ie, currently active glomerular nephritidies), renal cancer, single kidney, or recent (within last 6 months) renal surgery, or acute kidney injury.</li> </ul>
Trial Site(s):	Approximately 200 enrolling sites including, but not limited to, the following regions: North America, South America, Eastern Europe, Western Europe, Asia, and Australia.

Investigational Medicinal Product(s), Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration:	Tolvaptan tablets (15 or 30 mg) or matching placebo will be self-administered orally as split-dose regimens, once upon awakening and another approximately 8 to 9 hours later. Doses will be expressed as early dose/late dose (eg, 60/30). Placebo will be administered to all subjects during the placebo run-in period. Tolvaptan regimens include 30/15, 45/15, 60/30 and 90/30 mg and will be titrated to tolerability during the tolvaptan titration period, and then continued at the maximally tolerated dose through the tolvaptan run-in period, and throughout the double-blind, randomized treatment period for those subjects randomized to receive tolvaptan (placebo subjects will receive matching placebo tablets).
Trial Assessments:	<p><u>Screening:</u> Medical history, complete physical examination, urine pregnancy test (women of child-bearing potential only).</p> <p><u>Efficacy:</u> Serum creatinine for determination of eGFR, polycystic kidney disease (PKD) outcomes survey.</p> <p><u>Safety:</u> Vital signs, directed physical examination, AEs, hematology, urinalysis, and serum chemistry tests (including serum transaminases, alkaline phosphatase, bilirubin, serum sodium), biomarker plasma and urine samples, and DNA blood samples (for consenting subjects).</p> <p><u>Pharmacokinetic (PK):</u> Sparse blood samples for a possible population PK analysis, which would be reported separately, and confirmation of compliance.</p> <p><u>Pharmacodynamic (PD):</u> Urine osmolality (Uosm), specific gravity.</p>

Criteria for Evaluation:	<p><b>Primary Efficacy Endpoint:</b>  Treatment difference in the change of eGFR from pre-treatment baseline to post-treatment follow-up, normalized (divided) by each subject's treatment duration.</p> <p><b>Secondary Endpoints:</b></p> <p><b>Key Secondary Efficacy Endpoint:</b>  Treatment difference in annualized slope of eGFR calculated for individual subjects using an appropriate baseline and available post-randomization, on-treatment assessments.</p> <p><b>Safety Endpoints:</b></p> <ol style="list-style-type: none"> <li>1) AEs</li> <li>2) Vital signs</li> <li>3) Clinical laboratory tests, including serum transaminases, total bilirubin (BT), alkaline phosphatase (ALP), and serum sodium.</li> </ol> <p><b>PK Endpoints:</b> Plasma tolvaptan and metabolite(s), including DM-4103 plasma concentrations.</p> <p><b>PD Endpoints:</b> Uosm and specific gravity.</p> <p><b>Exploratory Endpoints:</b></p> <p><b>Safety (may be undertaken and reported separately from the clinical study report):</b></p> <ul style="list-style-type: none"> <li>• Urine and plasma biomarker concentrations for potential evaluation of metabolic or immunologic traits related to drug-induced liver injury (DILI) and/or etiology of, susceptibility to, activity of, or progress of ADPKD, as well as the potential development of tools for diagnosis, prognosis and response to treatment.</li> <li>• DNA samples for genetic evaluation of DILI and/or etiology of, susceptibility to, activity of, or progress of ADPKD, as well as the potential development of tools for diagnosis, prognosis and response to treatment.</li> </ul> <p><b>Efficacy:</b> Assessment of ADPKD outcomes.</p>
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Statistical Methods:	<p><u>Sample size:</u> Based on a Mixed Model Repeated Measurements analysis of the non-Japanese CKD-3 Subjects from trial 156-04-251, the treatment difference in renal function at Month 12 is 1.07 in our sample size calculation. It is expected that the residual variance and slope variance would be 22.13 and 5.27, respectively, assuming 4 to 5 pre-treatment and post-treatment observations taken in 2-week intervals. The power calculation estimates that, for a 2-sided alpha set at 0.05 for a power of 85% to 90%, and with an assumption of 15% dropout rate in the trial, a total sample size of 660 to 770 subjects (rounded up to 700 to 800 subjects) is needed.</p> <p><u>Key Datasets for analysis:</u> The following datasets are defined for this trial:</p> <ul style="list-style-type: none"><li>• Randomized Population: All subjects who are randomized in this trial.</li><li>• Randomized Safety Population: All subjects who are randomized in this trial and take at least 1 dose of IMP after randomization. This is the primary safety population.</li><li>• Primary Endpoint Efficacy Population: All subjects who are in the Randomized Population, take at least 1 dose of IMP after randomization, and have a primary endpoint baseline and at least 1 valid post-treatment evaluation in eGFR (ie, after at least 1 week off treatment).</li><li>• Key Secondary Endpoint Efficacy Population: All subjects who are in the Randomized Population, take at least 1 dose of IMP after randomization, and have a baseline and at least 1 post-randomization evaluation in eGFR.</li></ul> <p><u>Primary efficacy analysis:</u> The change in eGFR from pre-treatment baseline to post-treatment follow-up, annualized (divided) by each subject's IMP treatment duration, will be calculated. The annualized change in eGFR will be analyzed by analysis of covariance (ANCOVA) with treatment and randomization stratification factors as factor and covariate baselines.</p>
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Statistical Methods, cont.:	<p><u>Key secondary efficacy analysis:</u> The key secondary endpoint of the trial is the annualized rate (slope) of eGFR change. The linear mixed effect model with effects of time, treatment, time treatment interaction, acute hemodynamic effect, baseline and randomization stratification factors will be used for analysis of the key secondary endpoint, in which the intercept and time are both fixed effect and random effect. An un-structured variance covariance matrix is assumed for the random intercept and time.</p> <p><u>Safety analyses:</u> Safety analysis will be conducted based on standard safety variables, including AEs, clinical laboratory data, physical examinations and vital signs. Potentially clinically significant results in laboratory tests identified using prospectively defined criteria, including criteria on liver enzyme elevations, will also be summarized for the primary and secondary safety populations.</p>
Trial Duration:	The duration of the double-blind, randomized treatment period will be 12 months. The total duration of the trial (including the pre-randomization and follow-up periods) will be approximately 15 months.

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## List of Abbreviations and Definitions of Terms

<b><u>Abbreviation</u></b>	<b><u>Definition</u></b>
ADPKD	Autosomal dominant polycystic kidney disease
ADR	Adverse drug reactions
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC <sub>0-24</sub>	area under the concentration-time curve from time zero to 24 hours
AUC <sub>τ</sub>	Area under the concentration-time curve calculated to the last observable concentration
AVP	Arginine vasopressin
BT	Bilirubin, total
BUN	Blood urea nitrogen
cAMP	Cyclic adenosine monophosphate
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease-Epidemiology
CL/F	Apparent clearance of drug from plasma after extravascular administration
C <sub>max</sub>	Maximum (peak) plasma concentration
CrCL	Creatinine clearance
CRO	Clinical Research Organization
CSR	Clinical study report
CT	Computed tomography
CYP	Cytochrome P450
DILI	Drug-induced liver injury
DILIN	Drug-Induced Liver Injury Network
DNA	Deoxyribonucleic acid
DSMC	Data Safety and Monitoring Committee
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
eGFR <sub>CKD-EPI</sub>	Estimated glomerular filtration rate calculated using the Chronic Kidney Disease-Epidemiology formula
EMA	European Medicines Agency
EoTx	End of treatment
ESRD	End-stage renal disease
EU	European Union
FDA	(United States) Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
HgbA1c	Glycosylated hemoglobin
IB	Investigator's brochure
ICF	Informed consent form

<b><u>Abbreviation</u></b>	<b><u>Definition</u></b>
ICH	International Conference on Harmonisation
ID	Identification number
IDMC	Independent Data Monitoring Committee
IDMS	Isotope dilution mass spectroscopy
IEC	Independent ethics committee
IMP	Investigational medicinal product
IND	Investigative new drug
INR	International normalized ration
IRB	Institutional review board
IRE	Immediately reportable event
ITT	Intent-to-treat
IVRS	Interactive voice response system
LDH	Lactate dehydrogenase
MAR	Missing at random
MCHC	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measurements
MNAR	Missing not at random
MRI	Magnetic resonance imaging
NRC	National Research Council
NSAID	Non-steroidal anti-inflammatory drugs
OC	Observed cases
OPDC	Otsuka Pharmaceutical Development & Commercialization, Inc.
PD	Pharmacodynamic
PK	Pharmacokinetic
PKD	Polycystic kidney disease
PT	Prothrombin time
QD	Once daily
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
$t_{1/2,z}$	Elimination half-life
TKV	Total kidney volume
$t_{max}$	Time to maximum (peak) plasma concentration
Uosm	Urine osmolality
ULN	Upper limit of normal
US or USA	United States or United States of America
$V_2$	Vasopressin type 2 (receptor)
WBC	White blood cell
WOCBP	Women of childbearing potential

## 1 Introduction

Tolvaptan (OPC-41061) is a selective arginine vasopressin (AVP) type 2 ( $V_2$ ) receptor antagonist that is currently approved in the United States (US), Europe, Australia, Canada, China, Hong Kong, Indonesia, Japan, Philippines, Republic of Korea, Taiwan, Thailand, and Turkey, for various forms of hyponatremia, and in Japan also for volume overload in heart failure or liver cirrhosis.

Tolvaptan is also being investigated for the use in adults to treat autosomal dominant polycystic kidney disease (ADPKD), an inherited condition which leads to progressive destruction of normal kidney structure leading to end-stage renal disease (ESRD). The disease affects the structure of the kidneys through proliferation and growth of numerous fluid-filled cysts. The expanding cysts compress normal tissue and blood vessels resulting in ischemia, inflammation and fibrosis leading to progressive nephron loss. The remaining nephrons are initially able to compensate through glomerular hyperfiltration up to a point when nephron loss is so great that compensation is no longer adequate and renal function begins to decline. Clinical manifestations of kidney disease may be sporadic (hematuria, infections, pain) or chronic (hypertension, albuminuria, renal insufficiency) and indicate ongoing and cumulative damage to the kidney.

The number of diagnosed ADPKD cases was estimated at 116,228 in the US in 2009. The estimated prevalence of diagnosed ADPKD is similar in Europe and estimated to be < 5 per 10,000.<sup>1</sup> Though a rare genetic disease, it ranks as the 6<sup>th</sup> leading cause of ESRD in the US (2.3% of the new ESRD cases).<sup>2</sup> An estimated 45% to 70% of patients with ADPKD progress to ESRD by age 65.<sup>3</sup> Over the past 30 years, the age of onset for ESRD among ADPKD patients has remained the same (median age of 54). In contrast, effective therapy has delayed the onset of ESRD in patients with nephropathy due to hypertension, diabetes, and glomerulonephritis.

There are currently no therapies which can slow cyst growth or the deterioration of kidney function in ADPKD. Current management focuses on ameliorating symptoms of pain, control of blood pressure, and treatment of infections with antibiotics. None of these treatments target the underlying cause of the disease. Often, the only definitive intervention for renal complications in ADPKD is kidney transplantation, which typically occurs after years of hemodialysis.

In the US, the development program for tolvaptan for ADPKD was granted Fast-track designation on 20 Jan 2006 and orphan drug designation on 06 Apr 2012. Tolvaptan was

designated as an orphan drug for prevention of the progression of ADPKD in Japan on 11 Aug 2006. The European Medicines Agency (EMA) granted orphan designation for the use of tolvaptan for the treatment of ADPKD on 5 Aug 2013.

If approved, tolvaptan would be the first available therapy to slow kidney disease progression in adults with ADPKD.<sup>4,5</sup> Refer to the Tolvaptan Investigator's Brochure (IB) for more information.<sup>4</sup>

## **1.1 Nonclinical Data**

Rodent models of ADPKD and ex-vivo human ADPKD cell and tissue cultures have implicated AVP as a promoter of kidney cyst growth.<sup>6,7</sup> AVP-induced cyclic adenosine monophosphate (cAMP) increases proliferation of ADPKD renal tubular epithelium and chloride-mediated, intra-cystic, fluid secretion. This leads to cyst expansion which disrupts renal architecture leading to ischemia, kidney fibrosis, and irreversible damage to the kidney, ultimately impairing its function. Tolvaptan inhibits cAMP production by blocking AVP binding to the renal AVP-V<sub>2</sub> receptor. For information on nonclinical toxicology and absorption, distribution and metabolism data on tolvaptan please refer to the most current version of the Investigator's Brochure.<sup>4</sup>

## **1.2 Clinical Data**

Tolvaptan was clinically effective in delaying decline of renal function, as determined by changes in serum creatinine concentrations over 3 years, in an international, multicenter, clinical trial in subjects with chronic kidney disease (CKD) stage 1 to 3 due to ADPKD.<sup>8</sup> These effects were consistent across each of these CKD stages, supporting tolvaptan's potential utility in early to mid-stage disease (Table 1.2-1), and creating a compelling argument for long-term effectiveness in those initiating therapy at an early stage and adhering to therapy as the disease progresses. This trial also demonstrated an acute and persistent reduction on rate of kidney cystic growth. The reductions in rate of kidney growth correlated with reductions in kidney pain and with preservation of renal function. Similar correlations were observed in a smaller, matched-control study (Study 156-09-283).<sup>9</sup> Thus, the clinical data have confirmed the non-clinical effects seen in animals (see Section 1.1) and support approval of tolvaptan as the first agent to slow the progression of ADPKD.<sup>9</sup> This trial will serve to confirm prior results and extend our understanding of the safety and efficacy of tolvaptan into later stages of disease, specifically CKD stages 3b and 4.

**Table 1.2-1 Vasopressin Blockade Across Differing Severities of ADPKD:  
Effect on Rate of Estimated Glomerular Filtration Decline in  
Chronic Kidney Disease Stages 1-3**

CKD Stage by eGFR <sub>CKD-EPI</sub> (mL/min/1.73m <sup>2</sup> )	N (Tolvaptan/ Placebo)	eGFR Slope Tolvaptan	eGFR Slope Placebo	Effect Size	Relative Effect Size
Stage 1 ( $\geq 90$ )	330/173	-1.93	-2.86	0.94 <sup>a</sup>	33%
Stage 2 (60-90)	465/224	-2.64	-3.85	1.21 <sup>a</sup>	31%
Stage 3 <sup>b</sup> (30-60)	3a (45-60) 3b (30-45)	-3.51 -3.92	-5.23 -5.99	1.72 2.07	33% 35%

eGFR<sub>CKD-EPI</sub> = estimated glomerular filtration rate calculated by the Chronic Kidney Disease-Epidemiology (CKD-EPI) formula

<sup>a</sup>All p < 0.005

<sup>b</sup>CKD Stage 3: relative effect size (33%); N (tolvaptan/placebo; 163/84)

Source: Trial 156-04-251 clinical study report (CSR); Data on file

### 1.3 Pharmacokinetics/Pharmacodynamics

Following single oral doses to healthy subjects, tolvaptan maximum (peak) plasma concentration ( $C_{max}$ ) values show less than dose-proportional increases from 30 to 240 mg with mean values increasing from about 235 to 1000 ng/mL; values plateau at doses ranging from 240 to 480 mg. Following multiple once-daily (QD) dosing, tolvaptan pharmacokinetic (PK) values were also nonlinear. Mean  $C_{max}$  and area under the concentration-time curve calculated to the last observable concentration ( $AUC_{\tau}$ ) values were 4.2- and 6.4-fold higher for the 300 mg dose compared with the 30 mg dose. Across all doses, the median time to median (peak) plasma concentration ( $t_{max}$ ) value was 2 hours (range 1 to 12 hours). For 60- and 90-mg tablets, dosing with a high-fat meal increases tolvaptan  $C_{max}$  but has no effect on tolvaptan area under the concentration-time curve ( $AUC$ ).

Tolvaptan concentrations do not significantly accumulate following QD dosing, indicating that tolvaptan has a short elimination half-life ( $t_{1/2,z}$ ). Following single oral doses, the  $t_{1/2,z}$  of tolvaptan increases with increasing dose, with mean values around 3 hours for a 15 mg dose and 12 hours for 120 to 480 mg doses.

Tolvaptan excretion in urine is < 1% of the dose and in feces about 19% of the dose. Tolvaptan is eliminated primarily by cytochrome P450 (CYP)3A-mediated metabolism and is considered to be a weak substrate as the tolvaptan AUC was increased about 3.5-fold and the apparent clearance of drug from plasma after extravascular administration (CL/F) was decreased by 87% when co-administered with ketoconazole.

Mean  $C_{max}$  and AUC values in subjects with ADPKD and preserved renal function (average creatinine clearance [CrCL] > 60 mL/min) range from 15 to 60% higher when compared with healthy subject values, but rates of CL/F range from 14% slower to 27% faster, indicating that tolvaptan PK in ADPKD subjects with preserved renal function is similar to that in healthy subjects. Following multiple QD and split-dose regimens ranging from 30 to 120 mg/day, accumulation of tolvaptan concentrations is negligible. For split-dose regimens of 30, 60 and 120 mg/day, tolvaptan PK appears to be linear as mean values of AUC from time zero to 24 hours post-dose ( $AUC_{0-24h}$ ) approximately double with a doubling of daily dose.

Renal impairment reduces tolvaptan clearance and consequently plasma concentrations increase. Following a single 60 mg dose, tolvaptan AUC in subjects with CrCL < 30 mL/min was 1.9-fold higher compared to subjects with CrCL > 60 mL/min.

Tolvaptan is highly bound to plasma proteins (> 98%) and binding was unaffected by renal impairment.

Pharmacodynamic (PD) responses to tolvaptan were observed for subjects with ADPKD at CKD stages 1 to 4. At the recommended split-dose regimens of 45/15 mg to 90/30 mg daily, tolvaptan blocked AVP action at the V<sub>2</sub> receptor (ie, increased urine excretion rates and suppressed Uosm) for almost the entire 24-hour day in subjects with ADPKD (CKD Stage 1 to 2). The large increase in urine output that resulted from this inhibition was associated with the 5 most frequently reported adverse events (AEs; polyuria, pollakiuria, nocturia, thirst, and dry mouth) in clinical pharmacology or clinical efficacy trials. In 2 clinical pharmacology trials in subjects with ADPKD and estimated glomerular filtration rates (eGFR) > 60 mL/min/1.73m<sup>2</sup> administered a 90/30 mg dose regimen for at least 7 days, mean (standard deviation [SD]) 24-hour urine volumes were 7.464 (2.103) L and 6.532 (2.036) L. As renal function declined, the volume of urine produced for a given dose of tolvaptan decreased; following a 90/30 mg split-dose regimen, mean (SD) 24-hour urine volumes for subjects with ADPKD and eGFR 30 to 60 and < 30 mL/min/1.73m<sup>2</sup> were 6.233 (1.307) L and 5.024 (1.767) L, respectively. Therefore, despite an increase in tolvaptan concentration, the clinical effects of tolvaptan on the most common adverse events are diminished. Other adverse reactions, such as idiopathic liver injury, do not appear to be concentration-dependent.

Subjects with ADPKD are able to maintain a neutral fluid balance so increases in serum sodium and plasma osmolality were small, following tolvaptan treatment. Serum concentrations of creatinine, cystatin C, and uric acid were higher following tolvaptan treatment as tolvaptan reduced the eGFR approximately 6 to 8%, CrCL approximately 8 to 10%, and uric acid clearance approximately 20 to 25%; the changes appeared to

independent of baseline renal function for CKD stages 1 to 4. Urinary excretion of aquaporin 2 and cAMP were lower following tolvaptan treatment, supporting the hypothesis that tolvaptan inhibition of the V<sub>2</sub> receptor is successful in reducing cellular cAMP concentrations.

Following multiple oral doses, the tolvaptan metabolite DM-4103 accumulates, as its half-life is approximately 180 hours. This metabolite has no pharmacological activity at the concentrations expected to be achieved following the doses used in this trial 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 at about 80% of those expected to be achieved in this trial revealed no evidence of time-dependent toxicological effects.

For additional information on PK/PD responses from tolvaptan treatment, please refer to the Investigator's Brochure.<sup>4</sup>

#### **1.4 Known and Potential Risks and Benefits**

ADPKD is a devastating, progressive disease that places a tremendous burden on patients and their families. The risk a patient is willing to accept is a personal decision based on his/her individual and familial experience with the disease. Tolvaptan is potentially the first therapy that offers patients a treatment option to slow their disease progression; however, as of January 2014, it has not yet been approved for this indication. The treatment risks are well characterized, manageable, and must be weighed against the consequences of no treatment.

The most common observed risks of tolvaptan therapy include those arising from aquaresis (eg, polyuria, pollakiuria, nocturia, thirst, dry mouth), dehydration, electrolyte abnormalities, and gout. While aquaretic events did not contribute to significant patient morbidity over 3 years of study in the pivotal placebo-controlled trial (Trial 156-04-251), they do represent adverse drug reactions (ADRs) which occur early (within days to weeks) and are most likely to limit a subject's ability to continue therapy over a duration of treatment that is likely to provide benefit. Aquaretic ADRs are also likely to limit the efficacy of an unproven, yet often recommended, therapeutic strategy of increasing water ingestion.

While the proposal of increased water ingestion as a mechanism of ameliorating CKD<sup>10</sup> has not reached medical equipoise, in this trial we believe a general recommendation to do so is reasonable and would recommend ingestion of water adequate to avoid thirst. Typically, this would represent 2 to 3 liters of water per day in subjects with relatively intact renal function, and lesser amounts in those with more impaired function. Serum

sodium should be monitored during the trial to ensure a tendency toward hyponatremia (symptomatic or asymptomatic) is not produced.

The most notable safety issue associated with chronic tolvaptan use, newly identified in Trial 156-04-251, is the potential for idiosyncratic hepatic toxicity. An imbalance in the proportion of subjects with elevated transaminases (tolvaptan > placebo) led to identification of 3 subjects (total from both Trial 156-04-251 and its open-label extension trial, 156-08-271) with laboratory and clinical evidence of potentially serious drug-induced liver injury (DILI). Based on the available data from the afore-mentioned trials, the sponsor proposes that appropriate patient monitoring and management be implemented to mitigate this potential risk in the ADPKD population. For this trial, standard liver parameters will be measured at baseline and then monthly thereafter.

Significant events related to glaucoma and skin neoplasms were also observed; however the causal relationship to tolvaptan remains uncertain. These adverse reactions should be considered in light of the benefits of a reduced risk of ADPKD kidney complications, including renal pain, urinary tract infection, hematuria, anemia, and nephrolithiasis.<sup>5</sup>

The treatment risks of tolvaptan are well characterized, manageable, and must be weighed against the consequences of no adequate treatment. With sufficient knowledge of the benefits and risks and risk mitigation strategies, patients and their physicians may make informed decisions about tolvaptan treatment. In the final assessment, the overall benefit-risk profile of tolvaptan for the treatment of ADPKD appears favorable, offering a real opportunity to fill a longstanding unmet medical need.

## **2 Trial Rationale and Objectives**

### **2.1 Trial Rationale**

The current trial will extend the understanding of the efficacy and safety of tolvaptan treatment in ADPKD patients with late stage 2 to early stage 4 CKD. Focusing on the eGFR calculated by the Chronic Kidney Disease-Epidemiology (CKD-EPI) formula ( $eGFR_{CKD-EPI}$ , hereafter referred to as “eGFR”)<sup>11</sup>, this trial is expected to provide kidney function data that are complementary to the data demonstrating the benefits previously observed primarily in ADPKD subjects with earlier stages of disease.

Trial 156-04-251 utilized a post-randomization baseline to account for tolvaptan’s acute hemodynamic effect on eGFR. This hemodynamic effect has been well characterized in prior trials of up to 3-years duration. It has also been examined in subjects with kidney function ranging from normal to severely dysfunctional due to ADPKD or other

disorders.<sup>12,13</sup> The onset of hemodynamic effect is acute, it persists as long as treatment continues and is rapidly reversible upon discontinuation of treatment. A comparison of tolvaptan and placebo subjects able to complete Trial 156-04-251 indicated that the relative preservation of eGFR during treatment was sustained in the post-treatment follow-up phase and at baseline for Trial 156-08-271 (extending to at least 3 months). In an interim analysis of eGFR in the extension trial, both the prior-placebo and prior-tolvaptan groups exhibited this hemodynamic effect with open-label treatment with differences between groups being sustained for a further 2 years of treatment. (Data on file.)

However, in Trial 156-04-251, an early and imbalanced withdrawal of tolvaptan subjects led to missing baseline data for ~5% of tolvaptan subjects, complicating the interpretation of these results. The current trial will utilize tolvaptan treatment titration and tolerability run-in periods to exclude, prior to randomization, those subjects who report they are unlikely to be able to tolerate tolvaptan's aquaretic effects during long-term treatment. This, and a placebo run-in period, will be used to establish a pre-randomization baseline eGFR for each potential treatment assignment, thereby facilitating a straightforward calculation of the key secondary endpoint of eGFR slope for all subjects.

The trial's primary endpoint is defined as the absolute change in eGFR from pre-treatment to post-treatment, normalized by the subject's duration of treatment. To decrease variability, multiple serum creatinine measurements will be taken both pre- and post-treatment for each subject, and the eGFR values will then be averaged. Additionally, standardization of diet, exercise, and timing of serum collection and analysis of samples for serum creatinine are expected to reduce intra-subject variability.

In this trial, every effort will be made to avoid missing data by encouraging compliance and continuation of IMP. Furthermore, all subjects who do not specifically withdraw their consent will be followed as completely as possible for laboratory, health and vital status. This effort will begin during the informed consent process. Investigators, site personnel, and subjects will be provided with informational tools and educated regarding the importance of participation in clinical trials and adherence to all protocol specified visits and assessments. This will include training on relevant concepts from the National Academy of Sciences National Research Council (NRC) guideline on prevention and handling of missing data.<sup>14</sup> The informed consent form (ICF) will include a section codifying this understanding between the principal investigator and the prospective subject and can be withdrawn in stages accommodating each subject's willingness to provide follow-up of their medical information. Home nursing visits or local laboratory

visits will also be available for collection of follow-up blood samples and to continue health-status follow-up even if IMP is permanently discontinued.

Through more frequent (eg, monthly) monitoring of liver transaminases (aspartate aminotransferase [AST], alanine aminotransferase [ALT]), alkaline phosphatase (ALP), and bilirubin (total; BT), the current trial will more precisely define the potential for DILI previously observed in Trial 156-04-251. Frequent monitoring will also detect smaller elevations earlier permitting closer and more thorough evaluation and intervention (including drug interruption or discontinuation). This is expected to mitigate the risk of serious or irreversible injury.

Urine and plasma samples for potential biomarker testing and an optional blood sample for genetic deoxyribonucleic acid (DNA) testing will be collected and stored for a maximum of 15 years after the trial has ended. Potential analysis may include disease-related genes and genes involved in how tolvaptan is processed within the body. Therefore, the information gathered through genetic/biomarker analysis should improve the sponsor's understanding of the disease, its diagnosis, prognosis, and possibly treatment outcome by identifying which patients are more likely to respond to tolvaptan, and/or predicting which subjects are likely to progress to more severe disease states, and/or predicting which subjects may have an adverse event such as DILI, and/or lead to new opportunities for therapies. The aim of the genetic/biomarker testing is to further understand the causes and processes of ADPKD and the impact treatment with tolvaptan has on the progression of the disease and safety of the subject and future generations of patients.

## **2.2 Dosing Rationale**

Successful treatment of ADPKD appears to require early, constant inhibition of the vasopressin V<sub>2</sub> receptor. This treatment paradigm produced decreased rates of growth in kidney size in animal models. The clinical formulation of tolvaptan was optimized to increase bioavailability which necessitates split dosing to maintain suppression of AVP action across 24 hours. A higher dose is used early in the day, with a lower dose approximately 8 to 9 hours later in order to produce a maximal inhibition on waking with a gradual fall-off of effect during the night when frequent urination could lead to interruption of sleep.

Urine osmolality (Uosm) has been used as a surrogate of vasopressin V<sub>2</sub> receptor inhibition in Trials 156-03-248 and 156-03-249 to refine these doses. Normally, Uosm only increases above plasma osmolality (approximately 290 mOsm/L) when vasopressin is acting at the kidney's distal collecting ducts. When trough spot Uosm remains below

300 mOsm, effective V<sub>2</sub> receptor inhibition can be assumed. These trials also confirmed a phenomenon where the first day's therapy produces the most robust aquaresis, which then decreases approximately 20% by the 5<sup>th</sup> day of repeated dosing.<sup>15</sup>

Split dose regimens of 30/15, 45/15, 60/30, and 90/30 mg were available in the titration phase of the ongoing open-label extension trial in ADPKD (Trial 156-04-250). During this trial, both the tolerability of tolvaptan regimens and efficacy (as measured by suppression of Uosm) were determined in 46 subjects. Results of this trial confirm that suppression of trough Uosm improves with each higher dose of tolvaptan, and that "breakthrough" occurred less frequently with each regimen (breakthrough of 61%, 39%, 26%, 15% for 30/15, 45/15, 60/30, and 90/30 mg doses, respectively).<sup>16</sup>

While optimal efficacy (0% breakthrough at trough) could not be achieved at any of the dose regimens used in the titration for Trial 156-04-250, the limit of tolerability was reached with only 41% of subjects stating that they could tolerate a 90/30 mg dose.<sup>16</sup>

This trial will also implement a titration strategy in the pre-randomization period to establish, by self-report, a maximally tolerated dose of tolvaptan for each subject. In the tolvaptan titration period, all subjects will be given a split dose of 30/15 mg tolvaptan with upward titration every 3 to 4 days to 45/15 mg, 60/30 mg, up to a maximum dose of 90/30 mg per day over 2 weeks. All subjects will be encouraged to progress to 90/30 mg per day, as this is likely to be most effective. All subjects who tolerate tolvaptan at the 60/30 mg or 90/30 mg daily dose regimen may enter the tolvaptan run-in period at one of these doses for 3 additional weeks. Except for management of AEs, no dose adjustment will be permitted during the tolvaptan run-in period. Subjects unable to tolerate at least 3 weeks of daily tolvaptan treatment at 60/30 mg or 90/30 mg during the tolvaptan run-in period will not be eligible for randomization. This is expected to minimize post-randomization withdrawal due to inability to tolerate acute side effects of tolvaptan.

### **2.3 Trial Objectives**

Primary:

- To compare the efficacy of tolvaptan treatment in reducing the change in eGFR from pre-treatment baseline to post-treatment follow-up, as compared with placebo, in subjects with late-stage CKD due to ADPKD who tolerate tolvaptan during an initial run-in period.

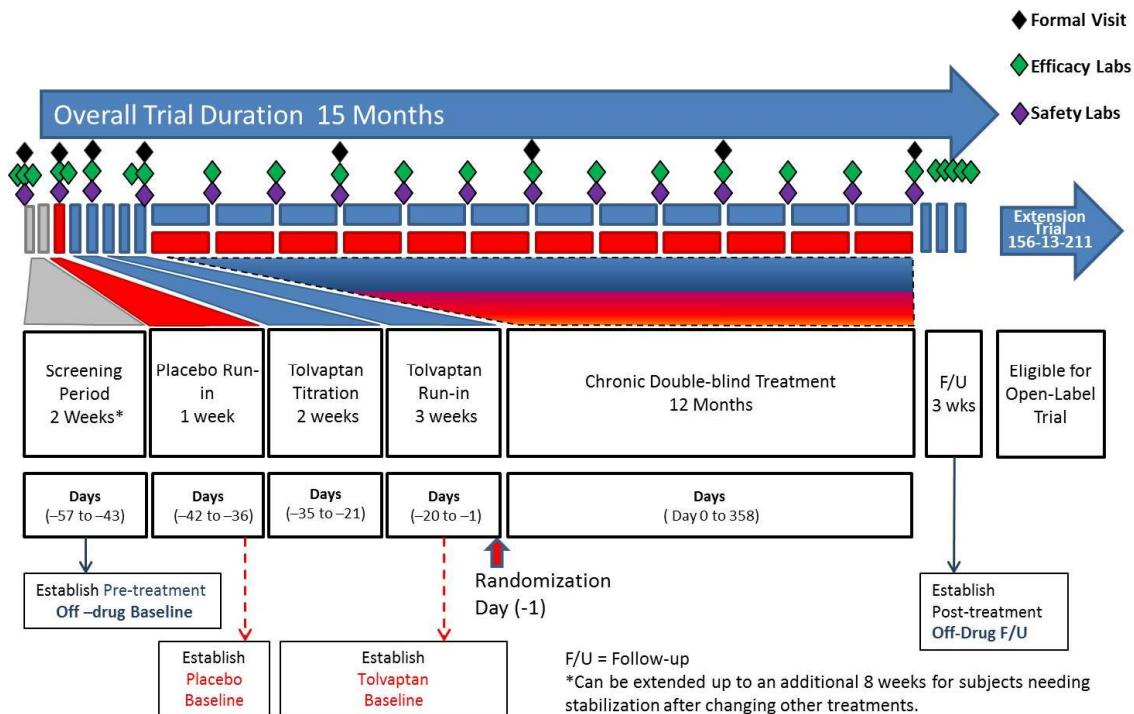
Secondary:

- To compare the efficacy of tolvaptan treatment in reducing the decline of annualized eGFR slope, as compared with placebo, in subjects with late-stage CKD due to ADPKD who tolerate tolvaptan during an initial run-in period.
- To compare overall and hepatic safety of tolvaptan with that of placebo and to compare incidence of ADPKD complications (outcomes) during the trial.

### 3 Trial Design

#### 3.1 Type/Design of Trial

This is a phase 3b, multi-center, randomized-withdrawal, placebo-controlled, double-blind, parallel-group trial to compare the efficacy and safety of tolvaptan in subjects with ADPKD and baseline kidney function as documented by an eGFR between 25-65 mL/min/1.73m<sup>2</sup>, inclusive. The overall design is illustrated in [Figure 3.1-1](#).



**Figure 3.1-1 Trial Design Schematic**

#### 3.2 Treatments

All subjects will be given investigational medicinal product (IMP; tolvaptan and/or placebo, according to trial period and randomization group) in a daily split dose, once upon awakening and another approximately 8 to 9 hours later. 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 maximize receptor suppression. Doses will be expressed as early dose/late dose (eg, 60/30 mg). Placebo will be administered to subjects randomized to that treatment in a form identical to the corresponding dose of tolvaptan tablets.

While taking IMP, 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 to 2 cups of water before bedtime regardless of perceived thirst and replenish fluids overnight with each episode of nocturia. Upon consent, all subjects should receive the recommendation for ingestion of at least 2-3 liters of fluid (including in solid, semi-solid, and liquid foods) per day, unless otherwise directed by your study doctor. This recommendation should start during screening and continue through the end of the trial.

### **3.2.1 Pre-randomization**

Subjects who provide informed consent, who meet the inclusion/exclusion criteria, and for whom preliminary eligibility is established, will enter an 8-week run-in period. This represents “pre-randomization”. This pre-randomization period consists of a screening period (typically 2 weeks for tolvaptan-naïve subjects; however, longer periods up to 8 additional weeks are acceptable for subjects withdrawing from tolvaptan or needing stabilization after changing other treatments, especially anti-hypertensives and diuretics), a placebo run-in period (1 week), a tolvaptan titration period (2 weeks), and a tolvaptan run-in period (3 weeks), described in more detail below.

#### **3.2.1.1 Screening Period**

No investigational treatments will be administered during the screening period. During this period, the subject's eligibility for the trial will be confirmed using historical imaging data of total kidney volume (TKV; if available) to support a diagnosis of ADPKD and to verify the level of CKD primarily due to ADPKD and not to other renal (hypoplasia) or metabolic (diabetic or hypertensive nephropathy) disorders. In addition, eligibility will be confirmed by the mean of eGFR calculated from the subjects' first 2 pre-treatment, central-lab, serum creatinine assessments. Subjects will be told that they will receive both tolvaptan and placebo during various subsequent periods of the trial and that the next period involves a dose escalation with multiple efficacy, safety, and tolerability assessments.

### **3.2.1.2 Placebo Run-in Period**

In the first week after the screening period, all subjects will begin the single-blind, placebo run-in period where they will be given placebo in a daily split dose of 0 mg (abbreviated 0/0 mg), in a form identical to tolvaptan tablets. The subject will remain blinded to treatment and receive a bottle of drug which they understand could be either tolvaptan or placebo. Those subjects unable to tolerate the placebo dose regimen will be considered “Run-in failures”, they will complete end of treatment (EoTx) visit assessments and be followed up after 7 days by phone call to assess any ongoing AEs.

### **3.2.1.3 Tolvaptan Titration Period**

During the single-blind, tolvaptan titration period (2 week duration), all subjects will receive 2 cartons of tolvaptan, 1 carton containing 2 bottles of 15 mg tablets and the other carton containing 2 bottles of 30 mg tablets. The tolvaptan tablets will appear identical to the placebo tablets dispensed in the prior period, and subjects will be told that they could be either tolvaptan or placebo. Subjects will be instructed to take tolvaptan starting at a split dose of 30/15 mg (as 2 tablets upon waking and 1 tablet approximately 8 to 9 hours later) and to titrate up every 3 to 4 days; first to 45/15 mg, then 60/30 mg, then up to the maximum dose of 90/30 mg. Titrating will be accomplished by increasing the number of tablets/dose and/or switching from 15 mg tablets to 30 mg tablets, as detailed in [Table 3.2.2-1](#), below. Prior to each upward titration, the subject’s tolerability to the current dose will be assessed by asking, “Could you tolerate this dose of trial medication for the rest of your life?” Those subjects unable to reach and tolerate at least a 60/30 mg tolvaptan dose regimen will be considered “Run-in failures”, they will complete end of EoTx visit assessments and be followed up after 7 days by phone call to assess any ongoing AEs.

### **3.2.1.4 Tolvaptan Run-in Period**

Subjects tolerating at least 60/30 mg tolvaptan may enter the tolvaptan run-in period (3 week duration). Subjects will continue on a stable 60/30 mg or 90/30 mg tolvaptan dose to confirm tolerability over a longer period and to establish a tolvaptan pre-randomization baseline.

At the end of the tolvaptan run-in period, subjects not tolerating at least 60/30 mg tolvaptan will be considered “Run-in failures”, they will complete EoTx visit assessments and be followed up after 7 days by phone call to assess any ongoing AEs.

### 3.2.2 Double-blind Randomized Treatment Period

Subjects completing the tolvaptan run-in period tolerating at least 60/30 mg of tolvaptan will be randomized upon entry to this double-blind period. Aside from the first required clinic visit and dispensing a new bottle of IMP, no distinction between the prior run-in period and the randomization period should be made for the subject.

After stratified randomization, subjects will enter the double-blind, randomized treatment period receiving either tolvaptan or placebo in a 1:1 ratio. Tolvaptan, or matching placebo, will be administered at 60/30 or 90/30 mg, as split doses, with down-titration to 45/15 mg and 30/15 mg as needed for tolerability. Planned down titration to 30/15 mg requires consultation with the medical monitor.

Subjects randomized to tolvaptan will continue to take the same dose that they received during the tolvaptan run-in period. Subjects randomized to placebo will receive placebo tablets matching their tolerated tolvaptan dose during the tolvaptan run-in period.

The treatment duration of these subjects will be 12 months from their date of randomization.

<b>Table 3.2.2-1 Dosing Schedule</b>		
<b>Trial Day</b>	<b>Nominal Time</b>	<b>Dose</b>
Day -56 to -43		<b>Screening</b> 2 weeks (No drug)
Day -42 to -36	8:00 am/ 4:00 to 5:00 pm	<b>Placebo run-in</b> Placebo (matching equivalent to tolvaptan)0 mg
Day -35 to -22	8:00 am/ 4:00 to 5:00 pm	<b>Tolvaptan titration</b> Tolvaptan split-dose titration (using 15 or 30 mg tablets) 30/15, 45/15, 60/30 then 90/30 mg (given as 2x15/1x15; 3x15/1x15; 2x30/1x30 or 3x30/1x30 mg tablets, respectively)
Day -21 to -1	8:00 am/ 4:00 to 5:00 pm	<b>Tolvaptan run-in</b> Tolvaptan stable dose (same as maximum tolerated dose from tolvaptan titration, either 60/30 or 90/30 mg) for 3 weeks, using 30 mg tablets Randomization 1:1 - tolvaptan:placebo (Day -1)

<b>Table 3.2.2-1 Dosing Schedule</b>		
<b>Trial Day</b>	<b>Nominal Time</b>	<b>Dose</b>
Day 1 to Month 12	8:00 am/ 4:00 to 5:00 pm	<p><b>Double-blind randomized treatment</b>            Tolvaptan or placebo at an equivalent dose given at last day of tolvaptan run-in (ie, Day -1, either 60/30 or 90/30 mg) using 30 mg or 0 mg tablets.</p> <p>30 mg or 0 mg tablets given 2 upon waking/1 at 8-9 hours later or 3 upon waking/1 at 8-9 hours later.</p> <p>Tolvaptan (subject continued at same dose as Day -1, but may down-titrate to 45/15 [or 30/15 mg, with medical monitor approval] using 15 mg tablets and return to previous maximal tolerated dose, if possible)</p> <p>Placebo (subject continued at same dose as Day -1, but may down-titrate to sham 45/15 or 30/15 mg using matching placebo tablets and return to previously maximal tolerated dose, if possible)</p>

### 3.2.3 Follow-up Period

For randomized subjects, a 3-week follow-up period will begin immediately after treatment cessation (early or planned). No IMP will be administered during this period.

### 3.3 Trial Population

This trial will consent and screen subjects in order to randomize approximately 800 subjects with ADPKD diagnosed by the presence of bilateral cysts per the Pei-Ravine criteria<sup>18,19</sup> (modified for computed tomography [CT] or magnetic resonance imaging [MRI], if needed). In order to maximize power and minimize the possibility of Type 2 error, trial enrollment will continue until a minimum of 700 subjects are randomized. Time allowing, the sponsor may, at its discretion, extend enrollment in order to randomize up to 1000 subjects to further improve the trial's power.

Adult subjects with more advanced ADPKD-renal dysfunction phenotype will be enrolled. Subjects who have advanced to an eGFR < 60 mL/min/1.73m<sup>2</sup> by age 55 or < 45 mL/min/1.73m<sup>2</sup> by age 65 remain at a significant risk of progression to ESRD before reaching average life expectancy. Renal function will be confirmed during screening by the mean of eGFR calculated from the subjects' first 2 pretreatment, central-lab serum creatinine assessments. See [Table 3.4.2-1](#) for additional inclusion criteria.

Consistent with this trial's pre-specified efficacy estimand, only subjects tolerating the single-blind run-in period of tolvaptan (60/30 or 90/30 mg per day) will be randomized to

the double-blind treatment period, to limit subsequent withdrawal due to lack of tolerability.

### **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 and of their role and responsibilities in the proposed research. This shall be documented on a written ICF that shall be approved by the same institutional review board/independent ethics committee (IRB/IEC) responsible for approval of this protocol. In addition, the protocol explanation may include recorded or electronic means of education, which will also meet IRB/IRC approval. Each ICF shall include the elements required by the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guideline<sup>20</sup> 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. 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.

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.

Subjects will have the option of consenting on the written ICF for collection of DNA samples. Subjects do not need to consent to the DNA sample collection in order to be

considered as a potential subject in the trial. Subjects who consent to the DNA sample collection may withdraw their consent to the sponsor's future analysis of that sample (by written request, as detailed in the ICF).

### **3.4.2 Inclusion Criteria**

Subjects are required to meet the following inclusion criteria:

<b>Table 3.4.2-1 Inclusion Criteria</b>	
1.	Male and female subjects age 18 to 55 years of age (inclusive) with eGFR between 25 and 65 mL/min/1.73m <sup>2</sup> -OR-
2.	Male and female subjects age 56 to < 66 years of age with eGFR between 25 and 44 mL/min/1.73m <sup>2</sup> (by medical monitor discretion, only).
3.	Diagnosis of ADPKD by modified Pei-Ravine criteria <sup>18 19</sup> : <ul style="list-style-type: none"> <li>• With family history: several cysts per kidney (3 if by sonography, 5 if by CT or MRI)</li> <li>• Without family history: 10 cysts per kidney (by any radiologic method, above) and exclusion of other cystic kidney diseases. 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.</li> </ul>
4.	Distribution and number of cysts consistent with the observed level of renal function deficit.

### **3.4.3 Exclusion Criteria**

Subjects will be excluded if they meet any of the following exclusion criteria during the pre-randomization period.

<b>Table 3.4.3-1 Exclusion Criteria</b>	
1.	Women of childbearing potential (WOCBP) who do not agree to practice 2 different methods of birth control or remain abstinent during the trial and for 30 days after the last dose of IMP. If employing birth control, 2 of the following precautions must be used: vasectomy of partner, tubal ligation, vaginal diaphragm, intrauterine device, birth control pill, birth control implant, birth control depot injection, condom, or sponge with spermicide.
2.	Women who are breast-feeding and/or who have a positive pregnancy test result prior to receiving IMP.
3.	Need for chronic diuretic use.
4.	Hepatic impairment or liver function abnormalities other than that expected for ADPKD with typical cystic liver disease during the pre-randomization period.
5.	Subjects with advanced diabetes (eg, glycosylated hemoglobin [HgbA1c] > 7.5 and/or glycosuria by dipstick), evidence of additional significant renal disease(s) (ie, currently active glomerular nephritidies), renal cancer, single kidney, or recent (within last 6 months) renal surgery or acute kidney injury.
6.	Subjects with contraindications to required trial assessments.
7.	Subjects who, in the opinion of the trial investigator or medical monitor, have a medical history or medical findings inconsistent with safety or compliance with trial assessments.

Non-childbearing potential in women is defined as female subjects who are surgically sterile (ie, have undergone bilateral oophorectomy or hysterectomy) or female subjects who have been postmenopausal for at least 12 consecutive months.

Subjects may be re-screened, at the discretion of the medical monitor, if the exclusion characteristic has changed or resolved. In the event that a subject is re-screened, a new ICF must be signed and a new screening number assigned and screening procedures repeated.

### **3.5      Outcome Endpoints**

#### **3.5.1      Primary Outcome Endpoint**

##### **3.5.1.1      Primary Efficacy Endpoint**

Treatment difference in the change of eGFR from pre-treatment baseline to post-treatment follow-up, normalized (divided) by each subject's treatment duration.

#### **3.5.2      Secondary Outcome Endpoints**

##### **3.5.2.1      Key Secondary Efficacy Endpoint**

Treatment difference in annualized slope of eGFR calculated for individual subjects using an appropriate baseline and available, post-randomization, on-treatment assessments.

##### **3.5.2.2      Safety Endpoints**

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

- 1) AEs
- 2) Vital signs
- 3) Clinical laboratory tests, including serum transaminases, BT, ALP, and serum sodium

##### **3.5.2.3      Pharmacokinetic/Pharmacodynamic Endpoints**

PK Endpoints: Determination of plasma tolvaptan and metabolite(s), including DM-4103 concentrations.

PD Endpoints: Uosm and specific gravity

### **3.5.3 Exploratory Outcome Endpoints**

#### **3.5.3.1 Exploratory Efficacy Endpoint**

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

#### **3.5.3.2 Exploratory Safety Endpoints**

- Urine and plasma biomarker concentrations for potential evaluation of metabolic or immunologic traits related to DILI and/or etiology of, susceptibility to, activity of, or progress of ADPKD, as well as the potential development of tools for diagnosis, prognosis and response to treatment.
- DNA samples for genetic evaluation of DILI and ADPKD genotyping and/or etiology of, susceptibility to, activity of, or progress of ADPKD, as well as the potential development of tools for diagnosis, prognosis and response to treatment.

Subjects will have the option of consenting for collection of the DNA sample. These analyses may be undertaken and reported separately from the clinical study report (CSR).

### **3.6 Measures to Minimize/Avoid Bias**

Only subjects who reach Day -1 and are who have indicated that they would likely be able to tolerate a dose of tolvaptan “for the rest of their lives” at a level of 60/30 mg or 90/30 mg will be eligible to enter the double-blind, randomized treatment period. In this period, neither the subject nor the investigator or his/her staff will know which treatment is assigned. Immediately prior to randomization, and at all subsequent visits or site-subject contacts, the subject will be reminded of the importance of their commitment to continue participation in the trial, however the subject will not be told that this day is the point at which randomization to long-term therapy occurs.

Randomization will be 1:1, tolvaptan (60/30 mg or 90/30 mg) to placebo, and will utilize an interactive voice response system (IVRS) to ensure appropriate stratification.

Estimated GFR is an important predictor of the rate of renal function decline; therefore, subjects will be stratified by their baseline eGFR at a threshold of  $\leq 45$  or  $> 45$  mL/min/1.73m<sup>2</sup> and by age ( $\leq 55$  or  $> 55$  years old). Subjects will also be stratified by total kidney volume (TKV;  $\leq 2000$  mL or  $> 2000$  mL), if known.

The prescription of additional fluid to subjects in this trial may serve to confound subject unblinding, but it is acknowledged that, with a randomized withdrawal design, a limitation of the main and exploratory analyses might include the subject’s perception of

their treatment assignment. Note, however, that calculation of eGFR is an objective measure and is expected to be unaffected by such perceptions.

### **3.7 Trial Procedures**

Trial assessment time points are summarized in [Table 3.7-1](#).

Assessment	Pre-randomization											Double-blind Randomized Treatment			Follow-up	
	Screening (2 weeks ± 1 day)		Placebo run-in (1 week ± 1 day) (Days -42 to -36)		Tolvaptan titration (2 weeks ± 1 day) (Days -35 to -22)			Tolvaptan run-in (3 weeks ± 1 day) (Days -21 to -1)			(Day 0)	Visits: monthly (± 2 days)	Month 12/ EoTx visit			
	Days -56 to -43 <sup>a</sup>		Day -42	Day -39 ± 1 day	Day -36	Days			Days			Day 0	Months 1 to 11	Month 12 /EoTx	Days +7 to +21 post-final visit <sup>a</sup>	
<b>Informed consent</b>	X															
<b>Inclusion/Exclusion</b>	X															
<b>Demographic/Medical history</b>	X															
<b>Vital signs</b> <sup>b</sup>	X	X			X			X		X		(X) <sup>b</sup>	X			X
<b>Physical examination<sup>c</sup></b>	X												X			
<b>Urine pregnancy test (WOCBP<sup>d</sup> only)</b>	X											(X) <sup>c</sup>	X			X
<b>Clinical laboratory samples<sup>e</sup>:</b>																
<b>Hematology and coagulation</b>	X															
<b>Urinalysis</b>	X	X			X					X			X			
<b>Serum Chemistry Panel</b>	X												X			X
<b>Liver Function Panel</b>	X				X			X		X	X		X	X		X
<b>Creatinine</b>	X	X	X		X	X		X		X	X		X	X	X	X
<b>Sodium</b>	X	X		X	X			X		X	X		X	X		
<b>PK plasma sample<sup>f</sup></b>										X		(X) <sup>f</sup>	X			X
<b>PD urine sample<sup>f</sup></b>			X		X			X		X		(X) <sup>f</sup>	X			X
<b>Biomarker urine and plasma sample<sup>f</sup></b>			X		X			X		X		(X) <sup>f</sup>	X			X
<b>DNA blood sample<sup>g</sup></b>	X															

**Table 3.7-1 Schedule of Assessments**

Assessment	Pre-randomization										Double-blind Randomized Treatment			Follow-up	
	Screening (2 weeks ± 1 day)		Placebo run-in (1 week ± 1 day) (Days -42 to -36)		Tolvaptan titration (2 weeks ± 1 day) (Days -35 to -22)		Tolvaptan run-in (3 weeks ± 1 day) (Days -21 to -1)		(Day 0)	Visits: monthly (± 2 days)	Month 12/ EoTx visit	3 weeks post-treatment			
	Days -56 to -43 <sup>a</sup>		Day -42	Day -39 ± 1 day	Day -36	Days		Days		Day 0	Months 1 to 11	Month 12 /EoTx	Days +7 to +21 post-final visit <sup>a</sup>		
Start newly dispensed IMP		X				X				X					
Tolerability/Dosing review				X		X	X	X	X		X		X	X	
Randomization											X				
Drug dispensation <sup>h</sup>		X			X				X		X				
Drug reconciliation <sup>h</sup>					X			X			X		X	X	
IVRS entry <sup>i</sup>	X	X			X	X	X	X		X		X	X	X	
Exploratory PKD outcomes <sup>j</sup>		X	-							X		X	X		
Adverse events	X	<----->													
Concomitant medications	X	<----->													

<sup>a</sup>The screening period may be extended up to an additional 8 weeks for subjects who require modification of medical care specifically for this trial. Visits during the screening and follow-up periods must be scheduled at least 24 hours (1 day) apart. At each visit, blood will be collected and analyzed centrally for serum creatinine concentrations, in addition to any other assessments listed. A visiting nurse house call or local laboratory visit may be substituted for visits where only blood/urine will be collected. Visits during the screening period must be scheduled within a 2-week period before the start of the placebo run-in period. Visits during the follow-up period must be scheduled during a 2-week period that begins 1 week after the end of treatment visit.

<sup>b</sup>The following visits (and all assessments required during those visits) should be performed in-clinic: screening, end of placebo run-in, end of tolvaptan titration, end of tolvaptan run-in, quarterly visits during the randomized, double-blind treatment period (eg, Months 3, 6, 9), Month 12/end of treatment (EoTx) visit, and the last follow-up visit. Vital signs at each of the above visits include sitting heart rate and blood pressure. Post-void body weight should be measured at the first screening visit and the Month 12/EoTx visit only. Height should be assessed at the first screening visit only. Either height or weight may be collected as an unscheduled measurement if its assessment was missed.

<sup>c</sup>A full physical examination is required at the first screening visit and the Month 12/EoTx visit. A “directed physical examination” may be performed at the quarterly visits (eg, Months 3, 6, 9) for assessment of signs or symptoms reported by the subject that might require further evaluation.

<sup>d</sup>During the trial, a pregnancy test should be completed at screening and at the quarterly visits. On suspicion of pregnancy, unscheduled urine or serum pregnancy testing will be performed. Positive urine pregnancy tests should be confirmed with a serum pregnancy test.

<sup>e</sup>The specifics and timing for clinical laboratory samples for central and local laboratory analyses are as follows:

**Screening period:** Subjects will have 3 blood draws on separate days between Day -56 and Day -43. The subject's eligibility will be confirmed by the mean of eGFR calculated from the subjects' first 2 pre-treatment, central laboratory serum creatinine assessments.

**Placebo run-in period:** Subjects will have 2 blood draws on separate days (at least 24 hours apart) between Days -42 to -36 with the last sample on Day -36.

**Tolvaptan titration period:** Subjects will have 1 blood draw at the end of 2 weeks with the sample being obtained on Day -22.

**Tolvaptan run-in period:** During the last 2 weeks of this period, blood will be drawn 2 times on separate days (at least 24 hours apart) with the last sample on Day -1.

**Double-blind treatment period:** Samples will be collected for central lab analysis monthly and at the Month 12/EoTx visit. Local standard of care laboratory tests will be performed monthly per the subject's individual clinical management needs. Local liver function panel analyses will also be performed more frequently, if necessary.

<sup>f</sup>During the double-blind, randomized treatment period, PK plasma samples, PD urine samples, and biomarker urine/plasma samples will be collected quarterly (eg, Months 3, 6, 9, 12/EoTx).

<sup>g</sup>Samples are optional.

<sup>h</sup>Drug dispensing and reconciliation will be done monthly and subjects will be reminded of the importance of their commitment to continue participation in the trial..

<sup>i</sup>If, during the titration contact, the determination is made to adjust the dose-regimen, the investigator will enter the subject's status in the IVRS and arrange for dispensation of a new IMP kit and reconciliation of returned IMP.

<sup>j</sup>Exploratory PKD outcomes will be completed either monthly over the phone or in person during quarterly clinic visits.

### **3.7.1 Schedule of Assessments**

#### **3.7.1.1 Pre-randomization Period**

After obtaining consent and upon establishing initial eligibility using inclusion/exclusion criteria, subjects will enter an initial 8-week, single-blind, pre-randomization period prior to actual randomization which will consist of:

- screening period (2 weeks; longer durations of up to 8 additional weeks may be required according to the investigator's judgment, as described below)
- placebo run-in period (1 week)
- tolvaptan titration period (2 weeks)
- tolvaptan run-in period (3 weeks)

There are 2 goals of this pre-randomization period: 1) to establish the degree to which a hemodynamic eGFR shift may occur for each potential treatment assignment (placebo and tolvaptan); and 2) to determine the maximally tolerated dose of tolvaptan for each subject by self-report.

Pre-randomization eGFR value(s) will be collected for each potential treatment assignment for all subjects. Having these data pre-randomization will allow for the following: equivalent evaluation of baseline characteristics, including the acute hemodynamic response to tolvaptan in all subjects who will contribute to the primary and key secondary endpoint; facilitate baseline assessments which appropriately accounts for placebo effect and tolvaptan hemodynamic onset effect of all randomized subjects who have a post-randomization eGFR. It also allows for comparison of randomized, completer and non-completer populations in terms of their hemodynamic response to tolvaptan.

To establish the pre-randomization eGFR, multiple serum creatinine values (isotope dilution mass spectroscopy [IDMS]-traceable) will be obtained under standardized conditions (see [Section 3.7.2.1](#)), each separated by one (minimum of 24 hours) to several days during the screening period and placebo run-in for the primary endpoint, and during each treatment's run-in period for the key secondary endpoint. The eGFR for each serum creatinine assessment will be calculated and then averaged, with the median of assessment dates being set as the subject's eGFR value's date.

##### **3.7.1.1.1 Screening Period (Days -56 to -43)**

The screening period will be for 2 weeks ( $\pm$  1 day) for tolvaptan-naive subjects. The screening period may be extended up to an additional 8 weeks for subjects who require modification of medical care specifically for this trial. This may include, for example,

stabilizing anti-hypertensive regimens for subjects discontinuing diuretics or “wash-out” of tolvaptan or other investigational agents for candidates who participated in previous trials.

The screening period will consist of three visits, each at least 24 hours apart. The first and last visits will be clinic visits, but a visiting nurse house call or local laboratory visit may be substituted for the other visit where only blood samples will be collected.

Assessments during the screening period will include (See [Table 3.7-1](#)):

- 1) Confirm diagnosis and determine whether the subject meets inclusion and exclusion criteria (first visit)
- 2) Record medical/PKD history, including demographic information (first visit)
- 3) Record concomitant medications and ensure subject's treatment meets current standard of care including lifestyle and dietary recommendations, especially for ingestion of at least 2-3 liters of fluid per day as appropriate, unless otherwise directed by your study doctor. (all visits)
- 4) Assess AEs (if reported; all visits)
- 5) Perform a full physical examination (first visit)
- 6) Assess vital signs (include sitting heart rate and blood pressure [first and last visits])
- 7) Assess post-void body weight and height (first visit)
- 8) Urine pregnancy test for WOCBP (first visit)
- 9) Collect urinalysis samples (first and last visits)
- 10) Collect blood for serum creatinine for eGFR calculation (3 collections, each at least 24 hours apart)
- 11) Collect blood for central clinical laboratory analyses (sodium [first and last visits], hematology, serum chemistry, and liver function panel [first visit] - see [Section 3.7.3.2](#)). If sodium, serum chemistry and/or liver function panel are collected at the same visit, a single tube of blood should be drawn for all assessments.
- 12) Collect PD urine sample (last visit)
- 13) Collect biomarker plasma and urine samples (last visit, see [Section 3.7.3.5](#))
- 14) Complete PKD history and outcomes surveys
- 15) Register subject status in IVRS
- 16) Collect blood for DNA sample (first visit, for consenting subjects only)
- 17) Dispense IMP for next period (last visit)

Preliminary eligibility for the trial will be initially assessed using the subjects' historical laboratory or imaging data. Eligibility will be confirmed by the mean of eGFR calculated from the subjects' first 2 pre-treatment, central-lab serum creatinine assessments.

Confirmation of ADPKD diagnosis (using the modified Pei Ravine criteria) may require

confirmatory imaging. Subjects will be told that they will receive both tolvaptan and placebo during various subsequent periods of the trial and that the next period involves a dose escalation with multiple efficacy, safety, and tolerability assessments.

### **3.7.1.1.2 Placebo Run-in Period (Days -42 to -36)**

The placebo run-in period will be 1 week ( $\pm$  1 day) and will be conducted in a single-blinded fashion. Subjects will be given placebo in a daily split dose of a single 0 mg tablet upon awakening and another 0 mg tablet approximately 8 to 9 hours later (abbreviated 0/0 mg), in a form identical to tolvaptan tablets.

Assessments during the placebo run-in period will include (See [Table 3.7-1](#)):

- 1) Record concomitant medications at all visits
- 2) Assess AEs at all visits
- 3) Assess vital signs (include sitting heart rate and blood pressure) on Day -36
- 4) Collect urinalysis sample on Day -36
- 5) Collect blood for serum creatinine for eGFR calculation (x2) and for assessment of sodium (x2) and liver function panel (x1) on separate days between Days -39 to -36 with the last sample being obtained on Day -36 (see [Section 3.7.3.2](#)). If sodium and liver function panel are collected at the same visit, a single tube of blood should be drawn for all assessments.
- 6) Collect PD urine sample on Day -36
- 7) Collect biomarker plasma and urine samples (see [Section 3.7.3.5](#)) on Day -36
- 8) Ask subject “Can you tolerate this dose of trial medication for the rest of your life?” on Day -36
- 9) Update subject status in IVRS on Day -36
- 10) IMP reconciliation on Day -36
- 11) Dispense IMP for next period on Day -36

### **3.7.1.1.3 Tolvaptan Titration Period (Days -35 to -22)**

The tolvaptan titration period will be a single-blind period that will last for 2 weeks ( $\pm$  1 day). All subjects will be given a split dose of 30/15 mg of tolvaptan with upward titration every 3 to 4 days to 45/15 mg, 60/30 mg, up to a maximum dose of 90/30 mg per day over 2 weeks. This titration will be monitored with telephone or clinic visits at each escalation level to assess tolerability.

Assessments during the tolvaptan titration period will include (See [Table 3.7-1](#)):

- 1) Record concomitant medications at all visits
- 2) Assess AEs at all visits
- 3) Assess vital signs (include sitting heart rate and blood pressure) on Day -22

- 4) Collect blood for serum creatinine for eGFR calculation and for assessment of sodium and liver function panel on Day -22 (see [Section 3.7.3.2](#)). If sodium and liver function panel are collected at the same visit, a single tube of blood should be drawn for all assessments.
- 5) Collect PD urine sample on Day -22
- 6) Collect biomarker plasma and urine samples (see [Section 3.7.3.5](#)) on Day -22
- 7) Ask subject “Can you tolerate this dose of trial medication for the rest of your life?” at each upward titration visit
- 8) Update subject status in IVRS at each upward titration visit
- 9) IMP reconciliation on Day -22
- 10) Dispense IMP for next period on Day -22

#### **3.7.1.1.4 Tolvaptan Run-In Period (Days -21 to -1)**

All subjects who tolerate tolvaptan at the 60/30 mg or 90/30 mg daily dose regimen will enter the tolvaptan run-in period at one of these doses for 3 weeks ( $\pm$  1 day). Except for management of AEs, no dose adjustment will be permitted during this period. Subjects unable to tolerate at least 3 weeks of daily tolvaptan treatment at 60/30 mg or 90/30 mg will not be eligible for randomization.

Subjects who reach Day -1 and are able to tolerate a given dose of tolvaptan “for the rest of their lives” at a level of 60/30 mg or 90/30 mg will be eligible to enter the double-blind, randomized treatment period. Randomization (Day -1) will be stratified by mean eGFR determined by available central isotope dilution mass spectroscopy (IDMS)-traceable serum creatinine measurements taken during the screening period and placebo run-in period. Subjects will be stratified in a 1:1 ratio to each treatment group as follows:

- CKD 2 to 3a stages [ $>45$  mL/min/1.73 m<sup>2</sup>] or
- CKD 3b to 4 stages [ $\leq 45$  mL/min/1.73 m<sup>2</sup>]

Ideally, a distribution of half of subjects being above or below this cut-off will be targeted. Therefore, enrollment may be adjusted if this ratio begins to vary by more than a 60:40 ratio. Subjects will also be stratified by age ( $\leq 55$  or  $> 55$  years old) and by total kidney volume (TKV;  $\leq 2000$  mL or  $> 2000$  mL), if known.

Assessments during the tolvaptan run-in period will include (See [Table 3.7-1](#)):

- 1) Record concomitant medications at all visits
- 2) Assess AEs at all visits
- 3) Assess vital signs (include sitting heart rate and calibrated blood pressure) on Day -1

- 4) Collect urinalysis sample on Day -1
- 5) Collect blood (2 times on separate days during the last 2 weeks of the period, with the last sample drawn on Day -1) for serum creatinine for eGFR calculation and for assessment of sodium and liver function panel (see [Section 3.7.3.2](#)). If sodium and liver function panel are collected at the same visit, a single tube of blood should be drawn for all assessments.
- 6) Collect PK plasma sample and PD urine sample on Day -1
- 7) Collect biomarker plasma and urine samples (see [Section 3.7.3.5](#)) on Day -1
- 8) Complete PKD outcomes survey on Day -1
- 9) Ask subject “Can you tolerate this dose of trial medication for the rest of your life?” on Day -1
- 10) Update subject status in IVRS on Day -1
- 11) IMP reconciliation on Day -1
- 12) Remind the subject of the importance of their commitment to continue participation in the trial on Day -1
- 13) Randomization on Day -1
- 14) Dispense IMP for next period on Day -1

### **3.7.1.2 Double-blind, Randomized Treatment Period (Day 0 to Month 12)**

Day 0 is the beginning of the double-blind, randomized treatment period. Only subjects who reach Day -1 and are able to tolerate a given dose of tolvaptan “for the rest of their lives” at a level of 60/30 mg or 90/30 mg will be eligible to enter this period. In this period, neither the subject nor the investigator or his/her staff will know with certainty which treatment is assigned. Immediately prior to randomization, and at each subsequent visit or site contact, the subject will be reminded of the importance of their commitment to continue participation in the trial; however, the subject will not be told that this day is the point at which randomization to long-term therapy occurs.

Post-randomization, the maximally-tolerated dose of tolvaptan established during the run-in period, or the equivalent as matching placebo tablets, will be dispensed according to the subject’s randomization outcome. Subjects must return any unused IMP from the pre-randomization period before continuing in the double-blind, randomized treatment period.

From this point forward, every effort to maintain adherence and continuation of the subjects until the end of the trial should be undertaken. If continued tolerability becomes an issue, subjects may titrate downward to 45/15 mg or 30/15 mg (with medical monitor approval) or temporarily interrupt treatment as needed. Return to higher doses is also allowed.

Assessments during the double-blind, randomized treatment period will include (See [Table 3.7-1](#)):

- 1) Remind the subject of the importance of their commitment to continue participation in the trial at all visits
- 2) Record concomitant medications at all visits
- 3) Assess AEs at all visits
- 4) Assess vital signs (including sitting heart rate and blood pressure) at Month 3, 6, 9, 12/ EoTx visits; include assessment of post-void body weight at the Month 12/EoTx visit only
- 5) Perform a full physical examination at Month 12/EoTx visit only (directed physical exam may be performed at Month 3, 6, 9 visits, if deemed necessary by the investigator)
- 6) Urine pregnancy test for WOCBP at Month 3, 6, 9, 12/EoTx visits (or if indicated)
- 7) Collect urinalysis sample at the Month 12/EoTx visit
- 8) Collect blood for serum creatinine for eGFR calculation and for assessment of sodium and liver function panel (see [Section 3.7.3.2](#)) monthly and at the Month 12/EoTx visit. Serum sodium and liver function panel should be determined from the same blood sample.
- 9) Collect blood for serum chemistry assessment at the Month 12/EoTx visit. The sodium, serum chemistry and liver function panel should be determined from a single tube of blood.
- 10) Collect plasma samples for PK analysis and PD urine samples at Month 3, 6, 9, 12/EoTx visits
- 11) Collect plasma and urine samples for potential biomarker analysis at Month 3, 6, 9, 12/EoTx visits (see [Section 3.7.3.5](#))
- 12) Complete PKD outcomes survey (monthly and at the Month 12/EoTx visit)
- 13) Update subject status in IVRS (monthly and at the Month 12/EoTx visit)
- 14) Dispense IMP at monthly visits up to and including Month 11
- 15) IMP reconciliation (monthly and at the Month 12/EoTx visit)

Visits during the treatment period will be scheduled monthly ( $\pm$  2 days), with a final visit at Month 12/EoTx.

Subjects discontinuing IMP in the placebo run-in period, tolvaptan titration period, or the tolvaptan run-in period should also have EoTx assessments performed (see [Section 3.8.3.3](#)).

All subjects have the right to withdraw their consent from further participation in the trial at any time without prejudice. In all cases of impending IMP discontinuation or consent withdrawal, the investigator should follow the procedures outlined in [Section 3.8.3.5.1](#) to

determine if the subject can continue participation in the trial if modifications to his/her treatment and/or schedule of assessments can be accommodated.

### **3.7.1.3 Follow-up Period (Month 12/End of Treatment to Day 21 Post-treatment)**

Randomized subjects will enter the follow-up period after they complete the double-blind, randomized treatment period, or after their EoTx visit, if they discontinued IMP. The follow-up period will be for 21 days in duration.

There will be no scheduled visits/assessments during the first week of the follow-up period. After the first week, 5 visits should be scheduled during the remaining 2 weeks of the follow-up period (between Day +7 and Day +21), with each visit at least 24 hours apart. These visits may be visiting nurse house calls or local laboratory visits when only blood samples will be collected, with the exception of the last visit, which will be a clinic visit.

Assessments during the last 2 weeks of the follow-up period will include (See [Table 3.7-1](#)):

- 1) Record concomitant medications at each visit
- 2) Assess AEs at each visit
- 3) Assess vital signs (including sitting heart rate and blood pressure) at the last visit
- 4) Urine pregnancy test for WOCBP at the last visit
- 5) Collect blood for central laboratory analysis of serum creatinine for eGFR calculations at each visit
- 6) Collect blood for assessment of sodium levels at the first visit (see [Section 3.7.3.2](#))
- 7) Collect blood for liver function panel assessments at the last visit (see [Section 3.7.3.2](#))
- 8) Collect plasma samples for PK analysis and PD urine samples at the last visit
- 9) Collect plasma and urine samples for potential biomarker analysis at the last visit (see [Section 3.7.3.5](#))
- 10) Update subject status in IVRS at the last visit

The above follow-up assessments will also be performed for a subject who interrupts IMP for  $\geq 7$  days, in order to collect their data in the event that they never restart IMP treatment (see [Section 3.8.3.2](#)).

### **3.7.2 Efficacy Assessments**

#### **3.7.2.1 Serum Creatinine for Estimated Glomerular Filtration Rate**

The serum creatinine concentration is related to eGFR and is commonly used to estimate renal function in clinical practice. Alteration in metabolism of creatinine and methodological interference in its measurements may impact accuracy of the serum creatinine and renal function estimation. Below are suggested measures to decrease serum creatinine variability prior to the monthly blood draws required by this protocol.

All trial subjects should:

- Maintain a stable dietary protein intake and avoid very different or high protein meals the day before each scheduled serum creatinine assessment.
- Maintain a stable exercise routine and avoid very different or heavy physical activity/exercise the day before each scheduled serum creatinine assessment.
- Maintain a stable water intake, aimed at avoiding thirst consistently throughout the trial - recommended ingestion of at least 2-3 liters of fluid (including in solid, semi-solid, and liquid foods) per day, unless otherwise directed by your study doctor.
- Plan to arrive at the same time for each blood-draw and clinic visit to better standardize time of the sample collection throughout the trial.
- Some medications may increase serum creatinine levels (eg, cimetidine, non-steroidal anti-inflammatory drugs [NSAID] medications like aspirin or ibuprofen, chemotherapy drugs, cephalosporin). Subjects should alert their trial doctor, and any other health-care providers, to take this into consideration when considering changes in their prescribed or over-the-counter medications, and all medication changes should be reported to their trial doctor or his/her staff.

Serum creatinine is stable when stored frozen; therefore, two samples/aliquots of blood will be collected for its analysis. While one blood sample will be analyzed by the central laboratory as soon as it is received and accessioned, the formal efficacy analyses will be based on duplicate samples/aliquots which are collected contemporaneously and frozen for later batched analysis to eliminate inter-day variability of the assay. Ongoing, batched analysis will be conducted for each subject upon his/her individual completion of all their assessments within the trial (not at the end of the trial).

The eGFR values will be calculated from the central-laboratory IDMS-traceable serum creatinine concentrations taken at screening and during every trial visit. In the screening period, serum creatinine assessments may not be repeated; the first two assessments must be used to determine the eGFR values that will be averaged for determination of meeting inclusion criteria. Further detail regarding eGFR calculations will be provided in the statistical analysis plan (SAP).

### **3.7.2.2 Polycystic Kidney Disease History and Outcomes Surveys**

A short PKD history survey will be completed once during screening to capture information from the subject's recollection, and documented past medical history where available. The survey should be updated at each visit if new information regarding past history becomes available.

The PKD outcomes survey will collect information relevant to the medical, social and economic consequences of new and ongoing PKD-related morbidities. New clinically relevant information and specific questions about outcomes will be collected at the following visits: screening, end of tolvaptan run-in, and during the double-blind randomized treatment period either monthly (over the phone or in person) or during quarterly clinic visits (in person).

If a subject who has been randomized and is taking IMP discontinues the use of IMP, PKD outcomes will be collected at the normally scheduled trial visits, or by telephone contact, to the date of the originally planned Month 12 visit, if the subject agrees.

## **3.7.3 Safety Assessments**

### **3.7.3.1 Adverse Events**

Refer to [Section 5, Reporting of Adverse Events](#).

### **3.7.3.2 Clinical Laboratory Assessments**

Blood and/or urine samples will be collected as indicated in the schedule of assessments, [Table 3.7-1](#). It is preferable to collect the clinical laboratory samples from each subject at a consistent time of day throughout the trial, and to recommend that the subject have a similar diet, avoiding variation in protein intake (especially cooked protein), and exercise pattern during these periods, in order to reduce variability in the samples over time (see [Section 3.7.2.1](#)).

A list of the specific clinical laboratory assessments is presented in [Table 3.7.3.2-1](#).

Clinical laboratory samples for analysis by the central laboratory will be collected at the following visits:

- during screening (3 visits at least 24 hours apart that occur during the 2 weeks prior to placebo run-in) - creatinine (all 3 visits), sodium and urinalysis (first and last visits), hematology and coagulation panel, serum chemistry panel, and liver function panel (first visit)
- during placebo run-in - urinalysis (Day -36), liver function panel, creatinine, and sodium (twice on separate days between Days -39 to -36 with the last sample being obtained on Day -36)

- during tolvaptan titration - liver function panel, creatinine, and sodium (Day -22)
- during tolvaptan run-in - urinalysis (Day -1), liver function panel, creatinine, and sodium (2 times on separate days during the last 2 weeks of the period, with the last sample drawn on Day -1)
- at monthly clinic visits during the double-blind, randomized treatment period - liver function panel, creatinine, and sodium
- at the Month 12/EoTx visit - serum chemistry panel, urinalysis, liver function panel, creatinine, and sodium
- during the follow-up period (5 visits at least 24 hours apart that begin 1 week after the Month 12/EoTx visit) - creatinine (all 5 visits), sodium (first visit), liver function panel and serum chemistry panel (last visit)

**Table 3.7.3.2-1 Clinical Laboratory Assessments**

<b>Hematology and coagulation panel:</b> <ul style="list-style-type: none"> <li>• hemoglobin</li> <li>• mean corpuscular hemoglobin (MCHC)</li> <li>• mean corpuscular volume (MCV)</li> <li>• red blood cell (RBC) count</li> <li>• white blood cell (WBC) count with differential</li> <li>• platelet count</li> <li>• prothrombin time (PT) as international normalized ration (INR)</li> <li>• activated partial thromboplastin time</li> </ul>	<b>Serum chemistry panel:</b> <ul style="list-style-type: none"> <li>• albumin</li> <li>• blood urea nitrogen (BUN)</li> <li>• serum calcium</li> <li>• serum chloride</li> <li>• carbon dioxide (CO<sub>2</sub>)</li> <li>• gamma-glutamyl transpeptidase (GGT)</li> <li>• glucose</li> <li>• lactate dehydrogenase (LDH)</li> <li>• phosphorus</li> <li>• potassium</li> <li>• total cholesterol</li> <li>• total protein</li> <li>• uric acid</li> </ul>
<b>Liver function panel:</b> <ul style="list-style-type: none"> <li>• alkaline phosphatase (ALP)</li> <li>• alanine transaminase (ALT)</li> <li>• aspartate aminotransferase (AST)</li> <li>• direct bilirubin</li> <li>• total bilirubin (BT)</li> </ul>	<b>Urinalysis panel:</b> <ul style="list-style-type: none"> <li>• appearance</li> <li>• color</li> <li>• blood</li> <li>• glucose</li> <li>• microscopic analysis (including WBC/RBC counts per high-powered field)</li> <li>• pH</li> <li>• protein</li> </ul>
<b>Creatinine</b>	<b>Sodium</b>

Liver panels will be analyzed more frequently during the double-blind, randomized treatment period if ALT > twice the upper limit of normal (2 x ULN), using both central and local labs, as needed, and per standard of care according to the subject's individual

medical needs. If liver function panel, sodium and/or serum chemistry assessments are scheduled at the same visit, all values should be determined from the same blood sample.

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 period) and at visits for Months 3, 6, and 9 during the double-blind randomized treatment period. Once enrolled into the trial, the subject should contact the clinic immediately on suspicion of pregnancy, and unscheduled urine or blood pregnancy testing will be performed. Positive urine pregnancy tests should be confirmed with a serum pregnancy test.

The following serum chemistry laboratory tests may be performed by the central laboratory at the request and approval of the medical monitor: calcium, phosphorus, parathyroid hormone, vitamin D, and bicarbonate levels. If performed, the results from these tests will be included in the clinical database.

### **3.7.3.3 Physical Examination and Vital Signs**

A full physical examination will be performed and documented at the first screening visit and the Month 12/EoTx visit. At other visits, a directed physical examination may be performed to focus on ADPKD-related signs and symptoms. In some geographic regions, more frequent subject visits may be the norm; however vital signs and clinically significant physical findings will be recorded as an unscheduled visit in the electronic case report form (eCRF) as applicable. Any changes in medication or AEs will be recorded in the eCRF.

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 examination. If the appointed designee is to perform the physical examination, he/she must be permitted to do so 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, where local regulations allow, while local regulations determine their being named in the ICF). Whenever possible, the same individual should perform all physical examinations. Any undesirable condition present at a post-treatment physical examination that was not present at the baseline examination should be documented as an AE and followed to a satisfactory conclusion.

Vital sign data, including seated blood pressure, heart rate, temperature, height, and weight, will be taken at the visits identified in the Schedule of Assessments ([Table 3.7-1](#)).

### **3.7.3.4 Assessment of Liver Symptoms, Signs or Test Abnormalities**

Testing for hepatic transaminase (ALT/AST), alkaline phosphatase, and BT will be performed during screening/run-in and at each monthly visit. Management of liver abnormalities is discussed in the paragraphs below.

#### **3.7.3.4.1 Requirements for Repeated Liver Testing**

##### **3.7.3.4.1.1 Repeated Liver Testing in Subjects with Normal Values at Screening**

The appearance of any suspicious symptom or sign should trigger prompt testing of hepatic function (ie, within 72 hours). Local laboratory testing is acceptable, ideally with a concurrent central laboratory sample for confirmation.

Any transaminase or bilirubin values which exceed 2 x ULN should also prompt immediate retesting within 72 hours. While values remain in an abnormal range, testing frequency should be increased to at least weekly for the first month, gradually returning to monthly as indicated by the results.

Subjects exhibiting such an increase during the tolvaptan titration/run-in phases will be disqualified from randomization on safety grounds and should not be randomized. Should the cause of the abnormality be determined to be unrelated to tolvaptan exposure (eg, having identified a plausible alternative explanation) such a subject may be re-screened only with medical monitor approval.

##### **3.7.3.4.1.2 Repeated Liver Testing in Subjects with Abnormal Values at Screening**

Subjects found to have liver laboratory abnormalities at screening or who have a history of non-ADPKD-related liver disease will require further evaluation. These subjects will need to have the special liver eCRF (see [Section 3.7.3.4.3](#)) completed and additional testing will be required during screening (to confirm the stability of the abnormality) and during the tolvaptan run-in phase at least 1 week prior to randomization (to confirm eligibility for randomization). Management of such subjects should be closely coordinated with the trial's Medical Monitor. In these subjects, further changes in liver test levels of > 2 x upper limit of their highest screening value at any point post-screening should prompt re-testing within 72 hours. Should such an increase occur in the tolvaptan titration/run-in phase, the subject will be disqualified from randomization.

#### **3.7.3.4.2 Liver Test Abnormalities and Interruption/Discontinuation of Investigational Medicinal Product**

Liver transaminase or bilirubin levels reaching or exceeding 2 x ULN that have an uncertain or rapidly increasing trajectory should prompt at least temporary IMP

interruption. IMP should not be resumed until monitoring indicates abnormalities have resolved, are stable or are not rapidly increasing, and then only with an increased frequency of monitoring.

Subjects would not typically be allowed to resume treatment with IMP if they have:

- transaminase levels rise above 8 x ULN,
- transaminase levels are > 5 x ULN for more than 2 weeks, or
- concurrent elevations of transaminase > 3 x ULN and BT > 2 x ULN.

Subjects with these levels of abnormality may be re-challenged with IMP if abnormalities were adjudicated as having a < 50% likelihood of being related to IMP (per DILI network [DILIN] probability criteria<sup>17</sup>) by an independent hepatic adjudication committee (see [Section 3.7.3.4.3](#)) and the investigator and medical monitor agree to an intensive monitoring plan to mitigate risk. The subject must also be willing to comply with these monitoring measures, be informed of the potential risks, and consent to IMP re-challenge.

#### **3.7.3.4.3 Requirements for Special Reporting Using the Liver Disease Electronic Case Report Form and Immediately Reportable Event Form**

The purpose of the liver disease eCRF and optional additional testing is to facilitate review of each subject who presents with, or develops a liver abnormality during the trial or to determine the probable cause(s) of these abnormalities. The review will be performed by a blinded, independent, hepatic, adjudication committee using DILIN probability criteria (< 25% = unlikely, 25% to 50% = possibly, 51% to 75% = probably, 76% to 95% = very likely, > 95% = definite).<sup>17</sup> The result of these analyses may be presented separately from the CSR.

The investigator must complete a special liver disease eCRF for any subject who:

- 1) discontinues treatment due to a liver-related AE,
- 2) reports a serious liver-related AE,
- 3) with normal screening levels develops ALT or AST levels  $\geq$  3 x ULN,
- 4) with normal screening levels develops BT levels  $\geq$  2 x ULN, or
- 5) with an abnormal screening liver test level develops abnormalities in that test that are  $>$  2 x the upper limit of their highest screening value.

All subjects meeting the above criteria will also be asked to provide an additional set of blood and urine biomarker samples at the time of the event. Additional clinical testing (such as testing for hepatitis serology) may also be indicated and their results reported according to local guidelines.

The liver eCRF and Immediately Reportable Event (IRE) form (see [Section 5.3](#)) should be updated as new information becomes available.

### **3.7.3.5 Other Safety Assessments**

#### **3.7.3.5.1 Biomarker Plasma Samples**

Blood samples (10 mL) for potential biomarker analysis will be collected at the following times:

- end of the screening period (Day -43)
- end of the placebo run-in period (Day -36)
- end of the tolvaptan titration period (Day -22)
- end of the tolvaptan run-in period (Day -1)
- during the double-blind, randomized treatment period at Months 3, 6, 9, 12/EoTx,
- at the last follow-up period visit
- during an episode of increased liver surveillance (due to AE or lab abnormality above set thresholds)

The blood sample will be taken following the PK sample at visits where both are collected, and processed similarly to the PK blood sample. Date and time of the blood sample, as well as the date and time of the last preceding dose should be noted in the eCRF.

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

#### **3.7.3.5.2 Biomarker Urine Samples**

A spot urine sample (20 mL) will be obtained at the following times:

- end of the screening period (Day -43)
- end of the placebo run-in period (Day -36)
- end of the tolvaptan titration period (Day -22)
- end of the tolvaptan run-in period (Day -1)
- during the double-blind, randomized treatment period at Months 3, 6, 9, 12/EoTx
- at the last follow-up period visit
- during an episode of increased liver surveillance (due to AE or lab abnormality above set thresholds)

This sample should be obtained prior to the subject eating breakfast, from the 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 of IMP, should be noted in the eCRF. This sample should be obtained from the same void as collected for the PD urine sample, when both samples are collected at the same visit.

All urine samples will be shipped to the central clinical laboratory for storage. Detailed handling and shipping instructions are in [Appendix 3](#).

### **3.7.3.5.3 DNA Blood Samples**

A blood sample for DNA collection will be obtained for every consenting subject at the beginning of the screening period.

All samples will be shipped to the central clinical laboratory. Detailed handling and shipping instructions are in [Appendix 3](#).

## **3.7.4 Pharmacokinetic/pharmacodynamic Assessments**

### **3.7.4.1 Pharmacokinetic Blood Samples**

Sparse samples will be taken for determination of plasma tolvaptan and metabolite(s), including DM-4103 concentrations. A 4 mL sample will be collected at the following times:

- end of the tolvaptan run-in period (Day -1)
- during the double-blind, randomized treatment period at Months 3, 6, 9, 12/EoTx,
- at the last follow-up visit

The date and time of collection of the PK sample and the date and time of administration of the last preceding dose of IMP must be recorded on the eCRF for all on-treatment and EoTx samples. The last dose time for the off-treatment follow-up sample will be assumed to be the same as for the Month12/EoTx sample. The exact time of sampling relative to the previous IMP 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](#).

### **3.7.4.2 Pharmacodynamic Urine Samples**

A spot urine sample for determination of Uosm and specific gravity will be obtained at the following times:

- end of the screening period (Day -43)
- end of the placebo run-in period (Day -36)
- end of the tolvaptan titration period (Day -22)

- end of the tolvaptan run-in period (Day -1)
- during the double-blind, randomized treatment period at Months 3, 6, 9, and 12/EoTx
- at the last follow-up visit

This sample should be obtained prior to the subject eating breakfast, from the 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 of IMP for all on-treatment and EoTx samples, should be noted in the eCRF. The last dose date for the off-treatment sample will be assumed to be the same as for the Month 12/EoTx PD urine sample.

All urine samples will be shipped to the central clinical laboratory for analysis. Detailed handling, including volume of sample needed, and shipping instructions is provided in [Appendix 3](#).

### **3.7.5 End of Treatment/End of Trial**

Randomized subjects will have their last scheduled treatment 12 months from their date of randomization.

If a subject discontinues IMP before Month 12, the last date that the subject received IMP will be recorded as EoTx. See [Section 3.8.3](#) and [Section 3.10](#) for more information on EoTx rules for this trial.

The end of trial date is defined as the last date of last contact with the subject. This does not refer to overall trial duration. The end of trial date and timing for follow-up assessments will be individualized for each subject.

### **3.7.6 Independent Data Monitoring Committee**

For trials in high morbidity and/or high mortality disease, where efficacy endpoints could be subject to expedited reporting, the integrity of the clinical trial may be compromised if the blind is broken. For this trial, an Independent Data Monitoring Committee (IDMC, also known as a Data Safety and Monitoring Committee [DSMC]) will be established. The role of the IDMC shall be delineated in a separate IDMC Charter document, but in general this group will meet on a regular basis 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 detailed in their Charter.

### **3.8 Stopping Rules, Withdrawal Criteria, and Procedures**

#### **3.8.1 Entire Trial or Treatment Arm(s)**

If the sponsor terminates or suspends the trial for safety or unanticipated other reasons, prompt notification will be given to investigators, IRBs/IECs, and regulatory authorities in accordance with regulatory requirements.

#### **3.8.2 Individual Site**

The investigator will notify the sponsor promptly if the trial is terminated by the investigator or the IRB/IEC at the site. If the investigator, IRB/IEC or sponsor decides to terminate or suspend the trial's conduct at a particular center for safety, non-enrollment of subjects, non-compliance with the protocol, 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 Discontinuation**

##### **3.8.3.1 Subjects Discontinued Prior to Randomization**

Subjects discontinued during the pre-randomization period will be designated as either a "Screen failure" or "Run-in failure". During the screening period, if a subject withdraws their consent or fails to meet all of the requirements to continue in the trial, that subject will be considered a "Screen failure". Subjects who fail to meet trial requirements during the screening period may be rescreened at a later date.

Screen failure subjects will be recorded as such on the eCRF. Screen failure subjects do not require follow-up and can be considered for rescreening if the reason for the screen failure was not that the subject withdrew their consent. If rescreened, the subject will sign a new informed consent, will be assigned a new screening number, and will repeat all screening procedures.

During the remainder of the pre-randomization period (placebo run-in, tolvaptan titration, or tolvaptan run-in periods), if a subject discontinues or is discontinued that subject will be considered a "Run-in failure". A subject may be considered a "Run-in failure" for any of the following reasons:

- Subject does not meet entry requirements (ie, subject cannot tolerate IMP treatment as specified for a particular pre-randomization period - see [Section 3.2.1](#)),
- Subject decides to formally withdraw consent and/or fails to return for subsequent appointments at the trial site, or
- Investigator considers the subject unsuitable for further participation.

Run-in failure subjects will be recorded as such on the eCRF. Run-in failure subjects will complete an EoTx visit upon withdrawal from the trial. The EoTx visit assessments will include: collect vital signs, physical examination, serum creatinine assessment, clinical laboratory assessments, collect PK/PD samples and biomarker urine/plasma samples. Run-in failure subjects will then be followed up after 7 days with a phone call to record any ongoing AEs (as specified in [Section 5.6](#)); unless the subject fully withdraws consent to any further follow-up by written documentation.

### **3.8.3.2 Treatment Interruption**

In this year-long trial, it is expected that subjects may have one or more treatment interruptions during the double-blind, randomized treatment period. If a subject's IMP treatment must be interrupted for medical or surgical reasons; liver test abnormalities; use of a prohibited concomitant medication; or other reasons (eg, hospital admission for an invasive procedure, a major medical condition, surgery, dental work, or a temporary situation that prevents subject compliance with the IMP administration schedule), the subject's IMP should be resumed as early as the situation allows (see [Section 3.8.3.4](#)).

Any IMP interruption of < 7 consecutive days will be recorded as missed doses rather than as a temporary interruption of IMP. The subject should immediately inform the investigator of any missed doses reaching or expected to be 2 days or more so that the investigator can continue to monitor the subject's treatments and prepare for a possible 7-day IMP interruption.

An IMP interruption that lasts  $\geq$  7 consecutive days will be recorded as a “7-day Treatment Interruption” on the eCRF and the subject will visit the clinic to collect vital signs, physical exam, serum creatinine assessment, clinical laboratory assessments, PK/PD samples, and biomarker urine/plasma samples. It is assumed that an interruption of this duration may become permanent, therefore the subject will have a total of 5 samples collected for serum creatinine measurements (in the 2-week period beginning on the 7th day and including the above-mentioned serum creatinine assessment).

Treatment may still be restarted during or after these assessments are completed. If treatment is restarted, and the subject continues to Month 12, the subject will complete the Month 12 visit and scheduled follow-up assessments; the 7-day Interruption assessments will be considered as unscheduled. This procedure is aimed at ensuring data for the primary endpoint will be collected from all subjects.

### **3.8.3.3 Treatment Discontinuation**

After randomization, a subject may stop treatment permanently before Month 12 for a variety of reasons. Treatment discontinuations may be initiated by a subject who is not

satisfied with treatment or may become medically necessary due to AEs or other issues, as determined by the investigator (see [Section 3.8.3.4](#)). However, each investigator must comprehensively review the circumstances and offer the subject options for continued treatment to the degree possible as described in [Section 3.8.3.5.1](#).

A subject who permanently discontinues treatment will be recorded as an IMP discontinuation on the eCRF. They will have an EoTx visit to collect vital signs, physical exam, serum creatinine assessment, clinical laboratory assessments, PK/PD samples, and biomarker urine/plasma samples. The subject will then enter the follow-up period as though they had reached the Month 12 visit. During the first week of the follow-up period, no procedures will be done. During the last two weeks of the follow-up period, the subject will have a total of 5 samples collected for serum creatinine measurements. After the follow-up period, the subject will continue with all assessments up to and including their scheduled Month 12 visit, but will not be required to complete follow-up beyond that visit.

### **3.8.3.4 Documenting Reasons for Treatment Interruption/Discontinuation**

A subject may temporarily interrupt or discontinue IMP for a number of reasons including those listed below:

- Reasons related to AE:
  - Subject decides to discontinue due annoyance or discomfort due to a non-serious AE which is not otherwise determined to be an undue hazard
  - Continuing IMP places the subject at undue hazard as determined by the investigator (eg, a safety concern that is possibly, probably, or likely related to IMP)
    - Serious adverse event (SAE)
    - eGFR decreased to a level requiring dialysis or kidney transplantation (confirmed by repeat testing)
    - Liver test abnormalities meeting criteria for permanent discontinuation (see [Section 3.7.3.4](#))
    - Clinical jaundice (requires an immediate interruption of IMP and prompt repeat testing to confirm abnormality)
- Death
- Reasons unrelated to medical condition (provide detail and review AE history with subject)
- Withdrawal of informed consent (complete written withdrawal of consent form)
- Lost to follow-up (Detailed procedures to prevent subjects from becoming “lost to follow-up will be provided in the operations manual. These procedures must be followed by the investigator, their staff or other designated trial personnel.)

- Pregnancy (see [Section 5.4](#))
- Termination of all or part of the trial by the sponsor

If the subject temporarily interrupts or discontinues IMP due to an AE, the investigator, or other trial personnel, will make every effort to follow the event until it has resolved or stabilized. Follow up procedures in [Section 3.8.3.2](#) and/or [Section 3.8.3.3](#) must be followed. If the subject's IMP is interrupted for a liver test abnormality or liver symptoms, procedures outlined in [Section 3.7.3.4](#) should be followed.

### **3.8.3.5      Withdrawal of Consent**

All subjects have the right to withdraw their consent from further participation in the trial at any time without prejudice. The investigator can also discontinue a subject's participation in the trial at any time if medically necessary. Unless the subject provides their written withdrawal of consent or there is other written documentation by the investigator confirming the subject's verbal intent to completely withdraw from the trial, subjects should be followed for all protocol-specified evaluations and assessments.

Complete withdrawal of consent requires a subject's refusal of ALL of the following methods of follow up (these methods of follow up will also be noted in the trial ICF):

- Participation in all follow-up procedures specified in the protocol (whether in-clinic, by telephone, or by an in-home visit).
- Participation in a subset of protocol specified follow-up procedures (by a frequency schedule and method as agreed by subject and staff)
- Contact of the subject by trial personnel, even if only by telephone, to assess current medical condition and obtain necessary medical or laboratory reports relevant to the trial's objectives.
- Contact of alternative person(s) who have been designated in source records as being available to discuss the subject's medical condition, even if only by telephone, mail or e-mail (eg, family, spouse, partner, legal representative, friend, neighbor, physician).
- Access to medical information from alternative sources (eg, hospital/clinic medical records, referring doctor's notes, public records, dialysis, transplantation or vital registries, social media sources).

Withdrawal of consent is a critical trial event and therefore should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a subject's intended withdrawal need to be completely understood, documented and managed to protect the rights of the subject and the integrity of the trial. A subject may initially express their desire to interrupt or discontinue IMP

administration, which is not equivalent to a complete withdrawal of consent for further participation (see [Section 3.8.3.2](#) through [Section 3.8.3.4](#)). A subject may, however, indicate that further trial participation is creating a burden on their work or social schedule. Therefore, the investigator should follow the procedures outlined in [Section 3.8.3.5.1](#) to determine if the subject can continue participation in the trial if modifications to his/her treatment and/or schedule of assessments can be accommodated. Only subjects who withdraw their permission for all of the above degrees of follow-up are considered to have completely withdrawn their consent to participate in the study.

### **3.8.3.5.1 Procedures to Encourage Continued Trial Participation**

In all cases of impending IMP discontinuation or consent withdrawal, investigators will be given instructions to meet and discuss with the subject their options of continuing in the trial, preferably on therapy. The investigator should ensure understanding and documentation of the reasons for the subject's desire to withdraw consent.

If a subject in the double-blind, randomized treatment period wishes to withdraw from the trial:

- 1) The investigator should first seek to understand the subject's motivation and wherever possible make accommodations to prevent treatment discontinuation or complete withdrawal of consent and maintain the fullest compliance with the protocol assessments (eg, provide necessary travel reimbursement, in-home visits, alternate visit scheduling, including during weekends). If the subject's wish is to discontinue study medication only, proceed to Step 2.
- 2) Ask the subject, "Would you be willing to continue if your dose of medication was lowered?" If the answer is "Yes" titrate the subject's dose down 1 level (eg, from 90/30 to 60/30, from 60/30 to 45/15, or from 45/15 to 30/15 [with medical monitor approval]). Repeat this step if the subject continues to request withdrawal of consent. If the answer is "No" or if, once the 30/15 dose is reached, the subject continues to request withdrawal of consent, go to Step 3.
- 3) Ask the subject, "If we temporarily interrupt your trial medication would you be willing to later resume medication and continue with all visits and sample collections?" If the answer is "Yes", interrupt IMP but continue to follow all other trial procedures for the subject until the subject restarts treatment. If the subject does not resume treatment with IMP after 7 days, perform 7-day Interruption assessments and follow-up (see [Section 3.8.3.2](#)) and then resume IMP and continue with all other monthly assessments to the end of the trial. If the subject still wishes to withdraw from the trial, go to Step 4.
- 4) Ask the subject, "If we discontinue your trial medication permanently, would you continue with all visits and sample collections?" If the answer is "Yes", discontinue IMP, perform an EoTx visit, complete the follow-up period, and then continue with all other monthly assessments to the end of the trial (see [Section 3.8.3.3](#)). If the answer is "No" go to Step 5.

- 5) If further trial support or interruption or permanent discontinuation of study medication does not resolve the subject's issues, further accommodations such as less frequent visits or blood draws may be used (so long as adequate safety monitoring can be ensured for those continuing IMP). Less frequent visits or procedures must be offered only if they are required to maintain access to the subject's medical information and/or to encourage the subject to continue in the trial.

### **3.8.3.5.2 Procedures to Prevent “Lost to Follow-up”**

The investigator must make every effort to contact subjects who fail to return for scheduled visits so that they will not be declared “lost to follow-up”. The following procedures should be followed at a minimum, with additional measures taken if unsuccessful.

- Contact all numbers for the subject and their listed contacts (to be collected in source at the subject's entry into the trial). This includes making calls after normal business hours or on holidays and weekends.
- Contact the subject's primary care physician, referring specialist, pharmacist or other health-care professional (using the contacts provided by the subject at entry to the trial).
- Send a text, e-mail and postal mail with certified (return-receipt requested) letters to all the subject's addresses and all contacts (as provided by the subject at entry to the trial).
- In-home visit at last address given.
- Review available medical records/notes for details of hospitalizations, clinic visits or other procedures which may indicate the status of subjects (as allowed through release of medical record forms to be completed by patient at trial entry).
- Utilize the internet to search for additional contact information (eg, reverse directory for phone numbers or new address information; facebook, linked-in or other social media for status updates)
- Check local, regional and national public records to locate the subject or search for mortality status as allowed by law.

Once all these actions have been exhausted (and documented), then the sponsor clinical research associate or medical monitor should be contacted for additional guidance.

### **3.9 Screen Failures**

A screen failure is a subject from whom informed consent is obtained and is documented in writing (ie, subject signs an ICF), but who withdraws consent from the trial or does not meet all of the requirements, during the screening period, to continue in the trial (ie, subject does not enter the placebo run-in period).

Screen failure subjects are permitted to be re-screened. In the event that the subject is re-screened, a new ICF must be signed.

### **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 consumes all doses of the IMP.

For purposes of this trial, subjects who are randomized, take IMP up to Month 12 (-7/+2 days), and complete some or all of their required trial visits/assessments to the end of the trial (including the Month 12 visit AND at least 1 follow-up serum creatinine assessment) will be defined as “On-treatment completers”.

Subjects who are randomized, take IMP but discontinue treatment prior to Day 358 (or never begin treatment), and complete some or all of their required trial visits/assessments to the end of the trial (including the Month 12 visit AND at least 1 follow-up serum creatinine assessment) will be defined as “Off-treatment completers”.

Subjects who are randomized, take IMP (or never begin treatment), but DO NOT complete the Month 12 visit AND at least 1 follow-up serum creatinine assessment will be defined as “Non-completers”.

Both On-treatment completers and Off-treatment completers will have the opportunity to enroll in a tolvaptan extension trial following their completion of this current trial.

Non-completers who took IMP may only enroll in the tolvaptan extension trial with medical monitor approval. Non-completers who never took IMP during the double-blind, randomized period may not enroll in the tolvaptan extension trial.

### **3.11      Definition of Subjects Lost to Follow-up**

Subjects who cannot be contacted on or before their last trial visit and who do not have a known reason for discontinuation (eg, withdrew consent or AE) will be classified as “lost to follow-up” as the reason for withdrawal.

Every effort will be made by the investigator, or trial personnel, to contact the subject before the subject is declared lost to follow-up (see [Section 3.8.3.5.2](#)).

### **3.12      Subject Compliance**

Dispensing of IMP and reconciliation will be done monthly during the randomized treatment period. Subject compliance will be monitored by pill counts as drug is returned. In addition, tolvaptan metabolite DM-4103 concentrations will be determined and evaluated for consistency with reported dosing.

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 (whichever is greater) will be deemed non-compliant. Depending on the circumstances leading to non-compliance, the subject may be discontinued from IMP administration by the investigator and/or sponsor. A subject who proactively wishes to discontinue IMP administration, or has IMP discontinued by the investigator, will be encouraged to continue limited participation in the trial, as described in [Section 3.8.3.3](#).

### **3.13 Protocol Deviations**

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, IMP dispensing or subject dosing error, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator or designee will contact the sponsor at the earliest possible time by telephone. The investigator and sponsor will come as quickly as possible to a 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 site monitor.

## **4 Restrictions**

### **4.1 Prohibited or Restricted 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 ribonucleic acid (RNA) therapies, tolvaptan, and other vasopressin antagonists (eg, OPC-31260 (mozavaptan), Vaprisol (conivaptan), or agonists (eg, desmopressin) 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 may be used intermittently, but not within 7 days of a urine assessment. Diuretics are not generally recommended in ADPKD due to their tendency to increase AVP levels through relative dehydration or volume depletion; thus, chronic use of diuretics (eg, for hypertension) will be prohibited due to potential endpoint interference and is an exclusionary criterion for this trial. Subjects 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. Some drugs

are known to alter creatinine concentrations so, while not prohibited, subjects should alert their trial doctor, and any other health-care providers, to take this into consideration when considering changes in their prescribed or over-the-counter medications. A brief list would include: cimetidine, NSAID medications like aspirin or ibuprofen, chemotherapy drugs, and cephalosporin.

Since tolvaptan is a weak cytochrome P450 (CYP) 3A4 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.

<b>Table 4.1-1                    CYP3A4 Inhibitors (Partial List)</b>			
boceprevir	clarithromycin	clotrimazole (if used orally)	indinavir
itraconazole	ketoconazole (if used orally)	lopinavir	mibefradil
nefazadone	nelfinavir	posaconazole	ritonavir
saquinavir	telaprevir	telithromycin	voriconazole

## **4.2        Dietary Restrictions and 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 advanced ADPKD, particularly if there is evidence for a propensity for rapid progression. In the absence of alternate regional practices, dietary salt < 5g/day and dietary protein < 1 g/kg/day and to limit caffeinated drinks/foods should also be given (no more than 2 coffee equivalents per day).

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. Upon consent, all subjects should receive the recommendation to ingestion of at least 2-3 liters of fluid (including in solid, semi-solid, and liquid foods) per day, unless otherwise directed by your study doctor. This recommendation should start during screening and continue through the end of the trial. Additionally, subjects should ingest 1 to 2 cups of water before bedtime regardless of perceived thirst and replenish fluids overnight with each episode of nocturia. Dehydration will be monitored by subject self-assessment of changes in body weight and reporting of symptoms. Acute changes of > 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.

Subjects should be advised that the ingestion of pomelo, grapefruit, or Seville orange products would be expected to increase tolvaptan concentrations and these should be avoided. In the event of an unintentional ingestion of such products, the investigator may ask the subject to temporarily interrupt IMP. Subjects should be informed of regionally appropriate recommendations in the trial ICF.

## **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 AEs may be associated with this disorder and are endpoints in this trial, including urine concentration defects, hypertension, renal pain, renal infection, nephrolithiasis, hematuria, and ESRD. As such, these events are considered “expected” in this trial population and will not qualify for the purposes of regulatory expedited reporting (eg, Suspected Unexpected Serious Adverse Reaction [SUSAR] and investigational new drug [IND] safety reports).

These blinded events will be evaluated on a regular basis by the trial’s Medical Monitor and the sponsor’s Safety group. The trial’s IDMC will include a separate statistical support group who will be provided the randomization codes so that partially or fully unblinded review of data may occur in closed session to better assess risk/benefit in the trial population.

### **5.1 Definitions**

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. For the purpose of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality. Additionally, in the European Union (EU), an adverse procedure-related reaction is any noxious or unintended response to a trial-related procedure and requires a SUSAR report.

A SAE includes any event that results in any of the following outcomes:

1. death
2. 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 that, had it occurred in a more severe form, might have caused death.
3. persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
4. requires in-patient hospitalization or prolongs hospitalization  
NOTE: A pre-scheduled hospitalization is not considered an SAE.
5. congenital anomaly/birth defect
6. other medically significant events that, based upon 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.

Non-serious AEs are all AEs that do not meet the criteria for a “serious” AE.

Immediately Reportable Event (IRE):

- Any SAE
- Any AE (whether serious or non-serious) that necessitates discontinuation of IMP.
- Any subject with a new liver test abnormality meeting the AE (whether serious or non-serious) or laboratory threshold criteria (whether considered an AE or not) for hepatic eCRF reporting.
- Any subject reporting an AE of special interest (eg, skin neoplasms or glaucoma).
- Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, it will mandate IMP discontinuation and must be reported on an IRE form to Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC). Pregnancy will only be documented on the AE eCRF if there is an abnormality or complication.
- Additionally, in the EU region, events involving overdose, misuse and abuse as well as reported lack of efficacy must also be reported as IREs.

Clinical Laboratory Changes: 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 an abnormal change from baseline for that subject, this is considered an AE.

**Severity:** Adverse events will be graded on a 3-point scale and reported as indicated on the eCRF. 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.

**IMP Causality:** Assessment of causal relationship of an AE to the use of the IMP

- Related:** There is a reasonable possibility of a causal relationship.
- Possibly related:** There is a reasonable causal relationship between the IMP and the AE. Dechallenge is lacking or unclear.
- Unlikely related:** There is a temporal relationship to IMP administration, but there is not a reasonable causal relationship between the IMP and the AE.
- Not Related:** There is no temporal or reasonable relationship to the IMP administration.

## **5.2 Eliciting and Reporting Adverse Events**

The investigator will periodically assess subjects for the occurrence of AEs. In order to avoid bias in eliciting AEs, subjects should be asked the following non-leading question: "How have you felt since your last visit?" All AEs (serious and non-serious) reported by the subject must be recorded on the source documents and eCRFs provided by the sponsor.

In addition, the sponsor must be notified immediately by telephone or fax of any immediately reportable events according to the procedure outlined below in [Section 5.3](#). Special attention should be paid to recording hospitalization and concomitant medications.

## **5.3 Immediately Reportable Events**

The investigator must immediately report within 24 hours after either the investigator or site personnel become aware of any SAE, new liver lab abnormality requiring special liver eCRF completion, or confirmed pregnancy, by telephone or by fax to the sponsor as outlined in Appendix 1. An IRE form must be completed and sent by fax or overnight courier to the sponsor. (Please note that the IRE form is NOT the AE eCRF.)

Non-serious events that require discontinuation of IMP (including laboratory abnormalities) should be reported to the sponsor within 3 working days. The IRE form must be completed and sent by fax or overnight courier to the sponsor.

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.

For subjects discontinued from IMP, vital status and scheduled laboratory data will continue to be collected at scheduled monthly visits and at trial termination.

#### **5.4      Pregnancy**

Women of childbearing potential who are sexually active must use an effective method of birth control during the course of the trial and for 30 days after the last dose of IMP in a manner such that risk of failure is minimized. Unless the subject is sterile (ie, women who have had a bilateral oophorectomy and/or hysterectomy or have been postmenopausal for at least 12 consecutive months) or remains abstinent, 2 of the following precautions must be used: vasectomy, tubal ligation, intrauterine device, birth control pills, birth control depot injection, birth control implant, condom or occlusive cap (diaphragm or cervical/vault caps) with spermicide. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy.

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

- General information.
- ICF.
- 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 informed consent form stating that the above-mentioned risk factors and the consequences were discussed with her.

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 IMP or be enrolled in the trial. If pregnancy is suspected while the subject is receiving treatment, IMP 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, IMP will be interrupted or withheld in an appropriate manner (eg, dose tapering if necessary for subject safety) and the subject will continue to be monitored for the duration of the remainder of the trial or of their pregnancy. Subjects who permanently discontinue IMP due to pregnancy may continue to be monitored in the same manner as other subjects to their 12-month visit and will be considered trial Off-treatment completers.

The investigator must immediately notify the sponsor of any pregnancy associated with IMP exposure during the trial and for 30 days after the last dose of IMP and record the event on the IRE form and forward it to the sponsor. The sponsor will forward Pregnancy Surveillance Form(s) for monitoring the outcome of the pregnancy.

Protocol required procedures for IMP 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 is encouraged to contact the sponsor/Clinical Research Organization (CRO) medical advisor to discuss their rationale for unblinding. However, to prevent delays to the investigator or medical personnel responding to a potentially emergent situation, unblinding of IMP will not be dependent upon the investigator receiving approval from the sponsor/CRO medical advisor (ie, the investigator will be able to obtain the code break information independent of the sponsor/CRO medical advisor). The investigator must contact the sponsor/CRO medical advisor by telephone with an explanation of the need for opening the treatment assignment code within 24 hours of opening the code. If the blind is broken, the sponsor's Clinical Safety and Pharmacovigilance department (contact information provided in Appendix 1) will 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. Once the blind is broken for a given subject, that subject may not reinitiate treatment with IMP.

## **5.6 Follow-up of Adverse Events**

For this trial, AEs will be followed up for 21 days after the last dose of IMP has been administered (follow-up period).

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.

For subjects who have discontinued IMP but have not withdrawn from the trial, vital status, AEs, concomitant medications, ESRD status, and scheduled laboratory data (including serum creatinine data) are planned to be collected regardless of IMP discontinuation until the scheduled end of the trial.

### **5.6.1 Follow-up of Non-serious Adverse Events**

Non-serious AEs that are identified on the last scheduled contact must be recorded on the AE eCRF with the current status noted. All non-serious events that are ongoing at this time will be recorded as ongoing on the eCRF.

### **5.6.2 Follow-up of Post-Trial Serious Adverse Events**

Serious AEs that are **identified on the last scheduled contact** must be recorded on the AE eCRF page and reported to the sponsor according to the reporting procedures outlined in [Section 5.3](#). This may include **unresolved previously reported** SAEs, or **new SAEs**. The investigator will follow 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 will continue to report any significant follow-up information to OPDC up to the point the event has been resolved.

### **5.6.3 Follow-up and Reporting of Serious Adverse Events Occurring after Last Scheduled Contact**

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 IMP, should be reported to OPDC. 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 potentially IMP-related SAEs 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 OPDC up to the point the event has been resolved.

## **6 Pharmacokinetic and Pharmacodynamic Analysis**

### **6.1 Pharmacokinetic**

Tolvaptan (OPC-41061) plasma concentrations may be used for a population PK analysis (that would be reported separately).

The DM-4103 metabolite has a half-life of approximately 180 hours and, consequently, is a good marker of long term compliance with dosing. DM-4103 concentrations will be reviewed for consistency with IMP dispensing and return records in order to determine compliance. Concentrations will be plotted by gender (male, female, total population) and modal dose within the previous treatment period and treatment day.

### **6.2 Pharmacodynamic**

Urine osmolality and specific gravity will be summarized by treatment (tolvaptan or placebo) and time point using descriptive statistics. Baseline values will be from the sample obtained at the end of the placebo run-in period.

## **7 Statistical Analysis**

### **7.1 Sample Size**

#### **7.1.1 Sample Size Estimation**

In this sample size estimation, it is assumed that 4 to 5 calculations of eGFR will be obtained at baseline during a 3-week interval during screening (2 weeks) and placebo run-in (1 week), and another 4 to 5 calculations will be obtained post-treatment during a 2-week interval that begins 1 week after the end of treatment (3-week post-treatment follow-up). The mean of the 4 to 5 eGFR values observed during the screening and placebo-run periods will be set as the baseline and the mean of the 4 to 5 eGFR values observed during the post-treatment follow-up period will be set as the renal function measurement post-treatment. The timing of the baseline and post-treatment observations will be set to the median of the observation times in the 2-week interval, respectively. Thus, the pre-treatment baseline will be set at approximately 6 weeks prior to randomization, and the post-treatment renal function measurement will be set at approximately 2 weeks after the end of treatment.

Based on a Mixed Model Repeated Measurements (MMRM) analysis of the non-Japan CKD-3 subjects from Trial 156-04-251, the treatment difference in renal function at Month 12, based on the post-randomization baseline, is 1.43 mL/min/1.73 m<sup>2</sup>. However, the US-FDA has expressed a concern that the onset and offset of tolvaptan's hemodynamic effect may not be equal (The sponsor believes it is not possible to determine if the small differences observed are due to a random error). Thus, with an assumption that the absolute value of the offset eGFR increase is 25% less than the absolute onset decrease in eGFR, we may assume the treatment difference in renal function is 1.07 mL/min/1.73 m<sup>2</sup> in our sample size calculation.

To investigate the reduction in intra-subject variation achieved by taking the mean of an increased number of observations at baseline and post-treatment follow-up, and its impact on the sample size, we have to estimate the intra-subject error and inter-subject error.

To derive the intra-subject variance and inter-subject variance, the approach provided by Dr. Lawrence, a FDA statistician, in a FDA communication to the sponsor (e-mail communication, 24Dec2014), was followed. For subject  $i$  randomized to the placebo group ( $i=1, \dots, n$ ), the eGFR at time  $t_j$  is assumed to be

$$Y_{i,j} = \alpha_i + \beta_i t_j + \varepsilon_{i,j} \quad (1)$$

For subject  $i$  randomized to the tolvaptan group ( $i= n+1, \dots, 2n$ ), the eGFR at time  $t_j$  is assumed to be

$$Y_{i,j} = \alpha_i + \beta_i t_j + \varepsilon_{i,j} \text{ if } j \text{ is observed at baseline} \quad (2)$$

$$Y_{i,j} = \alpha_i + \Delta + \beta_i t_j + \varepsilon_{i,j} \text{ if } j \text{ is observed at post-treatment follow-up} \quad (3)$$

$$Y_{i,j} = \alpha_i + \gamma + (\Delta + \beta_i) t_j + \varepsilon_{i,j} \text{ if } j \text{ is observed during the treatment period} \quad (4)$$

where  $\varepsilon_{i,j}$  are assumed iid  $N(0, \sigma^2)$ ,  $\beta_i$  are assumed iid  $N(\beta, \sigma_\beta^2)$ ,  $\varepsilon_{i,j}$  and  $\beta_i$  are mutually independent, and  $\Delta$  is treatment effect,  $\gamma$  is the hemodynamic onset effect. Based on this model, with baseline time is set to 0, the variance of change from baseline at a post-baseline visit is

$$\text{Var}(Y_{i,j} - Y_{i,0}) = \text{Var}(\beta_i t_j + \varepsilon_{i,j} - \varepsilon_{i,0}) = t_j^2 \sigma_\beta^2 + 2\sigma^2 \quad (5)$$

Dr. Lawrence's derivation is based on the assumption that an observation of eGFR is made at the end of a 2-week interval for  $k$  times (thus, totally  $2k$  weeks) at baseline and post-treatment follow-up visit respectively. Thus, Dr. Lawrence's variance of change from baseline to post-treatment follow-up is

$$(2/k) \sigma^2 + (1 + 1/12 + k/26)^2 \sigma_\beta^2 \quad (6)$$

If we change the assumption to this one that all these k observations are observed in the 2-week intervals mentioned in the first paragraph in this section, the variance would become

$$(2/k) \sigma^2 + (1 + 1/12 + 3/52)^2 \sigma_{\beta}^2 \quad (7)$$

This variance formula was used in our sample size calculation, since it matches our protocol design more closely.

If the model given by (1) to (4) is applied to the data of CKD-3 non-Japan subjects in Trial 156-04-251, with eGFR data from pre-randomization baseline to Follow-up Visit #2, the residual variance ( $\sigma^2$ ) and slope variance ( $\sigma_{\beta}^2$ ) are estimated as 22.13 and 5.27, respectively, which may be interpreted as intra- and inter-subject variances.

With a 2-sided alpha of 0.05 and 1:1 randomization to tolvaptan and placebo, using the parameters given above and sample size formula of 2-sample t-test, we have the following table:

<b>Table 7.1.1-1</b>		<b>Total Sample Size with k Observations and 15% Dropout Rate</b>				
k	1	2	3	4	5	6
85% Power	1884	1068	796	660	580	526
90% Power	2196	1246	930	770	676	612

The assumption of dropout rate of 15% is reasonable since the dropout rate was 20% in Trial 156-04-251, and it is expected that the inclusion of the tolvaptan run-in period in this trial will reduce the dropout rate in the double-blind treatment period. From this table, it seems that k = 4 would produce an acceptable sample size and not an excessive burden for enrolled subjects. Thus, with an assumption of 15% dropout rate in the trial, the total sample size (randomized subjects) would be from 660 to 770, and will be set as a range of between 700 and 1000 randomized subjects, with a goal of 800 subjects, depending also on the trial's ability to enroll and the accumulated number of subjects randomized up to the end of 2014. Because this information will be helpful in guiding the treatment of ADPKD patients with more advanced stages of CKD, and because marketing approval in many participating countries may be reached by 2015, it is critical to conclude enrollment near the end of 2014 or beginning of 2015. This will help avoid missing data due to subjects leaving the trial to seek commercially available treatment in those countries.

The desire for a small number of blood draws during these periods was emphasized by the trial's Steering Committee, which further suggested that measures be taken to minimize the intra-subject variability by standardizing, as much as possible, the timing and conditions by which serum creatinine was assessed (in particular recommending a similar diet, avoiding variation in protein, especially cooked protein, intake and exercise pattern during these periods). The Steering Committee also suggested that the intra-subject variance during the pre-treatment and post-treatment periods be monitored throughout the trial with a mandatory increase in serum creatinine sample numbers (ie, from a minimum of 4 to a minimum of 5) or subject numbers if observed variance was greater than that used in the power assumption (assessed using only baseline eGFR data in a power re-estimation procedure). They also favored the possibility that sample numbers, but not the minimum enrollment, be lowered (ie, to a maximum of 4 samples) if variance was significantly less due to these measures (see [Section 7.1.2. "Blinded Sample-Size Re-estimation"](#))

For the sample size of the key secondary endpoint, longitudinal analysis specified in the SAP of from Trial 156-04-251 was applied to the eGFR data of CKD-3 non-Japan subjects using post-randomization baseline, to obtain the estimates of the variance of inter-subject eGFR slope ( $4.39 \text{ mL/min}/1.73 \text{ m}^2$  per year) and the variance of intra-subject eGFR observations ( $22.45 \text{ mL/min}/1.73 \text{ m}^2$ ). The power calculation using the sample size formula provided by Lefante<sup>21</sup> assumes the following:

- 1) placebo subjects would have an eGFR decline of  $4.5 \text{ mL/min}/1.73 \text{ m}^2$  per year;
- 2) tolvaptan subjects would have an eGFR decline reduced 25% compared with placebo subjects;
- 3) treatment duration is 1 year with monthly observations in eGFR.

In addition, the 1:1 randomization and the alpha (0.05, 2-sided) specified above in the sample size of the primary endpoint are also assumed in the sample size calculation. It is then estimated that 315 subjects per group are required for 85% power and 367 subjects per group are required for 90% power. These sample sizes are very close to the sample size calculated using FDA statistician Dr. Lawrence's formula, for example, sample size of 368 per group with 90% power, when the variances provided above were used. Thus, with a total sample size of from 660 to 770 (rounded to 700 to 800), the key secondary endpoint will have at least 85% to more than 90% power in detecting a slope difference in this trial.

### 7.1.2 Blinded Sample Size Re-estimation

Blinded sample size re-estimation will be conducted when about half of the planned randomized subjects (350 to 400) have been randomized. This is expected to be conducted before the end of 2014 and thus before the availability of any post 12-month off-treatment follow-up eGFR data used for the primary analysis. The goal of this blinded sample size re-estimation is to check: 1) the differences between the observed variances and the variances used in the sample size calculation; 2) whether the approach of averaging the 4 to 5 baseline pre-treatment eGFR observation has achieved the goal of reducing the variance to the level planned. This sample size re-estimation is necessary, especially, as recommended by our vendor, a method to analyze for serum creatinine called Rate Blanked is to be used in this protocol, while the sample size calculation is based on the data from 156-04-251, in which another method called “Enzymatic” was used to analyze for serum creatinine. Based on these findings, the serum creatinine sample number and subject sample size of this trial may need to be adjusted. Detailed procedure of the blinded sample size re-estimation will be provided in the SAP.

### 7.2 Datasets for Analysis

The following datasets are defined for this trial:

- Randomized Population: All subjects who are randomized in this trial.
- Randomized Safety Population: All subjects who are randomized in this trial and take at least 1 dose of IMP after randomization. This is the primary safety population.
- Treated Safety Population: All subjects who take at least 1 dose of IMP during the tolvaptan titration/run-in periods. This is a secondary safety population.
- Primary Endpoint Efficacy Population: All subjects who are in the Randomized Population, take at least 1 dose of IMP after randomization, and have a baseline and at least 1 valid post-treatment evaluation in eGFR (ie, after at least 1 week off treatment). The primary endpoint's baseline is defined as the average of up to 5 eGFR values observed during the screening and placebo run-in periods.
- Key Secondary Endpoint Efficacy Population: All subjects who are in the Randomized Population, take at least 1 dose of IMP after randomization, and have a baseline and at least 1 post-randomization evaluation in eGFR during the double-blind treatment period. This is similar to the Primary Endpoint Efficacy Population, except that post-treatment evaluation in eGFR is replaced by a post-randomization evaluation.

The core subject population for all efficacy analyses is based on the intent-to-treat (ITT) population which consists of all randomized subjects who take at least one dose of IMP. As will be described below, in order to handle missing and restrictions imposed by

different types of analyses (eg, change from baseline analysis), datasets based on modified ITT population will be used in the efficacy analyses.

The Observed Cases (OC) dataset of this protocol is defined as the data observed at study specified visits. For the primary outcome variable of this protocol, the OC dataset consists of the pre-treatment baseline (average of eGFR observed in screening period and the first eGFR observed in placebo run-in period) and post-treatment follow-up (average of eGFR observed in a two-week interval which is one week post the last IMP dose). For the key secondary outcome variable of this protocol, the OC dataset within treatment period is defined as the data observed at study specified visits while subjects are taking IMP or within 24 hours of the last IMP dose.

### **7.3 Handling of Missing Data**

The eGFR estimated by the CKD-EPI formula is utilized as the primary efficacy assessment in this trial.

In this protocol, all data collected in the pre-treatment baseline and post-treatment follow-up periods (except the week immediately after treatment withdrawal) will be used and missing data will not be imputed in deriving the pre-treatment and post-treatment eGFR observations used for the primary analysis.

For sensitivity analyses of the primary analysis, in general, missing data will be handled by analysis using mixed model methodology under the assumption of “missing at random” (MAR). However, the possibility of “missing not at random” (MNAR) data can never be ruled out. Thus, every effort will be made to follow the subjects who discontinue IMP after randomization without withdrawing consent for follow-up of their eGFR assessments. When collected within the last 2 weeks of the 3 weeks immediately post IMP withdrawal, the data will be included in the primary analysis. Otherwise, eGFR assessments collected during or after this period will be included in the sensitivity analysis. Additional sensitivity analysis will be conducted for the key secondary endpoint for all subjects who withdraw consent or who are lost to follow-up, using multiple imputation methodology under appropriate assumptions. These sensitivity analyses are described in [Section 7.4.2.4](#) and more detail will be provided in the SAP.

### **7.4 Primary and Secondary Outcome Analysis**

This trial’s estimand is the difference in outcome improvement if all subjects tolerated and adhered to their treatment. To enrich this population, only subjects who can tolerate the tolvaptan titration and run-in periods will be randomized. This approach combines estimands #2 and #3 as recommended by the 2010 National Academy of Sciences’ NRC

report on prevention and treatment of missing data<sup>14</sup> where estimand #2 is "difference in outcome improvement in tolerators" and "estimand #3 is "difference in outcome improvement if all subjects tolerated or adhered". Thus, MAR data is assumed in the primary analysis. Sensitivity analysis will be provided to address the concern of MNAR data.

This estimand focuses on the efficacy of tolvaptan in slowing renal function decline. The objective of this trial is to confirm a causal effect of tolvaptan in slowing renal function decline, consistent with the selection of an efficacy rather than an effectiveness estimand.

An effectiveness estimand compares treatment policies and reasonably could include data acquired long after withdrawal from the trial (eg, when subjects discontinue tolvaptan but are followed for many weeks or months) or move to an alternate treatment regimen (eg, placebo subjects being prescribed commercial tolvaptan upon approval for ADPKD). In the absence of an approved and effective alternate treatment for ADPKD; it is premature to discuss treatment policies. Thus, while eGFR data collected in the second and third week post-withdrawal are used for the analysis of the primary endpoint, data collected long after withdrawal or after a subject moves to an alternate treatment regimen will be excluded in the primary analyses of both the primary and the key secondary endpoints.

#### **7.4.1 Primary Efficacy Outcome Analysis**

##### **7.4.1.1 Primary Endpoint Analysis**

The primary endpoint of this trial is the change in eGFR from pre-treatment baseline to post-treatment follow-up, annualized (divided) by each subjects' IMP treatment duration. This normalization is necessary, otherwise the treatment group having more dropouts or more earlier dropouts may assume an unfair advantage. To reduce the variation in this primary endpoint, 4 to 5 observations of eGFR will be obtained at baseline during a 3-week interval (screening and placebo run-in periods) and another 4 to 5 observations will be obtained post-treatment during a 2-week interval that begins 1 week after the end of treatment (3-week post-treatment follow-up). The average of the 4 to 5 eGFR values observed during the baseline period is set as the baseline and the average of the 4 to 5 eGFR values observed during the post-treatment follow-up period is set as the renal function measurement post-treatment. Timings of baseline and post-treatment follow-up observations are set to the median of the time of these observations in the respective 2 to 3-week intervals, and the duration is equal to the timing of baseline minus the timing of post-treatment follow-up plus 1.

Use of the duration to annualize the change is also reasonable since it will provide an “estimate” of annualized eGFR change in slope for each subject, though there is no estimate for intra-subject variation. Thus, analysis of covariance (ANCOVA) with effects of treatment and randomization stratification factors and covariate baseline will be applied to these “estimated slopes” as the primary analysis.

#### **7.4.1.2      Sensitivity Analysis of the Primary Endpoint**

Aligned with the desire to evaluate effects free from acute hemodynamic treatment effects, a sensitivity analysis of the primary endpoint will be performed including all available placebo data. In this sensitivity analysis, in addition to the 4 to 5 pre-treatment baseline observations and the 4 to 5 post-treatment follow-up observations, all post-randomization on-treatment eGFR observations in the protocol-specified visits for placebo subjects will also be included. The linear mixed effect model with effects of time (as a continuous variable), treatment, and time-treatment interaction, randomization stratification factors and baseline as covariate will be used to fit the eGFR data, in which the intercept and time are both a fixed effect and a random effect. An un-structured variance covariance matrix is assumed for the random intercept and time. The time variable used in the model may start from the first observation of eGFR baseline as mentioned in [Section 7.1.1](#), and this baseline will be used in the model. Missing data will be ignored in this analysis under the MAR assumption. Data acquired while taking tolvaptan cannot be used in this analysis without appropriate adjustment, but is evaluated in the key secondary efficacy endpoint of eGFR slope with a methodology which takes the acute hemodynamic drug effects of tolvaptan into account.

#### **7.4.1.3      Sensitivity Analysis Including Data from Subjects Who Discontinue IMP**

This sensitivity analysis deviates from the MAR assumption to include the post-discontinuation follow-up data in the analysis specified in the previous section. Subjects who discontinue IMP after randomization without withdrawing consent will be followed for additional off-treatment eGFR through to Month 12. These post “post-treatment follow-up” eGFR data will be included, with the data specified in the previous section, in a sensitivity analysis using the same analytic approach specified in the previous section.

### **7.4.2      Secondary Outcome Analyses**

In addition to the key secondary efficacy endpoint described below, safety variables will also be analyzed as secondary outcomes in this protocol (see [Section 7.6](#)).

#### **7.4.2.1 Key Secondary Endpoint Analysis**

The key secondary endpoint of the trial is the annualized rate of eGFR change, which is derived from each individual subject's eGFR slope using the CKD-EPI formula. Slope is preferred as a practical and clinically meaningful endpoint. In this analysis, all eGFR observations from placebo run-in, tolvaptan run-in (not including tolvaptan titration), double blind treatment, and post-treatment follow-up (not including data collected in the first week after the last IMP dose) periods will be included in the analysis, with the data from tolvaptan run-in and tolvaptan subjects in the double-blind treatment period flagged (yes = 1 and no = 0) for a tolvaptan acute hemodynamic effect.

The linear mixed effect model with effects of time (as a continuous variable), treatment, time-treatment interaction, acute hemodynamic effect, pre-treatment baseline (of the primary endpoint), and randomization stratification factors will be used to fit the GFR estimates, in which the intercept and time are both a fixed effect and a random effect. An un-structured variance covariance matrix is assumed for the random intercept and time. The time variable used in the model may start from the first observation of eGFR obtained from placebo run-in period.

#### **7.4.2.2 Sensitivity Analysis of the Key Secondary Endpoint**

This sensitivity analysis of the key secondary endpoint of this trial is to compare the linear trend of eGFR between tolvaptan and placebo groups. The advantage of this sensitivity analysis is that it does not depend on the assumption of linearity and equal tolvaptan hemodynamic onset and offset effects used in [Section 7.4.2.1](#). The change from the pre-treatment baseline during the on-treatment visits in the double-blind treatment period will be included in the analysis. Since the hemodynamic effects of tolvaptan are believed to begin to reverse within 1-2 days, on-treatment will be defined as within 24 hours of the last IMP dose.

Analysis of MMRM will be applied to the data of change from baseline in eGFR in each month from Month 1 to Month 12. The model will have fixed effect of treatment, visit, treatment visit interaction, randomization stratification factors, and covariate baseline and baseline visit interaction. An unstructured variance-covariance matrix is assumed for the repeated measurements. A linear contrast of the treatment differences in these 12 months will be used as the sensitivity analysis of the key secondary endpoint.

#### **7.4.2.3 Sensitivity Analysis Including Data from Subjects Who Discontinue IMP**

This sensitivity analysis deviates from the MAR assumption to include the post-discontinuation follow-up data in the analysis of the key secondary endpoint. Subjects

who discontinue treatment after randomization without withdrawing consent will be followed for additional eGFR (not including the eGFR observed in the 3-week follow-up period immediately after EoTx) up to Month 12. The data collected during this time will not be included in the key secondary endpoint analysis for the reasons given above. However, a sensitivity analysis including these data for the key secondary analysis will be performed. This analysis uses the same approach provided in [Section 7.4.2.1](#) for the analysis of the key secondary endpoint.

#### **7.4.2.4      Sensitivity Analysis Including Imputation of Missing Data**

Multiple imputation is commonly used in the analysis of MNAR data. For all randomized subjects who withdraw consent for further testing or who are lost to follow up, imputation of missing data will be applied to projected visits up to their planned end of the trial (12 months post-randomization). The subjects' reasons for discontinuation will be captured and categorized to help determine the missing data pattern (see [Section 3.8.3.4](#)). Imputation will be based on the MMRM model specified in [Section 7.4.2.2](#). For placebo subjects, and in the absence of evidence suggesting biased missing data pattern, the imputation will follow the placebo trend.

Post-withdrawal data from Trial 156-04-251 and Trial 156-08-271 interim analyses show that tolvaptan's eGFR benefits accumulate and are sustained after treatment discontinuation; therefore, imputation for subjects randomized to tolvaptan should reasonably begin at the value of their last eGFR. If a subject has the post-treatment follow-up in the two-week interval, imputation will be based on this post-treatment observation; if a subject does not have the post-treatment follow-up observation, imputation will be based on the last on-treatment observation and flagged with the tolvaptan acute hemodynamic effect mentioned in [Section 7.4.2.1](#).

Trial 156-04-251 data also support true disease modification and preservation of functioning kidney parenchyma through reduction of cyst growth. Thus, discontinuation of tolvaptan would not result in an immediate return to the placebo trend. Therefore, eGFR decline in subjects discontinuing tolvaptan will reasonably fall somewhere between the tolvaptan trend and placebo trend. This supports a series of analyses for imputation of missing data for tolvaptan subjects, which will begin using the tolvaptan trend, and move stepwise toward the placebo trend. Further details will be provided in the SAP.

### **7.4.3 Exploratory Analyses**

#### **7.4.3.1 ADPKD Outcomes**

Assessment of ADPKD outcomes is an exploratory endpoint in this protocol.

Exploratory analysis will be applied to each outcome as well as to a composite of those outcomes which are more closely related to kidney enlargement as potential events.

Analysis of time to multiple events will be applied. Detailed analysis procedures will be provided in the SAP.

#### **7.4.3.2 DNA and Urine and Plasma Biomarkers**

Investigations into possible risk factors and mechanisms underlying DILI as the result of tolvaptan exposure are currently ongoing. Urine and plasma biomarker concentrations may be evaluated for metabolic or immunologic traits related to DILI and/or etiology of, susceptibility to, activity of, or progress of ADPKD, as well as the potential development of tools for diagnosis, prognosis and response to treatment.

Consenting subjects may have DNA samples evaluated for genetic evaluation of DILI and/or etiology of, susceptibility to, activity of, or progress of ADPKD, as well as the potential development of tools for diagnosis, prognosis and response to treatment. The types of analyses that are planned are for genetic mutations of PKD1 and PKD2, which code for the proteins polycystin-1 and polycystin-2, respectively, in renal tubular cells and are responsible for approximately 85% (PKD1) and 15% (PKD2) of clinical cases of ADPKD. Genes involved with ADPKD's phenotypic manifestations (eg, other genes associated with high or low penetrance, non-renal manifestations of ADPKD such as liver or vascular disease, and accelerated versus slow progression of kidney failure) may also be analyzed. Genotyping for drug metabolizing enzymes and transporters by microarray is also envisioned. A potential link between genetic mutations of the genes coding for CYP3A4, the enzyme system primarily responsible for the metabolism of tolvaptan, or other enzymes and transporters involved in tolvaptan metabolism and transport into and out of the liver may be explored. Also, an experiment involving genotyping for human leukocyte antigen mutations may be explored that could be related to an immune-mediated response to tolvaptan treatment.

Samples from this trial may be analyzed as part of these investigations and may be reported separately.

### **7.5 Analysis of Demographic and Baseline Characteristics**

Demographic characteristics, disease severity, and medical history at (pre-treatment) baseline will be summarized by descriptive statistics, eg, proportion, mean, median,

standard deviation (SD), minimum and maximum values. These summary statistics will be reviewed to identify any potential lack of balance between the treatment groups.

## **7.6 Safety Analysis**

In general, baseline measurements of safety variables are defined as the last measurements prior to randomization for the primary Randomized Safety Population (except for serum creatinine, which is defined similarly to the baseline of eGFR assessment for the primary endpoint, see [Section 7.4.1.1](#)) and as their last measurements prior to the first dose of IMP for the secondary safety population (Treated Safety Population). Safety analyses will be conducted based on these safety populations, which are defined in [Section 7.2](#). Standard safety variables to be analyzed include AEs, clinical laboratory data, physical examinations, and vital signs. Safety variables will be summarized by descriptive statistics, (eg, proportion, mean, median, SD, minimum, and maximum values). In general, summary statistics, including changes from baseline, will be provided for safety variables based on all available data.

### **7.6.1 Adverse Events**

All AEs will be coded by system organ class and Medical Dictionary for Regulatory Activities (MedDRA) preferred term. The incidence of the following events will be summarized by treatment group for the primary safety population; summary of these events will also be provided for the secondary safety population:

- a) Treatment-emergent AEs (TEAEs) by severity
- b) TEAEs potentially causally related to the IMP
- c) TEAEs with an outcome of death
- d) Serious TEAEs
- e) Discontinuations due to TEAEs

### **7.6.2 Clinical Laboratory Data**

Summary statistics for changes from baseline in the central clinical laboratory measurements will be provided for the primary and secondary safety populations. Potentially clinically significant results in laboratory tests identified using prospectively defined criteria, including criteria for liver enzyme elevations, will also be summarized for the primary and secondary safety populations. In addition, by-subject listings will be provided for data of local laboratory tests.

In addition, laboratory measurements that signal the potential for Hy's Law will be reported. An incidence table and a listing will be provided for subjects who meet one or

combinations of following criteria, without initial findings of cholestasis (ALP activity  $> 2 \times \text{ULN}$ ):

- ALT or AST  $\geq 3 \times \text{ULN}$
- Bilirubin  $\geq 2 \times \text{ULN}$

### **7.6.3 Physical Examination and Vital Signs Data**

By-subject listings will be provided for physical examinations. Summary statistics for changes from baseline in vital signs and potentially clinically significant results in vital signs will be summarized for the primary safety population as well as the secondary safety population.

## **8 Management of Investigational Medicinal Product**

### **8.1 Packaging and Labeling**

All IMP will be provided to the investigator(s) by the sponsor or designated agent as tablets of 15 or 30 mg tolvaptan (OPC-41061) or matching placebo. Each bottle used in the dosing period will be labeled to clearly disclose the subject identification number (ID), compound ID, trial number, sponsor's name and address, instructions for use, route of administration, appropriate precautionary statements, and other information required by local regulatory authorities. Any region-specific requirements will appear in the official language of the country in which the investigational product is to be used.

One or more bottles of the designated IMP will be dispensed at the beginning of the placebo run-in period, the tolvaptan run in period, and monthly during the double-blind, randomized treatment period.

For the tolvaptan titration period, subjects will receive 2 cartons at the first visit; one with a yellow label (Kit A) and one with a blue label (Kit B). Subjects will be instructed to start with Kit A and told how many tablets to take per day. Kit A can accommodate the following doses for titration:

- 30/15 – 2 tablets upon waking and 1 tablet approximately 8 to 9 hours later
- 45/15 – 3 tablets upon waking and 1 tablet approximately 8 to 9 hours later

Once the subject is ready to titrate to the 60/30 dose, the site will instruct the subject to start taking IMP from Kit B. Kit B can accommodate the following doses for titration:

- 60/30 – 2 tablets upon waking and 1 tablet approximately 8 to 9 hours later

- 90/30 – 3 tablets upon waking and 1 tablet approximately 8 to 9 hours later

If the subject cannot tolerate the doses in Kit B, he/she will be instructed to return to Kit A for dosing.

## **8.2 Storage**

All IMPs will be stored in a securely locked cabinet or enclosure. Access will be limited to investigators and their designees. Neither investigators nor any designees may provide IMP to any subject not participating in this protocol.

The IMP should be stored according to the conditions specified in the IMP 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 IMP (including investigational, active control, or placebo) received, dispensed, administered, and returned.

## **8.4 Returns and Destruction**

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

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

# **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.

Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents 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;
- The date of the visit and the corresponding Visit or Day in the trial schedule;
- General subject status remarks, including any *significant* medical findings. The severity, frequency, duration, action taken, and outcome of any AEs and the investigator's assessment of relationship to IMP 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 each clinician (or designee) who made an entry in the progress notes.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above. Any changes to information in the trial progress notes and other source documents will be initialled and dated on the day the change is made by a site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data (so as not to obliterate the original 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 entered by investigative site personnel directly onto eCRFs in the sponsor's electronic data capture system. Changes to the data will be captured by an automatic audit trail.

## **9.3 File Management at the Trial Site**

The investigator will ensure that the trial site file is maintained in accordance with Section 8 of the ICH GCP Guideline and as required by applicable local regulations. The investigator/institution will 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 3 periods:

- A period of at least 2 years following the date on which approval to market the drug is obtained (or if IMP development is discontinued, the date regulatory authorities were notified of discontinuation); OR
- A period of at least 3 years after the sponsor notifies the investigator that the final report has been filed with regulatory authorities.
- Longer, region-specific storage requirements, if applicable.

The investigator must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) provision of an opportunity for sponsor to collect such records. The investigator will be responsible to maintain 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, due to relocation or 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 follow this trial carefully in a detailed and orderly manner in accordance with established research principles, the ICH GCP Guideline, and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the trial), the sponsor's monitors will visit the site during the trial, as well as communicate frequently via telephone and written communications.

### **10.2 Auditing**

The sponsor's Quality Management Unit (or representative) may conduct trial site audits. Audits will include but are not limited to drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. The investigator agrees to participate with audits.

Regulatory authorities may inspect the investigator site during or after the trial. The investigator will cooperate with such inspections and will contact the sponsor immediately if such an inspection occurs.

## **11 Ethics and Responsibility**

This trial must be conducted in compliance with the protocol, the ICH GCP Guideline, and applicable local laws and regulatory requirements. Each trial site will seek approval by an IRB or IEC according to regional requirements. The IRB/IEC will evaluate the ethical, scientific and medical appropriateness of the trial. Further, in preparing and handling eCRFs, 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.

Financial aspects, subject insurance and the publication policy for the trial will be documented in the agreement between the sponsor and the investigator.

## **12 Confidentiality**

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior written permission. Subject confidentiality requirements of the region(s) where the trial is conducted will be met. However, authorized regulatory officials and sponsor personnel (or their representatives) will be allowed full access to inspect and copy the records. All IMPs, 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 eCRFs. 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 the sponsor's prior written consent 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 will be written by the sponsor. Each amendment will be submitted to the IRB/IEC. Except for "administrative" or "non-substantial" amendments, investigators will wait for IRB/IEC approval of the amended protocol before implementing the change(s). Administrative amendments are defined as having no effect on the safety of subjects, conduct or management of the trial, trial design, or the quality or safety of IMP(s) used in the trial. A protocol change

intended to eliminate an apparent immediate hazard to subjects should be implemented immediately, followed by IRB/IEC notification within 5 working days. The sponsor will submit protocol amendments to the applicable regulatory agencies.

When the IRB/IEC, investigators, and/or the sponsor conclude that the protocol amendment 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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- <sup>2</sup> U S Renal Data System, USRDS 2012 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2012
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## Appendix 1

### Names of Sponsor Personnel

Report Immediately Reportable Events (serious adverse events, potential Hy's Law cases, pregnancies and adverse events requiring discontinuation of trial drug) to:

Quintiles  
Clinical Safety and Pharmacovigilance  
5927 South Miami Blvd  
Morrisville, NC 27560, USA  
Phone: +1-866-599-1341  
Fax: +1-866-599-1342

**For Medical Emergencies** (use only if sponsor personnel listed above are unavailable):

+1 301-990-0030

#### Global Project Leaders

Global Clinical Director/ Medical Director (Program Lead)	Frank Czerwic, MD, PhD Sr. Director, Global Clinical Development Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Blvd. Rockville, MD 20850, USA Phone: +1 240-683-3523; Fax +1 301-721-7523
Global Clinical Director/ Medical Director (Project Lead)	Olga Sergeyeva, MD, MPH Assoc. Director, Global Clinical Development Otsuka Pharmaceutical Development & Commercialization, Inc. 506 Carnegie Center Drive Suite 200 Princeton, NJ 08540, USA Phone: +1 609-249-6643; Fax +1-609-249-0643

#### Global Clinical Management

Global Clinical Management

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## Appendix 2                  Institutions Concerned With the Trial

<b>Lead Principal (Communicating) Investigator/Steering Committee Chair</b>	Vicente E. Torres, M.D., Ph.D. Chair, Division of Nephrology, Mayo Clinic 200 First St. S.W. Rochester, MN 55905, USA Phone: +1-501-266-7093
<b>Independent Data Monitoring Committee Chair</b>	Sidney Goldstein, M.D. Henry Ford Hospital 2799 West Grand Blvd Detroit, MI 48202, USA Phone: +1-313-303-5728
<b>Hepatic Adjudication Committee Chair</b>	Paul Watkins, MD Hamner-UNC Institute for Drug Safety Sciences Six Davis Drive PO Box 12137 Research Triangle Park, NC 27709, USA Phone: +1-919-226-3140 Fax: +1-919-226-3150
<b>Global Medical Monitoring</b>	Quintiles 5927 South Miami Blvd Morrisville, NC 27560, USA Phone: +1-214-505-6781 Mobile: +1-214-505-6781 Fax: +1-919-800-0095
<b>Study Management</b>	Quintiles 5927 South Miami Blvd Morrisville, NC 27560, USA Office: +1-262-361-4319 Mobile: +1-262-269-0199 Fax: +1-484-765-1823
<b>Safety Reporting</b>	Quintiles 5927 South Miami Blvd Morrisville, NC 27560, USA Phone: +1-866-599-1341 Fax: +1-866-599-1342
<b>Investigational Materials</b>	Almac 25 Fretz Rd Souderton, PA 18964, USA Phone: +1-215-660-8500
<b>Budget and Contract Negotiation</b>	INC Research, LLC 3201 Beechleaf Ct., #600 Raleigh, NC 27604, USA Phone: +1-919-876-9300
<b>Investigator Payments</b>	CFS Clinical 1000 Madison Ave, 1st Floor Audubon, PA 19403, USA Phone: +1-610-994-2754 Fax: +1-610-650-1895
<b>Electronic Data Capture</b>	MediData Solutions 79 Fifth Avenue, 8th Floor New York, NY 10003, USA Phone: +1-212-918-1800 Fax: +1-212-918-1818

<b>IRT Systems</b>	Almac Clinical Technologies 25 Fretz Road Souderton, PA 18964, USA US Tel: +1-877-738-8831 RoW Tel: +44 (0) 28 3835 2121
<b>Home Nursing Services</b>	Symphony Clinical Research <sup>SM</sup> 700 Deerpath Drive Vernon Hills, IL 60061, USA Phone: +1-847-215-0437 Fax: +1-847-215-0427
<b>Patient Recruitment and Retention</b>	Matthews Media Group (MMG) 700 King Farm Blvd, 5th Floor Rockville, MD 20850, USA Phone: +1-301-984-7191 Fax: +1-301-921-4405
<b>Traveling Coordinator Assistant</b>	Princeton Medical 349 Route 206 South Hillsborough, NJ 08844, USA Phone: +1-908-240-6884 Fax: +1-716-809-3642
<b>Central Laboratory Services</b>	Covance Central Laboratory Services 8211 SciCor Dr. Indianapolis, IN 46214, USA Phone: +1-317-273-7852 Toll-free: +1-800-462-8885 ext 7852 Fax: +1-317-616-2354
<b>PK/PD Analysis</b>	ICON 8282 Halsey Rd. Whitesboro, NY 13492, USA Phone: +1-315-768-2500
<b>DNA Sample Storage</b>	Gentris Corporation 133 Southcenter Court, Suite 400 Morrisville, NC 27560, USA Phone: +1-919-465-0100

## **Appendix 3            Handling and Shipment of Bioanalytical Samples**

### Handling of Specimens

All tubes must be labeled using the central laboratory's bar code labels provided with the sample collection kits. The central laboratory's requisition form must be completely filled out in regards to the all sample information. In addition, the subject ID number and date of collection must be hand-written on the sample tube. It is important to note the exact time of the blood collection on the eCRF.

Each specimen must be labeled using a waterproof pen. A label suitable for the storage conditions must contain the Subject ID number and date of collection, must correspond to the requisition form, and must be firmly attached. The requisition form must contain the name, address, and telephone number of the contact person from the trial site.

### Plasma PK Sample Collection

Collect blood samples to analyze tolvaptan and metabolite(s) concentrations using 4-mL draw collection tubes containing sodium heparin. After obtaining the blood sample, mix collection tube thoroughly by slowly inverting the collection tube 8-10 times. Place the collection tube in an ice/water bath. Within 45 minutes of collection, process collection tubes in a refrigerated centrifuge set at approximately 1300 g for 15 minutes at approximately 5°C. The separated plasma from the blood collection tube should then be divided equally between the 2 bar-code labeled polypropylene tubes. Within 90 minutes of collection, store both plasma aliquot samples at -70°C, except for brief periods on dry ice for shipment. If a -70°C freezer is unavailable, then the samples can be stored on dry ice for up to 1 week until a shipment to the central laboratory can be arranged.

### Plasma Biomarker Sample Collection

Collect blood samples for biomarker analysis using 10-mL draw collection tubes containing sodium heparin. After obtaining the blood sample, mix collection tube thoroughly by slowly inverting the collection tube 8-10 times. Place the collection tube in an ice/water bath. Within 45 minutes of collection, process collection tubes in a refrigerated centrifuge set at approximately 1300 g for 15 minutes at approximately 5°C. The separated plasma should then be divided between the bar-code labeled polypropylene tubes (number of aliquots will be defined in the operations manual). Within 90 minutes of collection, store plasma aliquot samples at -70°C, except for brief periods on dry ice for shipment. If a -70°C freezer is unavailable, then the samples can be stored on dry ice for up to one week until a shipment to the central laboratory can be arranged.

### Urine Biomarker Sample Collection

The 20 mL biomarker sample will be collected by the subject at home and transported to the site at room temperature. At the site, the sample should be immediately equally divided into the bar-code labeled polypropylene tubes (number of aliquots will be defined in the operations manual) and frozen. The samples must be stored -70°C, except for brief periods on dry ice for shipment. If a -70°C freezer is unavailable, then the samples can be stored on dry ice for up to 1 week until a shipment to the central laboratory can be arranged.

### Pharmacogenomic Sample Collection

Blood collection kits will be provided. These will include evacuator collection tubes, processing and storage instructions, and shipping supplies for each subject.

Approximately 8-10 mL of blood will be collected using the supplied evacuator tubes. The site will follow the instructions for collection, processing, storage, and shipment of blood samples as specified in the sample kits. All collection tubes must be labeled using the labels provided with the sample collection kits. The sample submission or lab requisition forms must be completely filled out. In addition, the subject number and date of collection must be hand-written on the sample tube using a waterproof marker.

### Sample Shipment

Plasma and urine samples must be neatly packed in the kits provided by the central lab and restrained in a Styrofoam container that is 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 or the central lab. Shipments from clinical sites will be via an overnight carrier to the central laboratory.

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, [insert compound number], 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 [insert compound number] 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 sub-investigators 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 trial in a cooperative publication prior to publication of efficacy and safety results on an individual basis.

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Principal or Coordinating Investigator Signature and Date

**Otsuka Pharmaceutical Development & Commercialization, Inc.**

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OPC-41061

**SIGNATURE PAGE**

**Document Name:** 156-13-210 Protocol

**Document Number:** 0001063982

**Document Version:** 2.0

<b>Signed by</b>	<b>Meaning of Signature</b>	<b>Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)</b>
Czerwiec_Frank	Clinical Approval	12-Feb-2014 14:06 GMT+00
Ouyang_John	Biostatistics Approval	12-Feb-2014 14:25 GMT+00
Shoaf_Susan	Clinical Pharmacology	12-Feb-2014 16:40 GMT+00

Otsuka Pharmaceutical  
Development & Commercialization, Inc.

Investigational Medicinal Product  
Tolvaptan (OPC-41061)

**REVISED CLINICAL PROTOCOL**

A Phase 3b, Multi-center, Randomized-withdrawal, Placebo-controlled, Double-blind, Parallel-group Trial to Compare the Efficacy and Safety of Tolvaptan (45 to 120 mg/day, Split-dose) in Subjects with Chronic Kidney Disease Between Late Stage 2 to Early Stage 4 Due to Autosomal Dominant Polycystic Kidney Disease

Protocol No. 156-13-210  
IND No. 72,975 EudraCT No. 2014-000226-38

**CONFIDENTIAL – PROPRIETARY INFORMATION**

Clinical Development Phase:	3b
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Boulevard Rockville, Maryland 20850, USA
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Sr. Manager, Clinical Development	Laurie Debuque Sr. Manager, Global Clinical Development Phone: +1-609-524-6894; Fax: +1-240-514-3994 E-mail: laurie.debuque@otsuka-us.com
Immediately Reportable Event	Clinical Safety and Pharmacovigilance Phone: +1-866-599-1341; Fax: +1-866-599-1342
Issue Date:	12 February 2014
Date of Administrative Change 1:	21 February 2014
Date of Amendment 1:	31 March 2014
Date of Administrative Change 2:	25 June 2014

Protocol 156-13-210

Date of Amendment 2: 26 November 2014

Date of Amendment 3: 26 March 2015

## Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc.	Protocol # 156-13-210 IND# 72,975
Name of Investigational Medicinal Product: Tolvaptan (OPC-41061)	EudraCT# 2014-000226-38
Protocol Title:	A Phase 3b, Multi-center, Randomized-withdrawal, Placebo-controlled, Double-blind, Parallel-group Trial to Compare the Efficacy and Safety of Tolvaptan (45 to 120 mg/day, Split-dose) in Subjects with Chronic Kidney Disease Between Late Stage 2 to Early Stage 4 Due to Autosomal Dominant Polycystic Kidney Disease
Clinical Phase/Trial Type:	Phase 3b/Therapeutic use
Treatment Indication:	Autosomal Dominant Polycystic Kidney Disease (ADPKD)
Objective(s):	<p>Primary: To compare the efficacy of tolvaptan treatment in reducing the change in estimated glomerular filtration rate (eGFR) from pre-treatment baseline to post-treatment follow-up, as compared with placebo, in subjects with late-stage chronic kidney disease (CKD) due to ADPKD who tolerate tolvaptan during an initial run-in period.</p> <p>Secondary: To compare the efficacy of tolvaptan treatment in reducing the decline of annualized eGFR slope, as compared with placebo, in subjects with late-stage CKD due to ADPKD who tolerate tolvaptan during an initial run-in period.</p> <p>To compare overall and hepatic safety of tolvaptan with placebo and to compare incidence of ADPKD complications (outcomes) during the trial.</p>

Trial Design:	<p>Multi-center, randomized-withdrawal, placebo-controlled, double-blind, parallel-group trial:</p> <p><u>Screening period (1-2 weeks):</u> Screening period may be extended up to an additional 8 weeks for subjects who require modification of medical care specifically for this trial. This may include, for example, stabilizing anti-hypertensive regimens for subjects discontinuing diuretics or “wash-out” of other investigational agents. Preliminary eligibility for the trial will be initially assessed using the subjects’ historical laboratory or imaging data. Eligibility will be confirmed by the mean of eGFR calculated from the subjects’ 2 pre-treatment, central-lab serum creatinine assessments (collected at least 24 hours apart). The final screening visit on Day -43 will not be scheduled until laboratory results from the second screening visit (V2) are received and evaluated. The eGFR values will be estimated based on the Chronic Kidney Disease-Epidemiology (CKD-EPI) formula (<math>eGFR_{CKD-EPI}</math>, hereafter referred to as eGFR). Confirmation of ADPKD diagnosis (using the modified Pei-Ravine criteria) may require confirmatory imaging.</p> <p><u>Placebo run-in period (1 week):</u> Subjects will be given placebo (as a single-blind “sham” 15/15 mg dose) in a daily split dose of a single 0 mg tablet upon awakening and another 0 mg tablet approximately 8 to 9 hours later (abbreviated 0/0 mg), in a form identical to tolvaptan tablets. Blood will be drawn once on the last day of the run-in period (Day -36) for efficacy and safety measures. Subjects unable to tolerate the placebo dose regimen will be considered “Run-in failures”, will complete an end of treatment (EoTx) visit and be followed up after 7 days by phone call to assess any ongoing adverse events (AEs).</p> <p><u>Tolvaptan titration period (2 weeks):</u> Subjects will be given a split dose of 30/15 mg tolvaptan (single-blind) with upward titration every 3 to 4 days to 45/15 mg, 60/30 mg, up to a maximum dose of 90/30 mg per day over 2 weeks. Subjects who are unable to tolerate at least 60/30 mg of daily tolvaptan will be considered “Run-in failures” and will complete an EoTx visit and be followed up after 7 days by phone call to assess any ongoing AEs. Subjects will have blood drawn on the last day of this period for efficacy and safety measures.</p>
Trial Design, cont.:	<u>Tolvaptan run-in period (3 weeks):</u> Subjects who tolerate the tolvaptan 60/30 mg or 90/30 mg daily dose regimen will enter the tolvaptan run-in period (single-blind) at the tolerated dose

for 3 additional weeks. Except for management of AEs, no dose adjustment will be permitted. Subjects unable to tolerate at least 3 weeks of daily tolvaptan treatment at 60/30 mg or higher will be considered “Run-in failures” and will complete an EoTx visit and be followed up after 7 days by phone call to assess any ongoing AEs. During the last 2 weeks of this period, blood will be drawn 2 times on separate days (at least 24 hours apart), including the last day of the run-in period, for efficacy and safety measures.

Double-blind, randomized treatment period (12 months): Only subjects who reach the end of the tolvaptan run-in period and are able to tolerate tolvaptan 60/30 mg or 90/30 mg daily “for the rest of their lives” are eligible to enter this period. Randomization will be 1:1, tolvaptan to placebo. Subjects will be stratified by their baseline eGFR, at a threshold of  $\leq 45$  or  $> 45$  mL/min/1.73m<sup>2</sup>, and by age ( $\leq 55$  or  $> 55$  years old). Subjects will also be stratified by three total kidney volume (TKV) criteria ( $\leq 2000$  mL,  $> 2000$  mL, or unknown). Post-randomization, the maximally-tolerated dose of tolvaptan established during the run-in period, or the equivalent as matching placebo tablets, will be dispensed according to the subject’s randomization outcome. If continued tolerability becomes an issue, subjects may titrate downward to 45/15 mg (or 30/15 mg, with medical monitor approval) or temporarily interrupt treatment as needed. Return to higher doses is also allowed. Subjects who discontinue IMP before the Month 12 visit will complete an EoTx visit, which should be scheduled as soon as possible after the subject’s last dose of investigational medicinal product (IMP) and complete the follow-up period.

Follow-up period (3 weeks): For all randomized subjects the follow-up period starts immediately after the last dose of IMP. No follow-up assessments will be taken during the first week of this period. During the last 2 weeks, Days 8 through 21, inclusive, 3 follow-up visits will be scheduled. The last follow-up visit will include measurements of efficacy and safety. Subjects will have blood drawn at each visit.

Subject Population:	<p>This trial will randomize approximately 1300 tolvaptan naïve subjects with ADPKD. Male and female adults will be enrolled, from 18-55 years of age with eGFR between 25 and 65 mL/min/1.73m<sup>2</sup> <b>or</b> 56 to &lt; 66 years of age with eGFR between 25 and 44 mL/min/1.73m<sup>2</sup> (with evidence of ADPKD progression and medical monitor approval). Only subjects tolerating a single-blind run-in period of tolvaptan (60/30 mg per day or 90/30 mg per day) will be randomized, to limit subsequent withdrawal due to lack of tolerability.</p>
Inclusion/Exclusion Criteria:	<p>Main inclusion criteria:</p> <ul style="list-style-type: none"> <li>• eGFR between 25 and 65 mL/min/1.73m<sup>2</sup> (18 to 55 years of age) or eGFR between 25 and 44 mL/min/1.73m<sup>2</sup> (56 to &lt; 66 years of age <b>with evidence of ADPKD progression, ie, eGFR decline of &gt; 2.0 mL/min/1.73 m<sup>2</sup> per year based on historical eGFR data and medical monitor discretion.</b></li> <li>• Tolvaptan naïve.</li> <li>• Diagnosis of ADPKD by modified Pei-Ravine criteria <ul style="list-style-type: none"> <li>• With family history: several cysts per kidney (3 if by sonography, 5 if by computed tomography or magnetic resonance imaging).</li> <li>• Without family history: 10 cysts per kidney (by any radiologic method above) and exclusion of other cystic kidney diseases. 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.</li> </ul> </li> <li>• Distribution and number of cysts consistent with the observed level of renal function deficit.</li> </ul> <p>Main exclusion criteria:</p> <ul style="list-style-type: none"> <li>• Need for chronic diuretic use.</li> <li>• Hepatic impairment or liver function abnormalities other than that expected for ADPKD with typical cystic liver disease during the pre-randomization period.</li> <li>• Subjects with advanced diabetes (eg, glycosylated hemoglobin [HgbA1c] &gt; 7.5, and/or glycosuria by dipstick, significant proteinuria, retinopathy), evidence of additional significant renal disease(s) (ie, currently active glomerular nephritides), renal cancer, single kidney, or recent (within last 6 months) renal surgery, or acute kidney injury.</li> </ul>

Trial Site(s):	Approximately 220 enrolling sites including, but not limited to, the following regions: North America, South America, Eastern Europe, Western Europe, Asia, and Australia.
Investigational Medicinal Product(s), Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration:	Tolvaptan tablets (15 or 30 mg) or matching placebo will be self-administered orally as split-dose regimens, once upon awakening and another approximately 8 to 9 hours later. Doses will be expressed as early dose/late dose (eg, 60/30 mg). Placebo will be administered to all subjects during the placebo run-in period as a single-blind "sham" 15/15 mg dose. Tolvaptan regimens include 30/15, 45/15, 60/30 and 90/30 mg and will be titrated to tolerability during the tolvaptan titration period, and then continued at the maximally tolerated dose through the tolvaptan run-in period, and throughout the double-blind, randomized treatment period for those subjects randomized to receive tolvaptan (placebo subjects will receive matching placebo tablets).
Trial Assessments:	<p><u>Screening:</u> Medical history, complete physical examination, urine pregnancy test (women of child-bearing potential only), and laboratory tests to determine initial eligibility.</p> <p><u>Efficacy:</u> Serum creatinine for determination of eGFR, polycystic kidney disease (PKD) outcomes survey.</p> <p><u>Safety:</u> Vital signs, directed physical examination, self-assessed tolerability, AEs, hematology, urinalysis, and serum chemistry tests (including serum transaminases, alkaline phosphatase, bilirubin, serum sodium), biomarker plasma and urine samples, and DNA blood samples (for consenting subjects).</p> <p><u>Pharmacokinetic (PK):</u> Sparse blood samples for a possible population PK analysis, which would be reported separately, and confirmation of compliance.</p> <p><u>Pharmacodynamic (PD):</u> Urine osmolality (Uosm), urine specific gravity.</p>

Criteria for Evaluation:	<p><b>Primary Efficacy Endpoint:</b> Treatment difference in the change of eGFR from pre-treatment baseline to post-treatment follow-up, annualized (divided) by each subject's IMP treatment duration.</p> <p><b>Secondary Endpoints:</b></p> <p><b>Key Secondary Efficacy Endpoint:</b> Treatment difference in annualized slope of eGFR calculated for individual subjects using an appropriate baseline and available post-randomization, on-treatment assessments.</p> <p><b>Safety Endpoints:</b></p> <ol style="list-style-type: none"><li>1) AEs</li><li>2) Vital signs</li><li>3) Clinical laboratory tests, including serum transaminases, total bilirubin (BT), alkaline phosphatase (ALP), and serum sodium.</li></ol> <p><b>PK Endpoints:</b> Plasma tolvaptan and metabolite(s), including DM-4103 plasma concentrations.</p> <p><b>PD Endpoints:</b> Uosm and urine specific gravity.</p> <p><b>Exploratory Endpoints:</b></p> <p><b>Safety (may be undertaken and reported separately from the clinical study report):</b></p> <ul style="list-style-type: none"><li>• Urine and plasma biomarker concentrations for potential evaluation of metabolic or immunologic traits related to drug-induced liver injury (DILI) and/or etiology of, susceptibility to, activity of, or progress of ADPKD, as well as the potential development of tools for diagnosis, prognosis and response to treatment.</li><li>• DNA samples for genetic evaluation of DILI and/or etiology of, susceptibility to, activity of, or progress of ADPKD, as well as the potential development of tools for diagnosis, prognosis and response to treatment.</li></ul> <p><b>Efficacy:</b> Assessment of ADPKD outcomes and analysis of efficacy based on modal doses.</p>
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Statistical Methods:	<p><u>Sample size:</u> Based on a Mixed Model Repeated Measurements analysis of the non-Japanese CKD-3 subjects from trial 156-04-251, the treatment difference in renal function at Month 12 is 1.07 in our sample size calculation. It is expected that the intra-subject variance is 14.2 and inter-subject variance is 28.05 at Month 12. With 3 repeated measures at pre-treatment baseline and post-treatment follow-up, respectively, the power calculation estimates that, for a 2-sided alpha set at 0.05 for a power of 90%, and with an assumption of 10% dropout rate in the trial, a total sample size of approximately 1300 subjects is needed.</p> <p><u>Key Datasets for analysis:</u> The following datasets are defined for this trial:</p> <ul style="list-style-type: none"><li>• Randomized Population: All subjects who are randomized in this trial.</li><li>• Randomized Safety Population: All subjects who are randomized in this trial and take at least 1 dose of IMP after randomization. This is the primary safety population.</li><li>• Primary Endpoint Efficacy Population: All subjects who are in the Randomized Population, take at least 1 dose of IMP after randomization, and have a primary endpoint baseline and at least 1 valid post-treatment evaluation in eGFR (ie, after at least 1 week off treatment).</li><li>• Key Secondary Endpoint Efficacy Population: All subjects who are in the Randomized Population, take at least 1 dose of IMP after randomization, and have a baseline and at least 1 post-randomization evaluation in eGFR.</li></ul> <p><u>Primary efficacy analysis:</u> The change in eGFR from pre-treatment baseline to post-treatment follow-up, annualized (divided) by each subject's IMP treatment duration, will be calculated. The annualized change in eGFR will be analyzed by a weighted analysis of covariance (ANCOVA) with treatment and randomization stratification factors as factor and covariate baselines. This weighted analysis is based on the reciprocal of the estimated variance of the "estimated slopes."</p>
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Statistical Methods, cont.:	<p><u>Key secondary efficacy analysis:</u> The key secondary endpoint of the trial is the annualized rate (slope) of eGFR change. The linear mixed effect model with effects of time, treatment, time treatment interaction, acute hemodynamic effect, baseline and randomization stratification factors will be used for analysis of the key secondary endpoint, in which the intercept and time are both fixed effect and random effect. An un-structured variance covariance matrix is assumed for the random intercept and time.</p> <p><u>Safety analyses:</u> Safety analysis will be conducted based on standard safety variables, including AEs, clinical laboratory data, physical examinations and vital signs. Potentially clinically significant results in laboratory tests identified using prospectively defined criteria, including criteria on liver enzyme elevations, will also be summarized for the primary and secondary safety populations.</p>
Trial Duration:	The duration of the double-blind, randomized treatment period will be 12 months. The total duration for each subject entered into the trial is approximately 15-17 months (including the pre-randomization and follow-up periods, and an additional 8 weeks for extension of the screening period in subjects for whom this is necessary).

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## List of Abbreviations and Definitions of Terms

<b>Abbreviation</b>	<b>Definition</b>
ADPKD	Autosomal dominant polycystic kidney disease
ADR	Adverse drug reactions
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC <sub>0-24</sub>	area under the concentration-time curve from time zero to 24 hours
AUC <sub>τ</sub>	Area under the concentration-time curve calculated to the last observable concentration
AVP	Arginine vasopressin
BT	Bilirubin, total
BUN	Blood urea nitrogen
cAMP	Cyclic adenosine monophosphate
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease-Epidemiology
CL/F	Apparent clearance of drug from plasma after extravascular administration
C <sub>max</sub>	Maximum (peak) plasma concentration
CrCL	Creatinine clearance
CRO	Clinical Research Organization
CSR	Clinical study report
CT	Computed tomography
CYP	Cytochrome P450
DILI	Drug-induced liver injury
DILIN	Drug-Induced Liver Injury Network
DNA	Deoxyribonucleic acid
DSMC	Data Safety and Monitoring Committee
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
eGFR <sub>CKD-EPI</sub>	Estimated glomerular filtration rate calculated using the Chronic Kidney Disease-Epidemiology formula
EMA	European Medicines Agency
EoTx	End of treatment
ESRD	End-stage renal disease
EU	European Union
FDA	(United States) Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
HAC	Hepatic adjudication committee
HgbA1c	Glycosylated hemoglobin
IA	Interim analysis

<b><u>Abbreviation</u></b>	<b><u>Definition</u></b>
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
ID	Identification number
IDMC	Independent Data Monitoring Committee
IDMS	Isotope dilution mass spectrometry
IEC	Independent ethics committee
IMP	Investigational medicinal product
IND	Investigative new drug
INR	International normalized ratio
IRB	Institutional review board
IRE	Immediately reportable event
ITT	Intent-to-treat
IVRS	Interactive voice response system
LDH	Lactate dehydrogenase
MAR	Missing at random
MCHC	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measurements
MNAR	Missing not at random
MRI	Magnetic resonance imaging
NRC	National Research Council
NSAID	Non-steroidal anti-inflammatory drugs
OC	Observed cases
OPDC	Otsuka Pharmaceutical Development & Commercialization, Inc.
PD	Pharmacodynamic
PK	Pharmacokinetic
PKD	Polycystic kidney disease
PT	Prothrombin time
QD	Once daily
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
$t_{1/2,z}$	Elimination half-life
TKV	Total kidney volume
$t_{max}$	Time to maximum (peak) plasma concentration
Uosm	Urine osmolality
ULN	Upper limit of normal
US or USA	United States or United States of America
V <sub>2</sub>	Vasopressin type 2 (receptor)

<b><u>Abbreviation</u></b>	<b><u>Definition</u></b>
WBC	White blood cell
WOCBP	Women of childbearing potential

## 1 Introduction

Tolvaptan (OPC-41061) is a selective arginine vasopressin (AVP) type 2 ( $V_2$ ) receptor antagonist that is currently approved in the United States (US), Europe, Australia, Canada, China, Hong Kong, Indonesia, Japan, Philippines, Republic of Korea, Taiwan, Thailand, and Turkey, for various forms of hyponatremia, and in Japan also for volume overload in heart failure or liver cirrhosis.

Tolvaptan is also being investigated for the use in adults to treat autosomal dominant polycystic kidney disease (ADPKD), an inherited condition which leads to progressive destruction of normal kidney structure leading to end-stage renal disease (ESRD). The disease affects the structure of the kidneys through proliferation and growth of numerous fluid-filled cysts. The expanding cysts compress normal tissue and blood vessels resulting in ischemia, inflammation and fibrosis leading to progressive nephron loss. The remaining nephrons are initially able to compensate through glomerular hyperfiltration up to a point when nephron loss is so great that compensation is no longer adequate and renal function begins to decline. Clinical manifestations of kidney disease may be sporadic (hematuria, infections, pain) or chronic (hypertension, albuminuria, renal insufficiency) and indicate ongoing and cumulative damage to the kidney.

The number of diagnosed ADPKD cases was estimated at 116,228 in the US in 2009. The estimated prevalence of diagnosed ADPKD is similar in Europe and estimated to be < 5 per 10,000.<sup>1</sup> Though a rare genetic disease, it ranks as the 6<sup>th</sup> leading cause of ESRD in the US (2.3% of the new ESRD cases).<sup>2</sup> An estimated 45% to 70% of patients with ADPKD progress to ESRD by age 65.<sup>3</sup> Over the past 30 years, the age of onset for ESRD among ADPKD patients has remained the same (median age of 54). In contrast, effective therapy has delayed the onset of ESRD in patients with nephropathy due to hypertension, diabetes, and glomerulonephritis.

There are currently no therapies which can slow cyst growth or the deterioration of kidney function in ADPKD. Current management focuses on ameliorating symptoms of pain, control of blood pressure, and treatment of infections with antibiotics. None of these treatments target the underlying cause of the disease. Often, the only definitive intervention for renal complications in ADPKD is kidney transplantation, which typically occurs after years of hemodialysis.

In the US, the development program for tolvaptan for ADPKD was granted Fast-track designation on 20 Jan 2006 and orphan drug designation on 06 Apr 2012. Tolvaptan was designated as an orphan drug for prevention of the progression of ADPKD in Japan on

11 Aug 2006. The European Medicines Agency (EMA) granted orphan designation for the use of tolvaptan for the treatment of ADPKD on 5 Aug 2013.

If approved, tolvaptan would be the first available therapy to slow kidney disease progression in adults with ADPKD.<sup>4,5</sup> Refer to the Tolvaptan Investigator's Brochure (IB) for more information.<sup>4</sup>

## **1.1 Nonclinical Data**

Rodent models of ADPKD and ex-vivo human ADPKD cell and tissue cultures have implicated AVP as a promoter of kidney cyst growth.<sup>6,7</sup> AVP-induced cyclic adenosine monophosphate (cAMP) increases proliferation of ADPKD renal tubular epithelium and chloride-mediated, intra-cystic, fluid secretion. This leads to cyst expansion which disrupts renal architecture leading to ischemia, kidney fibrosis, and irreversible damage to the kidney, ultimately impairing its function. Tolvaptan inhibits cAMP production by blocking AVP binding to the renal AVP-V<sub>2</sub> receptor. For information on nonclinical toxicology and absorption, distribution and metabolism data on tolvaptan please refer to the most current version of the Investigator's Brochure.<sup>4</sup>

## **1.2 Clinical Data**

Tolvaptan was clinically effective in delaying decline of renal function, as determined by changes in serum creatinine concentrations over 3 years, in an international, multicenter, clinical trial in subjects with chronic kidney disease (CKD) stage 1 to 3 due to ADPKD.<sup>8</sup> These effects were consistent across each of these CKD stages, supporting tolvaptan's potential utility in early to mid-stage disease (Table 1.2-1), and creating a compelling argument for long-term effectiveness in those initiating therapy at an early stage and adhering to therapy as the disease progresses. This trial also demonstrated an acute and persistent reduction on rate of kidney cystic growth. The reductions in rate of kidney growth correlated with reductions in kidney pain and with preservation of renal function. Similar correlations were observed in a smaller, matched-control study (Study 156-09-283).<sup>9</sup> Thus, the clinical data have confirmed the non-clinical effects seen in animals (see Section 1.1) and support approval of tolvaptan as the first agent to slow the progression of ADPKD.<sup>9</sup> This trial will serve to confirm prior results and extend our understanding of the safety and efficacy of tolvaptan into later stages of disease, specifically CKD stages 3b and 4.

<b>Table 1.2-1 Vasopressin Blockade Across Differing Severities of ADPKD: Effect on Rate of Estimated Glomerular Filtration Decline in Chronic Kidney Disease Stages 1-3</b>						
<b>CKD Stage by eGFR<sub>CKD-EPI</sub> (mL/min/1.73m<sup>2</sup>)</b>	<b>N (Tolvaptan/Placebo)</b>	<b>eGFR Slope Tolvaptan</b>	<b>eGFR Slope Placebo</b>	<b>Effect Size</b>	<b>Relative Effect Size</b>	
Stage 1 ( $\geq 90$ )	330/173	-1.93	-2.86	0.94 <sup>a</sup>	33%	
Stage 2 (60-90)	465/224	-2.64	-3.85	1.21 <sup>a</sup>	31%	
Stage 3 <sup>b</sup> (30-60)	3a (45-60) 3b (30-45)	135/70 28/14	-3.51 -3.92	-5.23 -5.99	1.72 2.07	33% 35%

eGFR<sub>CKD-EPI</sub> = estimated glomerular filtration rate calculated by the Chronic Kidney Disease-Epidemiology (CKD-EPI) formula

<sup>a</sup>All p < 0.005

<sup>b</sup>CKD Stage 3: relative effect size (33%); N (tolvaptan/placebo; 163/84)

Source: Trial 156-04-251 clinical study report (CSR); Data on file

### 1.3 Pharmacokinetics/Pharmacodynamics

Following single oral doses to healthy subjects, tolvaptan maximum (peak) plasma concentration ( $C_{max}$ ) values show less than dose-proportional increases from 30 to 240 mg with mean values increasing from about 235 to 1000 ng/mL; values plateau at doses ranging from 240 to 480 mg. Following multiple once-daily (QD) dosing, tolvaptan pharmacokinetic (PK) values were also nonlinear. Mean  $C_{max}$  and area under the concentration-time curve calculated to the last observable concentration ( $AUC_{\tau}$ ) values were 4.2- and 6.4-fold higher for the 300 mg dose compared with the 30 mg dose. Across all doses, the median time to median (peak) plasma concentration ( $t_{max}$ ) value was 2 hours (range 1 to 12 hours). For 60- and 90-mg tablets, dosing with a high-fat meal increases tolvaptan  $C_{max}$  but has no effect on tolvaptan area under the concentration-time curve ( $AUC$ ).

Tolvaptan concentrations do not significantly accumulate following QD dosing, indicating that tolvaptan has a short elimination half-life ( $t_{1/2,z}$ ). Following single oral doses, the  $t_{1/2,z}$  of tolvaptan increases with increasing dose, with mean values around 3 hours for a 15 mg dose and 12 hours for 120 to 480 mg doses.

Tolvaptan excretion in urine is < 1% of the dose and in feces about 19% of the dose. Tolvaptan is eliminated primarily by cytochrome P450 (CYP)3A-mediated metabolism and is considered to be a weak substrate as the tolvaptan AUC was increased about 3.5-fold and the apparent clearance of drug from plasma after extravascular administration (CL/F) was decreased by 87% when co-administered with ketoconazole.

Mean  $C_{max}$  and AUC values in subjects with ADPKD and preserved renal function (average creatinine clearance [CrCL] > 60 mL/min) range from 15 to 60% higher when compared with healthy subject values, but rates of CL/F range from 14% slower to 27% faster, indicating that tolvaptan PK in ADPKD subjects with preserved renal function is similar to that in healthy subjects. Following multiple QD and split-dose regimens ranging from 30 to 120 mg/day, accumulation of tolvaptan concentrations is negligible. For split-dose regimens of 30, 60 and 120 mg/day, tolvaptan PK appears to be linear as mean values of AUC from time zero to 24 hours post-dose ( $AUC_{0-24h}$ ) approximately double with a doubling of daily dose.

Renal impairment reduces tolvaptan clearance and consequently plasma concentrations increase. Following a single 60 mg dose, tolvaptan AUC in subjects with CrCL < 30 mL/min was 1.9-fold higher compared to subjects with CrCL > 60 mL/min.

Tolvaptan is highly bound to plasma proteins (> 98%) and binding was unaffected by renal impairment.

Pharmacodynamic (PD) responses to tolvaptan were observed for subjects with ADPKD at CKD stages 1 to 4. At the recommended split-dose regimens of 45/15 mg to 90/30 mg daily, tolvaptan blocked AVP action at the V<sub>2</sub> receptor (ie, increased urine excretion rates and suppressed Uosm) for almost the entire 24-hour day in subjects with ADPKD (CKD Stage 1 to 2). The large increase in urine output that resulted from this inhibition was associated with the 5 most frequently reported adverse events (AEs; polyuria, pollakiuria, nocturia, thirst, and dry mouth) in clinical pharmacology or clinical efficacy trials. In 2 clinical pharmacology trials in subjects with ADPKD and estimated glomerular filtration rates (eGFR) > 60 mL/min/1.73m<sup>2</sup> administered a 90/30 mg dose regimen for at least 7 days, mean (standard deviation [SD]) 24-hour urine volumes were 7.464 (2.103) L and 6.532 (2.036) L. As renal function declined, the volume of urine produced for a given dose of tolvaptan decreased; following a 90/30 mg split-dose regimen, mean (SD) 24-hour urine volumes for subjects with ADPKD and eGFR 30 to 60 and < 30 mL/min/1.73m<sup>2</sup> were 6.233 (1.307) L and 5.024 (1.767) L, respectively. Therefore, despite an increase in tolvaptan concentration, the clinical effects of tolvaptan on the most common adverse events are diminished. Other adverse reactions, such as idiopathic liver injury, do not appear to be concentration-dependent.

Subjects with ADPKD are able to maintain a neutral fluid balance so increases in serum sodium and plasma osmolality were small, following tolvaptan treatment. Serum concentrations of creatinine, cystatin C, and uric acid were higher following tolvaptan treatment as tolvaptan reduced the eGFR approximately 6 to 8%, CrCL approximately 8 to 10%, and uric acid clearance approximately 20 to 25%; the changes appeared to

independent of baseline renal function for CKD stages 1 to 4. Urinary excretion of aquaporin 2 and cAMP were lower following tolvaptan treatment, supporting the hypothesis that tolvaptan inhibition of the V<sub>2</sub> receptor is successful in reducing cellular cAMP concentrations.

Following multiple oral doses, the tolvaptan metabolite DM-4103 accumulates, as its half-life is approximately 180 hours. This metabolite has no pharmacological activity at the concentrations expected to be achieved following the doses used in this trial 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 at about 80% of those expected to be achieved in this trial revealed no evidence of time-dependent toxicological effects.

For additional information on PK/PD responses from tolvaptan treatment, please refer to the Investigator's Brochure.<sup>4</sup>

#### **1.4 Known and Potential Risks and Benefits**

ADPKD is a devastating, progressive disease that places a tremendous burden on patients and their families. The risk a patient is willing to accept is a personal decision based on his/her individual and familial experience with the disease. Tolvaptan is potentially the first therapy that offers patients a treatment option to slow their disease progression; however, as of January 2014, it has not yet been approved for this indication. The treatment risks are well characterized, manageable, and must be weighed against the consequences of no treatment.

The most common observed risks of tolvaptan therapy include those arising from aquaresis (eg, polyuria, pollakiuria, nocturia, thirst, dry mouth), dehydration, electrolyte abnormalities, and gout. While aquaretic events did not contribute to significant patient morbidity over 3 years of study in the pivotal placebo-controlled trial (Trial 156-04-251), they do represent adverse drug reactions (ADRs) which occur early (within days to weeks) and are most likely to limit a subject's ability to continue therapy over a duration of treatment that is likely to provide benefit. Aquaretic ADRs are also likely to limit the efficacy of an unproven, yet often recommended, therapeutic strategy of increasing water ingestion.

While the proposal of increased water ingestion as a mechanism of ameliorating CKD<sup>10</sup> has not reached medical equipoise, in this trial we believe a general recommendation to do so is reasonable and would recommend ingestion of water adequate to avoid thirst. Typically, this would represent a minimum of 2 to 3 liters of water per day in subjects with relatively intact renal function, and lesser amounts in those with more impaired

function. Serum sodium should be monitored during the trial to ensure a tendency toward hyponatremia (symptomatic or asymptomatic) is not produced.

The most notable safety issue associated with chronic tolvaptan use, newly identified in Trial 156-04-251, is the potential for idiosyncratic hepatic toxicity. With a once every 4-month monitoring scheme, an imbalance in the proportion of subjects with elevated transaminases (tolvaptan > placebo) led to identification of 3 subjects (total from both Trial 156-04-251 and its open-label extension trial, 156-08-271) with laboratory and clinical evidence of potentially serious drug-induced liver injury (DILI). Based on the available data from the afore-mentioned trials, the sponsor proposes that appropriate patient monitoring and management be implemented to mitigate this potential risk in the ADPKD population. For this trial, standard liver parameters will be measured at baseline and then monthly thereafter.

Significant events related to glaucoma and skin neoplasms were also observed; however the causal relationship to tolvaptan remains uncertain. These adverse events and the above attributable adverse reactions should be considered in light of the benefits of a reduced risk of ADPKD kidney complications, including renal pain, urinary tract infection, hematuria, anemia, and nephrolithiasis.<sup>5</sup>

The treatment risks of tolvaptan are well characterized, manageable, and must be weighed against the consequences of no adequate treatment. With sufficient knowledge of the benefits and risks and risk mitigation strategies, patients and their physicians may make informed decisions about tolvaptan treatment. In the final assessment, the overall benefit-risk profile of tolvaptan for the treatment of ADPKD appears favorable, offering a real opportunity to fill a longstanding unmet medical need.

## **2 Trial Rationale and Objectives**

### **2.1 Trial Rationale**

The current trial will extend the understanding of the efficacy and safety of tolvaptan treatment in ADPKD patients with late stage 2 to early stage 4 CKD. Focusing on the eGFR calculated by the Chronic Kidney Disease-Epidemiology (CKD-EPI) formula (eGFR<sub>CKD-EPI</sub>, hereafter referred to as “eGFR”)<sup>11</sup>, this trial is expected to provide kidney function data that are complementary to the data demonstrating the benefits previously observed primarily in ADPKD subjects with earlier stages of disease.

Trial 156-04-251 utilized a post-randomization baseline to account for tolvaptan’s acute hemodynamic effect on eGFR. This hemodynamic effect has been well characterized in prior trials of up to 3-years duration. It has also been examined in subjects with kidney

function ranging from normal to severely dysfunctional due to ADPKD or other disorders.<sup>12,13</sup> The onset of hemodynamic effect is acute, it persists as long as treatment continues and is rapidly reversible upon discontinuation of treatment. A comparison of tolvaptan and placebo subjects able to complete Trial 156-04-251 indicated that the relative preservation of eGFR during treatment was sustained in the post-treatment follow-up phase and at baseline for Trial 156-08-271 (extending to at least 3 months). In an interim analysis of eGFR in the extension trial, both the prior-placebo and prior-tolvaptan groups exhibited this hemodynamic effect with open-label treatment with differences between groups being sustained for a further 2 years of treatment. (Data on file).

However, in Trial 156-04-251, an early and imbalanced withdrawal of tolvaptan subjects led to missing baseline data for ~5% of tolvaptan subjects, complicating the interpretation of these results. The current trial will utilize tolvaptan treatment titration and tolerability run-in periods to exclude, prior to randomization, those subjects who report they are unlikely to be able to tolerate tolvaptan's aquaresic effects during long-term treatment. This, and a placebo run-in period, will be used to establish a pre-randomization baseline eGFR for each potential treatment assignment, thereby facilitating a straightforward calculation of the key secondary endpoint of eGFR slope for all subjects.

The trial's primary endpoint is defined as the absolute change in eGFR from pre-treatment to post-treatment, normalized by the subject's duration of treatment. To decrease variability, multiple serum creatinine measurements (isotope dilution mass spectrometry [IDMS]-traceable) will be taken both pre- and post-treatment for each subject, and the eGFR values will then be averaged. Additionally, standardization of diet, exercise, and timing of serum collection and analysis of samples for serum creatinine are expected to reduce intra-subject variability.

In this trial, every effort will be made to avoid missing data by encouraging compliance and continuation of IMP. Furthermore, all subjects who do not specifically withdraw their consent will be followed as completely as possible for laboratory, health and vital status. This effort will begin during the informed consent process. Investigators, site personnel, and subjects will be provided with informational tools and educated regarding the importance of participation in clinical trials and adherence to all protocol specified visits and assessments. This will include training on relevant concepts from the National Academy of Sciences National Research Council (NRC) guideline on prevention and handling of missing data.<sup>14</sup> The informed consent form (ICF) will include a section codifying this understanding between the principal investigator and the prospective subject and can be withdrawn in stages accommodating each subject's willingness to

provide follow-up of their medical information. Home nursing visits or local laboratory visits will also be available at most sites for collection of follow-up blood samples and to continue health-status follow-up even if IMP is permanently discontinued.

Through more frequent (eg, monthly) monitoring of liver transaminases (aspartate aminotransferase [AST], alanine aminotransferase [ALT]), alkaline phosphatase (ALP), and bilirubin (total; BT), the current trial will more precisely define the potential for DILI previously observed in Trial 156-04-251. Frequent monitoring will also detect smaller elevations earlier permitting closer and more thorough evaluation and intervention (including drug interruption or discontinuation). This is expected to mitigate the risk of serious or irreversible injury.

Urine and plasma samples for potential biomarker testing and an optional blood sample for genetic deoxyribonucleic acid (DNA) testing will be collected and stored for a maximum of 15 years after the trial has ended. Potential analysis may include disease-related genes and genes involved in how tolvaptan is processed within the body. Therefore, the information gathered through genetic/biomarker analysis should improve the sponsor's understanding of the disease, its diagnosis, prognosis, and possibly treatment outcome. This can be accomplished by identifying which subjects are more likely to respond to tolvaptan, and/or predicting which subjects are likely to progress to more severe disease states, and/or predicting which subjects may have an adverse event such as DILI, and/or lead to new opportunities for therapies. The aim of the genetic/biomarker testing is to further understand the causes and processes of ADPKD and the impact treatment with tolvaptan has on the progression of the disease and safety of the subject and future generations of patients.

## **2.2 Dosing Rationale**

Successful treatment of ADPKD appears to require early, constant inhibition of the vasopressin V<sub>2</sub> receptor. This treatment paradigm produced decreased rates of growth in kidney size in animal models. The clinical formulation of tolvaptan was optimized to increase bioavailability which necessitates split dosing to maintain suppression of AVP action across 24 hours. A higher dose is used early in the day, with a lower dose approximately 8 to 9 hours later in order to produce a maximal inhibition on waking with a gradual fall-off of effect during the night when frequent urination could lead to interruption of sleep.

Urine osmolality (Uosm) has been used as a surrogate of vasopressin V<sub>2</sub> receptor inhibition in Trials 156-03-248 and 156-03-249 to refine these doses. Normally, Uosm only increases above plasma osmolality (approximately 290 mOsm/L) when vasopressin

is acting at the kidney's distal collecting ducts. When trough spot Uosm remains below 300 mOsm, effective V<sub>2</sub> receptor inhibition can be assumed. These trials also confirmed a phenomenon where the first day's therapy produces the most robust aquaresis, which then decreases approximately 20% by the 5<sup>th</sup> day of repeated dosing.<sup>15</sup>

Split dose regimens of 30/15, 45/15, 60/30, and 90/30 mg were available in the titration phase of the ongoing open-label extension trial in ADPKD (Trial 156-04-250). During this trial, both the tolerability of tolvaptan regimens and efficacy (as measured by suppression of Uosm) were determined in 46 subjects. Results of this trial confirm that suppression of trough Uosm improves with each higher dose of tolvaptan, and that "breakthrough" occurred less frequently with each regimen (breakthrough of 61%, 39%, 26%, 15% for 30/15, 45/15, 60/30, and 90/30 mg doses, respectively).<sup>16</sup>

While optimal efficacy (0% breakthrough at trough) could not be achieved at any of the dose regimens used in the titration for Trial 156-04-250, the limit of tolerability was reached with only 41% of subjects stating that they could tolerate a 90/30 mg dose.<sup>16</sup>

This trial will also implement a titration strategy in the pre-randomization period to establish, by self-report, a maximally tolerated dose of tolvaptan for each subject.

In the tolvaptan titration period, all subjects will be given a split dose of 30/15 mg tolvaptan with upward titration every 3 to 4 days to 45/15 mg, 60/30 mg, up to a maximum dose of 90/30 mg per day over 2 weeks. All subjects will be encouraged to progress to 90/30 mg per day, as a higher dose is likely to be most effective. All subjects who tolerate tolvaptan at the 60/30 mg or 90/30 mg daily dose regimen may enter the tolvaptan run-in period at one of these doses for 3 additional weeks. Except for management of AEs, no dose adjustment will be permitted during the tolvaptan run-in period. Subjects unable to tolerate at least 3 weeks of daily tolvaptan treatment at 60/30 mg or 90/30 mg during the tolvaptan run-in period will not be eligible for randomization. This is expected to minimize post-randomization withdrawal due to inability to tolerate acute side effects of tolvaptan.

During the double-blind randomized treatment period, subjects will either be maintained on their maximally tolerated split dose of tolvaptan at 60/30 mg or 90/30 mg or randomized to placebo. To manage additional tolerability issues during this period, subjects may down-titrate blinded treatment to 45/15 mg or even 30/15 mg with medical monitor approval. Subjects will be encouraged to maintain maximally tolerated dose to optimize and maintain desired suppression. If down-titration occurs, subjects will be encouraged to return to previous maximal tolerated dose, if possible.

## **2.3 Trial Objectives**

Primary:

- To compare the efficacy of tolvaptan treatment in reducing the change in eGFR from pre-treatment baseline to post-treatment follow-up, as compared with placebo, in subjects with late-stage CKD due to ADPKD who tolerate tolvaptan during an initial run-in period.

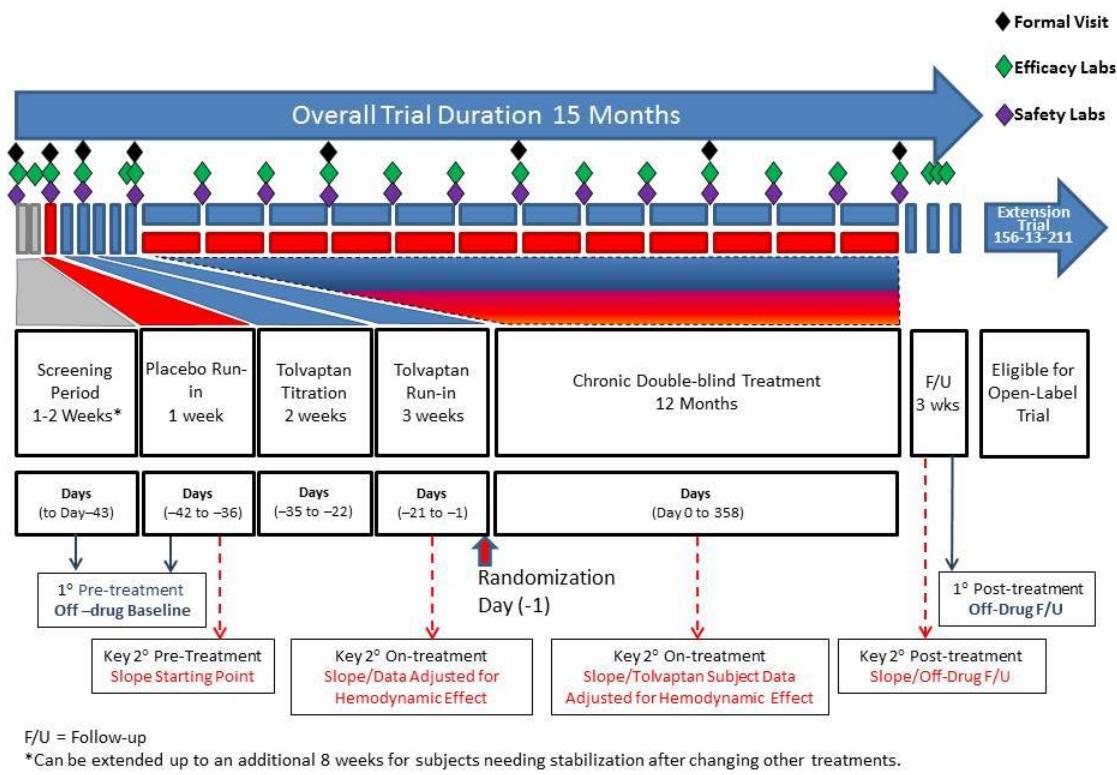
Secondary:

- To compare the efficacy of tolvaptan treatment in reducing the decline of annualized eGFR slope, as compared with placebo, in subjects with late-stage CKD due to ADPKD who tolerate tolvaptan during an initial run-in period.
- To compare overall and hepatic safety of tolvaptan with that of placebo and to compare incidence of ADPKD complications (outcomes) during the trial.

## **3 Trial Design**

### **3.1 Type/Design of Trial**

This is a phase 3b, multi-center, randomized-withdrawal, placebo-controlled, double-blind, parallel-group trial to compare the efficacy and safety of tolvaptan in subjects with ADPKD and baseline kidney function as documented by an eGFR between 25-65 mL/min/1.73m<sup>2</sup>, inclusive. The overall design is illustrated in [Figure 3.1-1](#).

**Figure 3.1-1 Trial Design Schematic**

### 3.2 Treatments

All subjects will be given investigational medicinal product (IMP; tolvaptan and/or placebo, according to trial period and randomization group) in a daily split dose, once upon awakening and another approximately 8 to 9 hours later. 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 maximize receptor suppression. Doses will be expressed as early dose/late dose (eg, 60/30 mg). Placebo will be administered to subjects randomized to that treatment in a form identical to the corresponding dose of tolvaptan tablets.

Upon consent, all subjects should receive the recommendation for ingestion of at least 2 to 3 liters of fluid (including in solid, semi-solid, and liquid foods) per day, unless otherwise directed by the investigator. This recommendation should start during screening and continue through the end of the trial.

While taking IMP, 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 to 2 cups of water before bedtime regardless of perceived thirst and replenish fluids overnight with each episode of nocturia.

### **3.2.1 Pre-randomization**

Subjects who provide informed consent and for whom preliminary eligibility is established will enter an 8-week run-in period. This represents “pre-randomization”. This pre-randomization period consists of a screening period (typically 1-2 weeks; however, longer periods up to 8 additional weeks are acceptable for subjects needing stabilization after changing other treatments, especially anti-hypertensives and diuretics, or who require additional assessments for qualification); a placebo run-in period (1 week), a tolvaptan titration period (2 weeks), and a tolvaptan run-in period (3 weeks).

During this period, subjects should be told “You will receive placebo or active treatment (tolvaptan) during the treatment phase, but you will not know which.” The subjects should not be told that there is a separate run-in phase and randomization phase, and they should not be told when formal randomization will occur. They should also be told “Your eligibility for continued participation will be assessed intermittently during the treatment period.”

#### **3.2.1.1 Screening Period (up to Day -43)**

No investigational treatments will be administered during the screening period. During this period, the subject’s eligibility for the trial will be confirmed using historical imaging data to support a diagnosis of ADPKD and to verify the level of CKD primarily due to ADPKD and not to other renal (hypoplasia) or metabolic (diabetic or hypertensive nephropathy) disorders. In addition, eligibility will be confirmed by the mean of eGFR calculated from the subjects’ 2 pre-treatment, central-lab, serum creatinine assessments. Subjects will be told that they will receive tolvaptan or placebo during various subsequent periods of the trial and that the next period involves a dose escalation with multiple efficacy, safety, and tolerability assessments. Trial medication will be dispensed on Day -43 after subject eligibility is confirmed. In exceptional circumstances, trial medication may be provided at the second screening visit with instruction not to take any medication until confirmation on Day -43 by the investigator. If trial medication is dispensed at the second screening visit, confirmation of eligibility and instructions to take medication will be provided by telephone on Day -43.

### **3.2.1.2 Placebo Run-in Period (Day -42 to Day -36)**

In the first week after the screening period, all subjects will begin the single-blind, placebo run-in period with placebo in a daily split dose of 0 mg (abbreviated 0/0 mg), in a form identical to tolvaptan tablets at the 15/15 mg dose. The subject will remain blinded to treatment, having received a bottle of trial drug during the screening period which they understood could be either tolvaptan or placebo. Those subjects unable to tolerate the placebo dose regimen will be considered “Run-in failures”, they will complete end of treatment (EoTx) visit assessments and be followed up after 7 days by phone call to assess any ongoing AEs.

### **3.2.1.3 Tolvaptan Titration Period (Day -35 to Day -22)**

During the single-blind, tolvaptan titration period (2 week duration), all subjects will receive 2 cartons of tolvaptan, 1 carton containing 2 bottles of 15 mg tablets and the other carton containing 2 bottles of 30 mg tablets. The tolvaptan tablets will appear identical to the placebo tablets dispensed in the prior period, and subjects will be told that they could be either tolvaptan or placebo. Subjects will be instructed to take tolvaptan starting at a split dose of 30/15 mg (as 2 tablets upon waking and 1 tablet approximately 8 to 9 hours later) and to titrate up every 3 to 4 days; first to 45/15 mg, then 60/30 mg, then up to the maximum dose of 90/30 mg. Titration will be accomplished by increasing the number of tablets/dose and/or switching from 15 mg tablets to 30 mg tablets, as detailed in [Table 3.2.2-1](#), below. Prior to each upward titration, the subject’s tolerability to the current dose will be assessed by asking, “Could you tolerate this dose of trial medication for the rest of your life?” Those subjects unable to reach and tolerate at least a 60/30 mg tolvaptan dose regimen will be considered “Run-in failures”, they will complete end of EoTx visit assessments and be followed up after 7 days by phone call to assess any ongoing AEs.

### **3.2.1.4 Tolvaptan Run-in Period (Day -21 to Day -1)**

Subjects tolerating at least 60/30 mg tolvaptan may enter the single-blind, tolvaptan run-in period (3 week duration). Subjects will continue on a stable 60/30 mg or 90/30 mg tolvaptan dose to confirm tolerability over a longer period and to establish a tolvaptan pre-randomization baseline.

At the end of the tolvaptan run-in period, subjects not tolerating at least 60/30 mg tolvaptan will be considered “Run-in failures”. They will complete EoTx visit assessments and be followed up after 7 days by phone call to assess any ongoing AEs.

### **3.2.2 Double-blind Randomized Treatment Period (Day 0 to Month 12)**

Subjects completing the tolvaptan run-in period tolerating at least 60/30 mg of tolvaptan will be randomized upon entry to this double-blind period. Aside from the first required clinic visit and dispensing new bottles of IMP, no distinction between the prior run-in period and the randomization period should be made for the subject.

After stratified randomization, by baseline eGFR (at a threshold of  $\leq 45$  or  $> 45$  mL/min/1.73m<sup>2</sup>), by age ( $\leq 55$  or  $> 55$  years old), and by three TKV criteria ( $\leq 2000$  mL,  $> 2000$  mL, or unknown), subjects will enter the double-blind, randomized treatment period receiving either tolvaptan or placebo in a 1:1 ratio. Tolvaptan, or matching placebo, will be administered at 60/30 or 90/30 mg, as split doses, with down-titrations to 45/15 mg and 30/15 mg as needed for tolerability. Planned down titration to 30/15 mg requires consultation with the medical monitor.

Subjects randomized to tolvaptan will continue to take the same dose that they received during the tolvaptan run-in period. Subjects randomized to placebo will receive placebo tablets matching their tolerated tolvaptan dose during the tolvaptan run-in period.

The treatment duration of these subjects will be 12 months from their date of randomization. Subjects not continuing in this trial will complete EoTx visit assessments and be followed for 21 days to assess any ongoing AEs.

**Table 3.2.2-1 Dosing Schedule**

Trial Day	Nominal Time	Dose
1 to 2 weeks (to Day -43)		<b>Screening</b> 1-2 weeks (No drug)
Day -42 to -36	8:00 am/ 4:00 to 5:00 pm	<b>Placebo run-in</b> Placebo (matching equivalent to tolvaptan) 0 mg
Day -35 to -22	8:00 am/ 4:00 to 5:00 pm	<b>Tolvaptan titration</b> Tolvaptan split-dose titration (using 15 or 30 mg tablets) 30/15, 45/15, 60/30 then 90/30 mg (given as 2x15/1x15; 3x15/1x15; 2x30/1x30 or 3x30/1x30 mg tablets, respectively)
Day -21 to -1	8:00 am/ 4:00 to 5:00 pm	<b>Tolvaptan run-in</b> Tolvaptan stable dose (same as maximum tolerated dose from tolvaptan titration, either 60/30 or 90/30 mg) for 3 weeks, using 30 mg tablets Randomization 1:1 - tolvaptan:placebo (Day -1)

<b>Table 3.2.2-1 Dosing Schedule</b>		
<b>Trial Day</b>	<b>Nominal Time</b>	<b>Dose</b>
Day 1 to Month 12	8:00 am/ 4:00 to 5:00 pm	<p><b>Double-blind randomized treatment</b></p> <p>Tolvaptan or placebo at an equivalent dose given at last day of tolvaptan run-in (ie, Day -1, either 60/30 or 90/30 mg) using 30 mg or matching placebo 0 mg tablets.</p> <p>30 mg or matching placebo 0 mg tablets given 2 upon waking/1 at 8-9 hours later or 3 upon waking/1 at 8-9 hours later.</p> <p>Tolvaptan (subject continued at same dose as Day -1, but may down-titrate to 45/15 [or 30/15 mg, with medical monitor approval] using 15 mg tablets and return to previous maximal tolerated dose, if possible)</p> <p>Placebo (subject continued at same dose as Day -1, but using matching placebo 0 mg tablets)</p>

### **3.2.3 Follow-up Period (Day +7 to Day +21)**

For randomized subjects, a 3-week follow-up period will begin immediately after treatment cessation (early or planned). No IMP will be administered during this period.

### **3.3 Trial Population**

This trial will consent and screen tolvaptan naïve subjects with ADPKD diagnosed by the presence of bilateral cysts per the Pei-Ravine criteria<sup>18,19</sup> (modified for computed tomography [CT] or magnetic resonance imaging [MRI], if needed). In order to maximize power and minimize the possibility of Type 2 error, trial enrollment will continue until approximately 1300 subjects are randomized.

Adult subjects with more advanced ADPKD-renal dysfunction phenotype will be enrolled. Subjects who have advanced to an eGFR < 60 mL/min/1.73m<sup>2</sup> by age 55 or < 45 mL/min/1.73m<sup>2</sup> by age 65 remain at a significant risk of progression to ESRD before reaching average life expectancy. Renal function will be confirmed during screening by the mean of eGFR calculated from the subjects' first 2 pretreatment, central-lab serum creatinine assessments. See [Table 3.4.2-1](#) for additional inclusion criteria.

Consistent with this trial's pre-specified efficacy estimand, only subjects tolerating the single-blind run-in period of tolvaptan (60/30 or 90/30 mg per day) will be randomized to the double-blind treatment period, to limit subsequent withdrawal due to lack of tolerability.

### **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 (without revealing details of its initial single-blind nature) and of their role and responsibilities in the proposed research. This shall be documented on a written ICF that shall be approved by the same institutional review board/independent ethics committee (IRB/IEC) responsible for approval of this protocol. In addition, the protocol explanation may include recorded or electronic means of education, which will also meet IRB/IRC approval. Each ICF shall include the elements required by the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guideline<sup>20</sup> 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. 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.

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 signed and dated by all subjects (or their guardian or legal representative, as applicable for local laws), 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.

Subjects will have the option of consenting on the written ICF for collection of DNA samples. Subjects do not need to consent to the DNA sample collection in order to be

considered as a potential subject in the trial. Subjects who consent to the DNA sample collection may withdraw their consent to the sponsor's future analysis of that sample (by written request, as detailed in the ICF).

### **3.4.2 Inclusion Criteria**

Subjects are required to meet the following inclusion criteria:

<b>Table 3.4.2-1 Inclusion Criteria</b>	
1.	Male and female subjects age 18 to 55 years of age (inclusive) with eGFR between 25 and 65 mL/min/1.73m <sup>2</sup> <b>-OR-</b>
2.	Male and female subjects age 56 to < 66 years of age with eGFR between 25 and 44 mL/min/1.73m <sup>2</sup> <b>with evidence of ADPKD progression, ie, eGFR decline of &gt; 2.0 mL/min/1.73 m<sup>2</sup> per year, based on historical eGFR data and medical monitor discretion.</b>
3.	Male and female subjects who are tolvaptan naïve.
4.	Diagnosis of ADPKD by modified Pei-Ravine criteria <sup>18 19</sup> : <ul style="list-style-type: none"> <li>• With family history: several cysts per kidney (3 if by sonography, 5 if by CT or MRI)</li> <li>• Without family history: 10 cysts per kidney (by any radiologic method, above) and exclusion of other cystic kidney diseases. 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.</li> <li>• Distribution and number of cysts consistent with the observed level of renal function deficit.</li> </ul>

### **3.4.3 Exclusion Criteria**

Subjects will be excluded if they meet any of the following exclusion criteria during the pre-randomization period.

<b>Table 3.4.3-1      Exclusion Criteria</b>	
1.	Women of childbearing potential (WOCBP) who do not agree to practice 2 different methods of birth control or remain abstinent during the trial and for 30 days after the last dose of IMP. If employing birth control, 2 of the following precautions must be used: vasectomy of partner, tubal ligation, vaginal diaphragm, intrauterine device, birth control pill, birth control implant, birth control depot injection, condom, or sponge with spermicide.
2.	Women who are breast-feeding and/or who have a positive pregnancy test result prior to receiving IMP.
3.	Need for chronic diuretic use.
4.	Hepatic impairment or liver function abnormalities other than that expected for ADPKD with typical cystic liver disease during the pre-randomization period.
5.	Subjects with advanced diabetes (eg, glycosylated hemoglobin [HgbA1c] > 7.5, and/or glycosuria by dipstick, significant proteinuria, retinopathy), evidence of additional significant renal disease(s) (ie, currently active glomerular nephritides), renal cancer, single kidney, or recent (within last 6 months) renal surgery or acute kidney injury.
6.	Subjects with contraindications to required trial assessments.
7.	Subjects who, in the opinion of the trial investigator or medical monitor, have a medical history or medical findings inconsistent with safety or compliance with trial assessments.
8.	Tolvaptan is contraindicated in patients who: are known to have hypersensitivity to tolvaptan or one of the excipients, are hypovolemic (volume depletion), cannot perceive thirst. Additionally, subjects with baseline screening abnormalities of serum sodium concentrations (hyponatremia or hypernatremia) may not be enrolled in the trial until these abnormalities resolve and then must be monitored accordingly.

Non-childbearing potential in women is defined as female subjects who are surgically sterile (ie, have undergone bilateral oophorectomy or hysterectomy) or female subjects who have been postmenopausal for at least 12 consecutive months.

Subjects may be re-screened, at the discretion of the medical monitor, if the exclusion characteristic has changed or resolved. In the event that a subject is re-screened, a new ICF must be signed and a new screening number assigned and screening procedures repeated.

### **3.5      Outcome Endpoints**

#### **3.5.1      Primary Outcome Endpoint**

##### **3.5.1.1      Primary Efficacy Endpoint**

Treatment difference in the change of eGFR from pre-treatment baseline to post-treatment follow-up, annualized (divided) by each subject's IMP treatment duration.

#### **3.5.2      Secondary Outcome Endpoints**

##### **3.5.2.1      Key Secondary Efficacy Endpoint**

Treatment difference in annualized slope of eGFR calculated for individual subjects using eGFR data observed in the placebo run-in, tolvaptan run-in (not including tolvaptan

titration), double-blind treatment, and post-treatment follow-up (not including data collected in the first week after the last IMP dose) periods.

### **3.5.2.2 Safety Endpoints**

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

- 1) AEs
- 2) Vital signs
- 3) Clinical laboratory tests, including serum transaminases, BT, ALP, and serum sodium

### **3.5.2.3 Pharmacokinetic/Pharmacodynamic Endpoints**

PK Endpoints: Determination of plasma tolvaptan and metabolite(s), including DM-4103 concentrations.

PD Endpoints: Uosm and urine specific gravity

### **3.5.3 Exploratory Outcome Endpoints**

#### **3.5.3.1 Exploratory Efficacy Endpoint**

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

#### **3.5.3.2 Exploratory Safety Endpoints**

- Urine and plasma biomarker concentrations for potential evaluation of metabolic or immunologic traits related to DILI and/or etiology of, susceptibility to, activity of, or progress of ADPKD, as well as the potential development of tools for diagnosis, prognosis and response to treatment.
- DNA samples for genetic evaluation of DILI and ADPKD genotyping and/or etiology of, susceptibility to, activity of, or progress of ADPKD, as well as the potential development of tools for diagnosis, prognosis and response to treatment.

Subjects will have the option of consenting for collection of the DNA sample. These analyses may be undertaken and reported separately from the clinical study report (CSR).

### **3.6 Measures to Minimize/Avoid Bias**

Only subjects who reach Day -1 and are who have indicated that they would likely be able to tolerate a dose of tolvaptan “for the rest of their lives” at a level of 60/30 mg or 90/30 mg will be eligible to enter the double-blind, randomized treatment period. In this

period, neither the subject nor the investigator or his/her staff will know which treatment is assigned. Immediately prior to randomization, and at all subsequent visits or site-subject contacts, the subject will be reminded of the importance of their commitment to continue participation in the trial, however the subject will not be told that this day is the point at which randomization to long-term therapy occurs.

Randomization will be 1:1, tolvaptan (60/30 mg or 90/30 mg) to placebo, and will utilize an interactive voice response system (IVRS) to ensure appropriate stratification.

Estimated GFR is an important predictor of the rate of renal function decline; therefore, subjects will be stratified by their baseline eGFR at a threshold of  $\leq 45$  or  $> 45$  mL/min/1.73m<sup>2</sup> and by age ( $\leq 55$  or  $> 55$  years old). Subjects will also be stratified by three TKV criteria ( $\leq 2000$  mL,  $> 2000$  mL, or unknown).

The prescription of additional fluid to subjects in this trial may serve to confound subject unblinding, but it is acknowledged that, with a randomized withdrawal design, a limitation of the main and exploratory analyses might include the subject's perception of their treatment assignment. Note, however, that calculation of eGFR is an objective measure and is expected to be unaffected by such perceptions.

### **3.7 Trial Procedures**

Trial assessment time points are summarized in [Table 3.7-1](#).

**Table 3.7-1 Schedule of Assessments**

Assessment	Pre-randomization										Double-blind Randomized Treatment			Follow-up						
	Screening <sup>a</sup> (1-2 weeks)			Placebo run-in (1 week ± 1 day) (Days -42 to -36)		Tolvaptan titration (2 weeks ± 1 day) (Days -35 to -22)			Tolvaptan run-in (3 weeks ± 1 day) (Days -21 to -1)		(Day 0)	Visits: monthly (± 2 days)	Month 12/ EoTx visit	3 weeks post-treatment <sup>a</sup>						
	V1	V2	Day -43	Day -42	Day -36	Days	-35	-32	-28	-24	-22	-21	-8	-1	Day 0	Months 1 to 11 <sup>b</sup>	Month 12 /EoTx	Days +8 to +21	V1	V2
Informed consent	X																			
Inclusion/Exclusion	X																			
Demographic/Medical history	X																			
Vital signs <sup>c</sup>	X	X				X						X			(X) <sup>c</sup>	X			X	
Physical examination <sup>d</sup>	X														(X) <sup>d</sup>	X				
Urine pregnancy test (WOCBP only) <sup>e</sup>	X					X									(X) <sup>e</sup>	X			X	
Chemistry Blood Sample <sup>c,f</sup> :																				
Serum Chemistry Panel	X															X			X	
Liver Function Panel	X	X				X						X	X		X	X			X	
Creatinine	X	X				X						X	X		X	X		X	X	X
Sodium	X	X				X						X			X	X			X	
Hematology and coagulation	X																			
PK plasma sample															(X) <sup>g</sup>	X			X	

**Table 3.7-1 Schedule of Assessments**

Assessment	Pre-randomization										Double-blind Randomized Treatment			Follow-up			
	Screening <sup>a</sup> (1-2 weeks)			Placebo run-in (1 week ± 1 day) (Days -42 to -36)		Tolvaptan titration (2 weeks ± 1 day) (Days -35 to -22)			Tolvaptan run-in (3 weeks ± 1 day) (Days -21 to -1)		(Day 0)	Visits: monthly (± 2 days)	Month 12/ EoTx visit	3 weeks post-treatment <sup>a</sup>			
	V1	V2	Day -43	Day -42	Day -36	Days -35	-32	-28	-24	-22	Day 0	Months 1 to 11 <sup>b</sup>	Month 12 /EoTx	Days +8 to +21	V1	V2	V3
Biomarker plasma sample		X			X					X			X	(X) <sup>g</sup>	X		X
DNA blood sample <sup>h</sup>		X															
Urinalysis	X	X			X							X			X		
PD and Biomarker urine sample		X <sup>g</sup>			X <sup>g</sup>					X <sup>g</sup>		X <sup>g</sup>	(X) <sup>g</sup>	X <sup>g</sup>			X <sup>g</sup>
Start newly dispensed IMP				X		X				X			X				
Tolerability/Dosing review					X		X	X	X	X		X		X	X		
Randomization												X					
Drug dispensation <sup>i</sup>			X		X					X		X		X			
Drug reconciliation <sup>i</sup>					X					X		X		X	X		
IVRS entry <sup>j</sup>	X		X		X					X		X		X	X		X
Exploratory PKD outcomes <sup>k</sup>		X									X		X	X			
Adverse events	X	<----->															
Concomitant medications	X	<----->															

<sup>a</sup>The screening period should be completed within 1-2 weeks before the start of the placebo run-in period. The screening period may be extended up to an additional 8 weeks for subjects who require modification of medical care specifically for this trial. Visits during the screening and follow-up periods must be scheduled at least 24 hours (1 day) apart. The Day -43 visit cannot occur until laboratory values from V2 are received. For two visits (V1, V2) during the screening period, blood will be collected and analyzed centrally for serum creatinine concentrations, in addition to any other assessments listed. A visiting nurse house call or local laboratory visit may be substituted for visits where only blood/urine will be collected during the follow-up (F/U) period. Three visits in the F/U period should be scheduled between Day 8 and Day 21 (inclusive) after the last dose of IMP. No F/U assessments will be taken during the first week of this period. Blood samples will be drawn at each visit for serum creatinine (V1, V2) and serum creatinine and other safety, efficacy, PK and PD measurements (V3).

<sup>b</sup>If IMP treatment is interrupted for  $\geq$  7 days during this period, procedures should be followed as detailed in [Section 3.8.3.2](#).

<sup>c</sup>The following visits (and all assessments required during those visits) should be performed in-clinic: screening (V1, V2, Day -43), end of placebo run-in, end of tolvaptan titration, end of tolvaptan run-in, quarterly visits during the randomized, double-blind treatment period (eg, Months 3, 6, 9), Month 12/end of treatment (EoTx) visit, and the last follow-up visit. Vital signs at each of the above visits include sitting heart rate and blood pressure. Post-void body weight should be measured at the first screening visit and the Month 12/EoTx visit only. Height should be assessed at the first screening visit only. Either height or weight may be collected as an unscheduled measurement if the planned assessment was missed. Weight may be assessed as necessary to assess changes in body weight.

<sup>d</sup>A full physical examination is required at screening (V1) and the Month 12/EoTx visit. A “directed physical examination” is performed at the quarterly visits (eg, Months 3, 6, 9) for assessment of signs or symptoms reported by the subject that might require further evaluation.

<sup>e</sup>During the trial, a pregnancy test should be completed at screening, end of placebo run-in and at the quarterly visits. On suspicion of pregnancy, unscheduled urine or serum pregnancy testing will be performed. Positive urine pregnancy tests should be confirmed with a serum pregnancy test.

<sup>f</sup>All serum creatinine samples will be analyzed by the central laboratory. The specifics and timing for all clinical laboratory samples for central and local laboratory analyses are as follows:

**All visits:** One or more tubes of blood may be collected to accommodate the needed tests.

**Screening period:** During the 1-2 weeks of the screening period, blood will be drawn 2 times on separate days (V1, V2) at least 24 hours apart. The subject's eligibility will be confirmed by the mean of eGFR calculated from the subjects' 2 pre-treatment (V1, V2), central laboratory serum creatinine assessments and entered in IVRS on Day -43.

**Placebo run-in period:** Subjects will have 1 blood draw at the end of 1 week with the sample being obtained on Day -36.

**Tolvaptan titration period:** Subjects will have 1 blood draw at the end of 2 weeks with the sample being obtained on Day -22.

**Tolvaptan run-in period:** During the last 2 weeks of this period, blood will be drawn 2 times on separate days (at least 24 hours apart) with the last sample on Day -1.

**Double-blind treatment period:** Samples will be collected for central lab analysis monthly and at the Month 12/EoTx visit. Local standard of care laboratory tests will be performed monthly per the subject's individual clinical management needs. Local liver function panel analyses will also be performed more frequently, if necessary.

**Follow-up period:** Subjects will have blood drawn on 3 visits at least 24 hours apart during the 3-week F/U period, which starts after the last dose of IMP. Visits should be scheduled between Days 8 and 21, inclusive.

Full Chemistry panel will be obtained during the following visits: Screening (V1), quarterly visit (M3, M6, M9, M12/EoTx, F/U period (V3).

Serum creatinine, serum sodium: Screening (V2), end of placebo period, end of tolvaptan titration, 2 times during tolvaptan run-in, monthly during double-blind treatment period, 3 times for serum creatinine and 1 time for serum sodium (V3) during the F/U period. Note that the first F/U visit will occur at least 7 days (Day 8) after the last dose of IMP.

Liver function panel: Screening (V2), end of placebo period, end of tolvaptan titration, 1 time during tolvaptan run-in, monthly during double blind treatment period, F/U period (V3).

<sup>g</sup>During the double-blind, randomized treatment period, PK plasma samples, PD urine samples, and biomarker urine/plasma samples will be collected quarterly (eg, Months 3, 6, 9, 12/EoTx). Urine biomarker samples should be collected as a mid-stream, clean-catch sample during the second morning void prior to the subject eating breakfast. Where necessary, supplies for collection should be dispensed prior to the visit with instructions to collect the urine sample on the day of the visit.

<sup>h</sup>DNA samples are optional and may be collected at subsequent visits with subject's consent.

<sup>i</sup>Drug dispensing and reconciliation will be done monthly (exceptions to allow dispensing/reconciliation at each 3-month clinic visit may be made by the medical monitor in exceptional circumstances, with instructions to take only one month's supply and start the next month only after acceptable safety lab results are confirmed by the investigator). Instructions to begin taking the next month's trial medication will be given during the time of IMP dispensation at each monthly visit or by telephone contact after the monthly LFT samples are collected. If LFT results are abnormal, the site will conduct a telephone contact with the trial subject to inform them that prompt immediate retesting (ie, within 72 hours) may be necessary (see [Section 3.7.3.4](#) for guidance) and to arrange for follow-up and adjustment of medication (as needed); if a down titration is required, the subject may need to return to the site or have new drug delivered. Subjects will be reminded of the importance of their commitment to continue participation in the trial. At the completion of the screening period, trial medication will be dispensed at Day -43 after subject eligibility is confirmed. In exceptional circumstances, trial medication may be dispensed at V2, with the instruction not to take any trial medication until eligibility is confirmed by the investigator. In these cases, confirmation of eligibility and instructions for taking trial medication will be provided by telephone on Day -43.

<sup>j</sup>At the end of the titration period, the subject's highest tolerated dose will be utilized for the 3-week tolvaptan run-in period.

<sup>k</sup>Exploratory PKD outcomes will be completed either monthly over the phone or in person during quarterly clinic visits.

### **3.7.1 Schedule of Assessments**

#### **3.7.1.1 Pre-randomization Period**

After obtaining consent and upon establishing initial eligibility using inclusion/exclusion criteria, subjects will enter an initial 8-week, single-blind, pre-randomization period prior to actual randomization which will consist of:

- screening period (1-2 weeks; longer durations of up to 8 additional weeks may be required according to the investigator's judgment, as described below)
- placebo run-in period (1 week)
- tolvaptan titration period (2 weeks)
- tolvaptan run-in period (3 weeks)

There are 2 goals of this pre-randomization period: 1) to establish the degree to which a hemodynamic eGFR shift may occur for each potential treatment assignment (placebo and tolvaptan); and 2) to determine the maximally tolerated dose of tolvaptan for each subject by self-report.

Pre-randomization eGFR value(s) will be calculated by CKD-EPI for each potential treatment assignment for all subjects. Having these data pre-randomization will allow for the following: equivalent evaluation of baseline characteristics, including the acute hemodynamic response to tolvaptan in all subjects who will contribute to the primary and key secondary endpoint; facilitate baseline assessments which appropriately accounts for placebo effect and tolvaptan hemodynamic onset effect of all randomized subjects who have a post-randomization eGFR. It also allows for comparison of randomized, completer and non-completer populations in terms of their hemodynamic response to tolvaptan.

To establish the pre-randomization eGFR, multiple serum creatinine values (IDMS-traceable) will be obtained under standardized conditions (see [Section 3.7.2.1](#)), each separated by one (minimum of 24 hours) to several days during the screening period and placebo run-in for the primary endpoint, and during each treatment's run-in period for the key secondary endpoint. The eGFR for each serum creatinine assessment will be calculated and then averaged, with the median of assessment dates being set as the subject's eGFR value's date.

##### **3.7.1.1.1 Screening Period (up to Day -43)**

The screening period will be for 1-2 weeks, but may be extended up to an additional 8 weeks for subjects who require modification of medical care or further medical evaluation specifically for this trial. This may include, for example, stabilizing

anti-hypertensive regimens for subjects discontinuing diuretics or “wash-out” of other investigational agents. As part of this stabilization or wash-out period, liver function and/or other lab safety tests may be performed, as needed.

The screening period should be completed within 1-2 weeks of the placebo run-in period, (unless extended as described above). Blood will be drawn 2 times on separate days (visit 1 and visit 2), at least 24 hours apart. The Day -43 visit will not be scheduled until laboratory results from the second visit are received and evaluated, so that the calculated mean eGFR result is available for eligibility assessment on Day -43.

Assessments during the screening period will include (See [Table 3.7-1](#)):

- 1) Confirm diagnosis and determine whether the subject meets inclusion and exclusion criteria (first visit)
- 2) Record medical/PKD history, including demographic information (first visit)
- 3) Record concomitant medications and ensure subject's treatment meets current standard of care including lifestyle and dietary recommendations, especially for ingestion of at least 2-3 liters of fluid per day as appropriate, unless otherwise directed by your study doctor. (all visits)
- 4) Assess AEs (if reported; all visits)
- 5) Perform a full physical examination (first visit)
- 6) Assess vital signs (include sitting heart rate and blood pressure [first and second visits])
- 7) Assess post-void body weight and height (first visit)
- 8) Urine pregnancy test for WOCBP (first visit)
- 9) Collect urinalysis samples (first and second visits)
- 10) Collect blood for serum creatinine for eGFR calculation (2 collections: first and second visits, at least 24 hours apart)
- 11) Collect blood for central clinical laboratory analyses (sodium [first and second visits]), hematology, serum chemistry, and liver function panel [first visit] - see Section 3.7.3.2). If sodium, serum chemistry and/or liver function panel are collected at the same visit, a single tube of blood should be drawn for all assessments.
- 12) Collect PD urine sample (second visit)
- 13) Collect biomarker plasma and urine samples (second visit, see Section 3.7.3.5)
- 14) Complete PKD history and outcomes surveys
- 15) Register subject status in IVRS
- 16) Collect blood for DNA sample (second visit, for consenting subjects only). DNA samples may be collected at a subsequent visit if subjects consent at a later date.

17) Dispense IMP for next period (last visit)

Preliminary eligibility for the trial will be initially assessed using the subjects' historical laboratory or imaging data. Eligibility will be confirmed by the mean of eGFR calculated from the subjects' 2 pre-treatment, central-lab serum creatinine assessments.

Confirmation of ADPKD diagnosis (using the modified Pei-Ravine criteria) may require confirmatory imaging. Subjects will be told that they will receive both tolvaptan and placebo during various subsequent periods of the trial and that the next period involves a dose escalation with multiple efficacy, safety, and tolerability assessments. Trial medication will be dispensed at Day -43 after subject eligibility is confirmed. In exceptional circumstances, trial medication may be dispensed at the second visit, with the instruction not to take any trial medication until eligibility is confirmed by the investigator. In these cases, confirmation of eligibility and instructions for taking trial medication will be provided by telephone on Day -43.

### **3.7.1.1.2 Placebo Run-in Period (Days -42 to -36)**

The placebo run-in period will be 1 week ( $\pm$  1 day) and will be conducted in a single-blinded fashion. Subjects will be given placebo in a daily split dose of a single 0 mg tablet upon awakening and another 0 mg tablet approximately 8 to 9 hours later (abbreviated 0/0 mg), in a form identical to 15/15 mg tolvaptan tablets.

Assessments during the placebo run-in period will include (See [Table 3.7-1](#)):

- 1) Record concomitant medications at all visits
- 2) Assess AEs at all visits
- 3) Assess vital signs (include sitting heart rate and blood pressure) on Day -36
- 4) Collect urinalysis sample on Day -36
- 5) Urine pregnancy test for WOCBP (Day -36)
- 6) Collect blood for serum creatinine for eGFR calculation and for assessment of sodium and liver function panel on Day -36 (see [Section 3.7.3.2](#)).
- 7) Collect PD urine sample on Day -36
- 8) Collect biomarker plasma and urine samples (see [Section 3.7.3.5](#)) on Day -36
- 9) Ask subject "Can you tolerate this dose of trial medication for the rest of your life?" on Day -36
- 10) Update subject status in IVRS on Day -36
- 11) IMP reconciliation on Day -36
- 12) Dispense IMP for next period on Day -36
- 13) Subjects found to be ineligible to continue in this trial after receiving IMP must have a 7-day follow-up visit (see [Section 3.8.3.1](#)).

### **3.7.1.3 Tolvaptan Titration Period (Days -35 to -22)**

The tolvaptan titration period will be a single-blind period that will last for 2 weeks ( $\pm 1$  day). All subjects will be given a split dose of 30/15 mg of tolvaptan with upward titration every 3 to 4 days to 45/15 mg, 60/30 mg, up to a maximum dose of 90/30 mg per day over 2 weeks. This titration will be monitored with telephone or clinic visits at each escalation level to assess tolerability.

Assessments during the tolvaptan titration period will include (See [Table 3.7-1](#)):

- 1) Record concomitant medications at all visits
- 2) Assess AEs at all visits
- 3) Assess vital signs (include sitting heart rate and blood pressure) on Day -22
- 4) Collect blood for serum creatinine for eGFR calculation and for assessment of sodium and liver function panel on Day -22 (see [Section 3.7.3.2](#)). If sodium and liver function panel are collected at the same visit, a single tube of blood should be drawn for all assessments.
- 5) Collect PD urine sample on Day -22
- 6) Collect biomarker plasma and urine samples (see [Section 3.7.3.5](#)) on Day -22
- 7) Ask subject “Can you tolerate this dose of trial medication for the rest of your life?” at each upward titration visit
- 8) Update subject status in IVRS on Day -22
- 9) IMP reconciliation on Day -22
- 10) Subjects not tolerating at least 60/30 mg dose should be informed they did not meet eligibility criteria for continuation
- 11) Dispense IMP for next period on Day -22
- 12) Subjects found to be ineligible to continue in this trial must have a 7-day follow-up visit (see [Section 3.8.3.1](#)).

### **3.7.1.4 Tolvaptan Run-In Period (Days -21 to -1)**

All subjects who tolerate tolvaptan at the 60/30 mg or 90/30 mg daily dose regimen will enter the tolvaptan run-in period at one of these doses for 3 weeks ( $\pm 1$  day). Except for management of AEs, no dose adjustment will be permitted during this period. Subjects unable to tolerate at least 3 weeks of daily tolvaptan treatment at 60/30 mg or 90/30 mg will not be eligible for randomization.

Subjects who reach Day -1 and are able to tolerate a given dose of tolvaptan “for the rest of their lives” at a level of 60/30 mg or 90/30 mg will be eligible to enter the double-blind, randomized treatment period. Randomization (Day -1) will be stratified by mean eGFR serum creatinine measurements taken during the screening period and

placebo run-in period. Subjects will be stratified in a 1:1 ratio to each treatment group as follows:

- CKD 2 to 3a stages [ $>45 \text{ mL/min}/1.73 \text{ m}^2$ ] or
- CKD 3b to 4 stages [ $\leq 45 \text{ mL/min}/1.73 \text{ m}^2$ ]

Ideally, a distribution of half of subjects being above or below this cut-off will be targeted. Therefore, enrollment may be adjusted if this ratio begins to vary by more than a 60:40 ratio. Subjects will also be stratified by age ( $\leq 55$  or  $> 55$  years old) and by three TKV criteria ( $\leq 2000 \text{ mL}$ ,  $> 2000 \text{ mL}$ , or unknown).

Assessments during the tolvaptan run-in period will include (See [Table 3.7-1](#)):

- 1) Record concomitant medications at all visits
- 2) Assess AEs at all visits
- 3) Assess vital signs (include sitting heart rate and calibrated blood pressure) on Day -1
- 4) Collect urinalysis sample on Day -1
- 5) Collect blood (2 times on separate days during the last 2 weeks of the period, with the last sample drawn on Day -1) for serum creatinine for eGFR calculation and for 1 assessment of sodium and liver function panel (see [Section 3.7.3.2](#)). If sodium and liver function panel are collected at the same visit, a single tube of blood should be drawn for all assessments.
- 6) Collect PK plasma sample and PD urine sample on Day -1
- 7) Collect biomarker plasma and urine samples (see [Section 3.7.3.5](#)) on Day -1
- 8) Complete PKD outcomes survey on Day -1
- 9) Ask subject “Can you tolerate this dose of trial medication for the rest of your life?” on Day -1
- 10) Update subject status in IVRS on Day -1
- 11) IMP reconciliation on Day -1
- 12) Remind the subject of the importance of their commitment to continue participation in the trial on Day -1
- 13) Randomization on Day -1
- 14) Dispense IMP for next period on Day -1
- 15) Subjects found ineligible to be randomized and continue in this trial must have a 7-day follow-up visit (see [Section 3.8.3.1](#)).

### **3.7.1.2 Double-blind, Randomized Treatment Period (Day 0 to Month 12)**

Day 0 is the beginning of the double-blind, randomized treatment period. Only subjects who reach Day -1 and are able to tolerate a given dose of tolvaptan “for the rest of their

lives” at a level of 60/30 mg or 90/30 mg will be eligible to enter this period. In this period, neither the subject nor the investigator or his/her staff will know with certainty which treatment is assigned. Immediately prior to randomization, and at each subsequent visit or site contact, the subject will be reminded of the importance of their commitment to continue participation in the trial; however, the subject will not be told that this day is the point at which randomization to long-term therapy occurs.

Post-randomization, the maximally-tolerated dose of tolvaptan established during the run-in period, or the equivalent as matching placebo tablets, will be dispensed according to the subject’s randomization outcome. Subjects must return any unused IMP from the pre-randomization period before continuing in the double-blind, randomized treatment period.

From this point forward, every effort to maintain adherence and continuation of the subjects until the end of the trial should be undertaken. If continued tolerability becomes an issue, subjects may titrate downward to 45/15 mg or 30/15 mg (with medical monitor approval) or temporarily interrupt treatment as needed. Return to higher doses is also allowed.

Assessments during the double-blind, randomized treatment period will include (See [Table 3.7-1](#)):

- 1) Remind the subject of the importance of their commitment to continue participation in the trial at all visits
- 2) Record concomitant medications at all visits
- 3) Assess AEs at all visits
- 4) Assess vital signs (including sitting heart rate and blood pressure) at Month 3, 6, 9, 12/ EoTx visits; include assessment of post-void body weight at the Month 12/EoTx visit only
- 5) Perform a full physical examination at Month 12/EoTx visit only (directed physical exam may be performed at Month 3, 6, 9 visits, if deemed necessary by the investigator)
- 6) Urine pregnancy test for WOCBP at Month 3, 6, 9, 12/EoTx visits (or if indicated)
- 7) Collect urinalysis sample at the Month 12/EoTx visit
- 8) Collect blood for serum creatinine for eGFR calculation and for assessment of sodium and liver function panel (see [Section 3.7.3.2](#)) monthly and at the Month 12/EoTx visit. Serum sodium and liver function panel should be determined from the same blood sample.
- 9) Collect blood for serum chemistry assessment at the Month 12/EoTx visit. The sodium, serum chemistry and liver function panel should be determined from a single tube of blood.

- 10) Collect plasma samples for PK analysis and PD urine samples at Month 3, 6, 9, 12/EoTx visits
- 11) Collect plasma and urine samples for potential biomarker analysis at Month 3, 6, 9, 12/EoTx visits (see [Section 3.7.3.5](#))
- 12) Complete PKD outcomes survey (monthly and at the Month 12/EoTx visit)
- 13) Ask subject “Can you tolerate this dose of trial medication for the rest of your life?” at each visit
- 14) Update subject status in IVRS (monthly and at the Month 12/EoTx visit)
- 15) Dispense IMP at monthly visits up to and including Month 11. In certain circumstances, with medical monitor approval, a 3-month drug supply may be provided; however, initiation of the next month’s supply must be directed by the site.
- 16) IMP reconciliation (monthly and at the Month 12/EoTx visit)
- 17) Subjects not continuing in this trial must have a 21-day follow-up period (see [Section 3.8.3.3](#)).

Visits during the treatment period will be scheduled monthly ( $\pm$  2 days), with a final visit at Month 12/EoTx.

Regardless of discontinuation of IMP, the subjects are expected to complete all monthly visits and assessments including the Month 12 visit (see [Section 3.8.3.3](#)).

All subjects have the right to withdraw their consent from further participation in the trial at any time without prejudice. In all cases of impending IMP discontinuation or consent withdrawal, the investigator should follow the procedures outlined in [Section 3.8.3.5.1](#) to determine if the subject can continue participation in the trial if modifications to his/her treatment and/or schedule of assessments can be accommodated.

### **3.7.1.3      Follow-up Period (Month 12/End of Treatment to Day 21 Post-treatment)**

For all randomized subjects, the 3-week follow-up period starts immediately after the last dose of IMP. No follow-up assessments will be taken during the first week of this period. During the last 2 weeks, Days 8 through 21, inclusive, 3 follow-up visits will be scheduled. The visits must occur at least 24 hours apart. Blood samples will be collected at each visit for serum creatinine measurements. The blood sample collected at the last follow-up visit will also include measurements of post-treatment efficacy and safety.

These visits may be visiting nurse house calls or local laboratory visits when only blood samples will be collected, with the exception of the last visit, which will be a clinic visit.

Assessments during the last 2 weeks of the follow-up period will include

(See [Table 3.7-1](#)):

- 1) Record concomitant medications at each visit
- 2) Assess AEs at each visit
- 3) Assess vital signs (including sitting heart rate and blood pressure) at the last visit
- 4) Urine pregnancy test for WOCBP at the last visit
- 5) Collect blood for central laboratory analysis of serum creatinine for eGFR calculations at each visit
- 6) Collect blood for assessment of sodium levels at the last visit (see [Section 3.7.3.2](#))
- 7) Collect blood for liver function panel assessments at the last visit (see [Section 3.7.3.2](#))
- 8) Collect plasma samples for PK analysis and PD urine samples at the last visit
- 9) Collect plasma and urine samples for potential biomarker analysis at the last visit (see [Section 3.7.3.5](#))
- 10) Update subject status in IVRS at the last visit

The above follow-up assessments will also be performed for a subject who interrupts IMP for  $\geq 7$  days, in order to collect their data in the event that they never restart IMP treatment (see [Section 3.8.3.2](#)).

### **3.7.2 Efficacy Assessments**

#### **3.7.2.1 Serum Creatinine for Estimated Glomerular Filtration Rate**

The serum creatinine concentration is related to eGFR and is commonly used to estimate renal function in clinical practice. Alteration in metabolism of creatinine and methodological interference in its measurements may impact accuracy of the serum creatinine and renal function estimation. Below are suggested measures to decrease serum creatinine variability prior to the monthly blood draws required by this protocol. All trial subjects should:

- Maintain a stable dietary protein intake and avoid very different or high cooked meat protein meals the day before each scheduled serum creatinine assessment.
- Maintain a stable exercise routine and avoid very different or heavy physical activity/exercise the day before each scheduled serum creatinine assessment.
- Maintain a stable water intake, aimed at avoiding thirst consistently throughout the trial - recommended ingestion of at least 2-3 liters of fluid (including in solid, semi-solid, and liquid foods) per day, unless otherwise directed by your study doctor.
- Plan to arrive at the same time for each blood-draw and clinic visit to better standardize time of the sample collection throughout the trial.

- Some medications may increase serum creatinine levels (eg, cimetidine, non-steroidal anti-inflammatory drugs [NSAID] medications like aspirin or ibuprofen, chemotherapy drugs, cephalosporin). Subjects should alert their trial doctor, and any other health-care providers, to take this into consideration when considering changes in their prescribed or over-the-counter medications, and all medication changes should be reported to their trial doctor or his/her staff.

Serum creatinine is stable when stored frozen; therefore, two samples/aliquots of blood will be collected for its analysis. While one blood sample will be analyzed by the central laboratory as soon as it is received and accessioned, the formal efficacy analyses will be based on duplicate samples/aliquots which are collected contemporaneously and frozen for later batched analysis to eliminate inter-day variability of the assay. Ongoing, batched analysis will be conducted for each subject upon his/her individual completion of all their assessments within the trial (not at the end of the trial).

The eGFR values will be calculated by CKD-EPI from the central-laboratory serum creatinine concentrations taken at screening and during every trial visit. In the screening period, serum creatinine assessments may not be repeated; the first two assessments must be used to determine the eGFR values that will be averaged for determination of meeting inclusion criteria. Further detail regarding eGFR calculations will be provided in the statistical analysis plan (SAP).

### **3.7.2.2 Polycystic Kidney Disease History and Outcomes Surveys**

A short PKD history survey will be completed once during screening to capture information from the subject's recollection, and documented past medical history where available. The survey should be updated at each visit if new information regarding past history becomes available.

The PKD outcomes survey will collect information relevant to the medical, social and economic consequences of new and ongoing PKD-related morbidities. New clinically relevant information and specific questions about outcomes will be collected at the following visits: screening, end of tolvaptan run-in, and during the double-blind randomized treatment period either monthly (over the phone or in person) or during quarterly clinic visits (in person).

If a subject who has been randomized discontinues the use of IMP, PKD outcomes will be collected at the normally scheduled trial visits, or by telephone contact, to the date of the originally planned Month 12 visit, if the subject agrees.

### **3.7.3 Safety Assessments**

#### **3.7.3.1 Adverse Events**

Refer to [Section 5, Reporting of Adverse Events](#).

#### **3.7.3.2 Clinical Laboratory Assessments**

Blood and/or urine samples will be collected as indicated in the schedule of assessments, ([Table 3.7-1](#)). It is preferable to collect the clinical laboratory samples from each subject at a consistent time of day throughout the trial, and to recommend that the subject have a similar diet, avoiding variation in protein intake (especially cooked meat protein), and exercise pattern during these periods, in order to reduce variability in the samples over time (see [Section 3.7.2.1](#)).

A list of the specific clinical laboratory assessments is presented in [Table 3.7.3.2-1](#).

Clinical laboratory samples for analysis by the central laboratory will be collected at the following visits:

- during screening (2 visits at least 24 hours apart that occur during the 1-2 weeks prior to placebo run-in) - creatinine (first and second visits), sodium and urinalysis (first and second visits), hematology and coagulation panel, serum chemistry panel, and liver function panel (first visit)
- during placebo run-in - urinalysis, liver function panel, creatinine, and sodium on Day -36)
- during tolvaptan titration - liver function panel, creatinine, and sodium (Day -22)
- during tolvaptan run-in - liver function panel (Day -8), urinalysis (Day -1), creatinine, (2 times on separate days during the last 2 weeks of the period, with the last sample drawn on Day -1), and sodium (Day -1)
- at monthly clinic visits during the double-blind, randomized treatment period - liver function panel, creatinine, and sodium
- at the Month 12/EoTx visit - serum chemistry panel, urinalysis, liver function panel, creatinine, and sodium
- during the 3-week follow-up period (3 visits that occur between Days 8 and 21, inclusive, after the last dose of IMP, and at least 24 hours apart) - creatinine (3 visits), sodium (last visit), liver function panel and serum chemistry panel (last visit)

<b>Table 3.7.3.2-1 Clinical Laboratory Assessments</b>	
<b>Hematology and coagulation panel:</b> <ul style="list-style-type: none"> <li>• hemoglobin,</li> <li>• mean corpuscular hemoglobin (MCHC)</li> <li>• mean corpuscular volume (MCV)</li> <li>• red blood cell (RBC) count</li> <li>• white blood cell (WBC) count with differential</li> <li>• platelet count</li> <li>• prothrombin time (PT) as international normalized ratio (INR)</li> <li>• activated partial thromboplastin time</li> </ul>	<b>Serum chemistry panel:</b> <ul style="list-style-type: none"> <li>• albumin</li> <li>• blood urea nitrogen (BUN)</li> <li>• serum calcium</li> <li>• serum chloride</li> <li>• carbon dioxide (CO<sub>2</sub>)</li> <li>• gamma-glutamyl transpeptidase (GGT)</li> <li>• glucose</li> <li>• lactate dehydrogenase (LDH)</li> <li>• phosphorus</li> <li>• potassium</li> <li>• total cholesterol</li> <li>• total protein</li> <li>• uric acid</li> </ul>
<b>Liver function panel:</b> <ul style="list-style-type: none"> <li>• alkaline phosphatase (ALP)</li> <li>• alanine transaminase (ALT)</li> <li>• aspartate aminotransferase (AST)</li> <li>• direct bilirubin</li> <li>• total bilirubin (BT)</li> </ul>	<b>Urinalysis panel:</b> <ul style="list-style-type: none"> <li>• appearance</li> <li>• color</li> <li>• blood</li> <li>• glucose</li> <li>• microscopic analysis (including WBC/RBC counts per high-powered field)</li> <li>• pH</li> <li>• protein</li> <li>• osmolality</li> <li>• specific gravity</li> <li>• urine creatinine</li> </ul>
<b>Creatinine</b>	<b>Sodium</b>

Liver panels will be analyzed more frequently during the double-blind, randomized treatment period if ALT > twice the upper limit of normal ( $2 \times \text{ULN}$ ), using both central and local laboratories, as needed, and per standard of care according to the subject's individual medical needs. If liver function panel, sodium and/or serum chemistry assessments are scheduled at the same visit, all values should be determined from the same blood sample.

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 period) and at visits for

Months 3, 6, and 9 during the double-blind randomized treatment period. Once enrolled into the trial, the subject should contact the clinic immediately on suspicion of pregnancy, and unscheduled urine or blood pregnancy testing will be performed. Positive urine pregnancy tests should be confirmed with a serum pregnancy test.

The following serum chemistry laboratory tests may be performed by the central laboratory at the request and approval of the medical monitor: calcium, phosphorus, parathyroid hormone, vitamin D, and bicarbonate levels. If performed, the results from these tests will be included in the clinical database.

### **3.7.3.3 Physical Examination and Vital Signs**

A full physical examination will be performed and documented at the first screening visit and the Month 12/EoTx visit. At other visits, a directed physical examination may be performed to focus on ADPKD-related signs and symptoms. In some geographic regions, more frequent subject visits may be the norm; however vital signs and clinically significant physical findings will be recorded as an unscheduled visit in the electronic case report form (eCRF) as applicable. Any changes in medication or AEs will be recorded in the eCRF.

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 examination. If the appointed designee is to perform the physical examination, he/she must be permitted to do so 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, where local regulations allow, while local regulations determine their being named in the ICF). Whenever possible, the same individual should perform all physical examinations. Any undesirable condition present at a post-treatment physical examination that was not present at the baseline examination should be documented as an AE and followed to a satisfactory conclusion.

Vital sign data, including seated blood pressure, heart rate, temperature, height, and weight, will be taken at the visits identified in the Schedule of Assessments ([Table 3.7-1](#)).

### **3.7.3.4 Assessment of Liver Symptoms, Signs or Test Abnormalities**

Testing for hepatic transaminase (ALT/AST), alkaline phosphatase, and BT will be performed during screening/run-in and at each monthly visit. Management of liver abnormalities is discussed in the paragraphs below.

### **3.7.3.4.1 Requirements for Repeated Liver Testing**

#### **3.7.3.4.1.1 Repeated Liver Testing in Subjects with Normal Values at Screening**

The appearance of any suspicious symptom or sign should trigger prompt testing of hepatic function (ie, within 72 hours). Local laboratory testing is acceptable, ideally with a concurrent central laboratory sample for confirmation.

Any transaminase or bilirubin values which exceed  $2 \times$  ULN should also prompt immediate retesting within 72 hours. While values remain in an abnormal range, testing frequency should be increased to at least weekly for the first month, gradually returning to monthly as indicated by the results.

Subjects exhibiting such an increase during the tolvaptan titration/run-in phases will be disqualified from randomization on safety grounds and should not be randomized.

Should the cause of the abnormality be determined to be unrelated to tolvaptan exposure (eg, having identified a plausible alternative explanation) such a subject may be re-screened only with medical monitor approval.

#### **3.7.3.4.1.2 Repeated Liver Testing in Subjects with Abnormal Values at Screening**

Subjects found to have liver laboratory abnormalities at screening or who have a history of non-ADPKD-related liver disease will require further evaluation. These subjects will need to have the special liver eCRF (see [Section 3.7.3.4.3](#)) completed and additional testing will be required during screening (to confirm the stability of the abnormality) and during the tolvaptan run-in phase at least 1 week prior to randomization (to confirm eligibility for randomization). Management of such subjects should be closely coordinated with the trial's Medical Monitor. In these subjects, further changes in liver test levels of  $> 2 \times$  upper limit of their highest screening value at any point post-screening should prompt re-testing within 72 hours. Should such an increase occur in the tolvaptan titration/run-in phase, the subject will be disqualified from randomization.

### **3.7.3.4.2 Liver Test Abnormalities and Interruption/Discontinuation of Investigational Medicinal Product**

Liver transaminase or bilirubin levels reaching or exceeding  $2 \times$  ULN that have an uncertain or rapidly increasing trajectory should prompt at least temporary IMP interruption. IMP should not be resumed until monitoring indicates abnormalities have resolved, are stable or are not rapidly increasing, and then only with an increased frequency of monitoring.

Subjects would not typically be allowed to resume treatment with IMP if they have:

- transaminase levels rise above  $8 \times$  ULN,
- transaminase levels are  $> 5 \times$  ULN for more than 2 weeks, or
- concurrent elevations of transaminase  $> 3 \times$  ULN and BT  $> 2 \times$  ULN.

Subjects with these levels of abnormality may be re-challenged with IMP if abnormalities were adjudicated as having a < 50% likelihood of being related to IMP (per DILI network [DILIN] probability criteria<sup>17</sup>) by an independent hepatic adjudication committee (HAC) (see [Section 3.7.3.4.3](#)) and the investigator and medical monitor agree to an intensive monitoring plan to mitigate risk. All elevations will be assessed by the medical monitoring team. The subject must also be willing to comply with these monitoring measures, be informed of the potential risks, and consent to IMP re-challenge.

#### **3.7.3.4.3 Requirements for Special Reporting Using the Liver Disease Electronic Case Report Form and Immediately Reportable Event Form**

The purpose of the liver disease eCRF and optional additional testing is to facilitate review of each subject who presents with, or develops a liver abnormality during the trial or and to determine the probable cause(s) of these abnormalities. The review will be performed by a blinded, independent HAC using DILIN probability criteria (< 25% = unlikely, 25% to 50% = possibly, 51% to 75% = probably, 76% to 95% = very likely, > 95% = definite).<sup>17</sup> The HAC will independently decide attribution and will communicate with the Independent Data Monitoring Committee (IDMC) that oversees the trial. The result of these analyses may be presented separately from the CSR.

The investigator must complete a special liver disease eCRF for any subject who:

- 1) discontinues treatment due to a liver-related AE,
- 2) reports a serious liver-related AE,
- 3) with normal screening levels develops ALT or AST levels  $\geq 3 \times$  ULN,
- 4) with normal screening levels develops BT levels  $\geq 2 \times$  ULN, or
- 5) with an abnormal screening liver test level develops abnormalities in that test that are  $> 2 \times$  the upper limit of their highest screening value.

All subjects meeting any one of the above criteria will also be asked to provide an additional set of blood and urine biomarker samples at the time of the event. Additional clinical testing (such as testing for hepatitis serology) may also be indicated and their results reported according to local guidelines.

The liver eCRF and Immediately Reportable Event (IRE) form (see [Section 5.3](#)) should be updated as new information becomes available.

### **3.7.3.5 Other Safety Assessments**

#### **3.7.3.5.1 Biomarker Plasma Samples**

Blood samples (10 mL) for potential biomarker analysis will be collected at the following times:

- second visit of the screening period
- end of the placebo run-in period (Day -36)
- end of the tolvaptan titration period (Day -22)
- end of the tolvaptan run-in period (Day -1)
- during the double-blind, randomized treatment period at Months 3, 6, 9, 12/EoTx
- at the last follow-up period visit
- during an episode of increased liver surveillance (due to AE or lab abnormality above set thresholds)

The blood sample will be taken following the PK sample at visits where both are collected, and processed similarly to the PK blood sample. Date and time of the blood sample, as well as the date and time of the last preceding dose should be noted in the eCRF.

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

#### **3.7.3.5.2 Biomarker Urine Samples**

A spot urine sample will be obtained at the following times:

- second visit of the screening period
- end of the placebo run-in period (Day -36)
- end of the tolvaptan titration period (Day -22)
- end of the tolvaptan run-in period (Day -1)
- during the double-blind, randomized treatment period at Months 3, 6, 9, 12/EoTx
- at the last follow-up period visit
- during an episode of increased liver surveillance (due to AE or lab abnormality above set thresholds)

This sample should be obtained prior to the subject eating breakfast, from the urine void taken after the first morning's void, and will ideally be provided as a mid-stream, clean-catch sample. To ensure a fasting urine sample is collected, subjects will be

provided with a sterile urine cup on the visit preceding the date of urine sample collection. Subjects will be instructed to collect a urine sample prior to eating breakfast, and to store the sample in the refrigerator until their clinic visit. Date and time of the urine sample, as well as the date and time of the last preceding dose of IMP, should be noted in the eCRF. This sample should be obtained from the same void as collected for the PD urine sample, when both samples are collected at the same visit.

All urine samples will be shipped to the central clinical laboratory for storage. Detailed handling and shipping instructions are in [Appendix 3](#).

### **3.7.3.5.3 DNA Blood Samples**

A blood sample for DNA collection will be obtained from every consenting subject at the second visit of the screening period. Samples may be collected at a subsequent visit if subjects provide consent after the second visit of the screening period.

All samples will be shipped to the central clinical laboratory. Detailed handling and shipping instructions are in [Appendix 3](#).

## **3.7.4 Pharmacokinetic/pharmacodynamic Assessments**

### **3.7.4.1 Pharmacokinetic Blood Samples**

Sparse samples will be taken for determination of plasma tolvaptan and metabolite(s), including DM-4103 concentrations. A 4 mL sample will be collected at the following times:

- end of the tolvaptan run-in period (Day -1)
- during the double-blind, randomized treatment period at Months 3, 6, 9, 12/EoTx
- at the last follow-up visit

The date and time of collection of the PK sample and the date and time of administration of the last preceding dose of IMP must be recorded on the eCRF for all on-treatment and EoTx samples. The last dose time for the off-treatment follow-up sample will be assumed to be the same as for the Month12/EoTx sample. The exact time of sampling relative to the previous IMP 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](#).

### **3.7.4.2      Pharmacodynamic Urine Samples**

A spot urine sample for determination of Uosm and specific gravity will be obtained at the following times:

- second visit of the screening period
- end of the placebo run-in period (Day -36)
- end of the tolvaptan titration period (Day -22)
- end of the tolvaptan run-in period (Day -1)
- during the double-blind, randomized treatment period at Months 3, 6, 9, and 12/EoTx
- at the last follow-up visit

This sample should be obtained prior to the subject eating breakfast, from the urine void taken after the first morning's void, and will ideally be provided as a mid-stream, clean-catch sample. To ensure a fasting urine sample is collected, subjects will be provided with a sterile urine cup on the visit preceding the date of urine sample collection. Subjects will be instructed to collect a urine sample prior to eating breakfast, and to store the sample in the refrigerator until their clinic visit.

Date and time of the urine sample, as well as the date and time of the last preceding dose of IMP for all on-treatment and EoTx samples, should be noted in the eCRF. The last dose date for the off-treatment sample will be assumed to be the same as for the Month 12/EoTx PD urine sample.

All urine samples will be shipped to the central clinical laboratory for analysis. Detailed handling, including volume of sample needed, and shipping instructions is provided in [Appendix 3](#).

### **3.7.5      End of Treatment/End of Trial**

Randomized subjects will have their last scheduled treatment 12 months from their date of randomization.

If a subject discontinues IMP before Month 12, the last date that the subject received IMP will be recorded as EoTx. See [Section 3.8.3](#) and [Section 3.10](#) for more information on EoTx rules for this trial.

The end of trial date is defined as the last date of last contact with the subject. This does not refer to overall trial duration. The end of trial date and timing for follow-up assessments will be individualized for each subject.

### **3.7.6      Independent Data Monitoring Committee**

For trials in high morbidity and/or high mortality disease, where efficacy endpoints could be subject to expedited reporting, the integrity of the clinical trial may be compromised if the blind is broken. For this trial, an IDMC, also known as a Data Safety and Monitoring Committee [DSMC]) will be established. The role of the IDMC shall be delineated in a separate IDMC Charter document, but in general this group will meet on a regular basis 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. Adjudication results as determined by the HAC will be reported to the IDMC on a quarterly basis or more frequently as necessary. 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 detailed in their Charter.

## **3.8      Stopping Rules, Withdrawal Criteria, and Procedures**

### **3.8.1      Entire Trial or Treatment Arm(s)**

If the sponsor terminates or suspends the trial for safety or unanticipated other reasons, prompt notification will be given to investigators, IRBs/IECs, and regulatory authorities in accordance with regulatory requirements.

### **3.8.2      Individual Site**

The investigator will notify the sponsor promptly if the trial is terminated by the investigator or the IRB/IEC at the site. If the investigator, IRB/IEC or sponsor decides to terminate or suspend the trial's conduct at a particular center for safety, non-enrollment of subjects, non-compliance with the protocol, 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 Discontinuation**

#### **3.8.3.1      Subjects Discontinued Prior to Randomization**

Subjects discontinued during the pre-randomization period will be designated as either a “Screen failure” or “Run-in failure”. During the screening period, if a subject withdraws their consent or fails to meet all of the requirements to continue in the trial, that subject will be considered a “Screen failure”. Subjects who fail to meet trial requirements during the screening period may be rescreened at a later date.

Screen failure subjects will be recorded as such on the eCRF. Screen failure subjects do not require follow-up and can be considered for rescreening if the reason for the screen failure was not that the subject withdrew their consent. If rescreened, the subject will sign a new informed consent, will be assigned a new screening number, and will repeat all screening procedures.

During the remainder of the pre-randomization period (placebo run-in, tolvaptan titration, or tolvaptan run-in periods), if a subject discontinues or is discontinued that subject will be considered a “Run-in failure”. A subject may be considered a “Run-in failure” for any of the following reasons:

- Subject does not meet entry requirements (ie, subject cannot tolerate IMP treatment as specified for a particular pre-randomization period - see [Section 3.2.1](#)),
- Subject decides to formally withdraw consent and/or fails to return for subsequent appointments at the trial site, or
- Investigator considers the subject unsuitable for further participation.

Run-in failure subjects will be recorded as such on the eCRF. Run-in failure subjects will complete an EoTx visit upon withdrawal from the trial. The EoTx visit assessments will include: collect vital signs, physical examination, serum creatinine assessment, clinical laboratory assessments, collect PK/PD samples and biomarker urine/plasma samples. Run-in failure subjects will then be followed up after 7 days with a phone call to record any ongoing AEs (as specified in [Section 5.6](#)); unless the subject fully withdraws consent to any further follow-up by written documentation.

### **3.8.3.2 Treatment Interruption**

In this year-long trial, it is expected that subjects may have one or more treatment interruptions during the double-blind, randomized treatment period. If a subject’s IMP treatment must be interrupted for medical or surgical reasons; liver test abnormalities; use of a prohibited concomitant medication; or other reasons (eg, hospital admission for an invasive procedure, a major medical condition, surgery; dental work, or a temporary situation that prevents subject compliance with the IMP administration schedule), the subject’s IMP should be resumed as early as the situation allows (see [Section 3.8.3.4](#)).

Any IMP interruption of < 7 consecutive days will be recorded as missed doses rather than as a temporary interruption of IMP. The subject should immediately inform the investigator of any missed doses reaching or expected to be 2 days or more so that the investigator can continue to monitor the subject’s treatments and prepare for a possible 7-day IMP interruption.

An IMP interruption that lasts  $\geq$  7 consecutive days will be recorded as a “7-day Treatment Interruption” on the eCRF and the subject will visit the clinic to collect vital signs, physical exam, serum creatinine assessment, clinical laboratory assessments, PK/PD samples, and biomarker urine/plasma samples. It is assumed that an interruption of this duration may become permanent, therefore the subject will have a total of 3 samples collected for serum creatinine measurements (in the 2-week period beginning on the 7th day and including the above-mentioned serum creatinine assessment). Treatment may still be restarted during or after these assessments are completed; any remaining serum creatinine assessments will not need to be completed if treatment is restarted during this period. If treatment is restarted, and the subject continues to Month 12, the subject will complete the Month 12 visit and scheduled follow-up assessments; the 7-day Interruption assessments will be considered as unscheduled. This procedure is aimed at ensuring data for the primary endpoint will be collected from all subjects.

### **3.8.3.3 Treatment Discontinuation**

After randomization, a subject may stop treatment permanently before Month 12 for a variety of reasons. Treatment discontinuations may be initiated by a subject who is not satisfied with treatment or may become medically necessary due to AEs or other issues, as determined by the investigator (see [Section 3.8.3.4](#)). However, each investigator must comprehensively review the circumstances and offer the subject options for continued treatment to the degree possible as described in [Section 3.8.3.5.1](#).

A subject who permanently discontinues treatment will be recorded as an IMP discontinuation on the eCRF. They will have an EoTx visit, which should be scheduled as soon as possible after the subject’s last dose of IMP, to collect vital signs, physical exam, serum creatinine assessment, clinical laboratory assessments, PK/PD samples, and biomarker urine/plasma samples. The subject’s follow-up period will be 3 weeks, as though they had reached the Month 12 visit, and the follow-up period will start after the last day of treatment, which may be a different day from the EoTx visit. No follow-up assessments will be taken during the first week of this period. There will be three visits in the follow-up period between Day 8 and Day 21. The first two will be for the collection of serum creatinine measurement and the third will have additional safety, efficacy, PK, and PD measurements. After the follow-up period, **the subject will continue with all assessments up to and including their scheduled Month 12 visit**, but will not be required to complete follow-up beyond that visit.

### **3.8.3.4 Documenting Reasons for Treatment Interruption/Discontinuation**

A subject may temporarily interrupt or discontinue IMP for a number of reasons including those listed below:

- Reasons related to AE:
  - Subject could not tolerate IMP due to an AE which is annoying or uncomfortable but not serious or hazardous
  - Physician determined that there are potential IMP related safety concern or SAE placing subject at undue hazard
  - Serious adverse event (SAE)
  - Progression of disease leading to dialysis, transplantation or eGFR decline as determined by the investigator
  - Liver test abnormalities meeting criteria for permanent discontinuation (see [Section 3.7.3.4](#))
  - Clinical signs of DILI (eg, jaundice, right upper quadrant pain)
- Death
- Reasons unrelated to medical condition (eg, pregnancy, trial too burdensome)
- Withdrawal of informed consent (partial related to IMP or complete from the trial)
- Lost to follow-up (Detailed procedures to prevent subjects from becoming “lost to follow-up will be provided in the operations manual. These procedures must be followed by the investigator, their staff or other designated trial personnel.)
- Termination of all or part of the trial by the sponsor
- Taking marketed product for tolvaptan (discontinued subjects only)

If the subject temporarily interrupts or discontinues IMP due to an AE, the investigator, or other trial personnel, will make every effort to follow the event until it has resolved or stabilized. Follow up procedures in [Section 3.8.3.2](#) and/or [Section 3.8.3.3](#) must be followed. If the subject’s IMP is interrupted for a liver test abnormality or liver symptoms, procedures outlined in [Section 3.7.3.4](#) should be followed.

### **3.8.3.5 Withdrawal of Consent**

All subjects have the right to withdraw their consent from further participation in the trial at any time without prejudice. The investigator can also discontinue a subject’s participation in the trial at any time if medically necessary. Unless the subject provides their written withdrawal of consent or there is other written documentation by the investigator confirming the subject’s verbal intent to completely withdraw from the trial, subjects should be followed for all protocol-specified evaluations and assessments.

Complete withdrawal of consent requires a subject's refusal of ALL of the following methods of follow up (these methods of follow up will also be noted in the trial ICF):

- Participation in all follow-up procedures specified in the protocol (whether in-clinic, by telephone, or by an in-home visit).
- Participation in a subset of protocol specified follow-up procedures (by a frequency schedule and method as agreed by subject and staff).
- Participation in all regularly scheduled, study-related follow-up visits and EoTx visits.
- Contact of the subject by trial personnel, even if only by telephone, to assess current medical condition and obtain necessary medical or laboratory reports relevant to the trial's objectives.
- Contact of alternative person(s) who have been designated in source records as being available to discuss the subject's medical condition, even if only by telephone, mail or e-mail (eg, family, spouse, partner, legal representative, friend, neighbor, physician).
- Access to medical information from alternative sources (eg, hospital/clinic medical records, referring doctor's notes, public records, dialysis, transplantation or vital registries, social media sources).

Withdrawal of consent is a critical trial event and therefore should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a subject's intended withdrawal need to be completely understood, documented and managed to protect the rights of the subject and the integrity of the trial. A subject may initially express their desire to interrupt or discontinue IMP administration, which is not equivalent to a complete withdrawal of consent for further participation (see [Section 3.8.3.2](#) through [Section 3.8.3.4](#)). A subject may, however, indicate that further trial participation is creating a burden on their work or social schedule. Therefore, the investigator should follow the procedures outlined in [Section 3.8.3.5.1](#) to determine if the subject can continue participation in the trial if modifications to his/her treatment and/or schedule of assessments can be accommodated. Only subjects who withdraw their permission for all of the above degrees of follow-up are considered to have completely withdrawn their consent to participate in the study.

### **3.8.3.5.1        Procedures to Encourage Continued Trial Participation**

In all cases of impending IMP discontinuation or consent withdrawal, investigators will be given instructions to meet and discuss with the subject their options of continuing in the trial, preferably on therapy. The investigator should ensure understanding and documentation of the reasons for the subject's desire to withdraw consent.

If a subject in the double-blind, randomized treatment period wishes to withdraw from the trial:

- 1) The investigator should first seek to understand the subject's motivation and wherever possible make accommodations to prevent treatment discontinuation or complete withdrawal of consent and maintain the fullest compliance with the protocol assessments (eg, provide necessary travel reimbursement, in-home visits, alternate visit scheduling, including during weekends). If the subject's wish is to discontinue study medication only, proceed to Step 2.
- 2) Ask the subject, "Would you be willing to continue if your dose of medication was lowered?" If the answer is "Yes" titrate the subject's dose down 1 level (eg, from 90/30 to 60/30, from 60/30 to 45/15, or from 45/15 to 30/15 [with medical monitor approval]). Repeat this step if the subject continues to request withdrawal of consent. If the answer is "No" or if, once the 30/15 dose is reached, the subject continues to request withdrawal of consent, go to Step 3.
- 3) Ask the subject, "If we temporarily interrupt your trial medication would you be willing to later resume medication and continue with all visits and sample collections?" If the answer is "Yes", interrupt IMP but continue to follow all other trial procedures for the subject until the subject restarts treatment. If the subject does not resume treatment with IMP after 7 days, perform 7-day Interruption assessments and follow-up (see [Section 3.8.3.2](#)) and then resume IMP and continue with all other monthly assessments to the end of the trial. If the subject still wishes to withdraw from the trial, go to Step 4.
- 4) Ask the subject, "If we discontinue your trial medication permanently, would you continue with all visits and sample collections?" If the answer is "Yes", discontinue IMP, perform an EoTx visit, complete the follow-up period, and then continue with all other monthly assessments to the end of the trial (see [Section 3.8.3.3](#)). If the answer is "No" go to Step 5.
- 5) If further trial support or interruption or permanent discontinuation of study medication does not resolve the subject's issues, further accommodations such as less frequent visits or blood draws may be used (so long as adequate safety monitoring can be ensured for those continuing IMP). Less frequent visits or procedures must be offered only if they are required to maintain access to the subject's medical information and/or to encourage the subject to continue in the trial.

### **3.8.3.5.2 Procedures to Prevent "Lost to Follow-up"**

The investigator must make every effort to contact subjects who fail to return for scheduled visits so that they will not be declared "lost to follow-up". The following procedures should be followed at a minimum, with additional measures taken if unsuccessful.

- Contact all numbers for the subject and their listed contacts (to be collected in source at the subject's entry into the trial). This includes making calls after normal business hours or on holidays and weekends.
- Contact the subject's primary care physician, referring specialist, pharmacist or other health-care professional (using the contacts provided by the subject at entry to the trial).
- Send a text, e-mail and postal mail with certified (return-receipt requested) letters to all the subject's addresses and all contacts (as provided by the subject at entry to the trial).
- In-home visit at last address given.
- Review available medical records/notes for details of hospitalizations, clinic visits or other procedures which may indicate the status of subjects (as allowed through release of medical record forms to be completed by patient at trial entry).
- Utilize the internet to search for additional contact information (eg, reverse directory for phone numbers or new address information; Facebook, Linked-In, or other social media for status updates).
- Check local, regional and national public records to locate the subject or search for mortality status as allowed by law.

Once all these actions have been exhausted (and documented), then the sponsor clinical research associate or medical monitor should be contacted for additional guidance.

### **3.9 Screen Failures**

A screen failure is a subject from whom informed consent is obtained and is documented in writing (ie, subject signs an ICF), but who withdraws consent from the trial or does not meet all of the requirements, during the screening period, to continue in the trial (ie, subject does not enter the placebo run-in period).

Screen failure subjects are permitted to be re-screened. In the event that the subject is re-screened, a new ICF must be signed.

### **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 consumes all doses of the IMP.

For purposes of this trial, subjects who are randomized, take IMP up to Month 12 (-7/+2 days), and complete some or all of their required trial visits/assessments to the end of the trial (including the Month 12 visit AND at least 1 follow-up serum creatinine assessment) will be defined as "On-treatment completers".

Subjects who are randomized, take IMP but discontinue treatment prior to Day 358 (or never begin treatment), and complete some or all of their required trial visits/assessments to the end of the trial (including the Month 12 visit AND at least 1 follow-up serum creatinine assessment) will be defined as “Off-treatment completers”.

Subjects who are randomized, take IMP (or never begin treatment), but DO NOT complete the Month 12 visit AND at least 1 EoTx follow-up serum creatinine assessment will be defined as “Non-completers”.

Both On-treatment completers and Off-treatment completers will have the opportunity to enroll in a tolvaptan extension trial following their completion of this current trial. Non-completers who took IMP may only enroll in the tolvaptan extension trial with medical monitor approval. Non-completers who never took IMP during the double-blind, randomized period may not enroll in the tolvaptan extension trial.

### **3.11     Definition of Subjects Lost to Follow-up**

Subjects who cannot be contacted on or before their last trial visit and who do not have a known reason for discontinuation (eg, withdrew consent or AE) will be classified as “lost to follow-up” as the reason for withdrawal.

Every effort will be made by the investigator, or trial personnel, to contact the subject before the subject is declared lost to follow-up (see [Section 3.8.3.5.2](#)).

### **3.12     Subject Compliance**

Dispensing of IMP and reconciliation will be done monthly during the randomized treatment period. Subject compliance will be monitored by pill counts as drug is returned. In addition, tolvaptan metabolite DM-4103 concentrations will be determined and evaluated for consistency with reported dosing.

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 (whichever is greater) will be deemed non-compliant. Depending on the circumstances leading to non-compliance, the subject may be discontinued from IMP administration by the investigator and/or sponsor. A subject who proactively wishes to discontinue IMP administration, or has IMP discontinued by the investigator, will be encouraged to continue limited participation in the trial, as described in [Section 3.8.3.3](#).

### **3.13     Protocol Deviations**

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, IMP dispensing or subject dosing

error, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator or designee will contact the medical monitor at the earliest possible time by telephone. The investigator and sponsor will come as quickly as possible to a 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 site monitor.

## **4      Restrictions**

### **4.1      Prohibited or Restricted 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 ribonucleic acid (RNA) therapies, tolvaptan, and other vasopressin antagonists eg, OPC-31260 (mozavaptan), Vaprisol (conivaptan), or agonists (eg, desmopressin) 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 may be used intermittently, but not within 7 days of a urine assessment. Diuretics are not generally recommended in ADPKD due to their tendency to increase AVP levels through relative dehydration or volume depletion; thus, chronic use of diuretics (eg, for hypertension) will be prohibited due to potential endpoint interference and is an exclusionary criterion for this trial. Subjects 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. Some drugs are known to alter creatinine concentrations so, while not prohibited, subjects should alert their trial doctor, and any other health-care providers, to take this into consideration when considering changes in their prescribed or over-the-counter medications. A brief list would include: cimetidine, NSAID medications like aspirin or ibuprofen, chemotherapy drugs, and cephalosporin.

Since tolvaptan is a weak cytochrome P450 (CYP) 3A4 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.

<b>Table 4.1-1 CYP3A4 Inhibitors (Partial List)</b>			
boceprevir	clarithromycin	clotrimazole (if used orally)	indinavir
itraconazole	ketoconazole (if used orally)	lopinavir	mibefradil
nefazadone	nelfinavir	posaconazole	ritonavir
saquinavir	telaprevir	telithromycin	voriconazole

## 4.2 Dietary Restrictions and Recommendations

Restriction of excess dietary sodium and cooked meat 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 advanced ADPKD, particularly if there is evidence for a propensity for rapid progression. In the absence of alternate regional practices, restrictions of dietary salt < 5g/day and dietary cooked meat protein < 1 g/kg/day and to limit caffeinated drinks/foods should also be given (no more than 2 coffee equivalents per day).

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. Upon consent, all subjects should receive the recommendation to ingestion of at least 2-3 liters of fluid (including in solid, semi-solid, and liquid foods) per day, unless otherwise directed by your study doctor. This recommendation should start during screening and continue through the end of the trial. Additionally, subjects should ingest 1 to 2 cups of water before bedtime regardless of perceived thirst and replenish fluids overnight with each episode of nocturia. Dehydration will be monitored by subject self-assessment of changes in body weight and reporting of symptoms. Acute changes of > 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.

Subjects should be advised that the ingestion of pomelo, grapefruit, or Seville orange products would be expected to increase tolvaptan concentrations and these should be avoided. In the event of an unintentional ingestion of such products, the investigator may ask the subject to temporarily interrupt IMP. Subjects should be informed of regionally appropriate recommendations in the trial ICF.

## 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 AEs may be associated with this disorder and are endpoints in this trial, including urine concentration defects, hypertension, renal pain, renal infection, nephrolithiasis, hematuria, and ESRD. As such, these events are considered “expected” in this trial population and will not qualify for the purposes of regulatory expedited reporting (eg, Suspected Unexpected Serious Adverse Reaction [SUSAR] and investigational new drug [IND] safety reports).

These blinded events will be evaluated on a regular basis by the trial’s Medical Monitor and the sponsor’s Safety group. The trial’s IDMC will include a separate statistical support group who will be provided the randomization codes so that partially or fully unblinded review of data may occur in closed session to better assess risk/benefit in the trial population.

### 5.1 Definitions

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. For the purpose of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality.

A SAE includes any event that results in any of the following outcomes:

1. death
2. 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 that, had it occurred in a more severe form, might have caused death.
3. persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
4. requires in-patient hospitalization or prolongs hospitalization  
NOTE: A pre-scheduled hospitalization is not considered an SAE.
5. congenital anomaly/birth defect

6. other medically significant events that, based upon 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.

Non-serious AEs are all AEs that do not meet the criteria for a “serious” AE.

Immediately Reportable Event (IRE):

- Any SAE
- Any AE (whether serious or non-serious) that necessitates discontinuation of IMP.
- Any subject with a new liver test abnormality meeting the AE (whether serious or non-serious) or laboratory threshold criteria (whether considered an AE or not) for hepatic eCRF reporting.
- Any subject reporting an AE of special interest (eg, skin neoplasms or glaucoma).
- Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, it will mandate IMP discontinuation and must be reported on an IRE form to Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC). Pregnancy will only be documented on the AE eCRF if there is an abnormality or complication.
- Additionally, in the EU region, events involving overdose, misuse and abuse as well as reported lack of efficacy must also be reported as IREs.

Clinical Laboratory Changes: 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 an abnormal change from baseline for that subject, this is considered an AE.

Severity: Adverse events will be graded on a 3-point scale and reported as indicated on the eCRF. 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.

IMP Causality: Assessment of causal relationship of an AE to the use of the IMP

- Related:** There is a reasonable possibility of a causal relationship.
- Possibly related:** There is a reasonable causal relationship between the IMP and the AE. Dechallenge is lacking or unclear.
- Unlikely related:** There is a temporal relationship to IMP administration, but there is not a reasonable causal relationship between the IMP and the AE.
- Not Related:** There is no temporal or reasonable relationship to the IMP administration.

## **5.2 Eliciting and Reporting Adverse Events**

The investigator will periodically assess subjects for the occurrence of AEs. In order to avoid bias in eliciting AEs, subjects should be asked the following non-leading question: "How have you felt since your last visit?" All AEs (serious and non-serious) reported by the subject must be recorded on the source documents and eCRFs provided by the sponsor.

In addition, the sponsor must be notified immediately by telephone or fax of any immediately reportable events according to the procedure outlined below in [Section 5.3](#). Special attention should be paid to recording hospitalization and concomitant medications.

## **5.3 Immediately Reportable Events**

The investigator must immediately report within 24 hours after either the investigator or site personnel become aware of any SAE, new liver lab abnormality requiring special liver eCRF completion, or confirmed pregnancy, by telephone or by fax to Quintiles drug safety services as outlined in Appendix 1. An IRE form must be completed and sent by fax or overnight courier to the sponsor. (Please note that the IRE form is NOT the AE eCRF.)

Non-serious events that require discontinuation of IMP (including laboratory abnormalities) should be reported to the sponsor within 3 working days. The IRE form must be completed and sent by fax or overnight courier to the sponsor.

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.

For subjects discontinued from IMP, vital status and scheduled laboratory data will continue to be collected at scheduled monthly visits and at trial termination.

#### **5.4      Pregnancy**

Women of childbearing potential who are sexually active must use an effective method of birth control during the course of the trial and for 30 days after the last dose of IMP in a manner such that risk of failure is minimized. Unless the subject is sterile (ie, women who have had a bilateral oophorectomy and/or hysterectomy or have been postmenopausal for at least 12 consecutive months) or remains abstinent, 2 of the following precautions must be used: vasectomy, tubal ligation, intrauterine device, birth control pills, birth control depot injection, birth control implant, condom or occlusive cap (diaphragm or cervical/vault caps) with spermicide. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy.

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

- General information.
- ICF.
- 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 informed consent form stating that the above-mentioned risk factors and the consequences were discussed with her.

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 IMP or be enrolled in the trial. If pregnancy is suspected while the subject is receiving treatment, IMP 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, IMP will be interrupted or withheld in an appropriate manner (eg, dose tapering if necessary for subject safety) and the

subject will continue to be monitored for the duration of the remainder of the trial or of their pregnancy. Subjects who permanently discontinue IMP due to pregnancy may continue to be monitored in the same manner as other subjects to their 12-month visit and will be considered trial Off-treatment completers.

The investigator must immediately notify the sponsor of any pregnancy associated with IMP exposure during the trial and for 30 days after the last dose of IMP and record the event on the IRE form and forward it to the sponsor. The sponsor will forward Pregnancy Surveillance Form(s) for monitoring the outcome of the pregnancy.

Protocol required procedures for IMP 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 is encouraged to contact the sponsor/Clinical Research Organization (CRO) medical advisor to discuss their rationale for unblinding. However, to prevent delays to the investigator or medical personnel responding to a potentially emergent situation, unblinding of IMP will not be dependent upon the investigator receiving approval from the sponsor/CRO medical advisor (ie, the investigator will be able to obtain the code break information independent of the sponsor/CRO medical advisor). The investigator must contact the sponsor/CRO medical advisor by telephone with an explanation of the need for opening the treatment assignment code within 24 hours of opening the code. If the blind is broken, the sponsor's Clinical Safety and Pharmacovigilance department (contact information provided in Appendix 1) will 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. Once the blind is broken for a given subject, that subject may not reinitiate treatment with IMP.

### **5.6 Follow-up of Adverse Events**

For this trial, AEs will be followed up for 7 days in subjects who discontinued prior to randomization and for 21 days after the last dose of IMP has been administered (follow-up period) in subjects who were randomized.

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.

For subjects who have discontinued IMP but have not withdrawn from the trial, vital status, AEs, concomitant medications, ESRD status, and scheduled laboratory data (including serum creatinine data) are planned to be collected regardless of IMP discontinuation until the scheduled end of the trial.

### **5.6.1 Follow-up of Non-serious Adverse Events**

Non-serious AEs that are identified on the last scheduled contact must be recorded on the AE eCRF with the current status noted. All non-serious events that are ongoing at this time will be recorded as ongoing on the eCRF.

### **5.6.2 Follow-up of Post-Trial Serious Adverse Events**

Serious AEs that are **identified on the last scheduled contact** must be recorded on the AE eCRF page and reported to the sponsor according to the reporting procedures outlined in [Section 5.3](#). This may include **unresolved previously reported SAEs, or new SAEs**. The investigator will follow 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 will continue to report any significant follow-up information to OPDC up to the point the event has been resolved.

### **5.6.3 Follow-up and Reporting of Serious Adverse Events Occurring after Last Scheduled Contact**

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 IMP, should be reported to OPDC. 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 potentially IMP-related SAEs 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 OPDC up to the point the event has been resolved.

## **6 Pharmacokinetic and Pharmacodynamic Analysis**

### **6.1 Pharmacokinetic**

Tolvaptan (OPC-41061) plasma concentrations may be used for a population PK analysis (that would be reported separately).

The DM-4103 metabolite has a half-life of approximately 180 hours and, consequently, is a good marker of long term compliance with dosing. DM-4103 concentrations will be reviewed for consistency with IMP dispensing and return records in order to determine compliance. Concentrations will be plotted by gender (male, female, total population) and modal dose within the previous treatment period and treatment day.

### **6.2 Pharmacodynamic**

Urine osmolality and specific gravity will be summarized by treatment (tolvaptan or placebo) and time point using descriptive statistics. Baseline values will be from the sample obtained at the end of the placebo run-in period.

## **7 Statistical Analysis**

### **7.1 Sample Size**

#### **7.1.1 Sample Size Estimation**

In this sample size estimation, it is assumed that 3 calculations of eGFR will be obtained at baseline during a 3-week interval during screening (1-2 weeks) and placebo run-in (1 week), and another 3 calculations will be obtained post-treatment during a 2-week interval that begins 1 week after the end of treatment (3-week post-treatment follow-up). The mean of the 3 eGFR values observed during the screening and placebo-run periods will be set as the baseline and the mean of the 3 eGFR values observed during the post-treatment follow-up period will be set as the renal function measurement post-treatment. The timing of the baseline and post-treatment observations will be set to the median of the observation times in the 2-week interval, respectively. Thus, the pre-treatment baseline will be set at approximately 6 weeks prior to randomization, and the post-treatment renal function measurement will be set at approximately 2 weeks after the end of treatment.

Based on a Mixed Model Repeated Measurements (MMRM) analysis of the non-Japan CKD-3 subjects from Trial 156-04-251, the treatment difference in renal function at Month 12, based on the post-randomization baseline, is  $1.43 \text{ mL/min}/1.73 \text{ m}^2$ . However, the US FDA has expressed a concern that the onset and offset of tolvaptan's

hemodynamic effect may not be equal (the sponsor believes it is not possible to determine if the small differences observed are due to a random error). Thus, with an assumption that the absolute value of the offset eGFR increase is 25% less than the absolute onset decrease in eGFR, we may assume the treatment difference in renal function is  $1.07 \text{ mL/min}/1.73 \text{ m}^2$  in our sample size calculation.

To investigate the reduction in intra-subject variation achieved by taking the mean of an increased number of observations at baseline and post-treatment follow-up, and its impact on the sample size, we have to estimate the intra-subject error and inter-subject error.

One of the approaches in sample size calculation for this protocol is to use MMRM to estimate the intra- and inter-subject variances. In the ADPKD phase 3 trial 156-04-251, there was a pre-treatment baseline visit and two post-treatment follow-up visits, along with other on-treatment visits. Assume these data follow the following model (denoted as  $j = 0$  for baseline and  $j = 37$  for follow-up, as well as  $j = 4, 8, 12, \dots, 36$ ):

$$Y_{i,0} = \alpha_i + \varepsilon_{i,0} \quad (1)$$

$$Y_{i,j} = \alpha_i + \delta_{i,j} + \varepsilon_{i,j} \quad (2)$$

where  $\delta_{i,j}$ , as a random effect of change from pre-treatment baseline at visit  $j$  for subject  $i$ . These  $\delta_{i,j}$ s jointly follow a multivariate normal distribution with means being  $\delta_{P,j}$  for placebo subjects and  $\delta_{T,j}$  for tolvaptan subjects. Their individual variance is assumed to be  $\sigma_{\delta,j}^2$ . These  $\delta_{i,j}$ s are supposed to be correlated; however, their correlations are not utilized for the purpose of sample size calculation in this protocol. In addition,  $\alpha_i$ s are assumed iid to have a normal distribution,  $\varepsilon_{i,j}$  are assumed iid  $N(0, \sigma^2)$ , and these random variables are mutually independent. Then, the change from baseline data follows this common MMRM model

$$Y_{i,j} - Y_{i,0} = \delta_{i,j} - \varepsilon_{i,0} + \varepsilon_{i,j} = \zeta_{i,j} + \varepsilon_{i,j} \quad (3)$$

where  $\zeta_{i,j} = \delta_{i,j} - \varepsilon_{i,0}$ . Note that the variance of  $\zeta_{i,j}$  (denoted by  $\sigma_{\zeta,j}^2$ ) is equal to  $\sigma_{\delta,j}^2 + \sigma^2$ . This model becomes a one-way random effect model if we only consider the post-treatment follow-up visits for a treatment group. Thus, applying a one-way random effect model to the change from pre-treatment baseline to post-treatment follow-up data of placebo and tolvaptan respectively, in subjects who had both follow-up visits and baseline in 156-04-251,  $\sigma^2$  is estimated as 8.52 for placebo and 5.68 for tolvaptan. Take the average of these two estimates of  $\sigma^2$  to obtain an estimate of  $\sigma^2$  as 7.1 to be used in this sample size calculation, which is the  $\sigma^2$  for Month 12 visit of 156-04-251. Note that

$$\text{Var}(Y_{i,j} - Y_{i,0}) = \sigma_{\delta,j}^2 + 2\sigma^2 \quad (4)$$

At Month 12, the SD (Standard Deviation) could be assumed as 6.5, based on CKD Stage 3 non-Japan subjects in 156-04-251. Then based on (4),  $\sigma_{\delta,j}^2$  at Month 12 is estimated as 28.05 ( $= 6.5^2 - 2 \times 7.1$ ).

With k repeated measurements at pre-treatment baseline and at 12 month post-treatment follow-up in this trial, the baseline intra-subject variance and the follow-up intra-subject variance are reduced from  $\sigma^2$  to  $\sigma^2/k$  respectively. Thus, the variance of average change from average baseline at Month 12 is  $(\sigma_{\delta,12}^2 + \sigma^2/k) + \sigma^2/k$ , which is estimated as 31.6 ( $= 28.05 + 7.1/4 + 7.1/4$ ) when k = 4 and 32.8 ( $= 28.05 + 7.1/3 + 7.1/3$ ) when k = 3. Here we have the following table of sample size:

<b>Table 7.1-1</b>		<b>Total Sample Size with Change = 1.07 and 10% Dropout Rate (Alpha = 0.05)</b>			
<b># of Blood draws</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	
90% power	1722	1434	1336	1288	
85% power	1477	1230	1146	1106	
80% power	1286	1070	998	962	

From the sample size table, the increase of repeated measurement at baseline and follow-up reduces the sample size significantly initially but quickly loses its effect when k is greater than 3. It seems that 3 repeated measurements may be appropriate in order to avoid subjects' burden. Thus, with an assumption of 10% dropout rate in the trial, the total sample size (randomized subjects) would be approximately 1300.

In order to avoid excessive blood draws, mechanisms were undertaken to minimize the intra-subject variability by standardizing, as much as possible, the timing and conditions by which serum creatinine was assessed (in particular recommending a similar diet, avoiding variation in protein, especially cooked meat protein, intake and exercise pattern during these periods). In addition to the efforts to reduce variability by standardizing subject diet at the time of blood draws, the number of scheduled blood draws will help establish precision in the estimated measurements.

For the sample size of the key secondary endpoint, longitudinal analysis specified in the SAP of from Trial 156-04-251 was applied to the eGFR data of CKD-3 non-Japan subjects using post-randomization baseline, to obtain the estimates of the variance of inter-subject eGFR slope ( $4.39 \text{ mL/min}/1.73 \text{ m}^2$  per year) and the variance of intra-subject eGFR observations ( $22.45 \text{ mL/min}/1.73 \text{ m}^2$ ). The power calculation using the sample size formula provided by Lefante<sup>21</sup> assumes the following:

- 1) placebo subjects would have an eGFR decline of  $4.5 \text{ mL/min}/1.73 \text{ m}^2$  per year;

- 2) tolvaptan subjects would have an eGFR decline reduced 25% compared with placebo subjects;
- 3) treatment duration is 1 year with monthly observations in eGFR.

In addition, the 1:1 randomization and the alpha (0.05, 2-sided) specified above in the sample size of the primary endpoint are also assumed in the sample size calculation. It is then estimated that 734 subjects are required for 90% power. Thus, with a total sample size of approximately 1300, the key secondary endpoint will have more than 90% power in detecting a slope difference in this trial.

### **7.1.2 Blinded Sample Size Re-estimation**

Blinded sample size re-estimation will be conducted when at least a third of the planned randomized subjects (400 to 500) have been randomized. This is expected to be conducted before the availability of any post 12-month off-treatment follow-up eGFR data used for the primary analysis. The goal of this blinded sample size re-estimation is to check: 1) the differences between the observed variances and the variances used in the sample size calculation; 2) whether the approach of averaging the 3 eGFR observations at pre-treatment baseline and post-treatment follow-up has achieved the goal of reducing the variance to the level planned. This sample size re-estimation is necessary, especially, as recommended by our vendor, a method to analyze for serum creatinine called Rate Blanked is to be used in this protocol, while the sample size calculation is based on the data from 156-04-251, in which another method called “Enzymatic” was used to analyze for serum creatinine. Based on these findings, the serum creatinine sample number and subject sample size of this trial may need to be adjusted. Detailed procedure of the blinded sample size re-estimation will be provided in the SAP.

## **7.2 Datasets for Analysis**

The following datasets are defined for this trial:

- Randomized Population: All subjects who are randomized in this trial.
- Randomized Safety Population: All subjects who are randomized in this trial and take at least 1 dose of IMP after randomization. This is the primary safety population.
- Treated Safety Population: All subjects who take at least 1 dose of IMP during the tolvaptan titration/run-in periods. This is a secondary safety population.
- Primary Endpoint Efficacy Population: All subjects who are in the Randomized Population, take at least 1 dose of IMP after randomization, and have a baseline and at least 1 valid post-treatment evaluation in eGFR (ie, after at least 1 week off treatment). The primary endpoint’s baseline is defined as the average of up to 3 eGFR values observed during the screening and placebo run-in periods.

- Key Secondary Endpoint Efficacy Population: All subjects who are in the Randomized Population, take at least 1 dose of IMP after randomization, and have a baseline and at least 1 post-randomization evaluation in eGFR during the double-blind treatment period. This is similar to the Primary Endpoint Efficacy Population, except that post-treatment evaluation in eGFR is replaced by a post-randomization evaluation.

The core subject population for all efficacy analyses is based on the intent-to-treat (ITT) population which consists of all randomized subjects who take at least one dose of IMP post randomization. As will be described below, in order to handle missing and restrictions imposed by different types of analyses (eg, change from baseline analysis), datasets based on modified ITT population will be used in the efficacy analyses.

The Observed Cases (OC) dataset of this protocol is defined as the data observed at study specified visits. For the primary outcome variable of this protocol, the OC dataset consists of the pre-treatment baseline (average of eGFR observed in screening period and the first eGFR observed in placebo run-in period) and post-treatment follow-up (average of eGFR observed in a two-week interval which is one week post the last IMP dose). For the key secondary outcome variable of this protocol, the OC dataset within treatment period is defined as the data observed at study specified visits while subjects are taking IMP or within 24 hours of the last IMP dose.

### **7.3 Handling of Missing Data**

The eGFR estimated by the CKD-EPI formula is utilized as the primary efficacy assessment in this trial.

In this protocol, all data collected in the pre-treatment baseline and post-treatment follow-up periods (except the week immediately after treatment withdrawal) will be used and missing data will not be imputed in deriving the pre-treatment and post-treatment eGFR observations used for the primary analysis.

For sensitivity analyses of the primary analysis, in general, missing data will be handled by analysis using mixed model methodology under the assumption of “missing at random” (MAR). However, the possibility of “missing not at random” (MNAR) data can never be ruled out. Thus, every effort will be made to follow the subjects who discontinue IMP after randomization without withdrawing consent for follow-up of their eGFR assessments. When collected within the last 2 weeks of the 3 weeks immediately post IMP withdrawal, the data will be included in the primary analysis. Otherwise, eGFR assessments collected during or after this period will be included in the sensitivity analysis. Additional sensitivity analysis will be conducted for the key secondary

endpoint for all subjects who withdraw consent or who are lost to follow-up, using multiple imputation methodology under appropriate assumptions. These sensitivity analyses are described in [Section 7.4.2.4](#) and more detail will be provided in the SAP.

## 7.4 Primary and Secondary Outcome Analysis

This trial's estimand is the difference in outcome improvement if all subjects tolerated and adhered to their treatment. To enrich this population, only subjects who can tolerate the tolvaptan titration and run-in periods will be randomized. This approach combines estimands #2 and #3 as recommended by the 2010 National Academy of Sciences' NRC report on prevention and treatment of missing data<sup>14</sup> where estimand #2 is "difference in outcome improvement in tolerators" and "estimand #3 is "difference in outcome improvement if all subjects tolerated or adhered". Thus, MAR data is assumed in the primary analysis. Sensitivity analysis will be provided to address the concern of MNAR data.

This estimand focuses on the efficacy of tolvaptan in slowing renal function decline. The objective of this trial is to confirm a causal effect of tolvaptan in slowing renal function decline, consistent with the selection of an efficacy rather than an effectiveness estimand.

An effectiveness estimand compares treatment policies and reasonably could include data acquired long after withdrawal from the trial (eg, when subjects discontinue tolvaptan but are followed for many weeks or months) or move to an alternate treatment regimen (eg, placebo subjects being prescribed commercial tolvaptan upon approval for ADPKD). In the absence of an approved and effective alternate treatment for ADPKD; it is premature to discuss treatment policies. Thus, while eGFR data collected in the second and third week post-withdrawal are used for the analysis of the primary endpoint, data collected long after withdrawal or after a subject moves to an alternate treatment regimen will be excluded in the primary analyses of both the primary and the key secondary endpoints.

### 7.4.1 Primary Efficacy Outcome Analysis

#### 7.4.1.1 Primary Endpoint Analysis

The primary endpoint of this trial is the change in eGFR (calculated by the CKD-EPI formula) from pre-treatment baseline to post-treatment follow-up, annualized (divided) by each subjects' IMP treatment duration. This normalization is necessary, otherwise the treatment group having more dropouts or more earlier dropouts may assume an unfair advantage. To reduce the variation in this primary endpoint, 3 observations of eGFR will be obtained at baseline during a 3-week interval (screening and placebo run-in periods)

and another 3 observations will be obtained post-treatment during a 2-week interval that begins 1 week after the end of treatment (3-week post-treatment follow-up). The average of the 3 eGFR values observed during the baseline period is set as the baseline and the average of the 3 eGFR values observed during the post-treatment follow-up period is set as the renal function measurement post-treatment. Timings of baseline and post-treatment follow-up observations are set to the median of the time of these observations in the respective 2 to 3-week intervals, and the duration is equal to the timing of baseline minus the timing of post-treatment follow-up plus 1.

Use of the duration to annualize the change is also reasonable since it will provide an “estimate” of annualized eGFR change in slope for each subject, though there is no estimate for intra-subject variation. Thus, a weighted analysis of covariance (ANCOVA) with effects of treatment and randomization stratification factors and covariate baseline will be applied to these “estimated slopes” as the primary analysis. This weighted analysis is based on the reciprocal of the estimated variance of the “estimated slopes,” and the detailed algorithm to derive the estimated variance is provided in Section 8.3 of the SAP.

#### **7.4.1.2      Sensitivity Analysis of the Primary Endpoint**

Aligned with the desire to evaluate effects free from acute hemodynamic treatment effects, a sensitivity analysis of the primary endpoint will be performed including all available placebo data. In this sensitivity analysis, in addition to the 3 pre-treatment baseline observations and the 3 post-treatment follow-up observations, all post-randomization on-treatment eGFR observations in the protocol-specified visits for placebo subjects will also be included. The linear mixed effect model with effects of time (as a continuous variable), treatment, and time-treatment interaction, randomization stratification factors and baseline as covariate will be used to fit the eGFR data, in which the intercept and time are both a fixed effect and a random effect. An un-structured variance covariance matrix is assumed for the random intercept and time. The time variable used in the model may start from the first observation of eGFR baseline as mentioned in [Section 7.1.1](#), and this baseline will be used in the model. Missing data will be ignored in this analysis under the MAR assumption. Data acquired while taking tolvaptan cannot be used in this analysis without appropriate adjustment, but is evaluated in the key secondary efficacy endpoint of eGFR slope with a methodology which takes the acute hemodynamic drug effects of tolvaptan into account.

#### **7.4.1.3 Sensitivity Analysis Including Data from Subjects Who Discontinue IMP**

This sensitivity analysis deviates from the MAR assumption to include the post-discontinuation follow-up data in the analysis specified in the primary analysis section. Subjects who discontinue IMP after randomization without withdrawing consent will be followed for additional off-treatment eGFR values up to Month 12. These post “post-treatment follow-up” eGFR data at Month 12 will be included to replace the data observed during post-treatment follow-up for the subjects who discontinue IMP early in a sensitivity analysis using the same analytic approach specified in the primary analysis section.

#### **7.4.2 Secondary Outcome Analyses**

In addition to the key secondary efficacy endpoint described below, safety variables will also be analyzed as secondary outcomes in this protocol (see [Section 7.6](#)).

##### **7.4.2.1 Key Secondary Endpoint Analysis**

The key secondary endpoint of the trial is the annualized rate of eGFR change, which is derived from each individual subject’s eGFR slope using the CKD-EPI formula. Slope is preferred as a practical and clinically meaningful endpoint. In this analysis, all eGFR observations from placebo run-in, tolvaptan run-in (not including tolvaptan titration), double blind treatment, and post-treatment follow-up (not including data collected in the first week after the last IMP dose) periods will be included in the analysis, with the data from tolvaptan run-in and tolvaptan subjects in the double-blind treatment period flagged (yes = 1 and no = 0) for a tolvaptan acute hemodynamic effect.

The linear mixed effect model with effects of time (as a continuous variable), treatment, time-treatment interaction, acute hemodynamic effect, pre-treatment baseline (of the primary endpoint), and randomization stratification factors will be used to fit the GFR estimates, in which the intercept and time are both a fixed effect and a random effect. An un-structured variance covariance matrix is assumed for the random intercept and time.

The time variable used in the model may start from the first observation of eGFR obtained from placebo run-in period. The covariate “acute hemodynamic effect” in the model is the flag variable with value of 0 and 1 specified earlier in this section for the data observed during tolvaptan run-in and the data observed for tolvaptan subjects during the double-blind treatment period. The starting point of this eGFR slope analysis is the eGFR observation during the placebo run-in period.

#### **7.4.2.2 Sensitivity Analysis of the Key Secondary Endpoint**

This sensitivity analysis of the key secondary endpoint of this trial is to compare the linear trend of eGFR between tolvaptan and placebo groups. The advantage of this sensitivity analysis is that it does not depend on the assumption of linearity and equal tolvaptan hemodynamic onset and offset effects used in [Section 7.4.2.1](#). The change from the pre-treatment baseline during the on-treatment visits in the double-blind treatment period will be included in the analysis. Since the hemodynamic effects of tolvaptan are believed to begin to reverse within 1-2 days, on-treatment will be defined as within 24 hours of the last IMP dose.

Analysis of MMRM will be applied to the data of change from baseline in eGFR in each month from Month 1 to Month 12. The model will have fixed effect of treatment, visit, treatment visit interaction, randomization stratification factors, and covariate baseline and baseline visit interaction. An unstructured variance-covariance matrix is assumed for the repeated measurements. A linear contrast of the treatment differences in these 12 months will be used as the sensitivity analysis of the key secondary endpoint.

#### **7.4.2.3 Sensitivity Analysis Including Data from Subjects Who Discontinue IMP**

This sensitivity analysis deviates from the MAR assumption to include the post-discontinuation follow-up data in the analysis of the key secondary endpoint. Subjects who discontinue treatment after randomization without withdrawing consent will be followed for additional eGFR (not including the eGFR observed in the 3-week follow-up period immediately after EoTx) up to Month 12. The data collected during this time will not be included in the key secondary endpoint analysis for the reasons given above. However, a sensitivity analysis including these data for the key secondary analysis will be performed. This analysis uses the same approach provided in [Section 7.4.2.1](#) for the analysis of the key secondary endpoint.

#### **7.4.2.4 Sensitivity Analysis Including Imputation of Missing Data**

Multiple imputation is commonly used in the analysis of MNAR data. For all randomized subjects who withdraw consent for further testing or who are lost to follow up, imputation of missing data will be applied to projected visits up to their planned end of the trial (12 months post-randomization). The subjects' reasons for discontinuation will be captured and categorized to help determine the missing data pattern (see [Section 3.8.3.4](#)). Imputation will be based on the MMRM model specified in [Section 7.4.2.2](#). For placebo subjects, and in the absence of evidence suggesting biased missing data pattern, the imputation will follow the placebo trend.

Post-withdrawal data from Trial 156-04-251 and Trial 156-08-271 interim analyses show that tolvaptan's eGFR benefits accumulate and are sustained after treatment discontinuation; therefore, imputation for subjects randomized to tolvaptan should reasonably begin at the value of their last eGFR. If a subject has the post-treatment follow-up in the two-week interval, imputation will be based on this post-treatment observation; if a subject does not have the post-treatment follow-up observation, imputation will be based on the last on-treatment observation and flagged with the tolvaptan acute hemodynamic effect mentioned in [Section 7.4.2.1](#).

Trial 156-04-251 data also support true disease modification and preservation of functioning kidney parenchyma through reduction of cyst growth. Thus, discontinuation of tolvaptan would not result in an immediate return to the placebo trend. Therefore, eGFR decline in subjects discontinuing tolvaptan will reasonably fall somewhere between the tolvaptan trend and placebo trend. This supports a series of analyses for imputation of missing data for tolvaptan subjects, which will begin using the tolvaptan trend, and move stepwise toward the placebo trend. Further details will be provided in the SAP.

### **7.4.3 Subgroup Efficacy Analysis**

Subgroup analyses will be provided for the primary and the key secondary endpoints by regions (US and non-US), gender (male and female), race (Caucasian and Other), age ( $\leq 55$  years,  $> 55$  years), baseline GFR level (eGFR  $\leq 45$  mL/min/1.73 m $^2$  and  $> 45$  mL/min/1.73 m $^2$ ) and three baseline TKV criteria ( $\leq 2000$  mL,  $> 2000$  mL, or unknown).

### **7.4.4 Exploratory Analyses**

#### **7.4.4.1 Analysis of Efficacy Based on Modal Doses**

Exploratory analyses will be applied to the primary and the key secondary endpoints with tolvaptan subjects coded by their modal doses in the trial, using the same analytic approaches specified for these endpoints.

#### **7.4.4.2 ADPKD Outcomes**

Assessment of ADPKD outcomes is an exploratory endpoint in this protocol.

Exploratory analysis will be applied to each outcome as well as to a composite of those outcomes which are more closely related to kidney enlargement as potential events.

Analysis of time to multiple events will be applied. Detailed analysis procedures will be provided in the SAP.

#### **7.4.4.3 DNA and Urine and Plasma Biomarkers**

Investigations into possible risk factors and mechanisms underlying DILI as the result of tolvaptan exposure are currently ongoing. Urine and plasma biomarker concentrations may be evaluated for metabolic or immunologic traits related to DILI and/or etiology of, susceptibility to, activity of, or progress of ADPKD, as well as the potential development of tools for diagnosis, prognosis and response to treatment.

Consenting subjects may have DNA samples evaluated for genetic evaluation of DILI and/or etiology of, susceptibility to, activity of, or progress of ADPKD, as well as the potential development of tools for diagnosis, prognosis and response to treatment. The types of analyses that are planned are for genetic mutations of PKD1 and PKD2, which code for the proteins polycystin-1 and polycystin-2, respectively, in renal tubular cells and are responsible for approximately 85% (PKD1) and 15% (PKD2) of clinical cases of ADPKD. Genes involved with ADPKD's phenotypic manifestations (eg, other genes associated with high or low penetrance, non-renal manifestations of ADPKD such as liver or vascular disease, and accelerated versus slow progression of kidney failure) may also be analyzed. Genotyping for drug metabolizing enzymes and transporters by microarray is also envisioned. A potential link between genetic mutations of the genes coding for CYP3A4, the enzyme system primarily responsible for the metabolism of tolvaptan, or other enzymes and transporters involved in tolvaptan metabolism and transport into and out of the liver may be explored. Also, an experiment involving genotyping for human leukocyte antigen mutations may be explored that could be related to an immune-mediated response to tolvaptan treatment.

Samples from this trial may be analyzed as part of these investigations and may be reported separately.

#### **7.4.5 Interim Analysis**

This trial is to be conducted over a critical time period during which tolvaptan may be approved as therapy for ADPKD in some of the participating regions. The European Medicines Agency's (EMA) decision for a pending marketing authorization application for the use of tolvaptan in treatment of ADPKD is expected in 2015. Following regulatory approval, reimbursement and commercial availability may have an impact on the ongoing ethical conduct of the trial. This may impact subjects enrolled in Europe who are continuing in the randomized, placebo-controlled treatment phase.

Therefore, the IDMC for this trial will be empowered to conduct an interim analysis (IA) of the primary endpoint once approximately half of enrolled subjects (600-700) are expected to complete their planned one-year treatment. The sponsor may decide the

actual timing of the IA to be conducted, based on the availability of commercial tolvaptan in ADPKD. This IA would use the O'Brian-Fleming spending function to apportion alpha and thus manage Type 1 error. Determination of the information time of the IA assumes total sample size in this trial to be set at 1300 if the trial is still randomizing subjects at the time of the IA. Alternatively, the actual total sample size will be used if the trial has stopped enrollment. For example, if the first 650 subjects out of 1300 total sample size are included, a p-value < 0.003051 is required to reject the null hypothesis, satisfy the objective of replicating efficacy, and offer a possibility for early trial completion. If a recommendation for early termination is accepted, all subjects remaining in the trial can be offered participation in a planned open-label extension trial. If the null hypothesis is not rejected at this interim evaluation, the trial would continue and the alpha of the final test of the primary endpoint would be 0.049002.

## **7.5 Analysis of Demographic and Baseline Characteristics**

Demographic characteristics, disease severity, and medical history at (pre-treatment) baseline will be summarized by descriptive statistics, eg, proportion, mean, median, standard deviation (SD), minimum and maximum values. These summary statistics will be reviewed to identify any potential lack of balance between the treatment groups.

## **7.6 Safety Analysis**

In general, baseline measurements of safety variables are defined as the last measurements prior to randomization for the primary Randomized Safety Population (except for serum creatinine, which is defined similarly to the baseline of eGFR assessment for the primary endpoint, see [Section 7.4.1.1](#)) and as their last measurements prior to the first dose of IMP for the secondary safety population (Treated Safety Population). Safety analyses will be conducted based on these safety populations, which are defined in [Section 7.2](#). Standard safety variables to be analyzed include AEs, self-reported tolerability, clinical laboratory data, physical examinations, and vital signs. Safety variables will be summarized by descriptive statistics, (eg, proportion, mean, median, SD, minimum, and maximum values). In general, summary statistics, including changes from baseline, will be provided for safety variables based on all available data.

### **7.6.1 Adverse Events**

All AEs will be coded by system organ class and Medical Dictionary for Regulatory Activities (MedDRA) preferred term. The incidence of the following events will be summarized by treatment group for the primary safety population; summary of these events will also be provided for the secondary safety population:

- a) Treatment-emergent AEs (TEAEs) by severity
- b) TEAEs potentially causally related to the IMP
- c) TEAEs with an outcome of death
- d) Serious TEAEs
- e) Discontinuations due to TEAEs

### **7.6.2 Clinical Laboratory Data**

Summary statistics for changes from baseline in the central clinical laboratory measurements will be provided for the primary and secondary safety populations. Potentially clinically significant results in laboratory tests identified using prospectively defined criteria, including criteria for liver enzyme elevations, will also be summarized for the primary and secondary safety populations. In addition, by-subject listings will be provided for data of local laboratory tests.

In addition, laboratory measurements that signal the potential for Hy's Law will be reported. An incidence table and a listing will be provided for subjects who meet one or combinations of following criteria, without initial findings of cholestasis (ALP activity  $> 2 \times$  ULN):

- ALT or AST  $\geq 3 \times$  ULN
- Bilirubin  $\geq 2 \times$  ULN

### **7.6.3 Physical Examination and Vital Signs Data**

By-subject listings will be provided for physical examinations. Summary statistics for changes from baseline in vital signs and potentially clinically significant results in vital signs will be summarized for the primary safety population as well as the secondary safety population.

## **8 Management of Investigational Medicinal Product**

### **8.1 Packaging and Labeling**

All IMP will be provided to the investigator(s) by the sponsor or designated agent as tablets of 15 or 30 mg tolvaptan (OPC-41061) or matching placebo. Each bottle used in the dosing period will be labeled to clearly disclose the subject identification number (ID), compound ID, trial number, sponsor's name and address, instructions for use, route of administration, appropriate precautionary statements, and other information required by local regulatory authorities. Any region-specific requirements will appear in the official language of the country in which the investigational product is to be used.

One or more bottles of the designated IMP will be dispensed at the beginning of the placebo run-in period, the tolvaptan run in period, and monthly during the double-blind, randomized treatment period.

For the tolvaptan titration period, subjects will receive 2 cartons at the first visit; one with a yellow label (Kit A) and one with a blue label (Kit B). Subjects will be instructed to start with Kit A and told how many tablets to take per day. Kit A can accommodate the following doses for titration:

- 30/15 – 2 tablets upon waking and 1 tablet approximately 8 to 9 hours later
- 45/15 – 3 tablets upon waking and 1 tablet approximately 8 to 9 hours later

Once the subject is ready to titrate to the 60/30 dose, the site will instruct the subject to start taking IMP from Kit B. Kit B can accommodate the following doses for titration:

- 60/30 – 2 tablets upon waking and 1 tablet approximately 8 to 9 hours later
- 90/30 – 3 tablets upon waking and 1 tablet approximately 8 to 9 hours later

If the subject cannot tolerate the doses in Kit B, he/she will be instructed to return to Kit A for dosing.

## **8.2 Storage**

All IMPs will be stored in a securely locked cabinet or enclosure. Access will be limited to investigators and their designees. Neither investigators nor any designees may provide IMP to any subject not participating in this protocol.

The IMP should be stored according to the conditions specified in the IMP 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 IMP (including investigational, active control, or placebo) received, dispensed, administered, and returned.

## **8.4 Returns and Destruction**

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

All IMP returned to the sponsor must be accompanied by appropriate documentation and be identified by protocol number with trial site number on the outermost shipping

container. Returned supplies should be in the original containers (eg, subject kits). The assigned trial monitor will facilitate the return of unused and/or partially used IMP.

## **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.

Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents 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;
- The date of the visit and the corresponding Visit or Day in the trial schedule;
- General subject status remarks, including any *significant* medical findings. The severity, frequency, duration, action taken, and outcome of any AEs and the investigator's assessment of relationship to IMP 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 each clinician (or designee) who made an entry in the progress notes.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above. Any changes to information in the trial progress notes and other source documents will be initialled and dated on the day the change is made by a site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data (so as not to obliterate the original 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 entered by investigative site personnel directly onto eCRFs in the sponsor's electronic data capture system. Changes to the data will be captured by an automatic audit trail.

### **9.3 File Management at the Trial Site**

The investigator will ensure that the trial site file is maintained in accordance with Section 8 of the ICH GCP Guideline and as required by applicable local regulations. The investigator/institution will 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 3 periods:

- A period of at least 2 years following the date on which approval to market the drug is obtained (or if IMP development is discontinued, the date regulatory authorities were notified of discontinuation); OR
- A period of at least 3 years after the sponsor notifies the investigator that the final report has been filed with regulatory authorities.
- Longer, region-specific storage requirements, if applicable.

The investigator must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) provision of an opportunity for sponsor to collect such records. The investigator will be responsible to maintain 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, due to relocation or 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 follow this trial carefully in a detailed and orderly manner in accordance with established research principles, the ICH GCP Guideline, and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the

progress of the trial), the sponsor's monitors will visit the site during the trial, as well as communicate frequently via telephone and written communications.

## **10.2 Auditing**

The sponsor's Quality Management Unit (or representative) may conduct trial site audits. Audits will include but are not limited to drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. The investigator agrees to participate with audits.

Regulatory authorities may inspect the investigator site during or after the trial. The investigator will cooperate with such inspections and will contact the sponsor immediately if such an inspection occurs.

## **11 Ethics and Responsibility**

This trial must be conducted in compliance with the protocol, the ICH GCP Guideline, and applicable local laws and regulatory requirements. Each trial site will seek approval by an IRB or IEC according to regional requirements. The IRB/IEC will evaluate the ethical, scientific and medical appropriateness of the trial. Further, in preparing and handling eCRFs, 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.

Financial aspects, subject insurance and the publication policy for the trial will be documented in the agreement between the sponsor and the investigator.

## **12 Confidentiality**

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior written permission. Subject confidentiality requirements of the region(s) where the trial is conducted will be met. However, authorized regulatory officials and sponsor personnel (or their representatives) will be allowed full access to inspect and copy the records. All IMPs, 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 eCRFs. 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 the sponsor's prior written consent 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 will be written by the sponsor. Each amendment will be submitted to the IRB/IEC. Except for "administrative" or "non-substantial" amendments, investigators will wait for IRB/IEC approval of the amended protocol before implementing the change(s). Administrative amendments are defined as having no effect on the safety of subjects, conduct or management of the trial, trial design, or the quality or safety of IMP(s) used in the trial. A protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately, followed by IRB/IEC notification within 5 working days. The sponsor will submit protocol amendments to the applicable regulatory agencies.

When the IRB/IEC, investigators, and/or the sponsor conclude that the protocol amendment 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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- <sup>2</sup> U S Renal Data System, USRDS 2012 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2012
- <sup>3</sup> Lentine KL, Xiao H, Machnicki G, Gheorghian A, Schnitzler MA. Renal function and healthcare costs in patients with polycystic kidney disease. *Clin J Am Soc Nephrol.* 2010 Aug;5(8):1471-9.
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## Appendix 1

### Names of Sponsor Personnel

Report Immediately Reportable Events (serious adverse events, potential Hy's Law cases, pregnancies and adverse events requiring discontinuation of trial drug) to:

Quintiles  
Clinical Safety and Pharmacovigilance  
5927 South Miami Blvd  
Morrisville, NC 27560, USA  
Phone: +1-866-599-1341  
Fax: +1-866-599-1342

**For Medical Emergencies** (use only if sponsor personnel listed above are unavailable):

+1 301-990-0030

#### Global Project Leaders

Global Clinical Director/ Medical Director (Program Lead)	Frank Czerwic, MD, PhD Sr. Director, Global Clinical Development Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Blvd. Rockville, MD 20850, USA Phone: +1 240-683-3523; Fax +1 301-721-7523
Global Clinical Director/ Medical Director (Project Lead)	Olga Sergeyeva, MD, MPH Assoc. Director, Global Clinical Development Otsuka Pharmaceutical Development & Commercialization, Inc. 506 Carnegie Center Drive Suite 200 Princeton, NJ 08540, USA Phone: +1 609-249-6643; Fax +1-609-249-0643

#### Global Clinical Management

Global Clinical Management

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## Appendix 2                  Institutions Concerned With the Trial

<b>Lead Principal (Communicating) Investigator/Steering Committee Chair</b>	Vicente E. Torres, M.D., Ph.D. Division of Nephrology, Mayo Clinic 200 First St. S.W. Rochester, MN 55905, USA Phone: +1-501-266-7093
<b>Independent Data Monitoring Committee Chair</b>	Sidney Goldstein, M.D. Henry Ford Hospital 2799 West Grand Blvd Detroit, MI 48202, USA Phone: +1-313-303-5728
<b>Hepatic Adjudication Committee Chair</b>	David H Alpers, MD William B Kountz Professor of Medicine Washington University School of Medicine St Louis, MO 63130, USA Phone: +1-314-362-8943 Fax: +1-314-362-8230
<b>Global Medical Monitoring</b>	Quintiles 5927 South Miami Blvd Morrisville, NC 27560, USA Phone: +1-214-505-6781 Mobile: +1-214-505-6781 Fax: +1-919-800-0095
<b>Study Management</b>	Quintiles 5927 South Miami Blvd Morrisville, NC 27560, USA Office: +1-262-361-4319 Mobile: +1-262-269-0199 Fax: +1-484-765-1823
<b>Safety Reporting</b>	Quintiles 5927 South Miami Blvd Morrisville, NC 27560, USA Phone: +1-866-599-1341 Fax: +1-866-599-1342
<b>Investigational Materials</b>	Almac 25 Fretz Rd Souderton, PA 18964, USA Phone: +1-215-660-8500
<b>Budget and Contract Negotiation</b>	INC Research, LLC 3201 Beechleaf Ct., #600 Raleigh, NC 27604, USA Phone: +1-919-876-9300
<b>Investigator Payments</b>	Quintiles 5927 South Miami Blvd Morrisville, NC 27560, USA Phone: +1-214-505-6781 Mobile: +1-214-505-6781 Fax: +1-919-800-0095
<b>Electronic Data Capture</b>	MediData Solutions 79 Fifth Avenue, 8th Floor New York, NY 10003, USA Phone: +1-212-918-1800 Fax: +1-212-918-1818

<b>IRT Systems</b>	Almac Clinical Technologies 25 Fretz Road Souderton, PA 18964, USA US Tel: +1-877-738-8831 RoW Tel: +44 (0) 28 3835 2121
<b>Home Nursing Services</b>	The Medical Research Network Ltd. 15 Presley Way Crownhill, Milton Keynes Buckinghamshire MK8 0ES Stuart Redding (Director) stuart.redding@themrn.co.uk Tel: 0800-032-2348 <a href="http://www.themrn.co.uk">www.themrn.co.uk</a>
<b>Patient Recruitment and Retention</b>	Matthews Media Group (MMG) 700 King Farm Blvd, 5th Floor Rockville, MD 20850, USA Phone: +1-301-984-7191 Fax: +1-301-921-4405
<b>Traveling Coordinator Assistant</b>	Princeton Medical 349 Route 206 South Hillsborough, NJ 08844, USA Phone: +1-908-240-6884 Fax: +1-716-809-3642
<b>Central Laboratory Services</b>	Covance Central Laboratory Services 8211 SciCor Dr. Indianapolis, IN 46214, USA Phone: +1-317-273-7852 Toll-free: +1-800-462-8885 ext 7852 Fax: +1-317-616-2354
<b>PK/PD Analysis</b>	ICON 8282 Halsey Rd. Whitesboro, NY 13492, USA Phone: +1-315-768-2500
<b>DNA Sample Storage</b>	Cancer Genetics, Inc. 133 Southcenter Court, Suite 400 Morrisville, NC 27560, USA Phone: +1-919-465-0100

## **Appendix 3            Handling and Shipment of Bioanalytical Samples**

### Handling of Specimens

All tubes must be labeled using the central laboratory's bar code labels provided with the sample collection kits. The central laboratory's requisition form must be completely filled out in regards to the all sample information. In addition, the subject ID number and date of collection must be hand-written on the sample tube. It is important to note the exact time of the blood collection on the eCRF.

Each specimen must be labeled using a waterproof pen. A label suitable for the storage conditions must contain the Subject ID number and date of collection, must correspond to the requisition form, and must be firmly attached. The requisition form must contain the name, address, and telephone number of the contact person from the trial site.

### Plasma PK Sample Collection

Collect blood samples to analyze tolvaptan and metabolite(s) concentrations using 4-mL draw collection tubes containing sodium heparin. After obtaining the blood sample, mix collection tube thoroughly by slowly inverting the collection tube 8-10 times. Place the collection tube in an ice/water bath. Within 45 minutes of collection, process collection tubes in a refrigerated centrifuge set at approximately 1300 g for 15 minutes at approximately 5°C. The separated plasma from the blood collection tube should then be divided equally between the 2 bar-code labeled polypropylene tubes. Within 90 minutes of collection, store both plasma aliquot samples at -70°C, except for brief periods on dry ice for shipment. If a -70°C freezer is unavailable, then the samples can be stored on dry ice for up to 1 week until a shipment to the central laboratory can be arranged.

### Plasma Biomarker Sample Collection

Collect blood samples for biomarker analysis using 10-mL draw collection tubes containing sodium heparin. After obtaining the blood sample, mix collection tube thoroughly by slowly inverting the collection tube 8-10 times. Place the collection tube in an ice/water bath. Within 45 minutes of collection, process collection tubes in a refrigerated centrifuge set at approximately 1300 g for 15 minutes at approximately 5°C. The separated plasma should then be divided between the bar-code labeled polypropylene tubes (number of aliquots will be defined in the operations manual). Within 90 minutes of collection, store plasma aliquot samples at -70°C, except for brief periods on dry ice for shipment. If a -70°C freezer is unavailable, then the samples can be stored on dry ice for up to one week until a shipment to the central laboratory can be arranged.

### Urine Biomarker Sample Collection

The PD/biomarker urine sample will be collected by the subject at home and transported to the site at room temperature. At the site, 20 mL of the sample should be immediately equally divided into the bar-code labeled polypropylene tubes (number of aliquots will be defined in the operations manual) and frozen. The samples must be stored -70°C, except for brief periods on dry ice for shipment. If a -70°C freezer is unavailable, then the samples can be stored on dry ice for up to 1 week until a shipment to the central laboratory can be arranged.

### Pharmacogenomic Sample Collection

Blood collection kits will be provided. These will include evacuator collection tubes, processing and storage instructions, and shipping supplies for each subject.

Approximately 8-10 mL of blood will be collected using the supplied evacuator tubes. The site will follow the instructions for collection, processing, storage, and shipment of blood samples as specified in the sample kits. All collection tubes must be labeled using the labels provided with the sample collection kits. The sample submission or lab requisition forms must be completely filled out. In addition, the subject number and date of collection must be hand-written on the sample tube using a waterproof marker.

### Sample Shipment

Plasma and urine samples must be neatly packed in the kits provided by the central lab and restrained in a Styrofoam container that is 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 or the central lab. Shipments from clinical sites will be via an overnight carrier to the central laboratory.

## Appendix 4              Administrative Changes/Protocol Amendments

**Administrative Change Number:** 1

**Issue Date:** 21 February 2014

**PURPOSE:**

This administrative change will not affect the safety of subjects, the scope of the investigation, or the scientific quality of the trial.

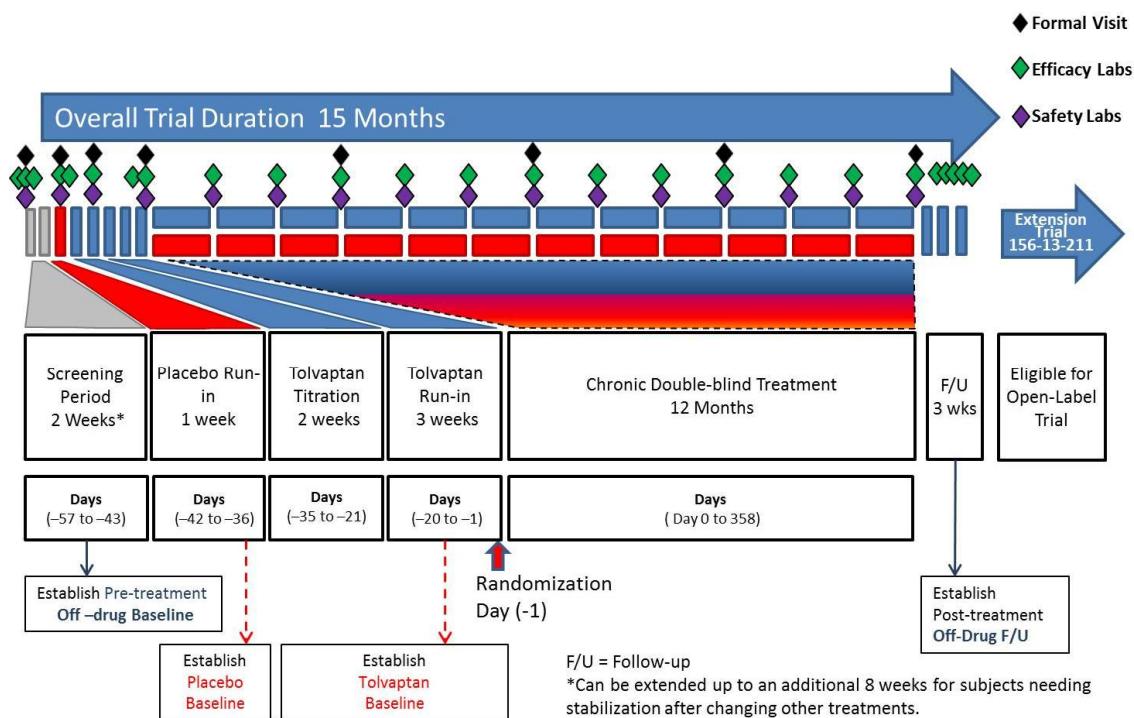
The purpose of this administrative change was to correct typographical errors and add additional clarifying information into Figure 3.1-1 - Trial Design Schematic.

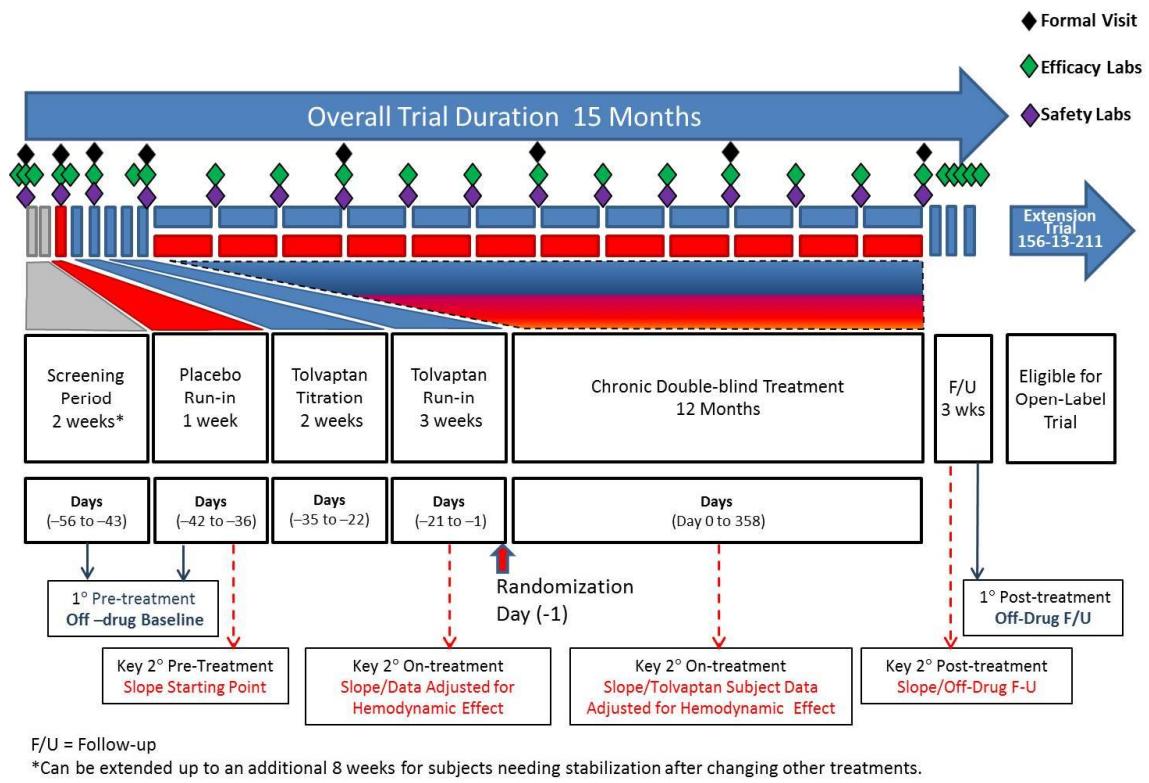
**BACKGROUND:**

In Figure 3.1-1: Typographical errors were corrected in the boxes for trial days and additional text boxes were added/modified to indicate specific periods of data collection for the primary and key secondary endpoints.

**MODIFICATIONS TO PROTOCOL:**

**Original Figure 3.1-1 - Trial Design Schematic:**



**Revised Figure 3.1-1 - Trial Design Schematic:****ADDITIONAL RISK TO THE SUBJECT:**

There is no additional risk to the subjects.

**Amendment Number** 1

**Issue Date:** 31 March 2014

**PURPOSE:**

The primary purpose of this amendment was to increase the sample size and period of enrollment to increase power for the primary and secondary endpoints.

In addition, information associated with a potential interim analysis was added, the number of creatinine blood draws was reduced, an inclusion criterion was added, and an exclusion criterion was modified. Minor revisions were also made to the protocol for clarity.

**BACKGROUND:**

**Increase in sample size**

In the original protocol, the sample size was calculated using the intra-and inter-subject variances derived from a slope analysis model. Then a method based on MMRM was developed and used to derive a new set of intra and inter-subject variances for the sample size calculation for the endpoint analysis for this protocol. This new sample size is more conservative.

**Addition of an interim analysis**

This trial is to be conducted over a critical time period during which tolvaptan may be approved as therapy for ADPKD in some of the participating regions. The European Medicines Agency's (EMA) decision for a pending marketing authorization application for use of tolvaptan in treatment of ADPKD is expected in 2015. Following regulatory approval, reimbursement and commercial availability may have an impact on the ongoing ethical conduct of the trial. This may impact subjects enrolled in Europe who are continuing in the randomized, placebo-controlled treatment phase. If an interim analysis is conducted and the results satisfy the null hypothesis, the trial may be terminated early and the existing enrolled subjects may be offered participation in an open-label trial.

**Decrease in blood draws for eGFR calculation**

With the increased sample size for this protocol, the number of blood samples collected for creatinine from each subject was reduced for both the pre-treatment and post-treatment eGFR calculations.

**Addition of an inclusion criterion to specify tolvaptan naïve subjects**

Due to the relatively short (12 months) treatment period during which treatment effect can be observed, and in order to minimize any carry over effect from previous exposure to the IMP, this study will enroll only tolvaptan naïve subjects. An inclusion criterion

was therefore added to specify that only tolvaptan naïve subjects will be permitted to enroll in this trial.

### Clarification of exclusion criterion # 5

A change was made to the exclusion criteria to further define subjects with “advanced diabetes” who would be excluded from the protocol.

### Other Revisions

It was decided that some of the language should be changed, or expanded, for clarity in specific sections of the document. Also, language was added to define the minimum “wash-out” period for subjects enrolled in the trial who were being treated with tolvaptan from previous trials.

Changes were made to the footnotes in the Schedule of Assessments table to correspond to changes in visit assessments, to clarify the analysis of serum creatinine samples, to specify visits that were in-clinic, and to define specifics like “cooked meat protein”, etc.

- Changed instances of “sham” to “matching placebo 0 mg tablets”.
- Clarified all instances of dietary “protein” to dietary “cooked meat protein”.
- Changed Chairman of the hepatic adjudication committee to Dr. David Alpers.
- Fixed typographical errors.

### Sectional Revisions

Location	Old Text	Updated Text
Synopsis, Trial Design, Screening Period	<p><u>Screening period (2 weeks):</u>  ... This may include, for example, stabilizing anti-hypertensive regimens for subjects discontinuing diuretics or “wash-out” of tolvaptan or other investigational agents for subjects who participated in previous trials.</p> <p>....Eligibility will be confirmed by the mean of eGFR calculated from the subjects' first 2 pre-treatment, central-lab serum creatinine assessments.</p>	<p><u>Screening period (1-2 weeks):</u>  ... This may include, for example, stabilizing anti-hypertensive regimens for subjects discontinuing diuretics or “wash-out” of other investigational agents.</p> <p>....Eligibility will be confirmed by the mean of eGFR calculated from the subjects' 2 pre-treatment, central-lab serum creatinine assessments (<b>collected at least 24 hours apart</b>). <b>The final screening visit on Day -43 will not be scheduled until laboratory results from the second screening visit (V2) are received and evaluated.</b></p>
Synopsis, Trial Design, Placebo Run-in period (1 week)	<p>Placebo run-in period (1 week):  Subjects will be given placebo in a daily split dose of a single 0 mg tablet upon awakening and another 0 mg tablet approximately 8 to 9 hours later</p>	<p>Placebo run-in period (1 week):  Subjects will be given placebo (<b>as a single-blind “sham” 15/15 mg dose</b>) in a daily split dose of a single 0 mg tablet upon awakening and</p>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
	(abbreviated 0/0 mg), in a form identical to tolvaptan tablets.  Blood will be drawn 2 times on separate days (at least 24 hours apart), including the last day of the run-in period,	another 0 mg tablet approximately 8 to 9 hours later (abbreviated 0/0 mg), in a form identical to tolvaptan tablets.  Blood will be drawn <b>once</b> on the last day of the run-in period ( <b>Day -36</b> ).
Synopsis, Trial Design, Tolvaptan Titration Period (2 weeks)	Tolvaptan titration period (2 weeks): Subjects will be given a split dose of 30/15 mg tolvaptan with upward titration every 3 to 4 days to 45/15 mg, 60/30 mg, up to a maximum dose of 90/30 mg per day over 2 weeks.	Tolvaptan titration period (2 weeks): Subjects will be given a split dose of 30/15 mg tolvaptan ( <b>single-blind</b> ) with upward titration every 3 to 4 days to 45/15 mg, 60/30 mg, up to a maximum dose of 90/30 mg per day over 2 weeks.
Synopsis, Trial Design, Tolvaptan Run-in Period (3 weeks)	Tolvaptan run-in period (3 weeks): Subjects who tolerate the tolvaptan 60/30 mg or 90/30 mg daily dose regimen will enter the tolvaptan run-in period at the tolerated dose for 3 additional weeks.	Tolvaptan run-in period (3 weeks): Subjects who tolerate the tolvaptan 60/30 mg or 90/30 mg daily dose regimen will enter the tolvaptan run-in period ( <b>single-blind</b> ) at the tolerated dose for 3 additional weeks.
Synopsis, Trial Design, Follow-up Period (3 weeks)	....No assessments will be taken for the first week of this period; however, 5 visits will be scheduled for the last 2 weeks of follow-up for post-treatment efficacy and safety measures.	....No assessments will be taken for the first week of this period; however, 3 visits will be scheduled for the last 2 weeks of follow-up for post-treatment efficacy and safety measures.
Synopsis, Subject Population	This trial will randomize approximately 800 subjects with ADPKD, with a minimum of 700 and a maximum of 1000 subjects planned to be enrolled.	This trial will randomize <b>approximately 1300 tolvaptan naïve</b> subjects with ADPKD.
Synopsis, Inclusion Criteria	N/A	<ul style="list-style-type: none"> <li>• Tolvaptan naïve</li> </ul>
Synopsis, Exclusion Criteria and Section 3.4.3, Table 3.4.3-1, Exclusion Criterion 5	<ul style="list-style-type: none"> <li>• Subjects with advanced diabetes (eg, glycosylated hemoglobin [HgbA1c] &gt; 7.5, and/or glycosuria by dipstick), evidence of additional significant renal disease(s) (ie, currently active glomerular nephritides), renal cancer, single kidney, or recent (within last 6 months) renal surgery, or acute kidney injury.</li> </ul>	<ul style="list-style-type: none"> <li>• Subjects with advanced diabetes (eg, glycosylated hemoglobin [HgbA1c] &gt; 7.5, and/or glycosuria by dipstick, <b>significant proteinuria, retinopathy</b>), evidence of additional significant renal disease(s) (ie, currently active glomerular nephritides), renal cancer, single kidney, or recent (within last 6 months) renal surgery, or acute kidney injury.</li> </ul>
Synopsis, Trial Site(s)	Approximately 200 enrolling sites including, but not limited to, the following regions: North America, South America, Eastern Europe, Western Europe, Asia, and Australia.	Approximately <b>220</b> enrolling sites including, but not limited to, the following regions: North America, South America, Eastern Europe, Western Europe, Asia, and Australia.

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
Synopsis, Investigational Product(s), etc	<p>Doses will be expressed as early dose/late dose (eg, 60/30).</p> <p>Placebo will be administered to all subjects during the placebo run-in period.</p>	<p>Doses will be expressed as early dose/late dose (eg, 60/30 <b>mg</b>).</p> <p>Placebo will be administered to all subjects during the placebo run-in period <b>as a single-blind “sham” 15/15 mg dose</b>.</p>
Synopsis, Trial Assessments	<p><b>Screening:</b> Medical history, complete physical examination, urine pregnancy test (women of child-bearing potential only).</p> <p><b>Safety:</b> Vital signs, directed physical examination, AEs, hematology, urinalysis, and serum chemistry tests (including serum transaminases, alkaline phosphatase, bilirubin, serum sodium), biomarker plasma and urine samples, and DNA blood samples (for consenting subjects).</p> <p><b>Pharmacodynamic (PD):</b> Urine osmolality (Uosm), specific gravity.</p>	<p><b>Screening:</b> Medical history, complete physical examination, urine pregnancy test (women of child-bearing potential only), <b>and laboratory tests to determine initial eligibility</b>.</p> <p><b>Safety:</b> Vital signs, directed physical examination, <b>self-assessed tolerability</b>, AEs, hematology, urinalysis, and serum chemistry tests (including serum transaminases, alkaline phosphatase, bilirubin, serum sodium), biomarker plasma and urine samples, and DNA blood samples (for consenting subjects).</p> <p><b>Pharmacodynamic (PD):</b> Urine osmolality (Uosm), <b>urine</b> specific gravity.</p>
Synopsis, Criteria for Evaluation	<p><b>Primary Efficacy Endpoint:</b> Treatment difference in the change of eGFR from pre-treatment baseline to post-treatment follow-up, normalized (divided) by each subject's treatment duration.</p> <p><b>PD Endpoints:</b> Uosm and specific gravity.</p> <p><b>Exploratory Endpoints:</b></p> <p><b>Efficacy:</b> Assessment of ADPKD outcomes.</p>	<p><b>Primary Efficacy Endpoint:</b> Treatment difference in the change of eGFR from pre-treatment baseline to post-treatment follow-up, <b>annualized</b> (divided) by each subject's <b>IMP</b> treatment duration.</p> <p><b>PD Endpoints:</b> Uosm and <b>urine</b> specific gravity.</p> <p><b>Exploratory Endpoints:</b></p> <p><b>Efficacy:</b> Assessment of ADPKD outcomes <b>and analysis of efficacy based on modal doses</b>.</p>
Synopsis, Statistical Methods, Sample Size	<p>Based on a Mixed Model Repeated Measurements analysis of the non-Japanese CKD-3 Subjects from trial 156-04-251, the treatment difference in renal function at Month 12 is 1.07 in our sample size calculation. It is expected that the residual variance and slope variance would be 22.13 and 5.27, respectively, assuming 4 to 5 pre-treatment and post-treatment observations taken in 2-week</p>	<p>Based on a Mixed Model Repeated Measurements analysis of the non-Japanese CKD-3 Subjects from trial 156-04-251, the treatment difference in renal function at Month 12 is 1.07 in our sample size calculation. <b>It is expected that the intra-subject variance is 14.2 and inter-subject variance is 28.05 at Month 12. With 3 repeated measures at pre-treatment baseline and post-</b></p>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
	<p>intervals. The power calculation estimates that, for a 2-sided alpha set at 0.05 for a power of 85% to 90%, and with an assumption of 15% dropout rate in the trial, a total sample size of approximately 660 to 770 subjects (rounded up to 700 to 800 subjects) is needed.</p>	<p><b>treatment follow-up, respectively</b> the power calculation estimates that, for a 2-sided alpha set at 0.05 for a power of 90%, and with an assumption of <b>10%</b> dropout rate in the trial, a total sample size of <b>approximately 1300</b> subjects is needed.</p>
Synopsis, Trial Duration	<p>The duration of the double-blind, randomized treatment period will be 12 months. The total duration of the trial (including pre-randomization and follow-up periods) will be approximately 15 months.</p>	<p>The duration of the double-blind, randomized treatment period will be 12 months. The total duration for <b>each subject entered into of the trial is approximately 15-17 months (including the pre-randomization and follow-up periods, and an additional 8 weeks for extension of the screening period in subjects for whom this is necessary).</b></p>
Section 1.4, Known and Potential Risks and Benefits	<p>Typically, this would represent 2 to 3 liters of water per day in subjects with relatively intact renal function, and lesser amounts in those with more impaired function.</p> <p>An imbalance in the proportion of subjects with elevated transaminases (tolvaptan &gt; placebo) led to identification of 3 subjects (total from both Trial 156-04-251 and its open-label extension trial, 156-08-271) with laboratory and clinical evidence of potentially serious drug-induced liver injury (DILI).</p> <p>These adverse reactions should be considered in light of the benefits of a reduced risk of ADPKD kidney complications, including renal pain, urinary tract infection, hematuria, anemia, and nephrolithiasis.</p>	<p>Typically, this would represent a <b>minimum of</b> 2 to 3 liters of water per day in subjects with relatively intact renal function, and lesser amounts in those with more impaired function.</p> <p><b>....With a once every 4-month monitoring scheme,</b> an imbalance in the proportion of subjects with elevated transaminases (tolvaptan &gt; placebo) led to identification of 3 subjects (total from both Trial 156-04-251 and its open-label extension trial, 156-08-271) with laboratory and clinical evidence of potentially serious drug-induced liver injury (DILI).</p> <p><b>....These adverse events and the above attributable</b> adverse reactions should be considered in light of the benefits of a reduced risk of ADPKD kidney complications, including renal pain, urinary tract infection, hematuria, anemia, and nephrolithiasis.</p>
Section 2.1, Trial Rationale	<p>....Home nursing visits or local laboratory visits will also be available for collection of follow-up blood samples and to continue health-status follow up even if IMP is permanently discontinued.</p> <p>Therefore, the information gathered</p>	<p>....Home nursing visits or local laboratory visits will also be available <b>at most sites</b> for collection of follow-up blood samples and to continue health-status follow up even if IMP is permanently discontinued.</p>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
	<p>through genetic/biomarker analysis should improve the sponsor's understanding of the disease, its diagnosis, prognosis, and possibly treatment outcome by identifying which patients are more likely to respond to tolvaptan, and/or predicting which subjects are likely to progress to more severe disease states, and/or predicting which subjects may have an adverse event such as DILI, and/or lead to new opportunities for therapies.</p>	<p>Therefore, the information gathered through genetic/biomarker analysis should improve the sponsor's understanding of the disease, its diagnosis, prognosis, and possibly treatment outcome. <b>This can be accomplished</b> by identifying which <b>subjects</b> are more likely to respond to tolvaptan, and/or predicting which subjects are likely to progress to more severe disease states, and/or predicting which subjects may have an adverse event such as DILI, and/or lead to new opportunities for therapies.</p>
Section 2.2, Dosing Rationale	<p>All subjects will be encouraged to progress to 90/30 mg per day, as this is likely to be most effective.</p>	<p>All subjects will be encouraged to progress to 90/30 mg per day, as <b>a higher dose</b> is likely to be most effective.</p> <p>During the double-blind randomized treatment period, subjects will either be maintained on their maximally tolerated split dose of tolvaptan at 60/30 mg or 90/30 mg or randomized to placebo. To manage additional tolerability issues during this period, subjects may down-titrate blinded treatment to 45/15 mg or even 30/15 mg with medical monitor approval. Subjects will be encouraged to maintain maximally tolerated dose to optimize and maintain desired suppression. If down-titration occurs, subjects will be encouraged to return to previous maximal tolerated dose, if possible.</p>
Section 3.1.1, Figure 3.1-1	See previous Figure below	See revised Figure below
Section 3.2.1, Pre-randomization	<p>Subjects who provide informed consent, who meet the inclusion/exclusion criteria, and for whom preliminary eligibility is established, will enter an 8-week run-in period.</p> <p>...This pre-randomization period consists of a screening period (typically 2 weeks for tolvaptan-naïve subjects; however, longer periods up to 8 additional weeks are acceptable for subjects withdrawing from tolvaptan, or needing stabilization after changing other treatments, and/or requiring additional assessments for qualification); a placebo run in</p>	<p>Subjects who provide informed consent, and for whom preliminary eligibility is established, will enter an 8-week run-in period.</p> <p>...This pre-randomization period consists of a screening period (typically <b>1-2 weeks</b>; however, longer periods up to 8 additional weeks are acceptable for subjects needing stabilization after changing other treatments, especially anti-hypertensives and diuretics, <b>or who require additional assessments for qualification</b>); a placebo run in</p>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
	especially anti-hypertensives and diuretics), a placebo run in period (1 week), a tolvaptan titration period (2 weeks), and a tolvaptan run-in period (3 weeks), described in more detail below.	period (1 week), a tolvaptan titration period (2 weeks), and a tolvaptan run-in period (3 weeks).
	N/A	During this period, subjects should be told “You will receive placebo or active treatment (tolvaptan) during the treatment phase, but you will not know which.” The subjects should not be told that there is a separate run-in phase and randomization phase, and they should not be told when formal randomization will occur. They should also be told “Your eligibility for continued participation will be assessed intermittently during the treatment period.”
Section 3.2.1.1, Screening Period	Subjects will be told that they will receive both tolvaptan and placebo during various subsequent periods of the trial and that the next period involves a dose escalation with multiple efficacy, safety, and tolerability assessments.	Subjects will be told that they will receive tolvaptan <b>or</b> placebo during various subsequent periods of the trial and that the next period involves a dose escalation with multiple efficacy, safety, and tolerability assessments.  Trial medication will be dispensed on Day -43 after subject eligibility is confirmed. In exceptional circumstances, trial medication may be provided at the second screening visit with instruction not to take any medication until confirmation on Day -43 by the investigator. If trial medication is dispensed at the second screening visit, confirmation of eligibility and instructions to take medication will be provided by telephone on Day -43.
Section 3.2.1.2, Placebo Run-in Period	In the first week after the screening period, all subjects will begin the single-blind, placebo run-in period where they will be given placebo in a daily split dose of 0 mg (abbreviated 0/0 mg), in a form identical to tolvaptan tablets. The subject will remain blinded to treatment and receive a bottle of drug which they understand could be either tolvaptan or placebo.	In the first week after the screening period, all subjects will begin the single-blind, placebo run-in period <b>with</b> placebo in a daily split dose of 0 mg (abbreviated 0/0 mg), in a form identical to tolvaptan tablets <b>at the 15/15 mg dose</b> . The subject will remain blinded to treatment, <b>having received</b> a bottle of <b>trial drug</b> <b>during the screening period</b> which they <b>understood</b> could be either tolvaptan or placebo.
Section 3.2.1.4,	Subjects tolerating at least 60/30 mg	Subjects tolerating at least 60/30 mg

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
Tolvaptan Run-in Period (Day -21 to Day -1)	tolvaptan may enter the tolvaptan run-in period (3 week duration).	tolvaptan may enter the <b>single-blind</b> , tolvaptan run-in period (3 week duration).
Section 3.2.2, Double-blind Randomized Treatment Period (Day 0 to Month 12)	N/A	Subjects not continuing in this trial will complete EoTx visit assessments and be followed for 21 days to assess any ongoing AEs.
Section 3.2.2, Table 3.2.2-1 Dosing Schedule	Trial Day Day -56 to -43	Trial Day <b>1 to 2 weeks (to Day -43)</b>
Section 3.3, Trial Population	<p>This trial will consent and screen subjects in order to randomize approximately 800 subjects with ADPKD....</p> <p>In order to maximize power and minimize the possibility of Type 2 error, trial enrollment will continue until a minimum of 700 subjects are randomized. Time allowing, the sponsor may, at its discretion, extend enrollment in order to randomize up to 1000 subjects to further improve the trial's power.</p>	<p>This trial will consent and screen tolvaptan naïve subjects with ADPKD....</p> <p>....In order to maximize power and minimize the possibility of Type 2 error, trial enrollment will continue until <b>approximately 1300</b> subjects are randomized.</p>
Section 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 and of their role and responsibilities in the proposed research.	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 ( <b>without revealing details of its initial single-blind nature</b> ) and of their role and responsibilities in the proposed research.
Section 3.4.2, Inclusion Criteria, Table 3.4.2-1	<p>3.....</p> <ul style="list-style-type: none"> <li>• Without family history: 10 cysts per kidney (by any radiologic method, above) and exclusion of other cystic kidney diseases. 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.</li> </ul> <p>4. Distribution and number of cysts consistent with the observed level of renal function deficit.</p>	<p><b>3. Male and female subjects who are tolvaptan naïve.</b></p> <p><b>4.....</b></p> <ul style="list-style-type: none"> <li>• Without family history: 10 cysts per kidney (by any radiologic method, above) and exclusion of other cystic kidney diseases. 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.</li> <li>• Distribution and number of cysts consistent with the observed level of renal function deficit.</li> </ul>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
Section 3.5.1.1, Primary Efficacy Endpoint	Treatment difference in the change of eGFR from pre-treatment baseline to post-treatment follow-up, normalized (divided) by each subject's treatment duration.	Treatment difference in the change of eGFR from pre-treatment baseline to post-treatment follow-up, <b>annualized</b> (divided) by each subject's <b>IMP</b> treatment duration.
Section 3.5.2.3, Pharmacokinetic/Pharmacodynamic Endpoints	PD Endpoints: Uosm and specific gravity	PD Endpoints: Uosm and <b>urine</b> specific gravity
Table 3.7-1, Schedule of Assessments	Previous Table is at the end of Appendix 4	Updated Table with tracked changes is at the end of Appendix 4
Section 3.7.1.1, Pre-randomization Period	<ul style="list-style-type: none"> <li>• screening period (2 weeks; longer durations of up to 8 additional weeks may be required according to the investigator's judgment, as described below)</li> </ul> <p>To establish the pre-randomization eGFR, multiple serum creatinine values (isotope dilution mass spectroscopy [IDMS]-traceable) will be obtained under standardized conditions.....</p>	<p>screening period (<b>1-2</b> weeks; longer durations of up to 8 additional weeks may be required according to the investigator's judgment, as described below)</p> <p>To establish the pre-randomization eGFR, multiple serum creatinine values will be obtained under standardized conditions.....</p>
Section 3.7.1.1.1, Screening Period	The screening period will be for 2 weeks ( $\pm$ 1 day) for tolvaptan-naïve subjects. The screening period may be extended up to an additional 8 weeks for subjects who require modification of medical care specifically for this trial.	The screening period will be for <b>1-2</b> weeks, but may be extended up to an additional 8 weeks for subjects who require modification of medical care <b>or further medical evaluation</b> specifically for this trial.
	This may include, for example, stabilizing anti hypertensive regimens for subjects discontinuing diuretics or "wash-out" of tolvaptan or other investigational agents for candidates who participated in previous trials. Subjects who were previously taking tolvaptan are required to sign an ICF and have at least a 2 week wash-out period prior to beginning the 1-2-week screening assessments.	This may include, for example, stabilizing anti hypertensive regimens for subjects discontinuing diuretics or "wash-out" of other investigational agents.
	The screening period will consist of three visits, each at least 24 hours apart. The first and last visits will be clinic visits, but a visiting nurse house call or local laboratory visit may be substituted for the other visit where only blood samples will be collected.	The screening period should be completed within <b>1-2 weeks</b> of the placebo run-in period ( <b>unless extended as described above</b> ). <b>Blood will be drawn 2 times on separate days (visit 1 and visit 2), at least 24 hours apart. The Day -43 visit will not be scheduled until laboratory results from the second visit are received and evaluated so that the calculated mean eGFR result is available for eligibility assessment on Day -43.</b>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
	<p>6) Assess vital signs (include sitting heart rate and blood pressure [first and last visits])</p> <p>9) Collect urinalysis samples (first and last visits)</p> <p>10) Collect blood for serum creatinine for eGFR calculation (3 collections, each at least 24 hours apart)</p> <p>11) Collect blood for central clinical laboratory analyses (sodium [first and last visits])</p> <p>12) Collect PD urine sample (last visit)</p> <p>13) Collect biomarker plasma and urine samples (last visit, see Section 3.7.3.5)</p> <p>16) Collect blood for DNA sample (first visit, for consenting subjects only)</p>	<p>6) Assess vital signs (include sitting heart rate and blood pressure [first and <b>second</b> visits])</p> <p>9) Collect urinalysis samples (first and <b>second</b> visits)</p> <p>10) Collect blood for serum creatinine for eGFR calculation (<b>2</b> collections, first <b>and second visits</b>, at least 24 hours apart)</p> <p>11) Collect blood for central clinical laboratory analyses (sodium [first and <b>second</b> visits])</p> <p>12) Collect PD urine sample (<b>second</b> visit)</p> <p>13) Collect biomarker plasma and urine samples (<b>second</b> visit, see Section 3.7.3.5)</p> <p>16) Collect blood for DNA sample (<b>second</b> visit, for consenting subjects only)</p>
	N/A	Trial medication will be dispensed at Day -43 after subject eligibility is confirmed. In exceptional circumstances, trial medication may be dispensed at the second visit, with the instruction not to take any trial medication until eligibility is confirmed by the investigator. In these cases, confirmation of eligibility and instructions for taking trial medication will be provided by telephone on Day -43.
Section 3.7.1.1.2, Placebo Run-in Period (Days -42 to -36)	<p>Subjects will be given placebo in a daily split dose of a single 0 mg tablet upon awakening and another 0 mg tablet approximately 8 to 9 hours later (abbreviated 0/0 mg), in a form identical to tolvaptan tablets.</p> <p>5) Collect blood for serum creatinine for eGFR calculation (x2) and for assessment of sodium (x2) and liver function panel (x1) on separate days between Days - 39 to - 36 with the last sample being obtained on Day - 36. If sodium and liver function panel are collected at the same visit, a single tube of blood should be drawn for all assessments.</p>	<p>Subjects will be given placebo in a daily split dose of a single 0 mg tablet upon awakening and another 0 mg tablet approximately 8 to 9 hours later (abbreviated 0/0 mg), in a form identical to <b>15/15 mg</b> tolvaptan tablets.</p> <p>5) Collect blood for serum creatinine for eGFR calculation and for assessment of sodium and liver function panel on Day -36.</p> <p>12) Subjects found to be ineligible to continue in this trial after receiving IMP must have a 7-day follow-up visit (see Section 3.8.3.1).</p>
Section 3.7.1.1.3, Tolvaptan Titration Period (Days -35 to - )	N/A	10) Subjects not tolerating at least 60/30 mg dose should be informed they did not meet

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
22)		<p>eligibility criteria for continuation</p> <p>12) Subjects found to be ineligible to continue in this trial must have a 7-day follow-up visit (see Section 3.8.3.1).</p>
Section 3.7.1.1.4, Tolvaptan Run-In Period (Days -21 to -1)	<p>Randomization (Day 1) will be stratified by mean eGFR determined by available central isotope dilution mass spectroscopy (IDMS) traceable serum creatinine measurements taken during the screening period and placebo run-in period.</p>	<p>Randomization (Day 1) will be stratified by mean eGFR serum creatinine measurements taken during the screening period and placebo run-in period.</p> <p>15) Subjects found ineligible to be randomized and continue in this trial must have a 7-day follow-up visit (see Section 3.8.3.1).</p>
Section 3.7.1.2, Double-blind, Randomized Treatment Period	<p>14) Dispense IMP at monthly visits up to and including Month 11</p> <p>Subjects discontinuing IMP in the placebo run-in period, tolvaptan titration period, or the tolvaptan run-in period should also have EoTx assessments performed (see Section 3.8.3.3).</p>	<p>14) Dispense IMP at monthly visits up to and including Month 11. <b>In certain circumstances, with medical monitor approval, a 3-month drug supply may be provided; however, initiation of the next month's supply must be directed by the site.</b></p> <p>16) Subjects not continuing in this trial must have a 21-day follow-up period (see Section 3.8.3.3).</p> <p>Regardless of discontinuation of IMP, the subjects are expected to complete all monthly visits and assessments including the Month 12 visit.</p>
Section 3.7.1.3, Follow-up Period (Month 12/End of Treatment to Day 21 Post treatment)	<p>There will be no scheduled visits/assessments during the first week of the follow-up period. After the first week, 5 visits should be scheduled during the remaining 2 weeks of the follow-up period (between Day +7 and Day +21), with each visit at least 24 hours apart.</p>	<p>There will be no scheduled visits/assessments during the first week of the follow-up period. After the first week, <b>3</b> visits should be scheduled during the remaining 2 weeks of the follow-up period (between Day +7 and Day +21). The first visit should be scheduled on approximately Day +7, the second visit on approximately Day +14 and the third visit on approximately Day +21 (-2 days).</p>
Section 3.7.2.1, Serum Creatinine for Estimated Glomerular Filtration Rate	<p>The eGFR values will be calculated from the central-laboratory IDMS-traceable serum creatinine concentrations taken at screening and during every trial visit.</p>	<p>The eGFR values will be calculated from the central-laboratory serum creatinine concentrations taken at screening and during every trial visit.</p>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
Section 3.7.3.2, Clinical Laboratory Assessments	<p>Clinical laboratory samples for analysis by the central laboratory will be collected at the following visits:</p> <ul style="list-style-type: none"> <li>• during screening (3 visits at least 24 hours apart that occur during the 2 weeks prior to placebo run-in) - creatinine (all 3 visits), sodium and urinalysis (first and last visits), hematology and coagulation panel, serum chemistry panel, and liver function panel (first visit)</li> <li>• during placebo run-in - urinalysis (Day - 36), liver function panel, creatinine, and sodium (twice on separate days between Days 39 to - 36 with the last sample being obtained on Day - 36)</li> <li>• during the follow-up period (5 visits at least 24 hours apart that begin 1 week after the Month 12/EoTx visit) - creatinine (all 5 visits), sodium (first visit), liver function panel and serum chemistry panel (last visit)</li> </ul>	<p>Clinical laboratory samples for analysis by the central laboratory will be collected at the following visits:</p> <ul style="list-style-type: none"> <li>• during screening (<b>2</b> visits at least 24 hours apart that occur during the <b>1-2</b> weeks prior to placebo run-in) - creatinine (<b>first and second</b> visits), sodium and urinalysis (<b>first and second</b> visits), hematology and coagulation panel, serum chemistry panel, and liver function panel (first visit)</li> <li>• during placebo run-in - urinalysis, liver function panel, creatinine, and sodium on Day -36</li> <li>• during the follow-up period (<b>3</b> visits that begin 1 week after the Month 12/EoTx visit) - creatinine (<b>3</b> visits), sodium (first visit), liver function panel and serum chemistry panel (last visit)</li> </ul>
Section 3.7.3.2, Table 3.7.3.2-1	N/A	<p>Urinalysis panel:</p> <ul style="list-style-type: none"> <li>• osmolality</li> <li>• specific gravity</li> <li>• urine creatinine</li> </ul>
Section 3.7.3.4.2, Liver Test Abnormalities and Interruption/Discontinuation of Investigational Medicinal Product	N/A	All elevations will be assessed by the medical monitoring team.
Section 3.7.3.4.3, Requirements for Special Reporting Using the Liver Disease Electronic Case Report Form and Immediately Reportable Event Form	N/A	The HAC will independently decide attribution and will communicate with the Independent Data Monitoring Committee (IDMC) that oversees the trial.
Section 3.7.3.5.1, Biomarker Plasma Samples	<p>Blood samples (10 mL) for potential biomarker analysis will be collected at the following times:</p> <ul style="list-style-type: none"> <li>• end of the screening period (Day - 43)</li> </ul>	<p>Blood samples (10 mL) for potential biomarker analysis will be collected at the following times:</p> <ul style="list-style-type: none"> <li>• <b>second visit</b> of the screening period</li> </ul>
Section 3.7.3.5.2, Biomarker Urine	A spot urine sample (20 mL) will be	A spot urine sample will be obtained at the following times:

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
Samples	<p>obtained at the following times:</p> <ul style="list-style-type: none"> <li>• end of the screening period (Day -43)</li> </ul>	<ul style="list-style-type: none"> <li>• <b>second visit</b> of the screening period</li> </ul> <p>To ensure a fasting urine sample is collected, subjects will be provided with a sterile urine cup on the visit preceding the date of urine sample collection. Subjects will be instructed to collect a urine sample prior to eating breakfast, and to store the sample in the refrigerator until their clinic visit.</p>
Section 3.7.3.5.3, DNA Blood Samples	A blood sample for DNA collection will be obtained for every consenting subject at the beginning of the screening period.	A blood sample for DNA collection will be obtained for every consenting subject at the <b>second visit</b> of the screening period.
Section 3.7.4.2, Pharmacodynamic Urine Samples	<p>A spot urine sample for determination of Uosm and specific gravity will be obtained at the following times:</p> <ul style="list-style-type: none"> <li>• end of the screening period (Day - 43)</li> </ul>	<p>A spot urine sample for determination of Uosm and specific gravity will be obtained at the following times:</p> <ul style="list-style-type: none"> <li>• <b>second visit</b> of the screening period</li> </ul> <p>To ensure a fasting urine sample is collected, subjects will be provided with a sterile urine cup on the visit preceding the date of urine sample collection. Subjects will be instructed to collect a urine sample prior to eating breakfast, and to store the sample in the refrigerator until their clinic visit.</p>
Section 3.7.6, Independent Data Monitoring Committee	N/A	....Adjudication results as determined by the HAC will be reported to the IDMC on a quarterly basis or more frequently as necessary....
Section 3.8.3.2, Treatment Interruption	.....It is assumed that an interruption of this duration may become permanent, therefore the subject will have a total of 5 samples collected for serum creatinine measurements....	.....It is assumed that an interruption of this duration may become permanent, therefore the subject will have a total of <b>3</b> samples collected for serum creatinine measurements....
	Treatment may still be restarted during or after these assessments are completed.	Treatment may still be restarted during or after these assessments are completed; <b>any remaining serum creatinine assessments will not need to be completed if treatment is restarted during this period.</b>
Section 3.8.3.3, Treatment Discontinuation	During the last two weeks of the follow-up period, the subject will have a total of 5 samples collected for serum creatinine measurements.	During the last two weeks of the follow-up period, the subject will have a total of <b>3</b> samples collected for serum creatinine measurements.
Section 3.8.3.4 Documenting Reasons	<ul style="list-style-type: none"> <li>• Subject decides to discontinue due annoyance or discomfort due</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Subject could not tolerate IMP due to an AE which is</b></li> </ul>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
for Treatment Interruption/Discontinuation	<p>to a non-serious AE which is not otherwise determined to be an undue hazard</p> <ul style="list-style-type: none"> <li>• Continuing IMP places the subject at undue hazard as determined by the investigator (eg, a safety concern that is possibly, probably, or likely related to IMP)</li> <li>• eGFR decreased to a level requiring dialysis or kidney transplantation (confirmed by repeat testing post IMP discontinuation)</li> <li>• Clinical jaundice (requires an immediate interruption of IMP and prompt repeat testing to confirm abnormality)</li> <li>• Reasons unrelated to medical condition (provide detail and review AE history with subject)</li> <li>• Withdrawal of informed consent (complete written withdrawal of consent form)</li> <li>• Pregnancy (see Section 5.4)</li> </ul>	<p><b>annoying or uncomfortable but not serious or hazardous</b></p> <ul style="list-style-type: none"> <li>• <b>Physician determined that there are potential IMP related safety concern or SAE placing subject at undue hazard</b></li> <li>• <b>Progression of disease leading to dialysis, transplantation or eGFR decline as determined by the investigator</b></li> <li>• <b>Clinical signs of DILI (eg, jaundice, right upper quadrant pain)</b></li> <li>• Reasons unrelated to medical condition (<b>eg, pregnancy, trial too burdensome</b>)</li> <li>• Withdrawal of informed consent (<b>partial related to IMP or complete from the trial</b>)</li> <li>• Taking marketed product for tolvaptan (discontinued subjects only)</li> </ul>
Section 3.8.3.5, Withdrawal of Consent	N/A	<ul style="list-style-type: none"> <li>• Participation in all regularly scheduled, study-related follow-up visits and end of treatment visits</li> </ul>
Section 3.10, Definition of Completed Subjects	Subjects who are randomized, take IMP (or never begin treatment), but DO NOT complete the Month 12 visit AND at least 1 follow-up serum creatinine assessment will be defined as “Non-completers”.	Subjects who are randomized, take IMP (or never begin treatment), but DO NOT complete the Month 12 visit AND at least 1 <b>EoTx</b> follow-up serum creatinine assessment will be defined as “Non-completers”.
Section 5.6, Follow-up of Adverse Events	For this trial, AEs will be followed up for 21 days after the last dose of IMP has been administered (follow-up period)	For this trial, AEs will be followed up for <b>7 days in subjects who discontinued prior to randomization</b> and for 21 days after the last dose of IMP has been administered (follow-up period) <b>in subjects who were randomized</b> .
Section 7.1.1, Sample Size Estimation	In this sample size estimation, it is assumed that 4 to 5 calculations of eGFR will be obtained at baseline during a 3-week interval during screening (2 weeks) and placebo run-in (1 week), and another 4 to 5 calculations will be obtained post-treatment during a 2-week interval that begins 1 week after the end of treatment (3-week post-treatment	In this sample size estimation, it is assumed that <b>3</b> calculations of eGFR will be obtained at baseline during a 3-week interval during screening ( <b>1-2 weeks</b> ) and placebo run-in (1 week), and another <b>3</b> calculations will be obtained post-treatment during a 2-week interval that begins 1 week after the end of treatment (3-week post-treatment follow-up).

Location	Old Text	Updated Text
	<p>follow-up). The mean of the 4 to 5 eGFR values observed during the screening and placebo-run periods will be set as the baseline and the mean of the 4 to 5 eGFR values observed during the post-treatment follow-up period will be set as the renal function measurement post-treatment.</p> <p>To derive the intra-subject variance and inter-subject variance, the approach provided by Dr. Lawrence, a FDA statistician, in a FDA communication to the sponsor (e-mail communication, 24Dec2013), was followed. For subject i randomized to the placebo group (<math>i=1, \dots, n</math>), the eGFR at time <math>t_j</math> is assumed to be</p> $Y_{i,j} = \alpha_i + \beta_i t_j + \epsilon_{i,j} \quad (1)$ <p>For subject i randomized to the tolvaptan group (<math>i= n+1, \dots, 2n</math>), the eGFR at time <math>t_j</math> is assumed to be</p> $Y_{i,j} = \alpha_i + \beta_i t_j + \epsilon_{i,j} \text{ if } j \text{ is observed at baseline} \quad (2)$ $Y_{i,j} = \alpha_i + \Delta + \beta_i t_j + \epsilon_{i,j} \text{ if } j \text{ is observed at post-treatment follow-up} \quad (3)$ $Y_{i,j} = \alpha_i + \gamma + (\Delta + \beta_i) t_j + \epsilon_{i,j} \text{ if } j \text{ is observed during the treatment period} \quad (4)$ <p>where <math>\epsilon_{i,j}</math> are assumed iid <math>N(0, \sigma^2)</math>, <math>\beta_i</math> are assumed iid <math>N(\beta, \sigma\beta^2)</math>, <math>\alpha_i</math> and <math>\beta_i</math> are mutually independent, and <math>\Delta</math> is treatment effect, <math>\gamma</math> is the hemodynamic onset effect. Based on this model, with baseline time is set to 0, the variance of change from baseline at a post-baseline visit is</p> $\text{Var}(Y_{i,j} - Y_{i,0}) = \text{Var}(\beta_i t_j + \epsilon_{i,j} - \epsilon_{i,0}) = t_j^2 \sigma\beta^2 + \sigma^2 \quad (5)$ <p>Dr. Lawrence's derivation is based on the assumption that an observation of eGFR is made at the end of a 2-week interval for k times (thus, totally 2k weeks) at baseline and post-treatment follow-up visit respectively. Thus, Dr. Lawrence's variance of change from baseline to post-treatment follow-up is</p> $(2/k) \sigma^2 + (1 + 1/12 + k/26)^2 \sigma\beta^2 \quad (6)$ <p>If we change the assumption to this one that all these k observations are observed in the 2-week intervals mentioned in the first paragraph in</p>	<p>The mean of the 3 eGFR values observed during the screening and placebo-run periods will be set as the baseline and the mean of the 3 eGFR values observed during the post-treatment follow-up period will be set as the renal function measurement post-treatment.</p> <p>One of the approaches in sample size calculation for this protocol is to use MMRM to estimate the intra- and inter-subject variances. In the ADPKD phase 3 trial 156-04-251, there was a pre-treatment baseline visit and two post-treatment follow-up visits, along with other on-treatment visits. Assume these data follow the following model (denoted as <math>j = 0</math> for baseline and <math>j = 37</math> for follow-up, as well as <math>j = 4, 8, 12, \dots, 36</math>):</p> $Y_{i,0} = \alpha_i + \epsilon_{i,0} \quad (1)$ $Y_{i,j} = \alpha_i + \delta_{i,j} + \epsilon_{i,j} \quad (2)$ <p>where <math>\delta_{i,j}</math> as a random effect of change from pre-treatment baseline at visit <math>j</math> for subject <math>i</math>. These <math>\delta_{i,j}</math>s jointly follow a multivariate normal distribution with means being <math>\delta_{P,j}</math> for placebo subjects and <math>\delta_{T,j}</math> for tolvaptan subjects. Their individual variance is assumed to be <math>\sigma\delta_{j,2}</math>. These <math>\delta_{i,j}</math>s are supposed to be correlated; however, their correlations are not utilized for the purpose of sample size calculation in this protocol. In addition, <math>\alpha_i</math>s are assumed iid to have a normal distribution, <math>\epsilon_{i,j}</math> are assumed iid <math>N(0, \sigma^2)</math>, and these random variables are mutually independent. Then, the change from baseline data follows this common MMRM model</p> $Y_{i,j} - Y_{i,0} = \delta_{i,j} - \epsilon_{i,0} + \epsilon_{i,j} = \zeta_{i,j} + \epsilon_{i,j} \quad (3)$ <p>where <math>\zeta_{i,j} = \delta_{i,j} - \epsilon_{i,0}</math>. Note that the variance of <math>\zeta_{i,j}</math> (denoted by <math>\sigma\zeta_{j,2}</math>) is equal to <math>\sigma\delta_{j,2} + \sigma^2</math>. This model becomes a one-way random effect model if we only consider the post-treatment follow-up visits for a treatment group. Thus, applying a one-way random effect model to the change from pre-treatment baseline to post-treatment follow-up data of</p>

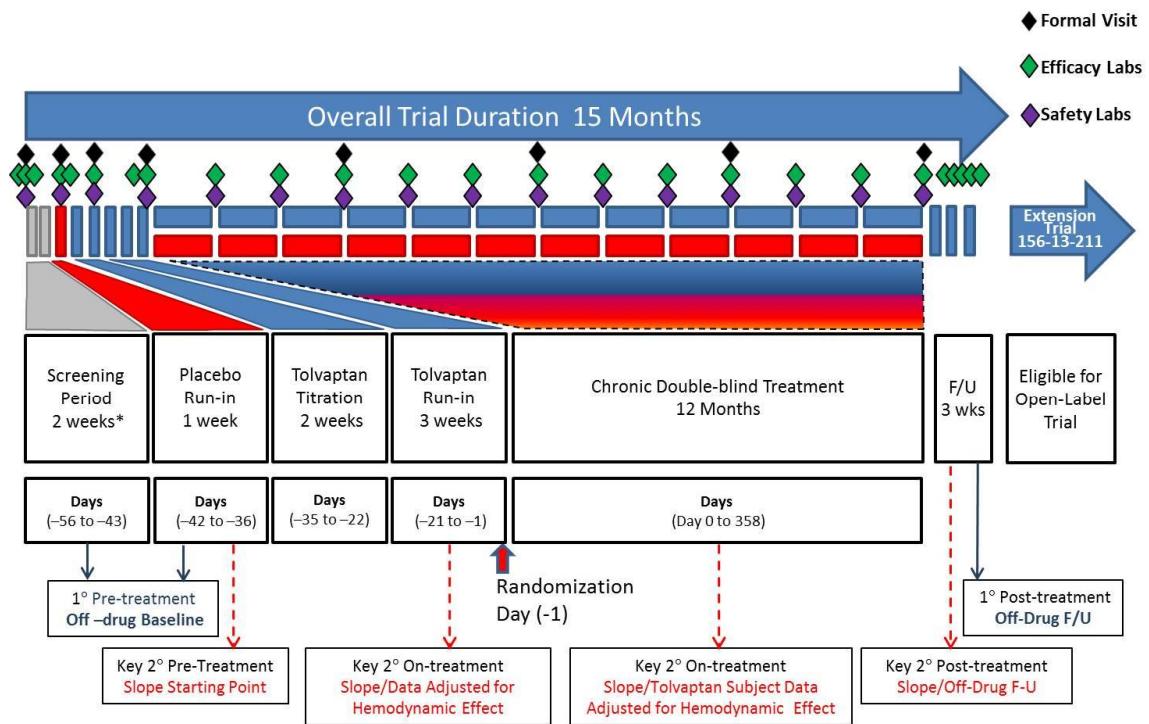
Location	Old Text	Updated Text
	<p>this section, the variance would <math>(2/k) \sigma^2 + (1 + 1/12 + 3/52)2 \sigma\beta^2</math> (7)</p> <p>This variance formula was used in our sample size calculation, since it matches our protocol design more closely.</p> <p>If the model given by (1) to (4) is applied to the data of CKD-3 non-Japan subjects in Trial 156-04-251, with eGFR data from pre-randomization baseline to Follow-up Visit #2, the residual variance (<math>\sigma^2</math>) and slope variance (<math>\sigma\beta^2</math>) are estimated as 22.13 and 5.27, respectively, which may be interpreted as intra- and inter-subject variances.</p> <p>With a 2-sided alpha of 0.05 and 1:1 randomization to tolvaptan and placebo, using the parameters given above and sample size formula of 2-sample t-test, we have the following table:</p> <p>(TABLE 7.1.1.1 deleted).</p> <p>The assumption of dropout rate of 15% is reasonable since the dropout rate was 20% in Trial 156-04-251, and it is expected that the inclusion of the tolvaptan run-in period in this trial will reduce the dropout rate in the double blind treatment period. From this table, it seems that <math>k = 4</math> would produce an acceptable sample size and not an excessive burden for enrolled subjects.</p>	<p>placebo and tolvaptan respectively, in subjects who had both follow-up visits and baseline in 156-04-251, <math>\sigma^2</math> is estimated as 8.52 for placebo and 5.68 for tolvaptan. Take the average of these two estimates of <math>\sigma^2</math> to obtain an estimate of <math>\sigma^2</math> as 7.1 to be used in this sample size calculation, which is the <math>\sigma^2</math> for Month 12 visit of 156-04-251. Note that</p> $\text{Var}(Y_{i,j} - Y_{i,0}) = \sigma\delta_{j,2} + 2\sigma^2 \quad (4)$ <p>At Month 12, the SD (Standard Deviation) could be assumed as 6.5, based on CKD Stage 3 non-Japan subjects in 156-04-251. Then based on (4), <math>\sigma\delta_{j,2}</math> at Month 12 is estimated as 28.05 (<math>= 6.52 - 2 \times 7.1</math>). With <math>k</math> repeated measurements at pre-treatment baseline and at 12 month post-treatment follow-up in this trial, the baseline intra-subject variance and the follow-up intra-subject variance are reduced from <math>\sigma^2</math> to <math>\sigma^2/k</math> respectively. Thus, the variance of average change from average baseline at Month 12 is <math>(\sigma\delta_{1,2} + \sigma^2/k) + \sigma^2/k</math>, which is estimated as 31.6 (<math>= 28.05 + 7.1/4 + 7.1/4</math>) when <math>k = 4</math> and 32.8 (<math>= 28.05 + 7.1/3 + 7.1/3</math>) when <math>k = 3</math>. Here we have the following table of sample size:</p> <p>(New TABLE 7.1.1.1 inserted)</p>
Section 7.1.1, Sample Size Estimation	<p>Thus, with an assumption of 15% dropout rate in the trial, the total sample size (randomized subjects) would be from 660 to 770, and will be set as a range of between 700 and 1000 randomized subjects, with a goal of 800 subjects, depending also on the trial's ability to enroll and the accumulated number of subjects randomized up to the end of 2014. Because this information will be helpful in guiding the treatment of ADPKD patients with more advanced stages of CKD, and because marketing approval in many participating countries may be reached by 2015, it is critical to conclude enrollment near the end of</p>	<p><b>From the sample size table, the increase of repeated measurement at baseline and follow-up reduces the sample size significantly initially but quickly loses its effect when <math>k</math> is greater than 3. It seems that 3 repeated measurements may be appropriate in order to avoid subjects' burden.</b> Thus, with an assumption of 10% dropout rate in the trial, the total sample size (randomized subjects) would be approximately 1300.</p>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
	2014 or beginning of 2015. This will help avoid missing data due to subjects leaving the trial to seek commercially available treatment in those countries.	
Section 7.1.1, Sample Size Estimation	<p>The desire for a small number of blood draws during these periods was emphasized by the trial's Steering Committee, which further suggested that measures be taken to minimize the intra-subject variability by standardizing, as much as possible, the timing and conditions by which serum creatinine was assessed (in particular recommending a similar diet, avoiding variation in protein, especially cooked protein, intake and exercise pattern during these periods). The Steering Committee also suggested that the intra subject variance during the pre-treatment and post-treatment periods be monitored throughout the trial with a mandatory increase in serum creatinine sample numbers (ie, from a minimum of 4 to a minimum of 5) or subject numbers if observed variance was greater than that used in the power assumption (assessed using only baseline eGFR data in a power re-estimation procedure).</p> <p>They also favored the possibility that sample numbers, but not the minimum enrollment, be lowered (ie, to a maximum of 4 samples) if variance was significantly less due to these measures (see Section 7.1.2. "Blinded Sample-Size Re-estimation").</p>	<p><b>In order to avoid excessive blood draws, mechanisms were undertaken</b> to minimize the intra-subject variability by standardizing, as much as possible, the timing and conditions by which serum creatinine was assessed (in particular recommending a similar diet, avoiding variation in protein, especially cooked meat protein, intake and exercise pattern during these periods). <b>In addition to the efforts to reduce variability by standardizing subject diet at the time of blood draws, the number of scheduled blood draws will help establish precision in the estimated measurements.</b></p>
Section 7.1.1, Sample Size Estimation	<p>In addition, the 1:1 randomization and the alpha (0.05, 2-sided) specified above in the sample size of the primary endpoint are also assumed in the sample size calculation. It is then estimated that 315 subjects per group are required for 85% power and 367 subjects per group are required for 90% power. These sample sizes are very close to the sample size calculated using FDA statistician Dr. Lawrence's formula, for example, sample size of 368 per group with 90% power, when the variances provided above were used. Thus, with a total sample size of from</p>	<p>In addition, the 1:1 randomization and the alpha (0.05, 2-sided) specified above in the sample size of the primary endpoint are also assumed in the sample size calculation. It is then estimated that <b>734 subjects are required for 90% power. Thus, with a total sample size of approximately 1300</b>, the key secondary endpoint will have more than 90% power in detecting a slope difference in this trial.</p>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
	660 to 770 (rounded to 700 to 800), the key secondary endpoint will have at least 85% to more than 90% power in detecting a slope difference in this trial.	
Section 7.1.2, Blinded Sample Size Re-estimation	<p>Blinded sample size re-estimation will be conducted when about half of the planned randomized subjects (350 to 400) have been randomized. This is expected to be conducted before the end of 2014 and thus before the availability of any post 12 month off-treatment follow-up eGFR data used for the primary analysis. The goal of this blinded sample size re-estimation is to check: 1) the differences between the observed variances and the variances used in the sample size calculation; 2) whether the approach of averaging the 4 to 5 baseline pre-treatment eGFR observations has achieved the goal of reducing the variance to the level planned.</p>	<p>Blinded sample size re-estimation will be conducted when <b>at least a third</b> of the planned randomized subjects (<b>400 to 500</b>) have been randomized. This is expected to be conducted before the availability of any post 12 month off-treatment follow-up eGFR data used for the primary analysis. The goal of this blinded sample size re-estimation is to check: 1) the differences between the observed variances and the variances used in the sample size calculation; 2) whether the approach of averaging the <b>3</b> eGFR observations <b>at pre-treatment baseline and post-treatment follow-up</b> has achieved the goal of reducing the variance to the level planned.</p>
Section 7.2, Datasets for Analysis, Primary Endpoint Efficacy Population:	<p>....The primary endpoint's baseline is defined as the average of up to 5 eGFR values observed during the screening and placebo run-in periods.</p> <p>The core subject population for all efficacy analyses is based on the intent-to-treat (ITT) population which consists of all randomized subjects who take at least one dose of IMP.</p>	<p>The primary endpoint's baseline is defined as the average of up to <b>3</b> eGFR values observed during the screening and placebo run-in periods.</p> <p>The core subject population for all efficacy analyses is based on the intent-to-treat (ITT) population which consists of all randomized subjects who take at least one dose of IMP <b>post randomization</b>.</p>
Section 7.4.1.1, Primary Endpoint Analysis	<p>To reduce the variation in this primary endpoint, 4 to 5 observations of eGFR will be obtained at baseline during a 3 week interval (screening and placebo run-in periods) and another 4 to 5 observations will be obtained post-treatment during a 2-week interval that begins 1 week after the end of treatment (3-week post-treatment follow-up). The average of the 4 to 5 eGFR values observed during the baseline period is set as the baseline and the average of the 4 to 5 eGFR values observed during the post-treatment follow-up period is set as the renal function measurement post-treatment</p>	<p>To reduce the variation in this primary endpoint, <b>3</b> observations of eGFR will be obtained at baseline during a 3 week interval (screening and placebo run-in periods) and another <b>3</b> observations will be obtained post-treatment during a 2-week interval that begins 1 week after the end of treatment (3-week post-treatment follow-up). The average of the <b>3</b> eGFR values observed during the baseline period is set as the baseline and the average of the <b>3</b> eGFR values observed during the post-treatment follow-up period is set as the renal function measurement post-treatment</p>

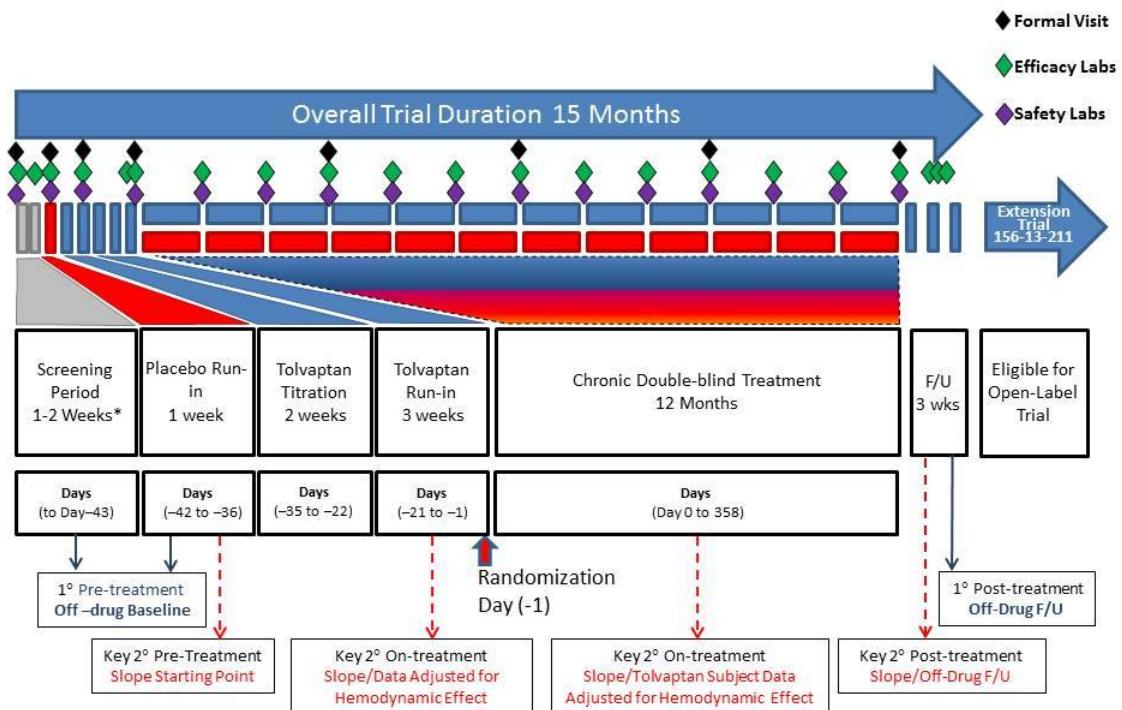
<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
Section 7.4.1.2, Sensitivity Analysis of the Primary Endpoint	Aligned with the desire to evaluate effects free from acute hemodynamic treatment effects, a sensitivity analysis of the primary endpoint will be performed including all available placebo data. In this sensitivity analysis, in addition to the 4 to 5 pre-treatment baseline observations and the 4 to 5 post-treatment follow-up observations, all post randomization on-treatment eGFR observations in the protocol-specified visits for placebo subjects will also be included	Aligned with the desire to evaluate effects free from acute hemodynamic treatment effects, a sensitivity analysis of the primary endpoint will be performed including all available placebo data. In this sensitivity analysis, in addition to the 3 pre-treatment baseline observations and the 3 post-treatment follow-up observations, all post randomization on-treatment eGFR observations in the protocol-specified visits for placebo subjects will also be included
Section 7.4.3, Subgroup Efficacy Analysis	N/A	Subgroup analyses will be provided for the primary and the key secondary endpoints by regions (US and non-US), gender (male and female), race (Caucasian and Other), age ( $\leq$ 55 years, $>$ 55 years), baseline GFR level (eGFR $\leq$ 45 mL/min/1.73 <sup>2</sup> m <sup>2</sup> and $>$ 45 mL/min/1.73 m <sup>2</sup> and baseline TKV ( $\leq$ 2000 mL, $>$ 2000 mL or unknown).
Section 7.4.4.1, Exploratory Analysis of Efficacy Based on Modal Doses	N/A	Exploratory analyses will be applied to the primary and key secondary endpoints will tolvaptan subjects coded by their modal doses in the trial, using the same analytic approached specified for these endpoints.
Section 7.4.5, Interim Analysis	N/A	This trial is to be conducted over a critical time period during which tolvaptan may be approved as therapy for ADPKD in some of the participating regions. The European Medicines Agency's (EMA) decision for a pending marketing authorization application for the use of tolvaptan in treatment of ADPKD is expected in 2015. Following regulatory approval, reimbursement and commercial availability may have an impact on the ongoing ethical conduct of the trial. This may impact subjects enrolled in Europe who are continuing in the randomized, placebo-controlled treatment phase. Therefore, the IDMC for this trial will be empowered to conduct an interim analysis (IA) of the primary endpoint once approximately half of enrolled subjects (600-700) are

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
		<p>expected to complete their planned one-year treatment. The sponsor may decide the actual timing of the IA to be conducted, based on the availability of commercial tolvaptan in ADPKD. This IA would use the O'Brian-Fleming spending function to apportion alpha and thus manage Type 1 error. Determination of the information time of the IA assumes total sample size in this trial to be set at 1300, if the trial is still randomizing subjects at the time of the IA. For example, if the first 650 subjects out of 1300 total sample size are included, a p-value &lt; 0.003051 is required to reject the null hypothesis, satisfy the objective of replicating efficacy, and offer a possibility for early trial completion. If a recommendation for early termination is accepted, all subjects remaining in the trial can be offered participation in a planned open-label extension trial. If the null hypothesis is not rejected at this interim evaluation, the trial would continue and the alpha of the final test of the primary endpoint would be 0.049002.</p>
Section 7.6, Safety Analysis	<p>Standard safety variables to be analyzed include AEs, clinical laboratory data, physical examinations, and vital signs.</p>	<p>Standard safety variables to be analyzed include AEs, <b>self-reported tolerability</b>, clinical laboratory data, physical examinations, and vital signs.</p>
Appendix 3, Handling and Shipment of Bioanalytical Samples	<p>The 20 mL biomarker sample will be collected by the subject at home and transported to the site at room temperature. At the site, the sample should be immediately equally divided into the bar-code labeled polypropylene tubes (number of aliquots will be defined in the operations manual) and frozen.</p>	<p>The PD/<b>biomarker urine</b> sample will be collected by the subject at home and transported to the site at room temperature. At the site, <b>20 mL</b> of the sample should be immediately equally divided into the bar-code labeled polypropylene tubes (number of aliquots will be defined in the operations manual) and frozen.</p>

**Previous Figure 3.1-1 - Trial Design Schematic:**

F/U = Follow-up

\*Can be extended up to an additional 8 weeks for subjects needing stabilization after changing other treatments.

**Revised Figure 3.3-1 Trial Design Schematic**

**Previous Schedule of Assessments****Table 10.2-1: Schedule of Assessments**

Assessment	Pre-randomization										Double-blind Randomized Treatment			Follow-up			
	Screening (2 weeks ± 1 day)		Placebo run-in (1 week ± 1 day) (Days -42 to -36)		Tolvaptan titration (2 weeks ± 1 day) (Days -35 to -22)				Tolvaptan run-in (3 weeks ± 1 day) (Days -21 to -1)			(Day 0)	Visits: monthly (± 2 days)	Month 12/ EoTx visit	3 weeks post-treatment		
	Days -56 to -43 <sup>a</sup>	Day -42	Day -39 ± 1 day	Day -36	-35	-32	-28	-24	-22	-21	-15	-8	-1	Day 0	Months 1 to 11	Month 12 /EoTx	Days +7 to +21 post-final visit <sup>a</sup>
Informed consent	X																
Inclusion/Exclusion	X																
Demographic/Medical history	X																
Vital signs <sup>b</sup>	X	X			X				X			X		(X) <sup>b</sup>	X		X
Physical examination <sup>c</sup>	X														X		
Urine pregnancy test (WOCBP only) <sup>d</sup>	X													(X) <sup>c</sup>	X		X
Clinical laboratory samples <sup>e</sup> :																	
Hematology and coagulation	X																
Urinalysis	X	X			X						X				X		
Serum Chemistry Panel	X														X		X
Liver Function Panel	X				X				X		X	X			X		X
Creatinine	X	X	X		X	X			X		X	X		X	X	X	X
Sodium	X	X		X	X			X		X	X		X	X	X		
PK plasma sample <sup>f</sup>											X			(X) <sup>f</sup>	X		X
PD urine sample <sup>f</sup>			X		X			X			X			(X) <sup>f</sup>	X		X
Biomarker urine and plasma			X		X			X			X			(X) <sup>f</sup>	X		X

**Table 10.2-1: Schedule of Assessments**

Assessment	Pre-randomization										Double-blind Randomized Treatment			Follow-up	
	Screening (2 weeks ± 1 day)		Placebo run-in (1 week ± 1 day) (Days -42 to -36)		Tolvaptan titration (2 weeks ± 1 day) (Days -35 to -22)		Tolvaptan run-in (3 weeks ± 1 day) (Days -21 to -1)		(Day 0)	Visits: monthly (± 2 days)	Month 12/ EoTx visit	3 weeks post-treatment			
	Days -56 to -43 <sup>a</sup>		Day -42	Day -39 ± 1 day	Day -36	Days		Days		Day 0	Months 1 to 11	Month 12 /EoTx	Days +7 to +21 post-final visit <sup>a</sup>		
<sup>f</sup> sample															
DNA blood sample <sup>g</sup>	X														
Start newly dispensed IMP			X			X			X			X			
Tolerability/Dosing review					X		X	X	X		X		X		
Randomization											X				
Drug dispensation <sup>h</sup>		X			X				X		X		X		
Drug reconciliation <sup>h</sup>					X				X		X		X		
IVRS entry <sup>i</sup>	X	X			X		X	X	X		X		X		X
Exploratory PKD outcomes <sup>j</sup>		X	-								X		X		
Adverse events	X	<----->													
Concomitant medications	X	<----->													

<sup>a</sup>The screening period may be extended up to an additional 8 weeks for subjects who require modification of medical care specifically for this trial. Visits during the screening and follow-up periods must be scheduled at least 24 hours (1 day) apart. At each visit, blood will be collected and analyzed centrally for serum creatinine concentrations, in addition to any other assessments listed. A visiting nurse house call or local laboratory visit may be substituted for visits where only blood/urine will be collected. Visits during the screening period must be scheduled within a 2-week period before the start of the placebo run-in period. Visits during the follow-up period must be scheduled during a 2-week period that begins 1 week after the end of treatment visit.

<sup>b</sup>The following visits (and all assessments required during those visits) should be performed in-clinic: screening, end of placebo run-in, end of tolvaptan titration, end of tolvaptan run-in, quarterly visits during the randomized, double-blind treatment period (eg, Months 3, 6, 9), Month 12/end of treatment (EoTx) visit, and the last follow-up visit. Vital signs at each of the above visits include sitting heart rate and blood pressure. Post-void body weight should

be measured at the first screening visit and the Month 12/EoTx visit only. Height should be assessed at the first screening visit only. Either height or weight may be collected as an unscheduled measurement if its assessment was missed.

<sup>c</sup>A full physical examination is required at the first screening visit and the Month 12/EoTx visit. A “directed physical examination” may be performed at the quarterly visits (eg, Months 3, 6, 9) for assessment of signs or symptoms reported by the subject that might require further evaluation.

<sup>d</sup>During the trial, a pregnancy test should be completed at screening and at the quarterly visits. On suspicion of pregnancy, unscheduled urine or serum pregnancy testing will be performed. Positive urine pregnancy tests should be confirmed with a serum pregnancy test.

<sup>e</sup>The specifics and timing for clinical laboratory samples for central and local laboratory analyses are as follows:

**Screening period:** Subjects will have 3 blood draws on separate days between Day -56 and Day -43. The subject's eligibility will be confirmed by the mean of eGFR calculated from the subjects' first 2 pre-treatment, central laboratory serum creatinine assessments.

**Placebo run-in period:** Subjects will have 2 blood draws on separate days (at least 24 hours apart) between Days -42 to -36 with the last sample on Day -36.

**Tolvaptan titration period:** Subjects will have 1 blood draw at the end of 2 weeks with the sample being obtained on Day -22.

**Tolvaptan run-in period:** During the last 2 weeks of this period, blood will be drawn 2 times on separate days (at least 24 hours apart) with the last sample on Day -1.

**Double-blind treatment period:** Samples will be collected for central lab analysis monthly and at the Month 12/EoTx visit. Local standard of care laboratory tests will be performed monthly per the subject's individual clinical management needs. Local liver function panel analyses will also be performed more frequently, if necessary.

<sup>f</sup>During the double-blind, randomized treatment period, PK plasma samples, PD urine samples, and biomarker urine/plasma samples will be collected quarterly (eg, Months 3, 6, 9, 12/EoTx).

<sup>g</sup>Samples are optional.

<sup>h</sup>Drug dispensing and reconciliation will be done monthly and subjects will be reminded of the importance of their commitment to continue participation in the trial..

<sup>i</sup>If, during the titration contact, the determination is made to adjust the dose-regimen, the investigator will enter the subject's status in the IVRS and arrange for dispensation of a new IMP kit and reconciliation of returned IMP.

<sup>j</sup>Exploratory PKD outcomes will be completed either monthly over the phone or in person during quarterly clinic visits.

**Revised Schedule of Assessments****Table 10.2-1 Schedule of Assessments**

Assessment	Pre-randomization										Double-blind Randomized Treatment			Follow-up			
	Screening <sup>a</sup> (1-2 weeks)			Placebo run-in (1 week ± 1 day) (Days -42 to -36)		Tolvaptan titration (2 weeks ± 1 day) (Days -35 to -22)			Tolvaptan run-in (3 weeks ± 1 day) (Days -21 to -1)		(Day 0)	Visits: monthly (± 2 days)	Month 12/ EoTx visit				
	V1	V2	Day -43	Day -42	Day -36	-35	-32	-28	-24	-22	-21	-15	-8	-1	Day 0	Months 1 to 11 <sup>b</sup>	Month 12 /EoTx
Informed consent	X																
Inclusion/Exclusion	X																
Demographic/Medical history	X																
Vital signs <sup>c</sup>	X	X			X				X			X		(X) <sup>c</sup>	X		X
Physical examination <sup>d</sup>	X													(X) <sup>d</sup>	X		
Urine pregnancy test (WOCBP only) <sup>e</sup>	X				X									(X) <sup>e</sup>	X		X
Chemistry Blood Sample <sup>c,f</sup> :																	
Serum Chemistry Panel	X														X		X
Liver Function Panel	X	X			X			X			X		X		X	X	X
Creatinine	X	X			X			X			X	X		X	X	X	X
Sodium	X	X			X			X			X		X		X		X
Hematology and coagulation	X																
PK plasma sample												X		(X) <sup>g</sup>	X		X
Biomarker plasma sample		X			X			X			X		X	(X) <sup>g</sup>	X		X
DNA blood sample <sup>h</sup>		X															

**Table 10.2-1 Schedule of Assessments**

Assessment	Pre-randomization										Double-blind Randomized Treatment			Follow-up				
	Screening <sup>a</sup> (1-2 weeks)			Placebo run-in (1 week ± 1 day) (Days -42 to -36)		Tolvaptan titration (2 weeks ± 1 day) (Days -35 to -22)			Tolvaptan run-in (3 weeks ± 1 day) (Days -21 to -1)		(Day 0)	Visits: monthly (± 2 days)	Month 12/ EoTx visit					
	V1	V2	Day -43	Day -42	Day -36	-35	-32	-28	-24	-22	-21	-15	-8	-1	Day 0	Months 1 to 11 <sup>b</sup> /EoTx	Month 12 /EoTx	
Urinalysis	X	X			X								X			X		
PD and Biomarker urine sample		X			X					X			X		(X) <sup>g</sup>	X		X
Start newly dispensed IMP				X		X				X			X					
Tolerability/Dosing review					X		X	X	X				X			X	X	
Randomization													X					
Drug dispensation <sup>1</sup>			X		X					X			X			X		
Drug reconciliation <sup>1</sup>					X					X			X			X	X	
IVRS entry <sup>j</sup>	X	X	X		X		X	X	X	X			X			X	X	X
Exploratory PKD outcomes <sup>k</sup>		X											X			X	X	
Adverse events	X	<----->																
Concomitant medications	X	<----->																

<sup>a</sup>The screening period should be completed within 1-2 weeks before the start of the placebo run-in period. The screening period may be extended up to an additional 8 weeks for subjects who require modification of medical care specifically for this trial. Visits during the screening and follow-up periods must be scheduled at least 24 hours (1 day) apart. The Day -43 visit cannot occur until laboratory values from V2 are received. For two visits (V1, V2) during the screening period, blood will be collected and analyzed centrally for serum creatinine concentrations, in addition to any other assessments listed. A visiting nurse house call or local laboratory visit may be substituted for visits where only blood/urine will be collected during the follow-up period. Visits during the follow-up period must be scheduled during a 2-week period that begins 1 week after the end of treatment visit.

<sup>b</sup>If IMP treatment is interrupted for ≥ 7 days during this period, procedures should be followed as detailed in [Section 3.8.3.2](#).

<sup>c</sup>The following visits (and all assessments required during those visits) should be performed in-clinic: screening (V1, V2, Day -43), end of placebo run-in, end of tolvaptan titration, end of tolvaptan run-in, quarterly visits during the randomized, double-blind treatment period (eg, Months 3, 6, 9), Month 12/end of treatment (EoTx) visit, and the last follow-up visit. Vital signs at each of the above visits include sitting heart rate and blood pressure. Post-void body weight should be measured at the first screening visit and the Month 12/EoTx visit only. Height should be assessed at the first screening visit only. Either height or weight may be collected as an unscheduled measurement if its assessment was missed.

<sup>d</sup>A full physical examination is required at screening (V1) and the Month 12/EoTx visit. A “directed physical examination” is performed at the quarterly visits (eg, Months 3, 6, 9) for assessment of signs or symptoms reported by the subject that might require further evaluation.

<sup>e</sup>During the trial, a pregnancy test should be completed at screening, end of placebo run-in and at the quarterly visits. On suspicion of pregnancy, unscheduled urine or serum pregnancy testing will be performed. Positive urine pregnancy tests should be confirmed with a serum pregnancy test.

<sup>f</sup>All serum creatinine samples will be analyzed by the central laboratory. The specifics and timing for all clinical laboratory samples for central and local laboratory analyses are as follows:

**All visits:** One or more tubes of blood may be collected to accommodate the needed tests.

**Screening period:** During the 1-2 weeks of the screening period, blood will be drawn 2 times on separate days (V1, V2) at least 24 hours apart. The subject's eligibility will be confirmed by the mean of eGFR calculated from the subjects' 2 pre-treatment (V1, V2), central laboratory serum creatinine assessments and entered in IVRS on Day -43.

**Placebo run-in period:** Subjects will have 1 blood draw at the end of 1 week with the sample being obtained on Day -36.

**Tolvaptan titration period:** Subjects will have 1 blood draw at the end of 2 weeks with the sample being obtained on Day -22.

**Tolvaptan run-in period:** During the last 2 weeks of this period, blood will be drawn 2 times on separate days (at least 24 hours apart) with the last sample on Day -1.

**Double-blind treatment period:** Samples will be collected for central lab analysis monthly and at the Month 12/EoTx visit. Local standard of care laboratory tests will be performed monthly per the subject's individual clinical management needs. Local liver function panel analyses will also be performed more frequently, if necessary.

**Follow-up period:** Subjects will have blood drawn on 3 visits over Days +7 to +21 post-treatment.

Full Chemistry panel will be obtained during following visit: Screening (V1), quarterly visit (M3, M6, M9, M12/EoTx, F/U period Day 21 Serum creatinine, serum sodium,: Screening (V2), end of placebo period, end of tolvaptan titration, 2 times during tolvaptan run-in, monthly during double blind treatment period, 2 times during F/U period

Liver function panel: Screening (V2), end of placebo period, end of tolvaptan titration, 2 times during tolvaptan run-in, monthly during double blind treatment period, F/U period Day 21

<sup>g</sup>During the double-blind, randomized treatment period, PK plasma samples, PD urine samples, and biomarker urine/plasma samples will be collected quarterly (eg, Months 3, 6, 9, 12/EoTx).

<sup>h</sup>DNA samples are optional.

<sup>i</sup>Drug dispensing and reconciliation will be done monthly (exceptions to allow dispensing/reconciliation at each 3-month clinic visit may be made by the medical monitor in exceptional circumstances, with instructions to take only one month's supply and start the next month only after acceptable safety lab results are confirmed by the investigator). Instructions to begin taking the next month's trial medication will be given by telephone contact. Subjects will

be reminded of the importance of their commitment to continue participation in the trial. At the completion of the screening period, trial medication will be dispensed at Day -43 after subject eligibility is confirmed. In exceptional circumstances, trial medication may be dispensed at V2, with the instruction not to take any trial medication until eligibility is confirmed by the investigator. In these cases, confirmation of eligibility and instructions for taking trial medication will be provided by telephone on Day -43.

j If, during the titration contact, the determination is made to adjust the dose-regimen, the investigator will enter the subject's status in the IVRS and arrange for dispensation of a new IMP kit and reconciliation of returned IMP. At the end of the titration period, the subject's highest tolerated dose will be utilized for the 3-week tolvaptan run-in period.

k Exploratory PKD outcomes will be completed either monthly over the phone or in person during quarterly clinic visits.

**Administrative Change Number:** 2**Issue Date:** 25 June 2014**PURPOSE:**

This administrative change will not affect the safety of subjects, the scope of the investigation, or the scientific quality of the trial.

The main purpose of this administrative change was to align the Statistical Analysis Plan with the protocol. In addition, an administrative change to Home Nursing Services was made, and several clarifications to the protocol were added.

**BACKGROUND:**

The US-FDA's Special Protocol Agreement (SPA) requested several modifications to the protocol to more closely align analyses with the Statistical Analysis Plan. The delegated Home Nursing Services vendor was also changed and is now updated.

**Sectional Revisions**

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
Synopsis, Trial Design, Double-blind, randomized treatment period (12 months):	...Subjects will also be stratified by total kidney volume (TKV; ≤ 2000 mL or > 2000 m), if known.	...Subjects will also be stratified by <b>three</b> total kidney volume ( <b>TKV</b> ) <b>criteria</b> (≤ 2000 mL, > 2000 mL, <b>or unknown</b> ).
Synopsis, Primary Efficacy Analysis	<u>Primary efficacy analysis:</u> The change in eGFR from pre-treatment baseline to post-treatment follow-up, annualized (divided) by each subject's IMP treatment duration, will be calculated. The annualized change in eGFR will be analyzed by analysis of covariance (ANCOVA) with treatment and randomization stratification factors as factor and covariate baselines.	<u>Primary efficacy analysis:</u> The change in eGFR from pre-treatment baseline to post-treatment follow-up, annualized (divided) by each subject's IMP treatment duration, will be calculated. The annualized change in eGFR will be analyzed by <b>a weighted</b> analysis of covariance (ANCOVA) with treatment and randomization stratification factors as factor and covariate baselines. <b>This weighted analysis is based on the reciprocal of the estimated variance of the “estimated slopes.”</b>
Abbreviations List		IDMS - Isotope dilution mass spectrometry
Section 2.1, Trial Rationale	To decrease variability, multiple serum creatinine measurements will be taken both pre- and post-treatment for each subject, and the eGFR values will then be averaged.	To decrease variability, multiple serum creatinine measurements ( <b>isotope dilution mass spectrometry [IDMS]-traceable</b> ) will be taken both pre- and post-treatment for each subject, and the eGFR values will then be averaged.
Section 3.2.2, Double-	After stratified randomization,	After stratified randomization, <b>by</b>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
blind Randomized Treatment Period (Day 0 to Month 12)	subjects will enter the double-blind, randomized treatment period receiving either tolvaptan or placebo in a 1:1 ratio.	<b>baseline eGFR (at a threshold of <math>\leq 45</math> or <math>&gt; 45 \text{ mL/min}/1.73\text{m}^2</math>), by age (<math>\leq 55</math> or <math>&gt; 55</math> years old), and by three TKV criteria (<math>\leq 2000 \text{ mL}</math>, <math>&gt; 2000 \text{ mL}</math>, or unknown),</b> subjects will enter the double-blind, randomized treatment period receiving either tolvaptan or placebo in a 1:1 ratio.
Section 3.4.1, Informed Consent	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),...	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 signed and dated by <b>all subjects (or their guardian or legal representative, as applicable for local laws)</b> , and the person obtaining consent (investigator or designee),..
Section 3.5.2.1, Key Secondary Efficacy Endpoint	Treatment difference in annualized slope of eGFR calculated for individual subjects using an appropriate baseline and available, post-randomization, on treatment assessments.	Treatment difference in annualized slope of eGFR calculated for individual subjects using <b>eGFR data observed in the placebo run-in, tolvaptan run-in (not including tolvaptan titration), double-blind treatment, and post-treatment follow-up (not including data collected in the first week after the last IMP dose) periods.</b>
Section 3.6, Measures to Minimize/Avoid Bias	Subjects will also be stratified by total kidney volume (TKV; $\leq 2000 \text{ mL}$ or $> 2000 \text{ mL}$ ), if known.	Subjects will also be stratified by <b>three TKV criteria (<math>\leq 2000 \text{ mL}</math>, <math>&gt; 2000 \text{ mL}</math>, or unknown).</b>
Section 3.7, Trial Procedures, Schedule of Assessments	c ...Either height or weight may be collected as an unscheduled measurement if its assessment was missed.	c ...Either height or weight may be collected as an unscheduled measurement if <b>the planned assessment was missed. Weight may be assessed as necessary to assess changes in body weight.</b>
	l...Instructions to begin taking the next month's trial medication will be given by telephone contact....	l...Instructions to begin taking the next month's trial medication will be given <b>during the time of IMP dispensation at each monthly visit or by telephone contact after the monthly LFT samples are collected. If LFT results are abnormal, the site will conduct a telephone contact with the trial subject to inform them that prompt immediate retesting (ie,</b>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
		<b>within 72 hours) may be necessary (see Section 3.7.3.4 for guidance) and to arrange for follow-up and adjustment of medication (as needed); if a down titration is required, the subject may need to return to the site or have new drug delivered.</b>
Section 3.7.1.1, Pre-randomization Period	<p>Pre-randomization eGFR value(s) will be collected for each potential treatment assignment for all subjects.</p> <p>To establish the pre-randomization eGFR, multiple serum creatinine values will be obtained under standardized conditions</p>	<p>Tolvaptan Run-in (3 weeks ± 1 day) Day - 15 column was deleted</p> <p>Pre-randomization eGFR value(s) will be <b>calculated by CKD-EPI</b> for each potential treatment assignment for all subjects.</p> <p>To establish the pre-randomization eGFR, multiple serum creatinine values (<b>IDMS-traceable</b>) will be obtained under standardized conditions</p>
Section 3.7.1.1.4, Tolvaptan Run-In Period (Days -21 to -1)	Subjects will also be stratified by age ( $\leq 55$ or $> 55$ years old) and by total kidney volume (TKV; $\leq 2000$ mL, or $> 2000$ mL), if known.	Subjects will also be stratified by age ( $\leq 55$ or $> 55$ years old) and by <b>three TKV criteria</b> ( $\leq 2000$ mL, $> 2000$ mL, <b>or unknown</b> ).
Section 3.7.2.1, Serum Creatinine for Estimated Glomerular Filtration Rate	The eGFR values will be calculated from the central-laboratory serum creatinine concentrations taken at screening and during every trial visit.	The eGFR values will be calculated by <b>CKD-EPI</b> from the central-laboratory serum creatinine concentrations taken at screening and during every trial visit.
Section 7.4.1.1, Primary Endpoint Analysis	The primary endpoint of this trial is the change in eGFR from pre-treatment baseline to post-treatment follow-up, annualized (divided) by each subjects' IMP treatment duration.	The primary endpoint of this trial is the change in eGFR ( <b>calculated by the CKD-EPI formula</b> ) from pre-treatment baseline to post-treatment follow-up, annualized (divided) by each subjects' IMP treatment duration.
	...Thus, analysis of covariance (ANCOVA) with effects of treatment and randomization stratification factors and covariate baseline will be applied to these "estimated slopes" as the primary analysis.	...Thus, <b>a weighted</b> analysis of covariance (ANCOVA) with effects of treatment and randomization stratification factors and covariate baseline will be applied to these "estimated slopes" as the primary analysis. <b>This weighted analysis is based on the reciprocal of the estimated variance of the "estimated slopes," and the detailed algorithm to derive the estimated variance is provided in Section 8.3 of the SAP.</b>
Section 7.4.1.3, Sensitivity Analysis Including Data from Subjects Who Discontinue IMP	This sensitivity analysis deviates from the MAR assumption to include the post-discontinuation follow-up data in the analysis specified in the previous section. Subjects who discontinue IMP after randomization	This sensitivity analysis deviates from the MAR assumption to include the post-discontinuation follow-up data in the analysis specified in the <b>primary analysis</b> section. Subjects who discontinue

Location	Old Text	Updated Text
	without withdrawing consent will be followed for additional off-treatment eGFR through to Month 12. These post “post-treatment follow-up” eGFR data will be included with the data specified in the previous section, in a sensitivity analysis using the same analytic approach specified in the previous section.	IMP after randomization without withdrawing consent will be followed for additional off-treatment eGFR <b>values up</b> to Month 12. These “post-treatment follow-up” eGFR data <b>at Month 12</b> will be included to replace the data <b>observed during post-treatment follow-up for the subjects who discontinue IMP early</b> , in a sensitivity analysis using the same analytic approach specified in the <b>primary analysis</b> section.
Section 7.4.2.1, Key Secondary Endpoint Analysis	The time variable used in the model may start from the first observation of eGFR obtained from placebo run-in period.	The time variable used in the model may start from the first observation of eGFR obtained from placebo run-in period. <b>The covariate “acute hemodynamic effect” in the model is the flag variable with value of 0 and 1 specified earlier in this section for the data observed during tolvaptan run-in and the data observed for tolvaptan subjects during the double blind treatment period. The starting point of this eGFR slope analysis is the eGFR observation during the placebo run-in period.</b>
Section 7.4.3, Subgroup Efficacy Analysis	Subgroup analyses will be provided for the primary and the key secondary endpoints by regions (US and non-US), gender (male and female), race, (Caucasian and Other), age ( $\leq 55$ years, $> 55$ years), baseline GFR level (eGFR $\leq 45$ mL/min/1.73 m <sup>2</sup> and $> 45$ mL/min/1.73 m <sup>2</sup> ) and baseline TKV ( $\leq 2000$ mL, $> 2000$ mL, or unknown).	Subgroup analyses will be provided for the primary and the key secondary endpoints by regions (US and non-US), gender (male and female), race (Caucasian and Other), age ( $\leq 55$ years, $> 55$ years), baseline GFR level (eGFR $\leq 45$ mL/min/1.73 m <sup>2</sup> and $> 45$ mL/min/1.73 m <sup>2</sup> ) and <b>three baseline TKV criteria</b> ( $\leq 2000$ mL, $> 2000$ mL, or unknown).
Appendix 2, Institutions Concerned With the Trial, Home Nursing Services	Symphony Clinical Research 700 Deerpath Drive Vernon Hills, IL 60061, USA Phone: +1-301-984-7191 Fax: +1-301-921-4405	The Medical Research Network Ltd. 15 Presley Way Crownhill, Milton Keynes Buckinghamshire MK8 0ES Stuart Redding (Director) <a href="mailto:stuart.redding@themrn.co.uk">stuart.redding@themrn.co.uk</a> Tel: 0800-032-2348 <a href="http://www.themrn.co.uk">www.themrn.co.uk</a>

**Amendment Number** 2**Issue Date:** 26 November 2014**PURPOSE:**

The primary purpose of this amendment was to add an additional exclusion criterion for France.

**BACKGROUND:**

A letter from the French health agency Agence nationale de sécurité du medicament (ANSM) requested verbiage be added to the exclusion criteria explaining contraindications of tolvaptan.

**Sectional Revisions**

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
Section 3.4.3, Exclusion Criteria, Table 3.4.3-1		8. Tolvaptan is contraindicated in patients who: are known to have hypersensitivity to tolvaptan or one of the excipients, are hypovolemic (volume depletion), cannot perceive thirst. Additionally, subjects with baseline screening abnormalities of serum sodium concentrations (hyponatremia or hypernatremia) may not be enrolled in the trial until these abnormalities resolve and then must be monitored accordingly.

**ADDITIONAL RISK TO THE SUBJECT:**

There is no additional risk to the subjects.

**Amendment Number** 3

**Issue Date:** 26 March 2015

**PURPOSE:**

The primary purpose of this amendment is to clarify the inclusion criterion for older subjects, and to correct a misstatement regarding SUSAR reporting for procedures. Other clarifications were added for consistency between the Schedule of Assessments table and text or to clarify sample collection process or timing. The DNA sample collection time was changed from the second screening visit only to any visit from the second screening visit onwards.

**BACKGROUND:**

**Clarification of Inclusion Criterion # 2 (other than synopsis, first appears in Section 3.4)**

A change is made to the inclusion criterion to clarify that subjects likely to have slowly progressive ADPKD due to their advanced age at entry be excluded if available renal function history confirms a progression rate inconsistent with the scientific goals of the trial. As this trial is only 1 year in duration, it is therefore important that enrolled subjects have a decrease of at least 2 mL/min/1.73 m<sup>2</sup> per year so that the expected measurable effect of tolvaptan (a 33% reduction in the rate of decline) may be determined.

**Clarification of Sample Collection (other than synopsis, first appears in Section 3.7)**

In order to ensure that urine samples are collected in the same manner at every site, wording is added to the Schedule of Assessments table to specify that urine samples will be collected during the second morning void as a mid-stream, clean-catch sample, and obtained prior to the subject's eating breakfast. This instruction was added to every visit where a urine sample is collected. Where necessary, all supplies for the collection should be provided to the subject prior to the next visit so the sample can be collected either in-clinic or at home on the day of the scheduled visit.

In the previous version of the protocol, serum creatinine samples are to be collected three times over the follow-up period. The language is clarified to emphasize that the first of 3 samples in the 3-week follow-up period occurs at least 7 days after the last dose of IMP to ensure the acute, reversible effects of tolvaptan on serum creatinine have a minimally reasonable time period to abate.

### Clarification of DNA Blood Samples (first appears in the Schedule of Assessments table, Section 3.7)

Language was added to allow flexibility in the timing of DNA blood sample collection in case subjects do not provide consent at the second screening visit, but consent to do so at a later visit. This eliminates potential protocol deviations that have no impact on the ability to interpret the data for the primary endpoint of this trial.

### Sectional Revisions

Location	Old Text	Updated Text
Synopsis, Trial Design	<p><u>Double-blind, randomized treatment period (12 months):</u> Only subjects who reach the end of the tolvaptan run-in period and are able to tolerate tolvaptan 60/30 mg or 90/30 mg daily “for the rest of their lives” are eligible to enter this period. Randomization will be 1:1, tolvaptan to placebo. Subjects will be stratified by their baseline eGFR, at a threshold of <math>\leq 45</math> or <math>&gt; 45 \text{ mL/min}/1.73\text{m}^2</math>, and by age (<math>\leq 55</math> or <math>&gt; 55</math> years old). Subjects will also be stratified by three total kidney volume (TKV) criteria (<math>\leq 2000 \text{ mL}</math>, <math>&gt; 2000 \text{ mL}</math>, or unknown). Post-randomization, the maximally-tolerated dose of tolvaptan established during the run-in period, or the equivalent as matching placebo tablets, will be dispensed according to the subject’s randomization outcome. If continued tolerability becomes an issue, subjects may titrate downward to 45/15 mg (or 30/15 mg, with medical monitor approval) or temporarily interrupt treatment as needed. Return to higher doses is also allowed.</p> <p><u>Follow-up period (3 weeks):</u> For randomized subjects, after Month 12 (or the EoTx visit, if a subject</p>	<p><u>Double-blind, randomized treatment period (12 months):</u> Only subjects who reach the end of the tolvaptan run-in period and are able to tolerate tolvaptan 60/30 mg or 90/30 mg daily “for the rest of their lives” are eligible to enter this period. Randomization will be 1:1, tolvaptan to placebo. Subjects will be stratified by their baseline eGFR, at a threshold of <math>\leq 45</math> or <math>&gt; 45 \text{ mL/min}/1.73\text{m}^2</math>, and by age (<math>\leq 55</math> or <math>&gt; 55</math> years old). Subjects will also be stratified by three total kidney volume (TKV) criteria (<math>\leq 2000 \text{ mL}</math>, <math>&gt; 2000 \text{ mL}</math>, or unknown). Post-randomization, the maximally-tolerated dose of tolvaptan established during the run-in period, or the equivalent as matching placebo tablets, will be dispensed according to the subject’s randomization outcome. If continued tolerability becomes an issue, subjects may titrate downward to 45/15 mg (or 30/15 mg, with medical monitor approval) or temporarily interrupt treatment as needed. Return to higher doses is also allowed. Subjects who discontinue IMP before the Month 12 visit will complete an EoTx visit, which should be scheduled as soon as possible after the subject’s last dose of investigational medicinal product (IMP) and complete the follow-up period.</p> <p><u>Follow-up period (3 weeks):</u> For all randomized subjects, the follow-up period starts immediately after the</p>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
	discontinues investigational medicinal product prematurely) each subject will enter a 3 week follow-up period. No assessments will be taken for the first week of this period; however, 3 visits will be scheduled for the last 2 weeks of follow-up for post-treatment efficacy and safety measures.	last dose of IMP. No follow-up assessments will be taken during the first week of this period. During the last 2 weeks, Days 8 through 21, inclusive, 3 follow-up visits will be scheduled. The last follow-up visit will include measurements of efficacy and safety. Subjects will have blood drawn at each visit.
Synopsis, Subject Population	This trial will randomize approximately 1300 tolvaptan naïve subjects with ADPKD. Male and female adults will be enrolled, from 18-55 years of age with eGFR between 25 and 65 mL/min/1.73m <sup>2</sup> or 56 to < 66 years of age with eGFR between 25 and 44 mL/min/1.73m <sup>2</sup> (with medical monitor approval),	This trial will randomize approximately 1300 tolvaptan naïve subjects with ADPKD. Male and female adults will be enrolled, from 18-55 years of age with eGFR between 25 and 65 mL/min/1.73m <sup>2</sup> or 56 to < 66 years of age with eGFR between 25 and 44 mL/min/1.73m <sup>2</sup> (with <b>evidence of ADPKD progression and</b> medical monitor approval).
Synopsis, Inclusion/Exclusion Criteria	<p>Main inclusion criteria:</p> <ul style="list-style-type: none"> <li>• eGFR between 25 and 65 mL/min/1.73m<sup>2</sup> (18 to 55 years) or eGFR between 25 and 44 mL/min/1.73m<sup>2</sup> (56 to &lt; 66 years, by medical monitor discretion only).</li> </ul>	<p>Main inclusion criteria:</p> <ul style="list-style-type: none"> <li>• eGFR between 25 and 65 mL/min/1.73m<sup>2</sup> (18 to 55 years of age) or eGFR between 25 and 44 mL/min/1.73m<sup>2</sup> (56 to &lt; 66 years of age, <b>with evidence of ADPKD progression, ie, eGFR decline of &gt; 2.0 mL/min/1.73 m<sup>2</sup> per year, based on historical eGFR data and</b> medical monitor discretion).</li> </ul>
Section 3.2.1.1, Screening Period (up to Day -43)	No investigational treatments will be administered during the screening period. During this period, the subject's eligibility for the trial will be confirmed using historical imaging data of total kidney volume (TKV; if available) to support a diagnosis of ADPKD and to verify the level of CKD primarily due to ADPKD and not to other renal (hypoplasia) or metabolic (diabetic or hypertensive nephropathy) disorders.	No investigational treatments will be administered during the screening period. During this period, the subject's eligibility for the trial will be confirmed using historical imaging data to support a diagnosis of ADPKD and to verify the level of CKD primarily due to ADPKD and not to other renal (hypoplasia) or metabolic (diabetic or hypertensive nephropathy) disorders.
Section 3.4.2, Inclusion Criteria, Table 3.4.2-1, Inclusion Criteria	2. Male and female subjects age 56 to < 66 years of age with eGFR between 25 and 44 mL/min/1.73m <sup>2</sup> (by medical monitor discretion, only).	2. Male and female subjects age 56 to < 66 years of age with eGFR between 25 and 44 mL/min/1.73m <sup>2</sup> <b>with evidence of ADPKD progression, ie, eGFR decline of &gt; 2.0 mL/min/1.73 m<sup>2</sup> per year, based on historical eGFR data and medical monitor discretion.</b>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
Section 3.7, Table 3.7-1, Schedule of Assessments	<p>Follow up column has the two subheaders below:      3 weeks post-treatment      Days +7 to +21 (-2 days) post final visit<sup>a</sup></p> <p>In the assessment row called Liver Function Panel, an X is marked for Day -1 during the tolvaptan run-in.</p> <p>In the assessment row called PD and Biomarker urine sample an X with footnote g occurs only once. All other Xs in this row do not have a footnote.</p> <p>In the IVRS entry row in the columns under Tolvaptan titration, Xs occur for Days -32, -28, -24, and -22.</p> <p>Footnote a      The screening period should be completed within 1-2 weeks before the start of the placebo run-in period. The screening period may be extended up to an additional 8 weeks for subjects who require modification of medical care specifically for this trial. Visits during the screening and follow-up periods must be scheduled at least 24 hours (1 day) apart. The Day -43 visit cannot occur until laboratory values from V2 are received. For two visits (V1, V2) during the screening period, blood will be collected and analyzed centrally for serum creatinine concentrations, in addition to any other assessments listed. A visiting nurse house call or local laboratory visit may be substituted for visits where only blood/urine will be collected during the follow-up period. Visits during the follow-up period must be scheduled during a 2-week period that begins 1 week after the end of treatment visit.</p>	<p>Follow up column has the two subheaders below:      3 weeks post-treatment<sup>a</sup>      Days +8 to +21</p> <p>The row beneath has V1, V2, and V3 added to show the three visit dates more clearly.</p> <p>In the assessment row called Liver Function Panel, an X is marked for Day -8 during the tolvaptan run-in, and the X marked for Day -1 has been deleted.</p> <p>Every X in the assessment row called PD and Biomarker urine sample has footnote g.</p> <p>In the IVRS entry row, the X for Screening V2 has been deleted, and in the columns under Tolvaptan titration, an X occurs for Day -22 only.</p> <p>Footnote a      The screening period should be completed within 1-2 weeks before the start of the placebo run-in period. The screening period may be extended up to an additional 8 weeks for subjects who require modification of medical care specifically for this trial. Visits during the screening and follow-up periods must be scheduled at least 24 hours (1 day) apart. The Day -43 visit cannot occur until laboratory values from V2 are received. For two visits (V1, V2) during the screening period, blood will be collected and analyzed centrally for serum creatinine concentrations, in addition to any other assessments listed. A visiting nurse house call or local laboratory visit may be substituted for visits where only blood/urine will be collected during the follow-up (F/U) period. Three visits in the F/U period should be scheduled between Day 8 and Day 21 (inclusive) after the last dose of IMP. No F/U assessments will be taken during the first week of this period. Blood samples will be</p>

Location	Old Text	Updated Text
	<p>Footnote f  <sup>f</sup>All serum creatinine samples will be analyzed by the central laboratory. The specifics and timing for all clinical laboratory samples for central and local laboratory analyses are as follows:</p> <p><b>All visits:</b> One or more tubes of blood may be collected to accommodate the needed tests.</p> <p><b>Screening period:</b> During the 1-2 weeks of the screening period, blood will be drawn 2 times on separate days (V1, V2) at least 24 hours apart. The subject's eligibility will be confirmed by the mean of eGFR calculated from the subjects' 2 pre-treatment (V1, V2), central laboratory serum creatinine assessments and entered in IVRS on Day -43.</p> <p><b>Placebo run-in period:</b> Subjects will have 1 blood draw at the end of 1 week with the sample being obtained on Day -36.</p> <p><b>Tolvaptan titration period:</b> Subjects will have 1 blood draw at the end of 2 weeks with the sample being obtained on Day -22.</p> <p><b>Tolvaptan run-in period:</b> During the last 2 weeks of this period, blood will be drawn 2 times on separate days (at least 24 hours apart) with the last sample on Day -1.</p> <p><b>Double-blind treatment period:</b> Samples will be collected for central lab analysis monthly and at the Month 12/EoTx visit. Local standard of care laboratory tests will be performed monthly per the subject's individual clinical management needs. Local liver function panel analyses will</p>	<p>drawn at each visit for serum creatinine (V1, V2) and serum creatinine and other safety, efficacy, PK and PD measurements (V3).</p> <p>Footnote f  <sup>f</sup>All serum creatinine samples will be analyzed by the central laboratory. The specifics and timing for all clinical laboratory samples for central and local laboratory analyses are as follows:</p> <p><b>All visits:</b> One or more tubes of blood may be collected to accommodate the needed tests.</p> <p><b>Screening period:</b> During the 1-2 weeks of the screening period, blood will be drawn 2 times on separate days (V1, V2) at least 24 hours apart. The subject's eligibility will be confirmed by the mean of eGFR calculated from the subjects' 2 pre-treatment (V1, V2), central laboratory serum creatinine assessments and entered in IVRS on Day -43.</p> <p><b>Placebo run-in period:</b> Subjects will have 1 blood draw at the end of 1 week with the sample being obtained on Day -36.</p> <p><b>Tolvaptan titration period:</b> Subjects will have 1 blood draw at the end of 2 weeks with the sample being obtained on Day -22.</p> <p><b>Tolvaptan run-in period:</b> During the last 2 weeks of this period, blood will be drawn 2 times on separate days (at least 24 hours apart) with the last sample on Day -1.</p> <p><b>Double-blind treatment period:</b> Samples will be collected for central lab analysis monthly and at the Month 12/EoTx visit. Local standard of care laboratory tests will be performed monthly per the subject's individual clinical management needs. Local liver function panel analyses will</p>

Location	Old Text	Updated Text
	<p>also be performed more frequently, if necessary.</p> <p><b>Follow-up period:</b> Subjects will have blood drawn on 3 visits over Days +7 to +21 post-treatment.</p> <p>Full Chemistry panel will be obtained during following visit: Screening (V1), quarterly visit (M3, M6, M9, M12/EoTx, F/U period Day 21</p> <p>Serum creatinine, serum sodium: Screening (V2), end of placebo period, end of tolvaptan titration, 2 times during tolvaptan run-in, monthly during double blind treatment period, 2 times during F/U period</p> <p>Liver function panel: Screening (V2), end of placebo period, end of tolvaptan titration, 2 times during tolvaptan run-in, monthly during double blind treatment period, F/U period Day 21</p> <p>Footnote g: gDuring the double-blind, randomized treatment period, PK plasma samples, PD urine samples, and biomarker urine/plasma samples will be collected quarterly (eg, Months 3, 6, 9, 12/EoTx).</p> <p>Footnote h: hDNA samples are optional.</p>	<p>also be performed more frequently, if necessary.</p> <p><b>Follow-up period:</b> Subjects will have blood drawn on 3 visits at least 24 hours apart during the 3-week period, which starts after the last dose of IMP. Visits should be scheduled between Days 8 and 21, inclusive.</p> <p>Full Chemistry panel will be obtained during the following visits: Screening (V1), quarterly visit (M3, M6, M9, M12/EoTx, F/U period (V3)</p> <p>Serum creatinine, serum sodium: Screening (V2), end of placebo period, end of tolvaptan titration, 2 times during tolvaptan run-in, monthly during double blind treatment period, 3 times for serum creatinine and 1 time for serum sodium (V3) during the F/U period. Note that the first F/U visit will occur at least 7 days (Day 8) after the last dose of IMP.</p> <p>Liver function panel: Screening (V2), end of placebo period, end of tolvaptan titration, 1 time during tolvaptan run-in, monthly during double blind treatment period, F/U period (V3).</p> <p>Footnote g: gDuring the double-blind, randomized treatment period, PK plasma samples, PD urine samples, and biomarker urine/plasma samples will be collected quarterly (eg, Months 3, 6, 9, 12/EoTx). Urine biomarkers should be collected as a mid-stream, clean-catch sample during the second morning void prior to the subject eating breakfast. Where necessary, supplies for collection should be dispensed prior to the visit with instructions to collect the urine sample on the day of the visit.</p> <p>Footnote h: hDNA samples are optional and may</p>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
	<p>Footnote j:</p> <p><sup>j</sup>If, during the titration contact, the determination is made to adjust the dose-regimen, the investigator will enter the subject's status in the IVRS and arrange for dispensation of a new IMP kit and reconciliation of returned IMP. At the end of the titration period, the subject's highest tolerated dose will be utilized for the 3-week tolvaptan run-in period.</p>	<p>be collected at subsequent visits with subject's consent.</p> <p>Footnote j:</p> <p><sup>j</sup>At the end of the titration period, the subject's highest tolerated dose will be utilized for the 3-week tolvaptan run-in period.</p>
Section 3.7.1.1.1, Screening Period (up to Day -43)	16) Collect blood for DNA sample (second visit, for consenting subjects only)	16) Collect blood for DNA sample (second visit, for consenting subjects only). DNA samples may be collected at a subsequent visit if subjects consent at a later date.
Section 3.7.1.1.3, Tolvaptan Titration Period (Days -35 to -22)	8) Update subject status in IVRS at each upward titration visit	8) Update subject status in IVRS on Day -22
Section 3.7.1.1.4, Tolvaptan Run-In Period (Days -21 to -1)	<p>Assessments during the tolvaptan run-in period will include (See Table 3.7-1):</p> <p>...</p> <p>5) Collect blood (2 times on separate days during the last 2 weeks of the period, with the last sample drawn on Day -1) for serum creatinine for eGFR calculation and for assessment of sodium and liver function panel (see Section 3.7.3.2). If sodium and liver function panel are collected at the same visit, a single tube of blood should be drawn for all assessments.</p>	<p>Assessments during the tolvaptan run-in period will include (See Table 3.7-1):</p> <p>...</p> <p>5) Collect blood (2 times on separate days during the last 2 weeks of the period, with the last sample drawn on Day -1) for serum creatinine for eGFR calculation and for 1 assessment of sodium and liver function panel (see Section 3.7.3.2). If sodium and liver function panel are collected at the same visit, a single tube of blood should be drawn for all assessments.</p>
Section 3.7.1.2, Double-blind, Randomized Treatment Period (Day 0 to Month 12)	<p>Regardless of discontinuation of IMP, the subjects are expected to complete all monthly visits and assessments including the Month 12 visit.</p> <p>... (enumerated list of assessments)</p> <p>13) Update subject status in IVRS (monthly and at the Month 12/EoTx visit)</p> <p>14) Dispense IMP at monthly visits up to and including Month 11. In certain circumstances, with medical monitor approval, a 3-month drug supply may be provided; however, initiation of the next month's supply must be directed by the site.</p>	<p>Regardless of discontinuation of IMP, the subjects are expected to complete all monthly visits and assessments including the Month 12 visit (see <a href="#">Section 3.8.3.3</a>).</p> <p>... (enumerated list of assessments)</p> <p><b>13) Ask subject “Can you tolerate this dose of trial medication for the rest of your life?” at each visit</b></p> <p>14) Update subject status in IVRS (monthly and at the Month 12/EoTx visit)</p> <p>15) Dispense IMP at monthly visits up to and including Month 11. In certain circumstances, with medical monitor approval, a 3-month drug supply may be provided; however,</p>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
Section 3.7.1.3, Follow-up Period (Month 12/End of Treatment to Day 21 Post-treatment)	<p>Randomized subjects will enter the follow-up period after they complete the double-blind, randomized treatment period, or after their EoTx visit, if they discontinued IMP. The follow-up period will be for 21 days in duration.</p> <p>There will be no scheduled visits/assessments during the first week of the follow-up period. After the first week, 3 visits should be scheduled during the remaining 2 weeks of the follow-up period (between Day +7 and Day +21). The first visit should be scheduled on approximately Day +7, the second visit on approximately Day +14 and the third visit on approximately Day +21 (-2 days). These visits may be visiting nurse house calls or local laboratory visits when only blood samples will be collected, with the exception of the last visit, which will be a clinic visit.</p> <p>Assessments during the last 2 weeks of the follow-up period will include (See Table 3.7-1):</p> <p>...</p> <p>6) Collect blood for assessment of sodium levels at the first visit (see <a href="#">Section 3.7.3.2</a>)</p>	<p>initiation of the next month's supply must be directed by the site.</p> <p>For all randomized subjects, the 3-week follow-up period starts immediately after the last dose of IMP. No follow-up assessments will be taken during the first week of this period. During the last 2 weeks, Days 8 through 21, inclusive, 3 follow-up visits will be scheduled. The visits must occur at least 24 hours apart. Blood samples will be collected at each visit for serum creatinine measurements. The blood sample collected at the last follow-up visit will also include measurements of post-treatment efficacy and safety.</p> <p>These visits may be visiting nurse house calls or local laboratory visits when only blood samples will be collected, with the exception of the last visit, which will be a clinic visit. Assessments during the last 2 weeks of the follow-up period will include (See Table 3.7-1):</p> <p>...</p> <p>6) Collect blood for assessment of sodium levels at the <b>last</b> visit (see <a href="#">Section 3.7.3.2</a>)</p>
Section 3.7.3.2, Clinical Laboratory Assessments	<ul style="list-style-type: none"> <li>• during tolvaptan run-in - urinalysis (Day -1), liver function panel, creatinine, and sodium (2 times on separate days during the last 2 weeks of the period, with the last sample drawn on Day -1)</li> <li>• during the follow-up period (3 visits that begin 1 week after the Month 12/EoTx visit) - creatinine (3 visits), sodium (first visit), liver function panel and serum chemistry panel (last visit)</li> </ul>	<ul style="list-style-type: none"> <li>• during tolvaptan run-in - liver function panel (Day-8), urinalysis (Day -1), creatinine, (2 times on separate days during the last 2 weeks of the period, with the last sample drawn on Day -1), and sodium (Day -1)</li> <li>• during the 3-week follow-up period (3 visits that occur between Days 8 and 21, inclusive, after the last dose of IMP, and at least 24 hours apart) - creatinine (3 visits), sodium (first visit), liver function panel and serum chemistry panel (last visit)</li> </ul>
Section 3.7.3.5.3, DNA Blood Samples	<p>A blood sample for DNA collection will be obtained for every consenting subject at the second visit of the screening period.</p>	<p>A blood sample for DNA collection will be obtained from every consenting subject at the second visit of the screening period. Samples may be collected at a subsequent visit if subjects provide consent after the</p>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
Section 3.8.3.3, Treatment Discontinuation	<p>A subject who permanently discontinues treatment will be recorded as an IMP discontinuation on the eCRF. They will have an EoTx visit to collect vital signs, physical exam, serum creatinine assessment, clinical laboratory assessments, PK/PD samples, and biomarker urine/plasma samples. The subject will then enter the follow-up period as though they had reached the Month 12 visit. During the first week of the follow-up period, no procedures will be done. During the last two weeks of the follow-up period, the subject will have a total of 3 samples collected for serum creatinine measurements.</p>	<p>A subject who permanently discontinues treatment will be recorded as an IMP discontinuation on the eCRF. They will have an EoTx visit, which should be scheduled as soon as possible after the subject's last dose of IMP, to collect vital signs, physical exam, serum creatinine assessment, clinical laboratory assessments, PK/PD samples, and biomarker urine/plasma samples. The subject's follow-up period will be 3 weeks as though they had reached the Month 12 visit, and the follow-up period will start after the last day of treatment, which may be a different day from the EoTx visit. No follow-up assessments will be taken during the first week of this period. There will be three visits in the follow up period between Day 8 and Day 21. The first two will be for the collection of serum creatinine measurement and the third will have additional safety, efficacy, PK, and PD measurements.</p>
Section 3.13, Protocol Deviations	<p>In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, IMP dispensing or subject dosing error, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator or designee will contact the sponsor at the earliest possible time by telephone.</p>	<p>In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, IMP dispensing or subject dosing error, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator or designee will contact the <b>medical monitor</b> at the earliest possible time by telephone.</p>
Section 5.1, Definitions	<p>A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality. Additionally, in the European Union (EU), an adverse procedure-related reaction is any noxious or unintended response to a trial-related procedure and requires a</p>	<p>A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality.</p>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
Section 5.3, Immediately Reportable Events	SUSAR report.  The investigator must immediately report within 24 hours after either the investigator or site personnel become aware of any SAE, new liver lab abnormality requiring special liver eCRF completion, or confirmed pregnancy, by telephone or by fax to the sponsor as outlined in Appendix 1. An IRE form must be completed and sent by fax or overnight courier to the sponsor. (Please note that the IRE form is NOT the AE eCRF.)	The investigator must immediately report within 24 hours after either the investigator or site personnel become aware of any SAE, new liver lab abnormality requiring special liver eCRF completion, or confirmed pregnancy, by telephone or by fax to <b>Quintiles drug safety services</b> as outlined in Appendix 1. An IRE form must be completed and sent by fax or overnight courier to the sponsor. (Please note that the IRE form is NOT the AE eCRF.)
Appendix 1	Global Clinical Management Laurie Debuque Sr. Manager, Global Clinical Development Otsuka Pharmaceutical Development & Commercialization, Inc. 1 University Square Drive Suite 500 Princeton, NJ 08540, USA Phone: +1-609-524-6894; Fax +1-240-514-3994	Global Clinical Management Laurie Debuque Sr. Manager, Global Clinical Development Otsuka Pharmaceutical Development & Commercialization, Inc. 506 Carnegie Center Princeton, NJ 08540, USA Phone: +1-609-524-6894; Fax +1-240-514-3994
Appendix 2	... Investigator Payments CFS Clinical 1000 Madison Ave, 1st Floor Audubon, PA 19403, USA Phone: +1-610-994-2754 Fax: +1-610-650-1895 ... DNA Sample Storage Gentris Corporation 133 Southcenter Court, Suite 400 Morrisville, NC 27560, USA Phone: +1-919-465-0100	... Investigator Payments Quintiles 5927 South Miami Blvd Morrisville, NC 27560, USA Phone: +1-214-505-6781 Mobile: +1-214-505-6781 Fax: +1-919-800-0095 ... DNA Sample Storage Cancer Genetics, Inc. 133 Southcenter Court, Suite 400 Morrisville, NC 27560, USA Phone: +1-919-465-0100

**Previous Schedule of Assessments****Table 3.7-1 Schedule of Assessments**

Assessment	Pre-randomization										Double-blind Randomized Treatment			Follow-up	
	Screening <sup>a</sup> (1-2 weeks)		Placebo run-in (1 week ± 1 day) (Days -42 to -36)		Tolvaptan titration (2 weeks ± 1 day) (Days -35 to -22)		Tolvaptan run-in (3 weeks ± 1 day) (Days -21 to -1)		(Day 0)	Visits: monthly (± 2 days)	Month 12/EoTx visit	3 weeks post-treatment			
	V1	V2	Day -43	Day -42	Day -36	Days		Days		Day 0	Months 1 to 11 <sup>b</sup>	Month 12/EoTx	Days +7 to +21 (-2 days) <sup>a</sup>		
Informed consent	X					-35	-32	-28	-24	-22	-21	-8	-1		
Inclusion/Exclusion	X														
Demographic/Medical history	X														
Vital signs <sup>c</sup>	X	X			X			X		X		(X) <sup>c</sup>	X		X
Physical examination <sup>d</sup>	X											(X) <sup>d</sup>	X		
Urine pregnancy test (WOCBP only) <sup>e</sup>	X				X							(X) <sup>e</sup>	X		X
Chemistry Blood Sample <sup>c,f</sup> :															
Serum Chemistry Panel	X												X		X
Liver Function Panel	X	X			X			X		X		X	X		X
Creatinine	X	X			X			X	X			X	X	X	X
Sodium	X	X			X			X		X		X	X		X
Hematology and coagulation	X														
PK plasma sample												(X) <sup>g</sup>	X		X
Biomarker plasma sample		X			X			X		X		(X) <sup>g</sup>	X		X

**Table 3.7-1 Schedule of Assessments**

Assessment	Pre-randomization										Double-blind Randomized Treatment			Follow-up	
	Screening <sup>a</sup> (1-2 weeks)			Placebo run-in (1 week ± 1 day) (Days -42 to -36)		Tolvaptan titration (2 weeks ± 1 day) (Days -35 to -22)			Tolvaptan run-in (3 weeks ± 1 day) (Days -21 to -1)		(Day 0)	Visits: monthly (± 2 days)	Month 12/EoTx visit		
	V1	V2	Day -43	Day -42	Day -36	Days			Days		Day 0	Months 1 to 11 <sup>b</sup>	Month 12/EoTx	Days +7 to +21 (-2 days) <sup>a</sup>	
DNA blood sample <sup>h</sup>		X				-35	-32	-28	-24	-22	-21	-8	-1		
Urinalysis	X	X			X							X		X	
PD and Biomarker urine sample		X			X				X			X	(X) <sup>g</sup>	X	X
Start newly dispensed IMP				X		X				X		X			
Tolerability/Dosing review					X		X	X	X	X		X		X	
Randomization											X				
Drug dispensation <sup>i</sup>			X		X				X			X			
Drug reconciliation <sup>i</sup>					X				X			X		X	
IVRS entry <sup>j</sup>	X	X	X		X	X	X	X			X		X	X	X
Exploratory PKD outcomes <sup>k</sup>		X									X		X	X	
Adverse events	X	<----->													
Concomitant medications	X	<----->													

<sup>a</sup>The screening period should be completed within 1-2 weeks before the start of the placebo run-in period. The screening period may be extended up to an additional 8 weeks for subjects who require modification of medical care specifically for this trial. Visits during the screening and follow-up periods must be scheduled at least 24 hours (1 day) apart. The Day -43 visit cannot occur until laboratory values from V2 are received. For two visits (V1, V2) during

the screening period, blood will be collected and analyzed centrally for serum creatinine concentrations, in addition to any other assessments listed. A visiting nurse house call or local laboratory visit may be substituted for visits where only blood/urine will be collected during the follow-up period. Visits during the follow-up period must be scheduled during a 2-week period that begins 1 week after the end of treatment visit.

<sup>b</sup>If IMP treatment is interrupted for  $\geq$  7 days during this period, procedures should be followed as detailed in [Section 3.8.3.2](#).

<sup>c</sup>The following visits (and all assessments required during those visits) should be performed in-clinic: screening (V1, V2, Day -43), end of placebo run-in, end of tolvaptan titration, end of tolvaptan run-in, quarterly visits during the randomized, double-blind treatment period (eg, Months 3, 6, 9), Month 12/end of treatment (EoTx) visit, and the last follow-up visit. Vital signs at each of the above visits include sitting heart rate and blood pressure. Post-void body weight should be measured at the first screening visit and the Month 12/EoTx visit only. Height should be assessed at the first screening visit only. Either height or weight may be collected as an unscheduled measurement if the planned assessment was missed. Weight may be assessed as necessary to assess changes in body weight.

<sup>d</sup>A full physical examination is required at screening (V1) and the Month 12/EoTx visit. A “directed physical examination” is performed at the quarterly visits (eg, Months 3, 6, 9) for assessment of signs or symptoms reported by the subject that might require further evaluation.

<sup>e</sup>During the trial, a pregnancy test should be completed at screening, end of placebo run-in and at the quarterly visits. On suspicion of pregnancy, unscheduled urine or serum pregnancy testing will be performed. Positive urine pregnancy tests should be confirmed with a serum pregnancy test.

<sup>f</sup>All serum creatinine samples will be analyzed by the central laboratory. The specifics and timing for all clinical laboratory samples for central and local laboratory analyses are as follows:

**All visits:** One or more tubes of blood may be collected to accommodate the needed tests.

**Screening period:** During the 1-2 weeks of the screening period, blood will be drawn 2 times on separate days (V1, V2) at least 24 hours apart. The subject's eligibility will be confirmed by the mean of eGFR calculated from the subjects' 2 pre-treatment (V1, V2), central laboratory serum creatinine assessments and entered in IVRS on Day -43.

**Placebo run-in period:** Subjects will have 1 blood draw at the end of 1 week with the sample being obtained on Day -36.

**Tolvaptan titration period:** Subjects will have 1 blood draw at the end of 2 weeks with the sample being obtained on Day -22.

**Tolvaptan run-in period:** During the last 2 weeks of this period, blood will be drawn 2 times on separate days (at least 24 hours apart) with the last sample on Day -1.

**Double-blind treatment period:** Samples will be collected for central lab analysis monthly and at the Month 12/EoTx visit. Local standard of care laboratory tests will be performed monthly per the subject's individual clinical management needs. Local liver function panel analyses will also be performed more frequently, if necessary.

**Follow-up period:** Subjects will have blood drawn on 3 visits over Days +7 to +21 post-treatment.

Full Chemistry panel will be obtained during following visit: Screening (V1), quarterly visit (M3, M6, M9, M12/EoTx, F/U period Day 21 Serum creatinine, serum sodium; Screening (V2), end of placebo period, end of tolvaptan titration, 2 times during tolvaptan run-in, monthly during double blind treatment period, 2 times during F/U period

Liver function panel: Screening (V2), end of placebo period, end of tolvaptan titration, 2 times during tolvaptan run-in, monthly during double blind treatment period, F/U period Day 21

<sup>g</sup>During the double-blind, randomized treatment period, PK plasma samples, PD urine samples, and biomarker urine/plasma samples will be collected quarterly (eg, Months 3, 6, 9, 12/EoTx).

<sup>h</sup>DNA samples are optional.

<sup>i</sup>Drug dispensing and reconciliation will be done monthly (exceptions to allow dispensing/reconciliation at each 3-month clinic visit may be made by the medical monitor in exceptional circumstances, with instructions to take only one month's supply and start the next month only after acceptable safety lab results are confirmed by the investigator). Instructions to begin taking the next month's trial medication will be given during the time of IMP dispensation at each monthly visit or by telephone contact after the monthly LFT samples are collected. If LFT results are abnormal, the site will conduct a telephone contact with the trial subject to inform them that prompt immediate retesting (ie, within 72 hours) may be necessary (see [Section 3.7.3.4](#) for guidance) and to arrange for follow-up and adjustment of medication (as needed); if a down titration is required, the subject may need to return to the site or have new drug delivered. Subjects will be reminded of the importance of their commitment to continue participation in the trial. At the completion of the screening period, trial medication will be dispensed at Day -43 after subject eligibility is confirmed. In exceptional circumstances, trial medication may be dispensed at V2, with the instruction not to take any trial medication until eligibility is confirmed by the investigator. In these cases, confirmation of eligibility and instructions for taking trial medication will be provided by telephone on Day -43.

<sup>j</sup>If, during the titration contact, the determination is made to adjust the dose-regimen, the investigator will enter the subject's status in the IVRS and arrange for dispensation of a new IMP kit and reconciliation of returned IMP. At the end of the titration period, the subject's highest tolerated dose will be utilized for the 3-week tolvaptan run-in period.

<sup>k</sup>Exploratory PKD outcomes will be completed either monthly over the phone or in person during quarterly clinic visits.

**Revised Schedule of Assessments****Table 3.7-1 Schedule of Assessments**

Assessment	Pre-randomization											Double-blind Randomized Treatment			Follow-up					
	Screening <sup>a</sup> (1-2 weeks)		Placebo run-in (1 week ± 1 day) (Days -42 to -36)		Tolvaptan titration (2 weeks ± 1 day) (Days -35 to -22)		Tolvaptan run-in (3 weeks ± 1 day) (Days -21 to -1)		(Day 0)	Visits: monthly (± 2 days)	Month 12/ EoTx visit	3 weeks post-treatment <sup>a</sup>			Day 0	Months 1 to 11 <sup>b</sup>	Month 12 /EoTx	Days +8 to +21		
	V1	V2	Day -43	Day -42	Day -36	-35	-32	-28	-24	-22	-21	-8	-1	V1			V2	V3		
Informed consent	X																			
Inclusion/Exclusion	X																			
Demographic/Medical history	X																			
Vital signs <sup>c</sup>	X	X			X				X			X		(X) <sup>c</sup>	X				X	
Physical examination <sup>d</sup>	X													(X) <sup>d</sup>	X					
Urine pregnancy test (WOCBP only) <sup>e</sup>	X				X									(X) <sup>e</sup>	X				X	
Chemistry Blood Sample <sup>c,f</sup> :																				
Serum Chemistry Panel	X														X				X	
Liver Function Panel	X	X			X				X		X			X	X				X	
Creatinine	X	X			X				X		X	X		X	X	X	X	X	X	
Sodium	X	X			X				X			X		X	X				X	
Hematology and coagulation	X																			
PK plasma sample													X	(X) <sup>g</sup>	X				X	
Biomarker plasma sample		X			X				X			X		(X) <sup>g</sup>	X				X	

**Table 3.7-1 Schedule of Assessments**

Assessment	Pre-randomization										Double-blind Randomized Treatment			Follow-up			
	Screening <sup>a</sup> (1-2 weeks)			Placebo run-in (1 week ± 1 day) (Days -42 to -36)		Tolvaptan titration (2 weeks ± 1 day) (Days -35 to -22)			Tolvaptan run-in (3 weeks ± 1 day) (Days -21 to -1)			(Day 0)	Visits: monthly (± 2 days)	Month 12/ EoTx visit	3 weeks post-treatment <sup>a</sup>		
	V1	V2	Day -43	Day -42	Day -36	Days			Days			Day 0	Months 1 to 11 <sup>b</sup>	Month 12 /EoTx	Days +8 to +21		
	-35	-32	-28	-24	-22	-21	-8	-1							V1	V2	V3
DNA blood sample <sup>h</sup>	X																
Urinalysis	X	X			X						X			X			
PD and Biomarker urine sample		X <sup>g</sup>			X <sup>g</sup>				X <sup>g</sup>		X <sup>g</sup>		(X) <sup>g</sup>	X <sup>g</sup>			X <sup>g</sup>
Start newly dispensed IMP				X		X			X			X					
Tolerability/Dosing review					X		X	X	X	X		X		X	X		
Randomization												X					
Drug dispensation <sup>i</sup>			X		X				X			X		X			
Drug reconciliation <sup>i</sup>					X				X			X		X	X		
IVRS entry <sup>j</sup>	X		X		X				X			X		X	X		X
Exploratory PKD outcomes <sup>k</sup>		X									X		X	X			
Adverse events	X	<----->															
Concomitant medications	X	<----->															

<sup>a</sup>The screening period should be completed within 1-2 weeks before the start of the placebo run-in period. The screening period may be extended up to an additional 8 weeks for subjects who require modification of medical care specifically for this trial. Visits during the screening and follow-up periods must be scheduled at least 24 hours (1 day) apart. The Day -43 visit cannot occur until laboratory values from V2 are received. For two visits (V1, V2) during

the screening period, blood will be collected and analyzed centrally for serum creatinine concentrations, in addition to any other assessments listed. A visiting nurse house call or local laboratory visit may be substituted for visits where only blood/urine will be collected during the follow-up (F/U) period. Three visits in the F/U period should be scheduled between Day 8 and Day 21 (inclusive) after the last dose of IMP. No F/U assessments will be taken during the first week of this period. Blood samples will be drawn at each visit for serum creatinine (V1, V2) and serum creatinine and other safety, efficacy, PK and PD measurements (V3).

<sup>b</sup>If IMP treatment is interrupted for  $\geq$  7 days during this period, procedures should be followed as detailed in [Section 3.8.3.2](#).

<sup>c</sup>The following visits (and all assessments required during those visits) should be performed in-clinic: screening (V1, V2, Day -43), end of placebo run-in, end of tolvaptan titration, end of tolvaptan run-in, quarterly visits during the randomized, double-blind treatment period (eg, Months 3, 6, 9), Month 12/end of treatment (EoTx) visit, and the last follow-up visit. Vital signs at each of the above visits include sitting heart rate and blood pressure. Post-void body weight should be measured at the first screening visit and the Month 12/EoTx visit only. Height should be assessed at the first screening visit only. Either height or weight may be collected as an unscheduled measurement if the planned assessment was missed. Weight may be assessed as necessary to assess changes in body weight.

<sup>d</sup>A full physical examination is required at screening (V1) and the Month 12/EoTx visit. A “directed physical examination” is performed at the quarterly visits (eg, Months 3, 6, 9) for assessment of signs or symptoms reported by the subject that might require further evaluation.

<sup>e</sup>During the trial, a pregnancy test should be completed at screening, end of placebo run-in and at the quarterly visits. On suspicion of pregnancy, unscheduled urine or serum pregnancy testing will be performed. Positive urine pregnancy tests should be confirmed with a serum pregnancy test.

<sup>f</sup>All serum creatinine samples will be analyzed by the central laboratory. The specifics and timing for all clinical laboratory samples for central and local laboratory analyses are as follows:

**All visits:** One or more tubes of blood may be collected to accommodate the needed tests.

**Screening period:** During the 1-2 weeks of the screening period, blood will be drawn 2 times on separate days (V1, V2) at least 24 hours apart. The subject's eligibility will be confirmed by the mean of eGFR calculated from the subjects' 2 pre-treatment (V1, V2), central laboratory serum creatinine assessments and entered in IVRS on Day -43.

**Placebo run-in period:** Subjects will have 1 blood draw at the end of 1 week with the sample being obtained on Day -36.

**Tolvaptan titration period:** Subjects will have 1 blood draw at the end of 2 weeks with the sample being obtained on Day -22.

**Tolvaptan run-in period:** During the last 2 weeks of this period, blood will be drawn 2 times on separate days (at least 24 hours apart) with the last sample on Day -1.

**Double-blind treatment period:** Samples will be collected for central lab analysis monthly and at the Month 12/EoTx visit. Local standard of care laboratory tests will be performed monthly per the subject's individual clinical management needs. Local liver function panel analyses will also be performed more frequently, if necessary.

**Follow-up period:** Subjects will have blood drawn on 3 visits at least 24 hours apart during the 3-week F/U period, which starts after the last dose of IMP. Visits should be scheduled between Days 8 and 21, inclusive.

Full Chemistry panel will be obtained during the following visits: Screening (V1), quarterly visit (M3, M6, M9, M12/EoTx, F/U period (V3).

Serum creatinine, serum sodium: Screening (V2), end of placebo period, end of tolvaptan titration, 2 times during tolvaptan run-in, monthly during double-blind treatment period, 3 times for serum creatinine and 1 time for serum sodium (V3) during the F/U period. Note that the first F/U visit will occur at least 7 days (Day 8) after the last dose of IMP.

Liver function panel: Screening (V2), end of placebo period, end of tolvaptan titration, 1 time during tolvaptan run-in, monthly during double blind treatment period, F/U period (V3).

<sup>g</sup>During the double-blind, randomized treatment period, PK plasma samples, PD urine samples, and biomarker urine/plasma samples will be collected quarterly (eg, Months 3, 6, 9, 12/EoTx). Urine biomarker samples should be collected as a mid-stream, clean-catch sample during the second morning void prior to the subject eating breakfast. Where necessary, supplies for collection should be dispensed prior to the visit with instructions to collect the urine sample on the day of the visit.

<sup>h</sup>DNA samples are optional and may be collected at subsequent visits with subject's consent.

<sup>i</sup>Drug dispensing and reconciliation will be done monthly (exceptions to allow dispensing/reconciliation at each 3-month clinic visit may be made by the medical monitor in exceptional circumstances, with instructions to take only one month's supply and start the next month only after acceptable safety lab results are confirmed by the investigator). Instructions to begin taking the next month's trial medication will be given during the time of IMP dispensation at each monthly visit or by telephone contact after the monthly LFT samples are collected. If LFT results are abnormal, the site will conduct a telephone contact with the trial subject to inform them that prompt immediate retesting (ie, within 72 hours) may be necessary (see [Section 3.7.3.4](#) for guidance) and to arrange for follow-up and adjustment of medication (as needed); if a down titration is required, the subject may need to return to the site or have new drug delivered. Subjects will be reminded of the importance of their commitment to continue participation in the trial. At the completion of the screening period, trial medication will be dispensed at Day -43 after subject eligibility is confirmed. In exceptional circumstances, trial medication may be dispensed at V2, with the instruction not to take any trial medication until eligibility is confirmed by the investigator. In these cases, confirmation of eligibility and instructions for taking trial medication will be provided by telephone on Day -43.

<sup>j</sup>At the end of the titration period, the subject's highest tolerated dose will be utilized for the 3-week tolvaptan run-in period.

<sup>k</sup>Exploratory PKD outcomes will be completed either monthly over the phone or in person during quarterly clinic visits.

**ADDITIONAL RISK TO THE SUBJECT:**

There is no additional risk to the subjects.

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, [insert compound number], 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 [insert compound number] 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 sub-investigators 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 trial in a cooperative publication prior to publication of efficacy and safety results on an individual basis.

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Principal or Coordinating Investigator Signature and Date

**Otsuka Pharmaceutical Development & Commercialization, Inc.**

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OPC-41061

**SIGNATURE PAGE**

**Document Name:** 156-13-210 Protocol AM3, France

**Document Number:** 0001154970

**Document Version:** 2.0

<b>Signed by</b>	<b>Meaning of Signature</b>	<b>Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)</b>
Ouyang_John	Biostatistics Approval	30-Mar-2015 14:25 GMT+00
Shoaf_Susan	Clinical Pharmacology	31-Mar-2015 16:16 GMT+00
Olga Sergeyeva	Clinical Approval	02-Apr-2015 13:03 GMT+00
Czerwiec_Frank	Clinical Approval	02-Apr-2015 20:53 GMT+0

## Appendix 4              Administrative Changes/Protocol Amendments

**Administrative Change Number:** 1

**Issue Date:** 21 February 2014

**PURPOSE:**

This administrative change will not affect the safety of subjects, the scope of the investigation, or the scientific quality of the trial.

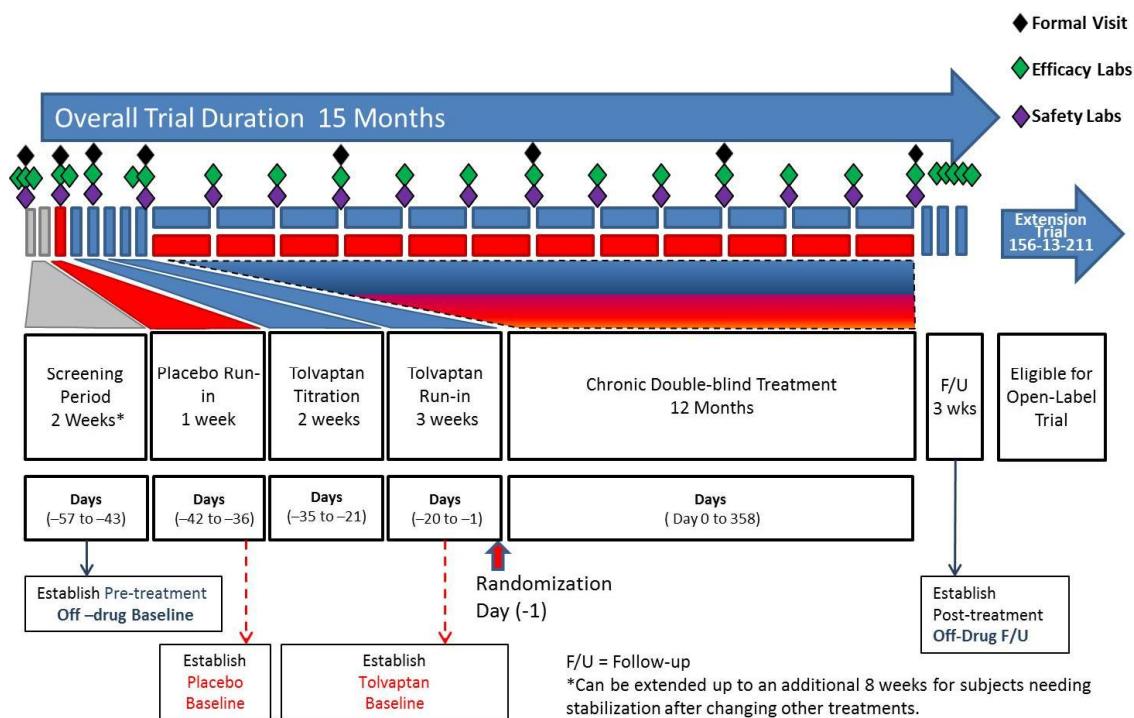
The purpose of this administrative change was to correct typographical errors and add additional clarifying information into Figure 3.1-1 - Trial Design Schematic.

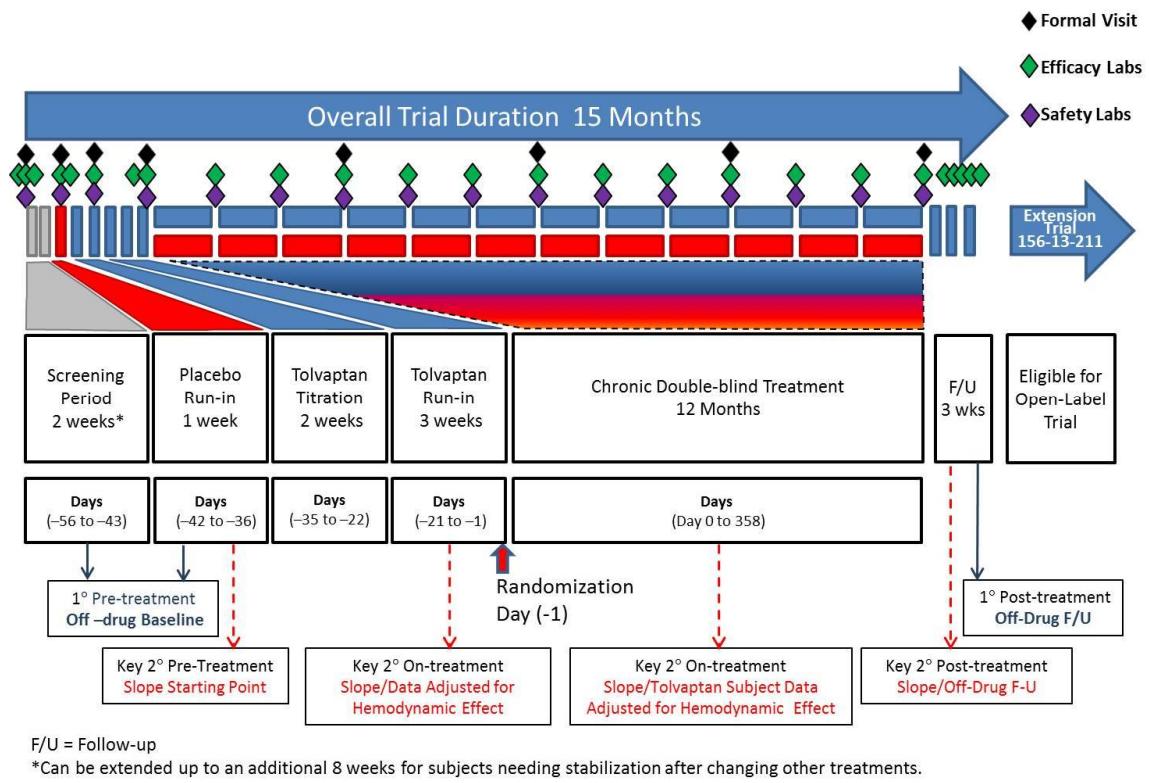
**BACKGROUND:**

In Figure 3.1-1: Typographical errors were corrected in the boxes for trial days and additional text boxes were added/modified to indicate specific periods of data collection for the primary and key secondary endpoints.

**MODIFICATIONS TO PROTOCOL:**

**Original Figure 3.1-1 - Trial Design Schematic:**



**Revised Figure 3.1-1 - Trial Design Schematic:****ADDITIONAL RISK TO THE SUBJECT:**

There is no additional risk to the subjects.

**Amendment Number** 1

**Issue Date:** 31 March 2014

**PURPOSE:**

The primary purpose of this amendment was to increase the sample size and period of enrollment to increase power for the primary and secondary endpoints.

In addition, information associated with a potential interim analysis was added, the number of creatinine blood draws was reduced, an inclusion criterion was added, and an exclusion criterion was modified. Minor revisions were also made to the protocol for clarity.

**BACKGROUND:**

**Increase in sample size**

In the original protocol, the sample size was calculated using the intra-and inter-subject variances derived from a slope analysis model. Then a method based on MMRM was developed and used to derive a new set of intra and inter-subject variances for the sample size calculation for the endpoint analysis for this protocol. This new sample size is more conservative.

**Addition of an interim analysis**

This trial is to be conducted over a critical time period during which tolvaptan may be approved as therapy for ADPKD in some of the participating regions. The European Medicines Agency's (EMA) decision for a pending marketing authorization application for use of tolvaptan in treatment of ADPKD is expected in 2015. Following regulatory approval, reimbursement and commercial availability may have an impact on the ongoing ethical conduct of the trial. This may impact subjects enrolled in Europe who are continuing in the randomized, placebo-controlled treatment phase. If an interim analysis is conducted and the results satisfy the null hypothesis, the trial may be terminated early and the existing enrolled subjects may be offered participation in an open-label trial.

**Decrease in blood draws for eGFR calculation**

With the increased sample size for this protocol, the number of blood samples collected for creatinine from each subject was reduced for both the pre-treatment and post-treatment eGFR calculations.

**Addition of an inclusion criterion to specify tolvaptan naïve subjects**

Due to the relatively short (12 months) treatment period during which treatment effect can be observed, and in order to minimize any carry over effect from previous exposure to the IMP, this study will enroll only tolvaptan naïve subjects. An inclusion criterion

was therefore added to specify that only tolvaptan naïve subjects will be permitted to enroll in this trial.

### Clarification of exclusion criterion # 5

A change was made to the exclusion criteria to further define subjects with “advanced diabetes” who would be excluded from the protocol.

### Other Revisions

It was decided that some of the language should be changed, or expanded, for clarity in specific sections of the document. Also, language was added to define the minimum “wash-out” period for subjects enrolled in the trial who were being treated with tolvaptan from previous trials.

Changes were made to the footnotes in the Schedule of Assessments table to correspond to changes in visit assessments, to clarify the analysis of serum creatinine samples, to specify visits that were in-clinic, and to define specifics like “cooked meat protein”, etc.

- Changed instances of “sham” to “matching placebo 0 mg tablets”.
- Clarified all instances of dietary “protein” to dietary “cooked meat protein”.
- Changed Chairman of the hepatic adjudication committee to Dr. David Alpers.
- Fixed typographical errors.

### Sectional Revisions

Location	Old Text	Updated Text
Synopsis, Trial Design, Screening Period	<p><u>Screening period (2 weeks):</u>  ... This may include, for example, stabilizing anti-hypertensive regimens for subjects discontinuing diuretics or “wash-out” of tolvaptan or other investigational agents for subjects who participated in previous trials.</p> <p>....Eligibility will be confirmed by the mean of eGFR calculated from the subjects' first 2 pre-treatment, central-lab serum creatinine assessments.</p>	<p><u>Screening period (1-2 weeks):</u>  ... This may include, for example, stabilizing anti-hypertensive regimens for subjects discontinuing diuretics or “wash-out” of other investigational agents.</p> <p>....Eligibility will be confirmed by the mean of eGFR calculated from the subjects' 2 pre-treatment, central-lab serum creatinine assessments (<b>collected at least 24 hours apart</b>). <b>The final screening visit on Day -43 will not be scheduled until laboratory results from the second screening visit (V2) are received and evaluated.</b></p>
Synopsis, Trial Design, Placebo Run-in period (1 week)	<p>Placebo run-in period (1 week):  Subjects will be given placebo in a daily split dose of a single 0 mg tablet upon awakening and another 0 mg tablet approximately 8 to 9 hours later</p>	<p>Placebo run-in period (1 week):  Subjects will be given placebo (<b>as a single-blind “sham” 15/15 mg dose</b>) in a daily split dose of a single 0 mg tablet upon awakening and</p>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
	(abbreviated 0/0 mg), in a form identical to tolvaptan tablets.  Blood will be drawn 2 times on separate days (at least 24 hours apart), including the last day of the run-in period,	another 0 mg tablet approximately 8 to 9 hours later (abbreviated 0/0 mg), in a form identical to tolvaptan tablets.  Blood will be drawn <b>once</b> on the last day of the run-in period ( <b>Day -36</b> ).
Synopsis, Trial Design, Tolvaptan Titration Period (2 weeks)	Tolvaptan titration period (2 weeks): Subjects will be given a split dose of 30/15 mg tolvaptan with upward titration every 3 to 4 days to 45/15 mg, 60/30 mg, up to a maximum dose of 90/30 mg per day over 2 weeks.	Tolvaptan titration period (2 weeks): Subjects will be given a split dose of 30/15 mg tolvaptan ( <b>single-blind</b> ) with upward titration every 3 to 4 days to 45/15 mg, 60/30 mg, up to a maximum dose of 90/30 mg per day over 2 weeks.
Synopsis, Trial Design, Tolvaptan Run-in Period (3 weeks)	Tolvaptan run-in period (3 weeks): Subjects who tolerate the tolvaptan 60/30 mg or 90/30 mg daily dose regimen will enter the tolvaptan run-in period at the tolerated dose for 3 additional weeks.	Tolvaptan run-in period (3 weeks): Subjects who tolerate the tolvaptan 60/30 mg or 90/30 mg daily dose regimen will enter the tolvaptan run-in period ( <b>single-blind</b> ) at the tolerated dose for 3 additional weeks.
Synopsis, Trial Design, Follow-up Period (3 weeks)	....No assessments will be taken for the first week of this period; however, 5 visits will be scheduled for the last 2 weeks of follow-up for post-treatment efficacy and safety measures.	....No assessments will be taken for the first week of this period; however, 3 visits will be scheduled for the last 2 weeks of follow-up for post-treatment efficacy and safety measures.
Synopsis, Subject Population	This trial will randomize approximately 800 subjects with ADPKD, with a minimum of 700 and a maximum of 1000 subjects planned to be enrolled.	This trial will randomize <b>approximately 1300 tolvaptan naïve</b> subjects with ADPKD.
Synopsis, Inclusion Criteria	N/A	<ul style="list-style-type: none"> <li>• Tolvaptan naïve</li> </ul>
Synopsis, Exclusion Criteria and Section 3.4.3, Table 3.4.3-1, Exclusion Criterion 5	<ul style="list-style-type: none"> <li>• Subjects with advanced diabetes (eg, glycosylated hemoglobin [HgbA1c] &gt; 7.5, and/or glycosuria by dipstick), evidence of additional significant renal disease(s) (ie, currently active glomerular nephritides), renal cancer, single kidney, or recent (within last 6 months) renal surgery, or acute kidney injury.</li> </ul>	<ul style="list-style-type: none"> <li>• Subjects with advanced diabetes (eg, glycosylated hemoglobin [HgbA1c] &gt; 7.5, and/or glycosuria by dipstick, <b>significant proteinuria, retinopathy</b>), evidence of additional significant renal disease(s) (ie, currently active glomerular nephritides), renal cancer, single kidney, or recent (within last 6 months) renal surgery, or acute kidney injury.</li> </ul>
Synopsis, Trial Site(s)	Approximately 200 enrolling sites including, but not limited to, the following regions: North America, South America, Eastern Europe, Western Europe, Asia, and Australia.	Approximately <b>220</b> enrolling sites including, but not limited to, the following regions: North America, South America, Eastern Europe, Western Europe, Asia, and Australia.

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
Synopsis, Investigational Product(s), etc	<p>Doses will be expressed as early dose/late dose (eg, 60/30).</p> <p>Placebo will be administered to all subjects during the placebo run-in period.</p>	<p>Doses will be expressed as early dose/late dose (eg, 60/30 <b>mg</b>).</p> <p>Placebo will be administered to all subjects during the placebo run-in period <b>as a single-blind “sham” 15/15 mg dose</b>.</p>
Synopsis, Trial Assessments	<p><b>Screening:</b> Medical history, complete physical examination, urine pregnancy test (women of child-bearing potential only).</p> <p><b>Safety:</b> Vital signs, directed physical examination, AEs, hematology, urinalysis, and serum chemistry tests (including serum transaminases, alkaline phosphatase, bilirubin, serum sodium), biomarker plasma and urine samples, and DNA blood samples (for consenting subjects).</p> <p><b>Pharmacodynamic (PD):</b> Urine osmolality (Uosm), specific gravity.</p>	<p><b>Screening:</b> Medical history, complete physical examination, urine pregnancy test (women of child-bearing potential only), <b>and laboratory tests to determine initial eligibility</b>.</p> <p><b>Safety:</b> Vital signs, directed physical examination, <b>self-assessed tolerability</b>, AEs, hematology, urinalysis, and serum chemistry tests (including serum transaminases, alkaline phosphatase, bilirubin, serum sodium), biomarker plasma and urine samples, and DNA blood samples (for consenting subjects).</p> <p><b>Pharmacodynamic (PD):</b> Urine osmolality (Uosm), <b>urine</b> specific gravity.</p>
Synopsis, Criteria for Evaluation	<p><b>Primary Efficacy Endpoint:</b> Treatment difference in the change of eGFR from pre-treatment baseline to post-treatment follow-up, normalized (divided) by each subject's treatment duration.</p> <p><b>PD Endpoints:</b> Uosm and specific gravity.</p> <p><b>Exploratory Endpoints:</b></p> <p><b>Efficacy:</b> Assessment of ADPKD outcomes.</p>	<p><b>Primary Efficacy Endpoint:</b> Treatment difference in the change of eGFR from pre-treatment baseline to post-treatment follow-up, <b>annualized</b> (divided) by each subject's <b>IMP</b> treatment duration.</p> <p><b>PD Endpoints:</b> Uosm and <b>urine</b> specific gravity.</p> <p><b>Exploratory Endpoints:</b></p> <p><b>Efficacy:</b> Assessment of ADPKD outcomes <b>and analysis of efficacy based on modal doses</b>.</p>
Synopsis, Statistical Methods, Sample Size	<p>Based on a Mixed Model Repeated Measurements analysis of the non-Japanese CKD-3 Subjects from trial 156-04-251, the treatment difference in renal function at Month 12 is 1.07 in our sample size calculation. It is expected that the residual variance and slope variance would be 22.13 and 5.27, respectively, assuming 4 to 5 pre-treatment and post-treatment observations taken in 2-week</p>	<p>Based on a Mixed Model Repeated Measurements analysis of the non-Japanese CKD-3 Subjects from trial 156-04-251, the treatment difference in renal function at Month 12 is 1.07 in our sample size calculation. <b>It is expected that the intra-subject variance is 14.2 and inter-subject variance is 28.05 at Month 12. With 3 repeated measures at pre-treatment baseline and post-</b></p>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
	<p>intervals. The power calculation estimates that, for a 2-sided alpha set at 0.05 for a power of 85% to 90%, and with an assumption of 15% dropout rate in the trial, a total sample size of approximately 660 to 770 subjects (rounded up to 700 to 800 subjects) is needed.</p>	<p><b>treatment follow-up, respectively</b> the power calculation estimates that, for a 2-sided alpha set at 0.05 for a power of 90%, and with an assumption of <b>10%</b> dropout rate in the trial, a total sample size of <b>approximately 1300</b> subjects is needed.</p>
Synopsis, Trial Duration	<p>The duration of the double-blind, randomized treatment period will be 12 months. The total duration of the trial (including pre-randomization and follow-up periods) will be approximately 15 months.</p>	<p>The duration of the double-blind, randomized treatment period will be 12 months. The total duration for <b>each subject entered into of the trial is approximately 15-17 months (including the pre-randomization and follow-up periods, and an additional 8 weeks for extension of the screening period in subjects for whom this is necessary).</b></p>
Section 1.4, Known and Potential Risks and Benefits	<p>Typically, this would represent 2 to 3 liters of water per day in subjects with relatively intact renal function, and lesser amounts in those with more impaired function.</p> <p>An imbalance in the proportion of subjects with elevated transaminases (tolvaptan &gt; placebo) led to identification of 3 subjects (total from both Trial 156-04-251 and its open-label extension trial, 156-08-271) with laboratory and clinical evidence of potentially serious drug-induced liver injury (DILI).</p> <p>These adverse reactions should be considered in light of the benefits of a reduced risk of ADPKD kidney complications, including renal pain, urinary tract infection, hematuria, anemia, and nephrolithiasis.</p>	<p>Typically, this would represent a <b>minimum of</b> 2 to 3 liters of water per day in subjects with relatively intact renal function, and lesser amounts in those with more impaired function.</p> <p><b>....With a once every 4-month monitoring scheme,</b> an imbalance in the proportion of subjects with elevated transaminases (tolvaptan &gt; placebo) led to identification of 3 subjects (total from both Trial 156-04-251 and its open-label extension trial, 156-08-271) with laboratory and clinical evidence of potentially serious drug-induced liver injury (DILI).</p> <p><b>....These adverse events and the above attributable</b> adverse reactions should be considered in light of the benefits of a reduced risk of ADPKD kidney complications, including renal pain, urinary tract infection, hematuria, anemia, and nephrolithiasis.</p>
Section 2.1, Trial Rationale	<p>....Home nursing visits or local laboratory visits will also be available for collection of follow-up blood samples and to continue health-status follow up even if IMP is permanently discontinued.</p> <p>Therefore, the information gathered</p>	<p>....Home nursing visits or local laboratory visits will also be available <b>at most sites</b> for collection of follow-up blood samples and to continue health-status follow up even if IMP is permanently discontinued.</p>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
	<p>through genetic/biomarker analysis should improve the sponsor's understanding of the disease, its diagnosis, prognosis, and possibly treatment outcome by identifying which patients are more likely to respond to tolvaptan, and/or predicting which subjects are likely to progress to more severe disease states, and/or predicting which subjects may have an adverse event such as DILI, and/or lead to new opportunities for therapies.</p>	<p>Therefore, the information gathered through genetic/biomarker analysis should improve the sponsor's understanding of the disease, its diagnosis, prognosis, and possibly treatment outcome. <b>This can be accomplished</b> by identifying which <b>subjects</b> are more likely to respond to tolvaptan, and/or predicting which subjects are likely to progress to more severe disease states, and/or predicting which subjects may have an adverse event such as DILI, and/or lead to new opportunities for therapies.</p>
Section 2.2, Dosing Rationale	<p>All subjects will be encouraged to progress to 90/30 mg per day, as this is likely to be most effective.</p>	<p>All subjects will be encouraged to progress to 90/30 mg per day, as <b>a higher dose</b> is likely to be most effective.</p> <p>During the double-blind randomized treatment period, subjects will either be maintained on their maximally tolerated split dose of tolvaptan at 60/30 mg or 90/30 mg or randomized to placebo. To manage additional tolerability issues during this period, subjects may down-titrate blinded treatment to 45/15 mg or even 30/15 mg with medical monitor approval. Subjects will be encouraged to maintain maximally tolerated dose to optimize and maintain desired suppression. If down-titration occurs, subjects will be encouraged to return to previous maximal tolerated dose, if possible.</p>
Section 3.1.1, Figure 3.1-1	See previous Figure below	See revised Figure below
Section 3.2.1, Pre-randomization	<p>Subjects who provide informed consent, who meet the inclusion/exclusion criteria, and for whom preliminary eligibility is established, will enter an 8-week run-in period.</p> <p>...This pre-randomization period consists of a screening period (typically 2 weeks for tolvaptan-naïve subjects; however, longer periods up to 8 additional weeks are acceptable for subjects withdrawing from tolvaptan, or needing stabilization after changing other treatments, and/or requiring additional assessments for qualification); a placebo run in</p>	<p>Subjects who provide informed consent, and for whom preliminary eligibility is established, will enter an 8-week run-in period.</p> <p>...This pre-randomization period consists of a screening period (typically <b>1-2 weeks</b>; however, longer periods up to 8 additional weeks are acceptable for subjects needing stabilization after changing other treatments, especially anti-hypertensives and diuretics, <b>or who require additional assessments for qualification</b>); a placebo run in</p>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
	especially anti-hypertensives and diuretics), a placebo run in period (1 week), a tolvaptan titration period (2 weeks), and a tolvaptan run-in period (3 weeks), described in more detail below.	period (1 week), a tolvaptan titration period (2 weeks), and a tolvaptan run-in period (3 weeks).
	N/A	During this period, subjects should be told “You will receive placebo or active treatment (tolvaptan) during the treatment phase, but you will not know which.” The subjects should not be told that there is a separate run-in phase and randomization phase, and they should not be told when formal randomization will occur. They should also be told “Your eligibility for continued participation will be assessed intermittently during the treatment period.”
Section 3.2.1.1, Screening Period	Subjects will be told that they will receive both tolvaptan and placebo during various subsequent periods of the trial and that the next period involves a dose escalation with multiple efficacy, safety, and tolerability assessments.	Subjects will be told that they will receive tolvaptan <b>or</b> placebo during various subsequent periods of the trial and that the next period involves a dose escalation with multiple efficacy, safety, and tolerability assessments.  Trial medication will be dispensed on Day -43 after subject eligibility is confirmed. In exceptional circumstances, trial medication may be provided at the second screening visit with instruction not to take any medication until confirmation on Day -43 by the investigator. If trial medication is dispensed at the second screening visit, confirmation of eligibility and instructions to take medication will be provided by telephone on Day -43.
Section 3.2.1.2, Placebo Run-in Period	In the first week after the screening period, all subjects will begin the single-blind, placebo run-in period where they will be given placebo in a daily split dose of 0 mg (abbreviated 0/0 mg), in a form identical to tolvaptan tablets. The subject will remain blinded to treatment and receive a bottle of drug which they understand could be either tolvaptan or placebo.	In the first week after the screening period, all subjects will begin the single-blind, placebo run-in period <b>with</b> placebo in a daily split dose of 0 mg (abbreviated 0/0 mg), in a form identical to tolvaptan tablets <b>at the 15/15 mg dose</b> . The subject will remain blinded to treatment, <b>having received</b> a bottle of <b>trial drug</b> <b>during the screening period</b> which they <b>understood</b> could be either tolvaptan or placebo.
Section 3.2.1.4,	Subjects tolerating at least 60/30 mg	Subjects tolerating at least 60/30 mg

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
Tolvaptan Run-in Period (Day -21 to Day -1)	tolvaptan may enter the tolvaptan run-in period (3 week duration).	tolvaptan may enter the <b>single-blind</b> , tolvaptan run-in period (3 week duration).
Section 3.2.2, Double-blind Randomized Treatment Period (Day 0 to Month 12)	N/A	Subjects not continuing in this trial will complete EoTx visit assessments and be followed for 21 days to assess any ongoing AEs.
Section 3.2.2, Table 3.2.2-1 Dosing Schedule	Trial Day Day -56 to -43	Trial Day <b>1 to 2 weeks (to Day -43)</b>
Section 3.3, Trial Population	<p>This trial will consent and screen subjects in order to randomize approximately 800 subjects with ADPKD....</p> <p>In order to maximize power and minimize the possibility of Type 2 error, trial enrollment will continue until a minimum of 700 subjects are randomized. Time allowing, the sponsor may, at its discretion, extend enrollment in order to randomize up to 1000 subjects to further improve the trial's power.</p>	<p>This trial will consent and screen tolvaptan naïve subjects with ADPKD....</p> <p>....In order to maximize power and minimize the possibility of Type 2 error, trial enrollment will continue until <b>approximately 1300</b> subjects are randomized.</p>
Section 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 and of their role and responsibilities in the proposed research.	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 ( <b>without revealing details of its initial single-blind nature</b> ) and of their role and responsibilities in the proposed research.
Section 3.4.2, Inclusion Criteria, Table 3.4.2-1	<p>3.....</p> <ul style="list-style-type: none"> <li>• Without family history: 10 cysts per kidney (by any radiologic method, above) and exclusion of other cystic kidney diseases. 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.</li> </ul> <p>4. Distribution and number of cysts consistent with the observed level of renal function deficit.</p>	<p><b>3. Male and female subjects who are tolvaptan naïve.</b></p> <p><b>4.....</b></p> <ul style="list-style-type: none"> <li>• Without family history: 10 cysts per kidney (by any radiologic method, above) and exclusion of other cystic kidney diseases. 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.</li> <li>• Distribution and number of cysts consistent with the observed level of renal function deficit.</li> </ul>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
Section 3.5.1.1, Primary Efficacy Endpoint	Treatment difference in the change of eGFR from pre-treatment baseline to post-treatment follow-up, normalized (divided) by each subject's treatment duration.	Treatment difference in the change of eGFR from pre-treatment baseline to post-treatment follow-up, <b>annualized</b> (divided) by each subject's <b>IMP</b> treatment duration.
Section 3.5.2.3, Pharmacokinetic/Pharmacodynamic Endpoints	PD Endpoints: Uosm and specific gravity	PD Endpoints: Uosm and <b>urine</b> specific gravity
Table 3.7-1, Schedule of Assessments	Previous Table is at the end of Appendix 4	Updated Table with tracked changes is at the end of Appendix 4
Section 3.7.1.1, Pre-randomization Period	<ul style="list-style-type: none"> <li>• screening period (2 weeks; longer durations of up to 8 additional weeks may be required according to the investigator's judgment, as described below)</li> </ul> <p>To establish the pre-randomization eGFR, multiple serum creatinine values (isotope dilution mass spectroscopy [IDMS]-traceable) will be obtained under standardized conditions.....</p>	<p>screening period (<b>1-2</b> weeks; longer durations of up to 8 additional weeks may be required according to the investigator's judgment, as described below)</p> <p>To establish the pre-randomization eGFR, multiple serum creatinine values will be obtained under standardized conditions.....</p>
Section 3.7.1.1.1, Screening Period	The screening period will be for 2 weeks ( $\pm$ 1 day) for tolvaptan-naïve subjects. The screening period may be extended up to an additional 8 weeks for subjects who require modification of medical care specifically for this trial.	The screening period will be for <b>1-2</b> weeks, but may be extended up to an additional 8 weeks for subjects who require modification of medical care <b>or further medical evaluation</b> specifically for this trial.
	This may include, for example, stabilizing anti hypertensive regimens for subjects discontinuing diuretics or "wash-out" of tolvaptan or other investigational agents for candidates who participated in previous trials. Subjects who were previously taking tolvaptan are required to sign an ICF and have at least a 2 week wash-out period prior to beginning the 1-2-week screening assessments.	This may include, for example, stabilizing anti hypertensive regimens for subjects discontinuing diuretics or "wash-out" of other investigational agents.
	The screening period will consist of three visits, each at least 24 hours apart. The first and last visits will be clinic visits, but a visiting nurse house call or local laboratory visit may be substituted for the other visit where only blood samples will be collected.	The screening period should be completed within <b>1-2 weeks</b> of the placebo run-in period ( <b>unless extended as described above</b> ). <b>Blood will be drawn 2 times on separate days (visit 1 and visit 2), at least 24 hours apart. The Day -43 visit will not be scheduled until laboratory results from the second visit are received and evaluated so that the calculated mean eGFR result is available for eligibility assessment on Day -43.</b>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
	<p>6) Assess vital signs (include sitting heart rate and blood pressure [first and last visits])</p> <p>9) Collect urinalysis samples (first and last visits)</p> <p>10) Collect blood for serum creatinine for eGFR calculation (3 collections, each at least 24 hours apart)</p> <p>11) Collect blood for central clinical laboratory analyses (sodium [first and last visits])</p> <p>12) Collect PD urine sample (last visit)</p> <p>13) Collect biomarker plasma and urine samples (last visit, see Section 3.7.3.5)</p> <p>16) Collect blood for DNA sample (first visit, for consenting subjects only)</p>	<p>6) Assess vital signs (include sitting heart rate and blood pressure [first and <b>second</b> visits])</p> <p>9) Collect urinalysis samples (first and <b>second</b> visits)</p> <p>10) Collect blood for serum creatinine for eGFR calculation (<b>2</b> collections, first <b>and second visits</b>, at least 24 hours apart)</p> <p>11) Collect blood for central clinical laboratory analyses (sodium [first and <b>second</b> visits])</p> <p>12) Collect PD urine sample (<b>second</b> visit)</p> <p>13) Collect biomarker plasma and urine samples (<b>second</b> visit, see Section 3.7.3.5)</p> <p>16) Collect blood for DNA sample (<b>second</b> visit, for consenting subjects only)</p>
	N/A	Trial medication will be dispensed at Day -43 after subject eligibility is confirmed. In exceptional circumstances, trial medication may be dispensed at the second visit, with the instruction not to take any trial medication until eligibility is confirmed by the investigator. In these cases, confirmation of eligibility and instructions for taking trial medication will be provided by telephone on Day -43.
Section 3.7.1.1.2, Placebo Run-in Period (Days -42 to -36)	<p>Subjects will be given placebo in a daily split dose of a single 0 mg tablet upon awakening and another 0 mg tablet approximately 8 to 9 hours later (abbreviated 0/0 mg), in a form identical to tolvaptan tablets.</p> <p>5) Collect blood for serum creatinine for eGFR calculation (x2) and for assessment of sodium (x2) and liver function panel (x1) on separate days between Days - 39 to - 36 with the last sample being obtained on Day - 36. If sodium and liver function panel are collected at the same visit, a single tube of blood should be drawn for all assessments.</p>	<p>Subjects will be given placebo in a daily split dose of a single 0 mg tablet upon awakening and another 0 mg tablet approximately 8 to 9 hours later (abbreviated 0/0 mg), in a form identical to <b>15/15 mg</b> tolvaptan tablets.</p> <p>5) Collect blood for serum creatinine for eGFR calculation and for assessment of sodium and liver function panel on Day -36.</p> <p>12) Subjects found to be ineligible to continue in this trial after receiving IMP must have a 7-day follow-up visit (see Section 3.8.3.1).</p>
Section 3.7.1.1.3, Tolvaptan Titration Period (Days -35 to - )	N/A	10) Subjects not tolerating at least 60/30 mg dose should be informed they did not meet

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
22)		<p>eligibility criteria for continuation</p> <p>12) Subjects found to be ineligible to continue in this trial must have a 7-day follow-up visit (see Section 3.8.3.1).</p>
Section 3.7.1.1.4, Tolvaptan Run-In Period (Days -21 to -1)	<p>Randomization (Day 1) will be stratified by mean eGFR determined by available central isotope dilution mass spectroscopy (IDMS) traceable serum creatinine measurements taken during the screening period and placebo run-in period.</p>	<p>Randomization (Day 1) will be stratified by mean eGFR serum creatinine measurements taken during the screening period and placebo run-in period.</p> <p>15) Subjects found ineligible to be randomized and continue in this trial must have a 7-day follow-up visit (see Section 3.8.3.1).</p>
Section 3.7.1.2, Double-blind, Randomized Treatment Period	<p>14) Dispense IMP at monthly visits up to and including Month 11</p> <p>Subjects discontinuing IMP in the placebo run-in period, tolvaptan titration period, or the tolvaptan run-in period should also have EoTx assessments performed (see Section 3.8.3.3).</p>	<p>14) Dispense IMP at monthly visits up to and including Month 11. <b>In certain circumstances, with medical monitor approval, a 3-month drug supply may be provided; however, initiation of the next month's supply must be directed by the site.</b></p> <p>16) Subjects not continuing in this trial must have a 21-day follow-up period (see Section 3.8.3.3).</p> <p>Regardless of discontinuation of IMP, the subjects are expected to complete all monthly visits and assessments including the Month 12 visit.</p>
Section 3.7.1.3, Follow-up Period (Month 12/End of Treatment to Day 21 Post treatment)	<p>There will be no scheduled visits/assessments during the first week of the follow-up period. After the first week, 5 visits should be scheduled during the remaining 2 weeks of the follow-up period (between Day +7 and Day +21), with each visit at least 24 hours apart.</p>	<p>There will be no scheduled visits/assessments during the first week of the follow-up period. After the first week, <b>3</b> visits should be scheduled during the remaining 2 weeks of the follow-up period (between Day +7 and Day +21). The first visit should be scheduled on approximately Day +7, the second visit on approximately Day +14 and the third visit on approximately Day +21 (-2 days).</p>
Section 3.7.2.1, Serum Creatinine for Estimated Glomerular Filtration Rate	<p>The eGFR values will be calculated from the central-laboratory IDMS-traceable serum creatinine concentrations taken at screening and during every trial visit.</p>	<p>The eGFR values will be calculated from the central-laboratory serum creatinine concentrations taken at screening and during every trial visit.</p>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
Section 3.7.3.2, Clinical Laboratory Assessments	<p>Clinical laboratory samples for analysis by the central laboratory will be collected at the following visits:</p> <ul style="list-style-type: none"> <li>• during screening (3 visits at least 24 hours apart that occur during the 2 weeks prior to placebo run-in) - creatinine (all 3 visits), sodium and urinalysis (first and last visits), hematology and coagulation panel, serum chemistry panel, and liver function panel (first visit)</li> <li>• during placebo run-in - urinalysis (Day - 36), liver function panel, creatinine, and sodium (twice on separate days between Days 39 to - 36 with the last sample being obtained on Day - 36)</li> <li>• during the follow-up period (5 visits at least 24 hours apart that begin 1 week after the Month 12/EoTx visit) - creatinine (all 5 visits), sodium (first visit), liver function panel and serum chemistry panel (last visit)</li> </ul>	<p>Clinical laboratory samples for analysis by the central laboratory will be collected at the following visits:</p> <ul style="list-style-type: none"> <li>• during screening (<b>2</b> visits at least 24 hours apart that occur during the <b>1-2</b> weeks prior to placebo run-in) - creatinine (<b>first and second</b> visits), sodium and urinalysis (<b>first and second</b> visits), hematology and coagulation panel, serum chemistry panel, and liver function panel (first visit)</li> <li>• during placebo run-in - urinalysis, liver function panel, creatinine, and sodium on Day -36</li> <li>• during the follow-up period (<b>3</b> visits that begin 1 week after the Month 12/EoTx visit) - creatinine (<b>3</b> visits), sodium (first visit), liver function panel and serum chemistry panel (last visit)</li> </ul>
Section 3.7.3.2, Table 3.7.3.2-1	N/A	<p>Urinalysis panel:</p> <ul style="list-style-type: none"> <li>• osmolality</li> <li>• specific gravity</li> <li>• urine creatinine</li> </ul>
Section 3.7.3.4.2, Liver Test Abnormalities and Interruption/Discontinuation of Investigational Medicinal Product	N/A	All elevations will be assessed by the medical monitoring team.
Section 3.7.3.4.3, Requirements for Special Reporting Using the Liver Disease Electronic Case Report Form and Immediately Reportable Event Form	N/A	The HAC will independently decide attribution and will communicate with the Independent Data Monitoring Committee (IDMC) that oversees the trial.
Section 3.7.3.5.1, Biomarker Plasma Samples	<p>Blood samples (10 mL) for potential biomarker analysis will be collected at the following times:</p> <ul style="list-style-type: none"> <li>• end of the screening period (Day - 43)</li> </ul>	<p>Blood samples (10 mL) for potential biomarker analysis will be collected at the following times:</p> <ul style="list-style-type: none"> <li>• <b>second visit</b> of the screening period</li> </ul>
Section 3.7.3.5.2, Biomarker Urine	A spot urine sample (20 mL) will be	A spot urine sample will be obtained at the following times:

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
Samples	<p>obtained at the following times:</p> <ul style="list-style-type: none"> <li>• end of the screening period (Day -43)</li> </ul>	<ul style="list-style-type: none"> <li>• <b>second visit</b> of the screening period</li> </ul> <p>To ensure a fasting urine sample is collected, subjects will be provided with a sterile urine cup on the visit preceding the date of urine sample collection. Subjects will be instructed to collect a urine sample prior to eating breakfast, and to store the sample in the refrigerator until their clinic visit.</p>
Section 3.7.3.5.3, DNA Blood Samples	A blood sample for DNA collection will be obtained for every consenting subject at the beginning of the screening period.	A blood sample for DNA collection will be obtained for every consenting subject at the <b>second visit</b> of the screening period.
Section 3.7.4.2, Pharmacodynamic Urine Samples	<p>A spot urine sample for determination of Uosm and specific gravity will be obtained at the following times:</p> <ul style="list-style-type: none"> <li>• end of the screening period (Day - 43)</li> </ul>	<p>A spot urine sample for determination of Uosm and specific gravity will be obtained at the following times:</p> <ul style="list-style-type: none"> <li>• <b>second visit</b> of the screening period</li> </ul> <p>To ensure a fasting urine sample is collected, subjects will be provided with a sterile urine cup on the visit preceding the date of urine sample collection. Subjects will be instructed to collect a urine sample prior to eating breakfast, and to store the sample in the refrigerator until their clinic visit.</p>
Section 3.7.6, Independent Data Monitoring Committee	N/A	....Adjudication results as determined by the HAC will be reported to the IDMC on a quarterly basis or more frequently as necessary....
Section 3.8.3.2, Treatment Interruption	.....It is assumed that an interruption of this duration may become permanent, therefore the subject will have a total of 5 samples collected for serum creatinine measurements....	.....It is assumed that an interruption of this duration may become permanent, therefore the subject will have a total of <b>3</b> samples collected for serum creatinine measurements....
	Treatment may still be restarted during or after these assessments are completed.	Treatment may still be restarted during or after these assessments are completed; <b>any remaining serum creatinine assessments will not need to be completed if treatment is restarted during this period.</b>
Section 3.8.3.3, Treatment Discontinuation	During the last two weeks of the follow-up period, the subject will have a total of 5 samples collected for serum creatinine measurements.	During the last two weeks of the follow-up period, the subject will have a total of <b>3</b> samples collected for serum creatinine measurements.
Section 3.8.3.4 Documenting Reasons	<ul style="list-style-type: none"> <li>• Subject decides to discontinue due annoyance or discomfort due</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Subject could not tolerate IMP due to an AE which is</b></li> </ul>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
for Treatment Interruption/Discontinuation	<p>to a non-serious AE which is not otherwise determined to be an undue hazard</p> <ul style="list-style-type: none"> <li>• Continuing IMP places the subject at undue hazard as determined by the investigator (eg, a safety concern that is possibly, probably, or likely related to IMP)</li> <li>• eGFR decreased to a level requiring dialysis or kidney transplantation (confirmed by repeat testing post IMP discontinuation)</li> <li>• Clinical jaundice (requires an immediate interruption of IMP and prompt repeat testing to confirm abnormality)</li> <li>• Reasons unrelated to medical condition (provide detail and review AE history with subject)</li> <li>• Withdrawal of informed consent (complete written withdrawal of consent form)</li> <li>• Pregnancy (see Section 5.4)</li> </ul>	<p><b>annoying or uncomfortable but not serious or hazardous</b></p> <ul style="list-style-type: none"> <li>• <b>Physician determined that there are potential IMP related safety concern or SAE placing subject at undue hazard</b></li> <li>• <b>Progression of disease leading to dialysis, transplantation or eGFR decline as determined by the investigator</b></li> <li>• <b>Clinical signs of DILI (eg, jaundice, right upper quadrant pain)</b></li> <li>• Reasons unrelated to medical condition (<b>eg, pregnancy, trial too burdensome</b>)</li> <li>• Withdrawal of informed consent (<b>partial related to IMP or complete from the trial</b>)</li> <li>• Taking marketed product for tolvaptan (discontinued subjects only)</li> </ul>
Section 3.8.3.5, Withdrawal of Consent	N/A	<ul style="list-style-type: none"> <li>• Participation in all regularly scheduled, study-related follow-up visits and end of treatment visits</li> </ul>
Section 3.10, Definition of Completed Subjects	Subjects who are randomized, take IMP (or never begin treatment), but DO NOT complete the Month 12 visit AND at least 1 follow-up serum creatinine assessment will be defined as “Non-completers”.	Subjects who are randomized, take IMP (or never begin treatment), but DO NOT complete the Month 12 visit AND at least 1 <b>EoTx</b> follow-up serum creatinine assessment will be defined as “Non-completers”.
Section 5.6, Follow-up of Adverse Events	For this trial, AEs will be followed up for 21 days after the last dose of IMP has been administered (follow-up period)	For this trial, AEs will be followed up for <b>7 days in subjects who discontinued prior to randomization</b> and for 21 days after the last dose of IMP has been administered (follow-up period) <b>in subjects who were randomized</b> .
Section 7.1.1, Sample Size Estimation	In this sample size estimation, it is assumed that 4 to 5 calculations of eGFR will be obtained at baseline during a 3-week interval during screening (2 weeks) and placebo run-in (1 week), and another 4 to 5 calculations will be obtained post-treatment during a 2-week interval that begins 1 week after the end of treatment (3-week post-treatment)	In this sample size estimation, it is assumed that <b>3</b> calculations of eGFR will be obtained at baseline during a 3-week interval during screening ( <b>1-2 weeks</b> ) and placebo run-in (1 week), and another <b>3</b> calculations will be obtained post-treatment during a 2-week interval that begins 1 week after the end of treatment (3-week post-treatment follow-up).

Location	Old Text	Updated Text
	<p>follow-up). The mean of the 4 to 5 eGFR values observed during the screening and placebo-run periods will be set as the baseline and the mean of the 4 to 5 eGFR values observed during the post-treatment follow-up period will be set as the renal function measurement post-treatment.</p> <p>To derive the intra-subject variance and inter-subject variance, the approach provided by Dr. Lawrence, a FDA statistician, in a FDA communication to the sponsor (e-mail communication, 24Dec2013), was followed. For subject i randomized to the placebo group (<math>i=1, \dots, n</math>), the eGFR at time <math>t_j</math> is assumed to be</p> $Y_{i,j} = \alpha_i + \beta_i t_j + \epsilon_{i,j} \quad (1)$ <p>For subject i randomized to the tolvaptan group (<math>i= n+1, \dots, 2n</math>), the eGFR at time <math>t_j</math> is assumed to be</p> $Y_{i,j} = \alpha_i + \beta_i t_j + \epsilon_{i,j} \text{ if } j \text{ is observed at baseline} \quad (2)$ $Y_{i,j} = \alpha_i + \Delta + \beta_i t_j + \epsilon_{i,j} \text{ if } j \text{ is observed at post-treatment follow-up} \quad (3)$ $Y_{i,j} = \alpha_i + \gamma + (\Delta + \beta_i) t_j + \epsilon_{i,j} \text{ if } j \text{ is observed during the treatment period} \quad (4)$ <p>where <math>\epsilon_{i,j}</math> are assumed iid <math>N(0, \sigma^2)</math>, <math>\beta_i</math> are assumed iid <math>N(\beta, \sigma\beta^2)</math>, <math>\alpha_i</math> and <math>\beta_i</math> are mutually independent, and <math>\Delta</math> is treatment effect, <math>\gamma</math> is the hemodynamic onset effect. Based on this model, with baseline time is set to 0, the variance of change from baseline at a post-baseline visit is</p> $\text{Var}(Y_{i,j} - Y_{i,0}) = \text{Var}(\beta_i t_j + \epsilon_{i,j} - \epsilon_{i,0}) = t_j^2 \sigma\beta^2 + \sigma^2 \quad (5)$ <p>Dr. Lawrence's derivation is based on the assumption that an observation of eGFR is made at the end of a 2-week interval for k times (thus, totally 2k weeks) at baseline and post-treatment follow-up visit respectively. Thus, Dr. Lawrence's variance of change from baseline to post-treatment follow-up is</p> $(2/k) \sigma^2 + (1 + 1/12 + k/26)^2 \sigma\beta^2 \quad (6)$ <p>If we change the assumption to this one that all these k observations are observed in the 2-week intervals mentioned in the first paragraph in</p>	<p>The mean of the 3 eGFR values observed during the screening and placebo-run periods will be set as the baseline and the mean of the 3 eGFR values observed during the post-treatment follow-up period will be set as the renal function measurement post-treatment.</p> <p>One of the approaches in sample size calculation for this protocol is to use MMRM to estimate the intra- and inter-subject variances. In the ADPKD phase 3 trial 156-04-251, there was a pre-treatment baseline visit and two post-treatment follow-up visits, along with other on-treatment visits. Assume these data follow the following model (denoted as <math>j = 0</math> for baseline and <math>j = 37</math> for follow-up, as well as <math>j = 4, 8, 12, \dots, 36</math>):</p> $Y_{i,0} = \alpha_i + \epsilon_{i,0} \quad (1)$ $Y_{i,j} = \alpha_i + \delta_{i,j} + \epsilon_{i,j} \quad (2)$ <p>where <math>\delta_{i,j}</math> as a random effect of change from pre-treatment baseline at visit <math>j</math> for subject <math>i</math>. These <math>\delta_{i,j}</math>s jointly follow a multivariate normal distribution with means being <math>\delta_{P,j}</math> for placebo subjects and <math>\delta_{T,j}</math> for tolvaptan subjects. Their individual variance is assumed to be <math>\sigma\delta_{j,2}</math>. These <math>\delta_{i,j}</math>s are supposed to be correlated; however, their correlations are not utilized for the purpose of sample size calculation in this protocol. In addition, <math>\alpha_i</math>s are assumed iid to have a normal distribution, <math>\epsilon_{i,j}</math> are assumed iid <math>N(0, \sigma^2)</math>, and these random variables are mutually independent. Then, the change from baseline data follows this common MMRM model</p> $Y_{i,j} - Y_{i,0} = \delta_{i,j} - \epsilon_{i,0} + \epsilon_{i,j} = \zeta_{i,j} + \epsilon_{i,j} \quad (3)$ <p>where <math>\zeta_{i,j} = \delta_{i,j} - \epsilon_{i,0}</math>. Note that the variance of <math>\zeta_{i,j}</math> (denoted by <math>\sigma\zeta_{j,2}</math>) is equal to <math>\sigma\delta_{j,2} + \sigma^2</math>. This model becomes a one-way random effect model if we only consider the post-treatment follow-up visits for a treatment group. Thus, applying a one-way random effect model to the change from pre-treatment baseline to post-treatment follow-up data of</p>

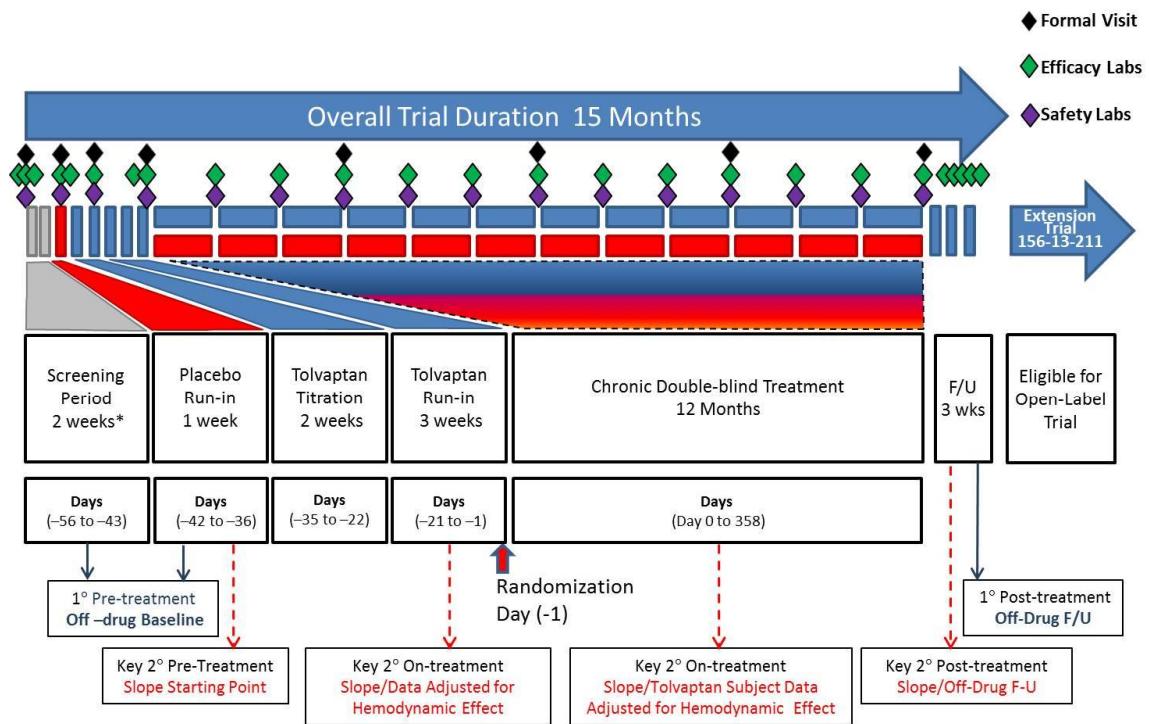
Location	Old Text	Updated Text
	<p>this section, the variance would <math>(2/k) \sigma^2 + (1 + 1/12 + 3/52)2 \sigma\beta^2</math> (7)</p> <p>This variance formula was used in our sample size calculation, since it matches our protocol design more closely.</p> <p>If the model given by (1) to (4) is applied to the data of CKD-3 non-Japan subjects in Trial 156-04-251, with eGFR data from pre-randomization baseline to Follow-up Visit #2, the residual variance (<math>\sigma^2</math>) and slope variance (<math>\sigma\beta^2</math>) are estimated as 22.13 and 5.27, respectively, which may be interpreted as intra- and inter-subject variances.</p> <p>With a 2-sided alpha of 0.05 and 1:1 randomization to tolvaptan and placebo, using the parameters given above and sample size formula of 2-sample t-test, we have the following table:</p> <p>(TABLE 7.1.1.1 deleted).</p> <p>The assumption of dropout rate of 15% is reasonable since the dropout rate was 20% in Trial 156-04-251, and it is expected that the inclusion of the tolvaptan run-in period in this trial will reduce the dropout rate in the double blind treatment period. From this table, it seems that <math>k = 4</math> would produce an acceptable sample size and not an excessive burden for enrolled subjects.</p>	<p>placebo and tolvaptan respectively, in subjects who had both follow-up visits and baseline in 156-04-251, <math>\sigma^2</math> is estimated as 8.52 for placebo and 5.68 for tolvaptan. Take the average of these two estimates of <math>\sigma^2</math> to obtain an estimate of <math>\sigma^2</math> as 7.1 to be used in this sample size calculation, which is the <math>\sigma^2</math> for Month 12 visit of 156-04-251. Note that</p> $\text{Var}(Y_{i,j} - Y_{i,0}) = \sigma\delta_{j,2} + 2\sigma^2 \quad (4)$ <p>At Month 12, the SD (Standard Deviation) could be assumed as 6.5, based on CKD Stage 3 non-Japan subjects in 156-04-251. Then based on (4), <math>\sigma\delta_{j,2}</math> at Month 12 is estimated as 28.05 (<math>= 6.52 - 2 \times 7.1</math>). With <math>k</math> repeated measurements at pre-treatment baseline and at 12 month post-treatment follow-up in this trial, the baseline intra-subject variance and the follow-up intra-subject variance are reduced from <math>\sigma^2</math> to <math>\sigma^2/k</math> respectively. Thus, the variance of average change from average baseline at Month 12 is <math>(\sigma\delta_{1,2} + \sigma^2/k) + \sigma^2/k</math>, which is estimated as 31.6 (<math>= 28.05 + 7.1/4 + 7.1/4</math>) when <math>k = 4</math> and 32.8 (<math>= 28.05 + 7.1/3 + 7.1/3</math>) when <math>k = 3</math>. Here we have the following table of sample size:</p> <p>(New TABLE 7.1.1.1 inserted)</p>
Section 7.1.1, Sample Size Estimation	<p>Thus, with an assumption of 15% dropout rate in the trial, the total sample size (randomized subjects) would be from 660 to 770, and will be set as a range of between 700 and 1000 randomized subjects, with a goal of 800 subjects, depending also on the trial's ability to enroll and the accumulated number of subjects randomized up to the end of 2014. Because this information will be helpful in guiding the treatment of ADPKD patients with more advanced stages of CKD, and because marketing approval in many participating countries may be reached by 2015, it is critical to conclude enrollment near the end of</p>	<p><b>From the sample size table, the increase of repeated measurement at baseline and follow-up reduces the sample size significantly initially but quickly loses its effect when <math>k</math> is greater than 3. It seems that 3 repeated measurements may be appropriate in order to avoid subjects' burden.</b> Thus, with an assumption of 10% dropout rate in the trial, the total sample size (randomized subjects) would be approximately 1300.</p>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
	2014 or beginning of 2015. This will help avoid missing data due to subjects leaving the trial to seek commercially available treatment in those countries.	
Section 7.1.1, Sample Size Estimation	<p>The desire for a small number of blood draws during these periods was emphasized by the trial's Steering Committee, which further suggested that measures be taken to minimize the intra-subject variability by standardizing, as much as possible, the timing and conditions by which serum creatinine was assessed (in particular recommending a similar diet, avoiding variation in protein, especially cooked protein, intake and exercise pattern during these periods). The Steering Committee also suggested that the intra subject variance during the pre-treatment and post-treatment periods be monitored throughout the trial with a mandatory increase in serum creatinine sample numbers (ie, from a minimum of 4 to a minimum of 5) or subject numbers if observed variance was greater than that used in the power assumption (assessed using only baseline eGFR data in a power re-estimation procedure).</p> <p>They also favored the possibility that sample numbers, but not the minimum enrollment, be lowered (ie, to a maximum of 4 samples) if variance was significantly less due to these measures (see Section 7.1.2. "Blinded Sample-Size Re-estimation").</p>	<p><b>In order to avoid excessive blood draws, mechanisms were undertaken</b> to minimize the intra-subject variability by standardizing, as much as possible, the timing and conditions by which serum creatinine was assessed (in particular recommending a similar diet, avoiding variation in protein, especially cooked meat protein, intake and exercise pattern during these periods). <b>In addition to the efforts to reduce variability by standardizing subject diet at the time of blood draws, the number of scheduled blood draws will help establish precision in the estimated measurements.</b></p>
Section 7.1.1, Sample Size Estimation	<p>In addition, the 1:1 randomization and the alpha (0.05, 2-sided) specified above in the sample size of the primary endpoint are also assumed in the sample size calculation. It is then estimated that 315 subjects per group are required for 85% power and 367 subjects per group are required for 90% power. These sample sizes are very close to the sample size calculated using FDA statistician Dr. Lawrence's formula, for example, sample size of 368 per group with 90% power, when the variances provided above were used. Thus, with a total sample size of from</p>	<p>In addition, the 1:1 randomization and the alpha (0.05, 2-sided) specified above in the sample size of the primary endpoint are also assumed in the sample size calculation. It is then estimated that <b>734 subjects are required for 90% power. Thus, with a total sample size of approximately 1300</b>, the key secondary endpoint will have more than 90% power in detecting a slope difference in this trial.</p>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
	660 to 770 (rounded to 700 to 800), the key secondary endpoint will have at least 85% to more than 90% power in detecting a slope difference in this trial.	
Section 7.1.2, Blinded Sample Size Re-estimation	<p>Blinded sample size re-estimation will be conducted when about half of the planned randomized subjects (350 to 400) have been randomized. This is expected to be conducted before the end of 2014 and thus before the availability of any post 12 month off-treatment follow-up eGFR data used for the primary analysis. The goal of this blinded sample size re-estimation is to check: 1) the differences between the observed variances and the variances used in the sample size calculation; 2) whether the approach of averaging the 4 to 5 baseline pre-treatment eGFR observations has achieved the goal of reducing the variance to the level planned.</p>	<p>Blinded sample size re-estimation will be conducted when <b>at least a third</b> of the planned randomized subjects (<b>400 to 500</b>) have been randomized. This is expected to be conducted before the availability of any post 12 month off-treatment follow-up eGFR data used for the primary analysis. The goal of this blinded sample size re-estimation is to check: 1) the differences between the observed variances and the variances used in the sample size calculation; 2) whether the approach of averaging the <b>3</b> eGFR observations <b>at pre-treatment baseline and post-treatment follow-up</b> has achieved the goal of reducing the variance to the level planned.</p>
Section 7.2, Datasets for Analysis, Primary Endpoint Efficacy Population:	<p>....The primary endpoint's baseline is defined as the average of up to 5 eGFR values observed during the screening and placebo run-in periods.</p> <p>The core subject population for all efficacy analyses is based on the intent-to-treat (ITT) population which consists of all randomized subjects who take at least one dose of IMP.</p>	<p>The primary endpoint's baseline is defined as the average of up to <b>3</b> eGFR values observed during the screening and placebo run-in periods.</p> <p>The core subject population for all efficacy analyses is based on the intent-to-treat (ITT) population which consists of all randomized subjects who take at least one dose of IMP <b>post randomization</b>.</p>
Section 7.4.1.1, Primary Endpoint Analysis	<p>To reduce the variation in this primary endpoint, 4 to 5 observations of eGFR will be obtained at baseline during a 3 week interval (screening and placebo run-in periods) and another 4 to 5 observations will be obtained post-treatment during a 2-week interval that begins 1 week after the end of treatment (3-week post-treatment follow-up). The average of the 4 to 5 eGFR values observed during the baseline period is set as the baseline and the average of the 4 to 5 eGFR values observed during the post-treatment follow-up period is set as the renal function measurement post-treatment</p>	<p>To reduce the variation in this primary endpoint, <b>3</b> observations of eGFR will be obtained at baseline during a 3 week interval (screening and placebo run-in periods) and another <b>3</b> observations will be obtained post-treatment during a 2-week interval that begins 1 week after the end of treatment (3-week post-treatment follow-up). The average of the <b>3</b> eGFR values observed during the baseline period is set as the baseline and the average of the <b>3</b> eGFR values observed during the post-treatment follow-up period is set as the renal function measurement post-treatment</p>

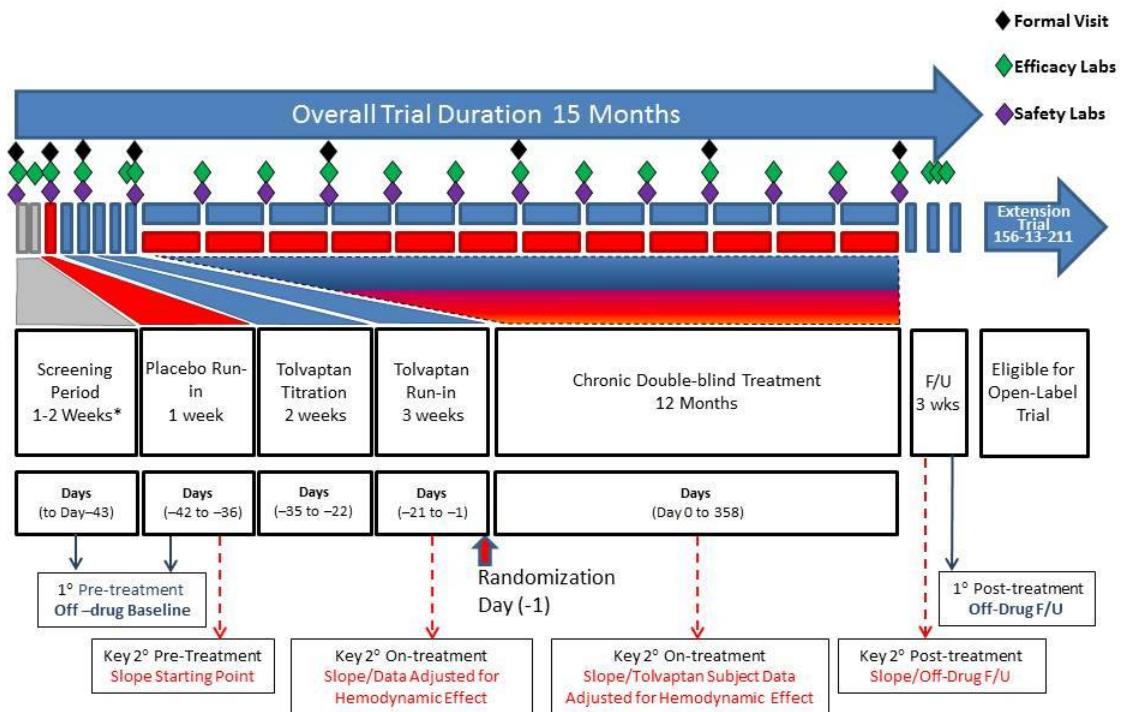
<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
Section 7.4.1.2, Sensitivity Analysis of the Primary Endpoint	Aligned with the desire to evaluate effects free from acute hemodynamic treatment effects, a sensitivity analysis of the primary endpoint will be performed including all available placebo data. In this sensitivity analysis, in addition to the 4 to 5 pre-treatment baseline observations and the 4 to 5 post-treatment follow-up observations, all post randomization on-treatment eGFR observations in the protocol-specified visits for placebo subjects will also be included	Aligned with the desire to evaluate effects free from acute hemodynamic treatment effects, a sensitivity analysis of the primary endpoint will be performed including all available placebo data. In this sensitivity analysis, in addition to the 3 pre-treatment baseline observations and the 3 post-treatment follow-up observations, all post randomization on-treatment eGFR observations in the protocol-specified visits for placebo subjects will also be included
Section 7.4.3, Subgroup Efficacy Analysis	N/A	Subgroup analyses will be provided for the primary and the key secondary endpoints by regions (US and non-US), gender (male and female), race (Caucasian and Other), age ( $\leq$ 55 years, $>$ 55 years), baseline GFR level (eGFR $\leq$ 45 mL/min/1.73 <sup>2</sup> m <sup>2</sup> and $>$ 45 mL/min/1.73 m <sup>2</sup> and baseline TKV ( $\leq$ 2000 mL, $>$ 2000 mL or unknown).
Section 7.4.4.1, Exploratory Analysis of Efficacy Based on Modal Doses	N/A	Exploratory analyses will be applied to the primary and key secondary endpoints will tolvaptan subjects coded by their modal doses in the trial, using the same analytic approached specified for these endpoints.
Section 7.4.5, Interim Analysis	N/A	This trial is to be conducted over a critical time period during which tolvaptan may be approved as therapy for ADPKD in some of the participating regions. The European Medicines Agency's (EMA) decision for a pending marketing authorization application for the use of tolvaptan in treatment of ADPKD is expected in 2015. Following regulatory approval, reimbursement and commercial availability may have an impact on the ongoing ethical conduct of the trial. This may impact subjects enrolled in Europe who are continuing in the randomized, placebo-controlled treatment phase. Therefore, the IDMC for this trial will be empowered to conduct an interim analysis (IA) of the primary endpoint once approximately half of enrolled subjects (600-700) are

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
		<p>expected to complete their planned one-year treatment. The sponsor may decide the actual timing of the IA to be conducted, based on the availability of commercial tolvaptan in ADPKD. This IA would use the O'Brian-Fleming spending function to apportion alpha and thus manage Type 1 error. Determination of the information time of the IA assumes total sample size in this trial to be set at 1300, if the trial is still randomizing subjects at the time of the IA. For example, if the first 650 subjects out of 1300 total sample size are included, a p-value &lt; 0.003051 is required to reject the null hypothesis, satisfy the objective of replicating efficacy, and offer a possibility for early trial completion. If a recommendation for early termination is accepted, all subjects remaining in the trial can be offered participation in a planned open-label extension trial. If the null hypothesis is not rejected at this interim evaluation, the trial would continue and the alpha of the final test of the primary endpoint would be 0.049002.</p>
Section 7.6, Safety Analysis	<p>Standard safety variables to be analyzed include AEs, clinical laboratory data, physical examinations, and vital signs.</p>	<p>Standard safety variables to be analyzed include AEs, <b>self-reported tolerability</b>, clinical laboratory data, physical examinations, and vital signs.</p>
Appendix 3, Handling and Shipment of Bioanalytical Samples	<p>The 20 mL biomarker sample will be collected by the subject at home and transported to the site at room temperature. At the site, the sample should be immediately equally divided into the bar-code labeled polypropylene tubes (number of aliquots will be defined in the operations manual) and frozen.</p>	<p>The PD/<b>biomarker urine</b> sample will be collected by the subject at home and transported to the site at room temperature. At the site, <b>20 mL</b> of the sample should be immediately equally divided into the bar-code labeled polypropylene tubes (number of aliquots will be defined in the operations manual) and frozen.</p>

**Previous Figure 3.1-1 - Trial Design Schematic:**

F/U = Follow-up

\*Can be extended up to an additional 8 weeks for subjects needing stabilization after changing other treatments.

**Revised Figure 3.3-1 Trial Design Schematic**

**Previous Schedule of Assessments****Table 10.2-1: Schedule of Assessments**

Assessment	Pre-randomization										Double-blind Randomized Treatment			Follow-up			
	Screening (2 weeks ± 1 day)		Placebo run-in (1 week ± 1 day) (Days -42 to -36)		Tolvaptan titration (2 weeks ± 1 day) (Days -35 to -22)				Tolvaptan run-in (3 weeks ± 1 day) (Days -21 to -1)			(Day 0)	Visits: monthly (± 2 days)	Month 12/ EoTx visit	3 weeks post-treatment		
	Days -56 to -43 <sup>a</sup>	Day -42	Day -39 ± 1 day	Day -36	-35	-32	-28	-24	-22	-21	-15	-8	-1	Day 0	Months 1 to 11	Month 12 /EoTx	Days +7 to +21 post-final visit <sup>a</sup>
Informed consent	X																
Inclusion/Exclusion	X																
Demographic/Medical history	X																
Vital signs <sup>b</sup>	X	X			X				X			X		(X) <sup>b</sup>	X		X
Physical examination <sup>c</sup>	X														X		
Urine pregnancy test (WOCBP only) <sup>d</sup>	X													(X) <sup>c</sup>	X		X
Clinical laboratory samples <sup>e</sup> :																	
Hematology and coagulation	X																
Urinalysis	X	X			X						X				X		
Serum Chemistry Panel	X														X		X
Liver Function Panel	X				X				X		X	X			X		X
Creatinine	X	X	X		X	X			X		X	X		X	X	X	X
Sodium	X	X		X	X			X		X	X		X	X	X		
PK plasma sample <sup>f</sup>											X			(X) <sup>f</sup>	X		X
PD urine sample <sup>f</sup>			X		X			X			X			(X) <sup>f</sup>	X		X
Biomarker urine and plasma			X		X			X			X			(X) <sup>f</sup>	X		X

**Table 10.2-1: Schedule of Assessments**

Assessment	Pre-randomization										Double-blind Randomized Treatment			Follow-up	
	Screening (2 weeks ± 1 day)		Placebo run-in (1 week ± 1 day) (Days -42 to -36)		Tolvaptan titration (2 weeks ± 1 day) (Days -35 to -22)		Tolvaptan run-in (3 weeks ± 1 day) (Days -21 to -1)		(Day 0)	Visits: monthly (± 2 days)	Month 12/ EoTx visit	3 weeks post-treatment			
	Days -56 to -43 <sup>a</sup>	Day -42	Day -39 ± 1 day	Day -36	Days		Days		Day 0	Months 1 to 11	Month 12 /EoTx	Days +7 to +21 post-final visit <sup>a</sup>			
<sup>f</sup> sample					-35	-32	-28	-24	-22	-21	-15	-8	-1		
DNA blood sample <sup>g</sup>	X														
Start newly dispensed IMP			X		X				X			X			
Tolerability/Dosing review					X	X	X	X			X		X		
Randomization											X				
Drug dispensation <sup>h</sup>		X			X				X		X		X		
Drug reconciliation <sup>h</sup>					X				X		X		X		
IVRS entry <sup>i</sup>	X	X			X	X	X	X			X		X		X
Exploratory PKD outcomes <sup>j</sup>		X	-								X		X		
Adverse events	X	<----->													
Concomitant medications	X	<----->													

<sup>a</sup>The screening period may be extended up to an additional 8 weeks for subjects who require modification of medical care specifically for this trial. Visits during the screening and follow-up periods must be scheduled at least 24 hours (1 day) apart. At each visit, blood will be collected and analyzed centrally for serum creatinine concentrations, in addition to any other assessments listed. A visiting nurse house call or local laboratory visit may be substituted for visits where only blood/urine will be collected. Visits during the screening period must be scheduled within a 2-week period before the start of the placebo run-in period. Visits during the follow-up period must be scheduled during a 2-week period that begins 1 week after the end of treatment visit.

<sup>b</sup>The following visits (and all assessments required during those visits) should be performed in-clinic: screening, end of placebo run-in, end of tolvaptan titration, end of tolvaptan run-in, quarterly visits during the randomized, double-blind treatment period (eg, Months 3, 6, 9), Month 12/end of treatment (EoTx) visit, and the last follow-up visit. Vital signs at each of the above visits include sitting heart rate and blood pressure. Post-void body weight should

be measured at the first screening visit and the Month 12/EoTx visit only. Height should be assessed at the first screening visit only. Either height or weight may be collected as an unscheduled measurement if its assessment was missed.

<sup>c</sup>A full physical examination is required at the first screening visit and the Month 12/EoTx visit. A “directed physical examination” may be performed at the quarterly visits (eg, Months 3, 6, 9) for assessment of signs or symptoms reported by the subject that might require further evaluation.

<sup>d</sup>During the trial, a pregnancy test should be completed at screening and at the quarterly visits. On suspicion of pregnancy, unscheduled urine or serum pregnancy testing will be performed. Positive urine pregnancy tests should be confirmed with a serum pregnancy test.

<sup>e</sup>The specifics and timing for clinical laboratory samples for central and local laboratory analyses are as follows:

**Screening period:** Subjects will have 3 blood draws on separate days between Day -56 and Day -43. The subject's eligibility will be confirmed by the mean of eGFR calculated from the subjects' first 2 pre-treatment, central laboratory serum creatinine assessments.

**Placebo run-in period:** Subjects will have 2 blood draws on separate days (at least 24 hours apart) between Days -42 to -36 with the last sample on Day -36.

**Tolvaptan titration period:** Subjects will have 1 blood draw at the end of 2 weeks with the sample being obtained on Day -22.

**Tolvaptan run-in period:** During the last 2 weeks of this period, blood will be drawn 2 times on separate days (at least 24 hours apart) with the last sample on Day -1.

**Double-blind treatment period:** Samples will be collected for central lab analysis monthly and at the Month 12/EoTx visit. Local standard of care laboratory tests will be performed monthly per the subject's individual clinical management needs. Local liver function panel analyses will also be performed more frequently, if necessary.

<sup>f</sup>During the double-blind, randomized treatment period, PK plasma samples, PD urine samples, and biomarker urine/plasma samples will be collected quarterly (eg, Months 3, 6, 9, 12/EoTx).

<sup>g</sup>Samples are optional.

<sup>h</sup>Drug dispensing and reconciliation will be done monthly and subjects will be reminded of the importance of their commitment to continue participation in the trial..

<sup>i</sup>If, during the titration contact, the determination is made to adjust the dose-regimen, the investigator will enter the subject's status in the IVRS and arrange for dispensation of a new IMP kit and reconciliation of returned IMP.

<sup>j</sup>Exploratory PKD outcomes will be completed either monthly over the phone or in person during quarterly clinic visits.

**Revised Schedule of Assessments****Table 10.2-1 Schedule of Assessments**

Assessment	Pre-randomization										Double-blind Randomized Treatment			Follow-up			
	Screening <sup>a</sup> (1-2 weeks)			Placebo run-in (1 week ± 1 day) (Days -42 to -36)		Tolvaptan titration (2 weeks ± 1 day) (Days -35 to -22)			Tolvaptan run-in (3 weeks ± 1 day) (Days -21 to -1)		(Day 0)	Visits: monthly (± 2 days)	Month 12/ EoTx visit				
	V1	V2	Day -43	Day -42	Day -36	-35	-32	-28	-24	-22	-21	-15	-8	-1	Day 0	Months 1 to 11 <sup>b</sup>	Month 12 /EoTx
Informed consent	X																
Inclusion/Exclusion	X																
Demographic/Medical history	X																
Vital signs <sup>c</sup>	X	X			X				X			X		(X) <sup>c</sup>	X		X
Physical examination <sup>d</sup>	X													(X) <sup>d</sup>	X		
Urine pregnancy test (WOCBP only) <sup>e</sup>	X				X									(X) <sup>e</sup>	X		X
Chemistry Blood Sample <sup>c,f</sup> :																	
Serum Chemistry Panel	X														X		X
Liver Function Panel	X	X			X			X			X		X		X	X	X
Creatinine	X	X			X			X			X	X		X	X	X	X
Sodium	X	X			X			X			X		X		X		X
Hematology and coagulation	X																
PK plasma sample												X		(X) <sup>g</sup>	X		X
Biomarker plasma sample		X			X			X			X		X	(X) <sup>g</sup>	X		X
DNA blood sample <sup>h</sup>		X															

**Table 10.2-1 Schedule of Assessments**

Assessment	Pre-randomization										Double-blind Randomized Treatment			Follow-up				
	Screening <sup>a</sup> (1-2 weeks)			Placebo run-in (1 week ± 1 day) (Days -42 to -36)		Tolvaptan titration (2 weeks ± 1 day) (Days -35 to -22)			Tolvaptan run-in (3 weeks ± 1 day) (Days -21 to -1)		(Day 0)	Visits: monthly (± 2 days)	Month 12/ EoTx visit					
	V1	V2	Day -43	Day -42	Day -36	-35	-32	-28	-24	-22	-21	-15	-8	-1	Day 0	Months 1 to 11 <sup>b</sup> /EoTx	Month 12 /EoTx	
Urinalysis	X	X			X								X			X		
PD and Biomarker urine sample		X			X					X			X		(X) <sup>g</sup>	X		X
Start newly dispensed IMP				X		X				X			X					
Tolerability/Dosing review					X		X	X	X				X			X	X	
Randomization													X					
Drug dispensation <sup>1</sup>			X		X					X			X			X		
Drug reconciliation <sup>1</sup>					X					X			X			X	X	
IVRS entry <sup>j</sup>	X	X	X		X		X	X	X	X			X			X	X	X
Exploratory PKD outcomes <sup>k</sup>		X											X			X	X	
Adverse events	X	<----->																
Concomitant medications	X	<----->																

<sup>a</sup>The screening period should be completed within 1-2 weeks before the start of the placebo run-in period. The screening period may be extended up to an additional 8 weeks for subjects who require modification of medical care specifically for this trial. Visits during the screening and follow-up periods must be scheduled at least 24 hours (1 day) apart. The Day -43 visit cannot occur until laboratory values from V2 are received. For two visits (V1, V2) during the screening period, blood will be collected and analyzed centrally for serum creatinine concentrations, in addition to any other assessments listed. A visiting nurse house call or local laboratory visit may be substituted for visits where only blood/urine will be collected during the follow-up period. Visits during the follow-up period must be scheduled during a 2-week period that begins 1 week after the end of treatment visit.

<sup>b</sup>If IMP treatment is interrupted for ≥ 7 days during this period, procedures should be followed as detailed in [Section 3.8.3.2](#).

<sup>c</sup>The following visits (and all assessments required during those visits) should be performed in-clinic: screening (V1, V2, Day -43), end of placebo run-in, end of tolvaptan titration, end of tolvaptan run-in, quarterly visits during the randomized, double-blind treatment period (eg, Months 3, 6, 9), Month 12/end of treatment (EoTx) visit, and the last follow-up visit. Vital signs at each of the above visits include sitting heart rate and blood pressure. Post-void body weight should be measured at the first screening visit and the Month 12/EoTx visit only. Height should be assessed at the first screening visit only. Either height or weight may be collected as an unscheduled measurement if its assessment was missed.

<sup>d</sup>A full physical examination is required at screening (V1) and the Month 12/EoTx visit. A “directed physical examination” is performed at the quarterly visits (eg, Months 3, 6, 9) for assessment of signs or symptoms reported by the subject that might require further evaluation.

<sup>e</sup>During the trial, a pregnancy test should be completed at screening, end of placebo run-in and at the quarterly visits. On suspicion of pregnancy, unscheduled urine or serum pregnancy testing will be performed. Positive urine pregnancy tests should be confirmed with a serum pregnancy test.

<sup>f</sup>All serum creatinine samples will be analyzed by the central laboratory. The specifics and timing for all clinical laboratory samples for central and local laboratory analyses are as follows:

**All visits:** One or more tubes of blood may be collected to accommodate the needed tests.

**Screening period:** During the 1-2 weeks of the screening period, blood will be drawn 2 times on separate days (V1, V2) at least 24 hours apart. The subject's eligibility will be confirmed by the mean of eGFR calculated from the subjects' 2 pre-treatment (V1, V2), central laboratory serum creatinine assessments and entered in IVRS on Day -43.

**Placebo run-in period:** Subjects will have 1 blood draw at the end of 1 week with the sample being obtained on Day -36.

**Tolvaptan titration period:** Subjects will have 1 blood draw at the end of 2 weeks with the sample being obtained on Day -22.

**Tolvaptan run-in period:** During the last 2 weeks of this period, blood will be drawn 2 times on separate days (at least 24 hours apart) with the last sample on Day -1.

**Double-blind treatment period:** Samples will be collected for central lab analysis monthly and at the Month 12/EoTx visit. Local standard of care laboratory tests will be performed monthly per the subject's individual clinical management needs. Local liver function panel analyses will also be performed more frequently, if necessary.

**Follow-up period:** Subjects will have blood drawn on 3 visits over Days +7 to +21 post-treatment.

Full Chemistry panel will be obtained during following visit: Screening (V1), quarterly visit (M3, M6, M9, M12/EoTx, F/U period Day 21 Serum creatinine, serum sodium,: Screening (V2), end of placebo period, end of tolvaptan titration, 2 times during tolvaptan run-in, monthly during double blind treatment period, 2 times during F/U period

Liver function panel: Screening (V2), end of placebo period, end of tolvaptan titration, 2 times during tolvaptan run-in, monthly during double blind treatment period, F/U period Day 21

<sup>g</sup>During the double-blind, randomized treatment period, PK plasma samples, PD urine samples, and biomarker urine/plasma samples will be collected quarterly (eg, Months 3, 6, 9, 12/EoTx).

<sup>h</sup>DNA samples are optional.

<sup>i</sup>Drug dispensing and reconciliation will be done monthly (exceptions to allow dispensing/reconciliation at each 3-month clinic visit may be made by the medical monitor in exceptional circumstances, with instructions to take only one month's supply and start the next month only after acceptable safety lab results are confirmed by the investigator). Instructions to begin taking the next month's trial medication will be given by telephone contact. Subjects will

be reminded of the importance of their commitment to continue participation in the trial. At the completion of the screening period, trial medication will be dispensed at Day -43 after subject eligibility is confirmed. In exceptional circumstances, trial medication may be dispensed at V2, with the instruction not to take any trial medication until eligibility is confirmed by the investigator. In these cases, confirmation of eligibility and instructions for taking trial medication will be provided by telephone on Day -43.

j If, during the titration contact, the determination is made to adjust the dose-regimen, the investigator will enter the subject's status in the IVRS and arrange for dispensation of a new IMP kit and reconciliation of returned IMP. At the end of the titration period, the subject's highest tolerated dose will be utilized for the 3-week tolvaptan run-in period.

k Exploratory PKD outcomes will be completed either monthly over the phone or in person during quarterly clinic visits.

**Administrative Change Number:** 2**Issue Date:** 25 June 2014**PURPOSE:**

This administrative change will not affect the safety of subjects, the scope of the investigation, or the scientific quality of the trial.

The main purpose of this administrative change was to align the Statistical Analysis Plan with the protocol. In addition, an administrative change to Home Nursing Services was made, and several clarifications to the protocol were added.

**BACKGROUND:**

The US-FDA's Special Protocol Agreement (SPA) requested several modifications to the protocol to more closely align analyses with the Statistical Analysis Plan. The delegated Home Nursing Services vendor was also changed and is now updated.

**Sectional Revisions**

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
Synopsis, Trial Design, Double-blind, randomized treatment period (12 months):	...Subjects will also be stratified by total kidney volume (TKV; ≤ 2000 mL or > 2000 m), if known.	...Subjects will also be stratified by <b>three</b> total kidney volume ( <b>TKV</b> ) <b>criteria</b> (≤ 2000 mL, > 2000 mL, <b>or unknown</b> ).
Synopsis, Primary Efficacy Analysis	<u>Primary efficacy analysis:</u> The change in eGFR from pre-treatment baseline to post-treatment follow-up, annualized (divided) by each subject's IMP treatment duration, will be calculated. The annualized change in eGFR will be analyzed by analysis of covariance (ANCOVA) with treatment and randomization stratification factors as factor and covariate baselines.	<u>Primary efficacy analysis:</u> The change in eGFR from pre-treatment baseline to post-treatment follow-up, annualized (divided) by each subject's IMP treatment duration, will be calculated. The annualized change in eGFR will be analyzed by <b>a weighted</b> analysis of covariance (ANCOVA) with treatment and randomization stratification factors as factor and covariate baselines. <b>This weighted analysis is based on the reciprocal of the estimated variance of the “estimated slopes.”</b>
Abbreviations List		IDMS - Isotope dilution mass spectrometry
Section 2.1, Trial Rationale	To decrease variability, multiple serum creatinine measurements will be taken both pre- and post-treatment for each subject, and the eGFR values will then be averaged.	To decrease variability, multiple serum creatinine measurements ( <b>isotope dilution mass spectrometry [IDMS]-traceable</b> ) will be taken both pre- and post-treatment for each subject, and the eGFR values will then be averaged.
Section 3.2.2, Double-	After stratified randomization,	After stratified randomization, <b>by</b>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
blind Randomized Treatment Period (Day 0 to Month 12)	subjects will enter the double-blind, randomized treatment period receiving either tolvaptan or placebo in a 1:1 ratio.	<b>baseline eGFR (at a threshold of <math>\leq 45</math> or <math>&gt; 45 \text{ mL/min}/1.73\text{m}^2</math>), by age (<math>\leq 55</math> or <math>&gt; 55</math> years old), and by three TKV criteria (<math>\leq 2000 \text{ mL}</math>, <math>&gt; 2000 \text{ mL}</math>, or unknown),</b> subjects will enter the double-blind, randomized treatment period receiving either tolvaptan or placebo in a 1:1 ratio.
Section 3.4.1, Informed Consent	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),...	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 signed and dated by <b>all subjects (or their guardian or legal representative, as applicable for local laws)</b> , and the person obtaining consent (investigator or designee),..
Section 3.5.2.1, Key Secondary Efficacy Endpoint	Treatment difference in annualized slope of eGFR calculated for individual subjects using an appropriate baseline and available, post-randomization, on treatment assessments.	Treatment difference in annualized slope of eGFR calculated for individual subjects using <b>eGFR data observed in the placebo run-in, tolvaptan run-in (not including tolvaptan titration), double-blind treatment, and post-treatment follow-up (not including data collected in the first week after the last IMP dose) periods.</b>
Section 3.6, Measures to Minimize/Avoid Bias	Subjects will also be stratified by total kidney volume (TKV; $\leq 2000 \text{ mL}$ or $> 2000 \text{ mL}$ ), if known.	Subjects will also be stratified by <b>three TKV criteria (<math>\leq 2000 \text{ mL}</math>, <math>&gt; 2000 \text{ mL}</math>, or unknown).</b>
Section 3.7, Trial Procedures, Schedule of Assessments	c ...Either height or weight may be collected as an unscheduled measurement if its assessment was missed.	c ...Either height or weight may be collected as an unscheduled measurement if <b>the planned assessment was missed. Weight may be assessed as necessary to assess changes in body weight.</b>
	l...Instructions to begin taking the next month's trial medication will be given by telephone contact....	l...Instructions to begin taking the next month's trial medication will be given <b>during the time of IMP dispensation at each monthly visit or by telephone contact after the monthly LFT samples are collected. If LFT results are abnormal, the site will conduct a telephone contact with the trial subject to inform them that prompt immediate retesting (ie,</b>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
		<b>within 72 hours) may be necessary (see Section 3.7.3.4 for guidance) and to arrange for follow-up and adjustment of medication (as needed); if a down titration is required, the subject may need to return to the site or have new drug delivered.</b>
Section 3.7.1.1, Pre-randomization Period	<p>Pre-randomization eGFR value(s) will be collected for each potential treatment assignment for all subjects.</p> <p>To establish the pre-randomization eGFR, multiple serum creatinine values will be obtained under standardized conditions</p>	<p>Tolvaptan Run-in (3 weeks ± 1 day) Day - 15 column was deleted</p> <p>Pre-randomization eGFR value(s) will be <b>calculated by CKD-EPI</b> for each potential treatment assignment for all subjects.</p> <p>To establish the pre-randomization eGFR, multiple serum creatinine values (<b>IDMS-traceable</b>) will be obtained under standardized conditions</p>
Section 3.7.1.1.4, Tolvaptan Run-In Period (Days -21 to -1)	Subjects will also be stratified by age ( $\leq 55$ or $> 55$ years old) and by total kidney volume (TKV; $\leq 2000$ mL, or $> 2000$ mL), if known.	Subjects will also be stratified by age ( $\leq 55$ or $> 55$ years old) and by <b>three TKV criteria</b> ( $\leq 2000$ mL, $> 2000$ mL, <b>or unknown</b> ).
Section 3.7.2.1, Serum Creatinine for Estimated Glomerular Filtration Rate	The eGFR values will be calculated from the central-laboratory serum creatinine concentrations taken at screening and during every trial visit.	The eGFR values will be calculated by <b>CKD-EPI</b> from the central-laboratory serum creatinine concentrations taken at screening and during every trial visit.
Section 7.4.1.1, Primary Endpoint Analysis	The primary endpoint of this trial is the change in eGFR from pre-treatment baseline to post-treatment follow-up, annualized (divided) by each subjects' IMP treatment duration.	The primary endpoint of this trial is the change in eGFR ( <b>calculated by the CKD-EPI formula</b> ) from pre-treatment baseline to post-treatment follow-up, annualized (divided) by each subjects' IMP treatment duration.
	...Thus, analysis of covariance (ANCOVA) with effects of treatment and randomization stratification factors and covariate baseline will be applied to these "estimated slopes" as the primary analysis.	...Thus, <b>a weighted</b> analysis of covariance (ANCOVA) with effects of treatment and randomization stratification factors and covariate baseline will be applied to these "estimated slopes" as the primary analysis. <b>This weighted analysis is based on the reciprocal of the estimated variance of the "estimated slopes," and the detailed algorithm to derive the estimated variance is provided in Section 8.3 of the SAP.</b>
Section 7.4.1.3, Sensitivity Analysis Including Data from Subjects Who Discontinue IMP	This sensitivity analysis deviates from the MAR assumption to include the post-discontinuation follow-up data in the analysis specified in the previous section. Subjects who discontinue IMP after randomization	This sensitivity analysis deviates from the MAR assumption to include the post-discontinuation follow-up data in the analysis specified in the <b>primary analysis</b> section. Subjects who discontinue

Location	Old Text	Updated Text
	without withdrawing consent will be followed for additional off-treatment eGFR through to Month 12. These post “post-treatment follow-up” eGFR data will be included with the data specified in the previous section, in a sensitivity analysis using the same analytic approach specified in the previous section.	IMP after randomization without withdrawing consent will be followed for additional off-treatment eGFR <b>values up</b> to Month 12. These “post-treatment follow-up” eGFR data <b>at Month 12</b> will be included to replace the data <b>observed during post-treatment follow-up for the subjects who discontinue IMP early</b> , in a sensitivity analysis using the same analytic approach specified in the <b>primary analysis</b> section.
Section 7.4.2.1, Key Secondary Endpoint Analysis	The time variable used in the model may start from the first observation of eGFR obtained from placebo run-in period.	The time variable used in the model may start from the first observation of eGFR obtained from placebo run-in period. <b>The covariate “acute hemodynamic effect” in the model is the flag variable with value of 0 and 1 specified earlier in this section for the data observed during tolvaptan run-in and the data observed for tolvaptan subjects during the double blind treatment period. The starting point of this eGFR slope analysis is the eGFR observation during the placebo run-in period.</b>
Section 7.4.3, Subgroup Efficacy Analysis	Subgroup analyses will be provided for the primary and the key secondary endpoints by regions (US and non-US), gender (male and female), race, (Caucasian and Other), age ( $\leq 55$ years, $> 55$ years), baseline GFR level (eGFR $\leq 45$ mL/min/1.73 m <sup>2</sup> and $> 45$ mL/min/1.73 m <sup>2</sup> ) and baseline TKV ( $\leq 2000$ mL, $> 2000$ mL, or unknown).	Subgroup analyses will be provided for the primary and the key secondary endpoints by regions (US and non-US), gender (male and female), race (Caucasian and Other), age ( $\leq 55$ years, $> 55$ years), baseline GFR level (eGFR $\leq 45$ mL/min/1.73 m <sup>2</sup> and $> 45$ mL/min/1.73 m <sup>2</sup> ) and <b>three baseline TKV criteria</b> ( $\leq 2000$ mL, $> 2000$ mL, or unknown).
Appendix 2, Institutions Concerned With the Trial, Home Nursing Services	Symphony Clinical Research 700 Deerpath Drive Vernon Hills, IL 60061, USA Phone: +1-301-984-7191 Fax: +1-301-921-4405	The Medical Research Network Ltd. 15 Presley Way Crownhill, Milton Keynes Buckinghamshire MK8 0ES Stuart Redding (Director) <a href="mailto:stuart.redding@themrn.co.uk">stuart.redding@themrn.co.uk</a> Tel: 0800-032-2348 <a href="http://www.themrn.co.uk">www.themrn.co.uk</a>

**Amendment Number** 2**Issue Date:** 26 November 2014**PURPOSE:**

The primary purpose of this amendment was to add an additional exclusion criterion for France.

**BACKGROUND:**

A letter from the French health agency Agence nationale de sécurité du medicament (ANSM) requested verbiage be added to the exclusion criteria explaining contraindications of tolvaptan.

**Sectional Revisions**

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
Section 3.4.3, Exclusion Criteria, Table 3.4.3-1		8. Tolvaptan is contraindicated in patients who: are known to have hypersensitivity to tolvaptan or one of the excipients, are hypovolemic (volume depletion), cannot perceive thirst. Additionally, subjects with baseline screening abnormalities of serum sodium concentrations (hyponatremia or hypernatremia) may not be enrolled in the trial until these abnormalities resolve and then must be monitored accordingly.

**ADDITIONAL RISK TO THE SUBJECT:**

There is no additional risk to the subjects.

**Amendment Number** 3

**Issue Date:** 26 March 2015

**PURPOSE:**

The primary purpose of this amendment is to clarify the inclusion criterion for older subjects, and to correct a misstatement regarding SUSAR reporting for procedures. Other clarifications were added for consistency between the Schedule of Assessments table and text or to clarify sample collection process or timing. The DNA sample collection time was changed from the second screening visit only to any visit from the second screening visit onwards.

**BACKGROUND:**

**Clarification of Inclusion Criterion # 2 (other than synopsis, first appears in Section 3.4)**

A change is made to the inclusion criterion to clarify that subjects likely to have slowly progressive ADPKD due to their advanced age at entry be excluded if available renal function history confirms a progression rate inconsistent with the scientific goals of the trial. As this trial is only 1 year in duration, it is therefore important that enrolled subjects have a decrease of at least 2 mL/min/1.73 m<sup>2</sup> per year so that the expected measurable effect of tolvaptan (a 33% reduction in the rate of decline) may be determined.

**Clarification of Sample Collection (other than synopsis, first appears in Section 3.7)**

In order to ensure that urine samples are collected in the same manner at every site, wording is added to the Schedule of Assessments table to specify that urine samples will be collected during the second morning void as a mid-stream, clean-catch sample, and obtained prior to the subject's eating breakfast. This instruction was added to every visit where a urine sample is collected. Where necessary, all supplies for the collection should be provided to the subject prior to the next visit so the sample can be collected either in-clinic or at home on the day of the scheduled visit.

In the previous version of the protocol, serum creatinine samples are to be collected three times over the follow-up period. The language is clarified to emphasize that the first of 3 samples in the 3-week follow-up period occurs at least 7 days after the last dose of IMP to ensure the acute, reversible effects of tolvaptan on serum creatinine have a minimally reasonable time period to abate.

### Clarification of DNA Blood Samples (first appears in the Schedule of Assessments table, Section 3.7)

Language was added to allow flexibility in the timing of DNA blood sample collection in case subjects do not provide consent at the second screening visit, but consent to do so at a later visit. This eliminates potential protocol deviations that have no impact on the ability to interpret the data for the primary endpoint of this trial.

### Sectional Revisions

Location	Old Text	Updated Text
Synopsis, Trial Design	<p><u>Double-blind, randomized treatment period (12 months):</u> Only subjects who reach the end of the tolvaptan run-in period and are able to tolerate tolvaptan 60/30 mg or 90/30 mg daily “for the rest of their lives” are eligible to enter this period. Randomization will be 1:1, tolvaptan to placebo. Subjects will be stratified by their baseline eGFR, at a threshold of <math>\leq 45</math> or <math>&gt; 45 \text{ mL/min}/1.73\text{m}^2</math>, and by age (<math>\leq 55</math> or <math>&gt; 55</math> years old). Subjects will also be stratified by three total kidney volume (TKV) criteria (<math>\leq 2000 \text{ mL}</math>, <math>&gt; 2000 \text{ mL}</math>, or unknown). Post-randomization, the maximally-tolerated dose of tolvaptan established during the run-in period, or the equivalent as matching placebo tablets, will be dispensed according to the subject’s randomization outcome. If continued tolerability becomes an issue, subjects may titrate downward to 45/15 mg (or 30/15 mg, with medical monitor approval) or temporarily interrupt treatment as needed. Return to higher doses is also allowed.</p> <p><u>Follow-up period (3 weeks):</u> For randomized subjects, after Month 12 (or the EoTx visit, if a subject</p>	<p><u>Double-blind, randomized treatment period (12 months):</u> Only subjects who reach the end of the tolvaptan run-in period and are able to tolerate tolvaptan 60/30 mg or 90/30 mg daily “for the rest of their lives” are eligible to enter this period. Randomization will be 1:1, tolvaptan to placebo. Subjects will be stratified by their baseline eGFR, at a threshold of <math>\leq 45</math> or <math>&gt; 45 \text{ mL/min}/1.73\text{m}^2</math>, and by age (<math>\leq 55</math> or <math>&gt; 55</math> years old). Subjects will also be stratified by three total kidney volume (TKV) criteria (<math>\leq 2000 \text{ mL}</math>, <math>&gt; 2000 \text{ mL}</math>, or unknown). Post-randomization, the maximally-tolerated dose of tolvaptan established during the run-in period, or the equivalent as matching placebo tablets, will be dispensed according to the subject’s randomization outcome. If continued tolerability becomes an issue, subjects may titrate downward to 45/15 mg (or 30/15 mg, with medical monitor approval) or temporarily interrupt treatment as needed. Return to higher doses is also allowed. Subjects who discontinue IMP before the Month 12 visit will complete an EoTx visit, which should be scheduled as soon as possible after the subject’s last dose of investigational medicinal product (IMP) and complete the follow-up period.</p> <p><u>Follow-up period (3 weeks):</u> For all randomized subjects, the follow-up period starts immediately after the</p>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
	discontinues investigational medicinal product prematurely) each subject will enter a 3 week follow-up period. No assessments will be taken for the first week of this period; however, 3 visits will be scheduled for the last 2 weeks of follow-up for post-treatment efficacy and safety measures.	last dose of IMP. No follow-up assessments will be taken during the first week of this period. During the last 2 weeks, Days 8 through 21, inclusive, 3 follow-up visits will be scheduled. The last follow-up visit will include measurements of efficacy and safety. Subjects will have blood drawn at each visit.
Synopsis, Subject Population	This trial will randomize approximately 1300 tolvaptan naïve subjects with ADPKD. Male and female adults will be enrolled, from 18-55 years of age with eGFR between 25 and 65 mL/min/1.73m <sup>2</sup> or 56 to < 66 years of age with eGFR between 25 and 44 mL/min/1.73m <sup>2</sup> (with medical monitor approval),	This trial will randomize approximately 1300 tolvaptan naïve subjects with ADPKD. Male and female adults will be enrolled, from 18-55 years of age with eGFR between 25 and 65 mL/min/1.73m <sup>2</sup> or 56 to < 66 years of age with eGFR between 25 and 44 mL/min/1.73m <sup>2</sup> (with <b>evidence of ADPKD progression and</b> medical monitor approval).
Synopsis, Inclusion/Exclusion Criteria	<p>Main inclusion criteria:</p> <ul style="list-style-type: none"> <li>• eGFR between 25 and 65 mL/min/1.73m<sup>2</sup> (18 to 55 years) or eGFR between 25 and 44 mL/min/1.73m<sup>2</sup> (56 to &lt; 66 years, by medical monitor discretion only).</li> </ul>	<p>Main inclusion criteria:</p> <ul style="list-style-type: none"> <li>• eGFR between 25 and 65 mL/min/1.73m<sup>2</sup> (18 to 55 years of age) or eGFR between 25 and 44 mL/min/1.73m<sup>2</sup> (56 to &lt; 66 years of age, <b>with evidence of ADPKD progression, ie, eGFR decline of &gt; 2.0 mL/min/1.73 m<sup>2</sup> per year, based on historical eGFR data and</b> medical monitor discretion).</li> </ul>
Section 3.2.1.1, Screening Period (up to Day -43)	No investigational treatments will be administered during the screening period. During this period, the subject's eligibility for the trial will be confirmed using historical imaging data of total kidney volume (TKV; if available) to support a diagnosis of ADPKD and to verify the level of CKD primarily due to ADPKD and not to other renal (hypoplasia) or metabolic (diabetic or hypertensive nephropathy) disorders.	No investigational treatments will be administered during the screening period. During this period, the subject's eligibility for the trial will be confirmed using historical imaging data to support a diagnosis of ADPKD and to verify the level of CKD primarily due to ADPKD and not to other renal (hypoplasia) or metabolic (diabetic or hypertensive nephropathy) disorders.
Section 3.4.2, Inclusion Criteria, Table 3.4.2-1, Inclusion Criteria	2. Male and female subjects age 56 to < 66 years of age with eGFR between 25 and 44 mL/min/1.73m <sup>2</sup> (by medical monitor discretion, only).	2. Male and female subjects age 56 to < 66 years of age with eGFR between 25 and 44 mL/min/1.73m <sup>2</sup> <b>with evidence of ADPKD progression, ie, eGFR decline of &gt; 2.0 mL/min/1.73 m<sup>2</sup> per year, based on historical eGFR data and medical monitor discretion.</b>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
Section 3.7, Table 3.7-1, Schedule of Assessments	<p>Follow up column has the two subheaders below:      3 weeks post-treatment      Days +7 to +21 (-2 days) post final visit<sup>a</sup></p> <p>In the assessment row called Liver Function Panel, an X is marked for Day -1 during the tolvaptan run-in.</p> <p>In the assessment row called PD and Biomarker urine sample an X with footnote g occurs only once. All other Xs in this row do not have a footnote.</p> <p>In the IVRS entry row in the columns under Tolvaptan titration, Xs occur for Days -32, -28, -24, and -22.</p> <p>Footnote a      The screening period should be completed within 1-2 weeks before the start of the placebo run-in period. The screening period may be extended up to an additional 8 weeks for subjects who require modification of medical care specifically for this trial. Visits during the screening and follow-up periods must be scheduled at least 24 hours (1 day) apart. The Day -43 visit cannot occur until laboratory values from V2 are received. For two visits (V1, V2) during the screening period, blood will be collected and analyzed centrally for serum creatinine concentrations, in addition to any other assessments listed. A visiting nurse house call or local laboratory visit may be substituted for visits where only blood/urine will be collected during the follow-up period. Visits during the follow-up period must be scheduled during a 2-week period that begins 1 week after the end of treatment visit.</p>	<p>Follow up column has the two subheaders below:      3 weeks post-treatment<sup>a</sup>      Days +8 to +21</p> <p>The row beneath has V1, V2, and V3 added to show the three visit dates more clearly.</p> <p>In the assessment row called Liver Function Panel, an X is marked for Day -8 during the tolvaptan run-in, and the X marked for Day -1 has been deleted.</p> <p>Every X in the assessment row called PD and Biomarker urine sample has footnote g.</p> <p>In the IVRS entry row, the X for Screening V2 has been deleted, and in the columns under Tolvaptan titration, an X occurs for Day -22 only.</p> <p>Footnote a      The screening period should be completed within 1-2 weeks before the start of the placebo run-in period. The screening period may be extended up to an additional 8 weeks for subjects who require modification of medical care specifically for this trial. Visits during the screening and follow-up periods must be scheduled at least 24 hours (1 day) apart. The Day -43 visit cannot occur until laboratory values from V2 are received. For two visits (V1, V2) during the screening period, blood will be collected and analyzed centrally for serum creatinine concentrations, in addition to any other assessments listed. A visiting nurse house call or local laboratory visit may be substituted for visits where only blood/urine will be collected during the follow-up (F/U) period. Three visits in the F/U period should be scheduled between Day 8 and Day 21 (inclusive) after the last dose of IMP. No F/U assessments will be taken during the first week of this period. Blood samples will be</p>

Location	Old Text	Updated Text
	<p>Footnote f  <sup>f</sup>All serum creatinine samples will be analyzed by the central laboratory. The specifics and timing for all clinical laboratory samples for central and local laboratory analyses are as follows:</p> <p><b>All visits:</b> One or more tubes of blood may be collected to accommodate the needed tests.</p> <p><b>Screening period:</b> During the 1-2 weeks of the screening period, blood will be drawn 2 times on separate days (V1, V2) at least 24 hours apart. The subject's eligibility will be confirmed by the mean of eGFR calculated from the subjects' 2 pre-treatment (V1, V2), central laboratory serum creatinine assessments and entered in IVRS on Day -43.</p> <p><b>Placebo run-in period:</b> Subjects will have 1 blood draw at the end of 1 week with the sample being obtained on Day -36.</p> <p><b>Tolvaptan titration period:</b> Subjects will have 1 blood draw at the end of 2 weeks with the sample being obtained on Day -22.</p> <p><b>Tolvaptan run-in period:</b> During the last 2 weeks of this period, blood will be drawn 2 times on separate days (at least 24 hours apart) with the last sample on Day -1.</p> <p><b>Double-blind treatment period:</b> Samples will be collected for central lab analysis monthly and at the Month 12/EoTx visit. Local standard of care laboratory tests will be performed monthly per the subject's individual clinical management needs. Local liver function panel analyses will</p>	<p>drawn at each visit for serum creatinine (V1, V2) and serum creatinine and other safety, efficacy, PK and PD measurements (V3).</p> <p>Footnote f  <sup>f</sup>All serum creatinine samples will be analyzed by the central laboratory. The specifics and timing for all clinical laboratory samples for central and local laboratory analyses are as follows:</p> <p><b>All visits:</b> One or more tubes of blood may be collected to accommodate the needed tests.</p> <p><b>Screening period:</b> During the 1-2 weeks of the screening period, blood will be drawn 2 times on separate days (V1, V2) at least 24 hours apart. The subject's eligibility will be confirmed by the mean of eGFR calculated from the subjects' 2 pre-treatment (V1, V2), central laboratory serum creatinine assessments and entered in IVRS on Day -43.</p> <p><b>Placebo run-in period:</b> Subjects will have 1 blood draw at the end of 1 week with the sample being obtained on Day -36.</p> <p><b>Tolvaptan titration period:</b> Subjects will have 1 blood draw at the end of 2 weeks with the sample being obtained on Day -22.</p> <p><b>Tolvaptan run-in period:</b> During the last 2 weeks of this period, blood will be drawn 2 times on separate days (at least 24 hours apart) with the last sample on Day -1.</p> <p><b>Double-blind treatment period:</b> Samples will be collected for central lab analysis monthly and at the Month 12/EoTx visit. Local standard of care laboratory tests will be performed monthly per the subject's individual clinical management needs. Local liver function panel analyses will</p>

Location	Old Text	Updated Text
	<p>also be performed more frequently, if necessary.</p> <p><b>Follow-up period:</b> Subjects will have blood drawn on 3 visits over Days +7 to +21 post-treatment.</p> <p>Full Chemistry panel will be obtained during following visit: Screening (V1), quarterly visit (M3, M6, M9, M12/EoTx, F/U period Day 21</p> <p>Serum creatinine, serum sodium: Screening (V2), end of placebo period, end of tolvaptan titration, 2 times during tolvaptan run-in, monthly during double blind treatment period, 2 times during F/U period</p> <p>Liver function panel: Screening (V2), end of placebo period, end of tolvaptan titration, 2 times during tolvaptan run-in, monthly during double blind treatment period, F/U period Day 21</p> <p>Footnote g: gDuring the double-blind, randomized treatment period, PK plasma samples, PD urine samples, and biomarker urine/plasma samples will be collected quarterly (eg, Months 3, 6, 9, 12/EoTx).</p> <p>Footnote h: hDNA samples are optional.</p>	<p>also be performed more frequently, if necessary.</p> <p><b>Follow-up period:</b> Subjects will have blood drawn on 3 visits at least 24 hours apart during the 3-week period, which starts after the last dose of IMP. Visits should be scheduled between Days 8 and 21, inclusive.</p> <p>Full Chemistry panel will be obtained during the following visits: Screening (V1), quarterly visit (M3, M6, M9, M12/EoTx, F/U period (V3)</p> <p>Serum creatinine, serum sodium: Screening (V2), end of placebo period, end of tolvaptan titration, 2 times during tolvaptan run-in, monthly during double blind treatment period, 3 times for serum creatinine and 1 time for serum sodium (V3) during the F/U period. Note that the first F/U visit will occur at least 7 days (Day 8) after the last dose of IMP.</p> <p>Liver function panel: Screening (V2), end of placebo period, end of tolvaptan titration, 1 time during tolvaptan run-in, monthly during double blind treatment period, F/U period (V3).</p> <p>Footnote g: gDuring the double-blind, randomized treatment period, PK plasma samples, PD urine samples, and biomarker urine/plasma samples will be collected quarterly (eg, Months 3, 6, 9, 12/EoTx). Urine biomarkers should be collected as a mid-stream, clean-catch sample during the second morning void prior to the subject eating breakfast. Where necessary, supplies for collection should be dispensed prior to the visit with instructions to collect the urine sample on the day of the visit.</p> <p>Footnote h: hDNA samples are optional and may</p>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
	<p>Footnote j:</p> <p><sup>j</sup>If, during the titration contact, the determination is made to adjust the dose-regimen, the investigator will enter the subject's status in the IVRS and arrange for dispensation of a new IMP kit and reconciliation of returned IMP. At the end of the titration period, the subject's highest tolerated dose will be utilized for the 3-week tolvaptan run-in period.</p>	<p>be collected at subsequent visits with subject's consent.</p> <p>Footnote j:</p> <p><sup>j</sup>At the end of the titration period, the subject's highest tolerated dose will be utilized for the 3-week tolvaptan run-in period.</p>
Section 3.7.1.1.1, Screening Period (up to Day -43)	16) Collect blood for DNA sample (second visit, for consenting subjects only)	16) Collect blood for DNA sample (second visit, for consenting subjects only). DNA samples may be collected at a subsequent visit if subjects consent at a later date.
Section 3.7.1.1.3, Tolvaptan Titration Period (Days -35 to -22)	8) Update subject status in IVRS at each upward titration visit	8) Update subject status in IVRS on Day -22
Section 3.7.1.1.4, Tolvaptan Run-In Period (Days -21 to -1)	<p>Assessments during the tolvaptan run-in period will include (See Table 3.7-1):</p> <p>...</p> <p>5) Collect blood (2 times on separate days during the last 2 weeks of the period, with the last sample drawn on Day -1) for serum creatinine for eGFR calculation and for assessment of sodium and liver function panel (see Section 3.7.3.2). If sodium and liver function panel are collected at the same visit, a single tube of blood should be drawn for all assessments.</p>	<p>Assessments during the tolvaptan run-in period will include (See Table 3.7-1):</p> <p>...</p> <p>5) Collect blood (2 times on separate days during the last 2 weeks of the period, with the last sample drawn on Day -1) for serum creatinine for eGFR calculation and for 1 assessment of sodium and liver function panel (see Section 3.7.3.2). If sodium and liver function panel are collected at the same visit, a single tube of blood should be drawn for all assessments.</p>
Section 3.7.1.2, Double-blind, Randomized Treatment Period (Day 0 to Month 12)	<p>Regardless of discontinuation of IMP, the subjects are expected to complete all monthly visits and assessments including the Month 12 visit.</p> <p>... (enumerated list of assessments)</p> <p>13) Update subject status in IVRS (monthly and at the Month 12/EoTx visit)</p> <p>14) Dispense IMP at monthly visits up to and including Month 11. In certain circumstances, with medical monitor approval, a 3-month drug supply may be provided; however, initiation of the next month's supply must be directed by the site.</p>	<p>Regardless of discontinuation of IMP, the subjects are expected to complete all monthly visits and assessments including the Month 12 visit (see <a href="#">Section 3.8.3.3</a>).</p> <p>... (enumerated list of assessments)</p> <p><b>13) Ask subject “Can you tolerate this dose of trial medication for the rest of your life?” at each visit</b></p> <p>14) Update subject status in IVRS (monthly and at the Month 12/EoTx visit)</p> <p>15) Dispense IMP at monthly visits up to and including Month 11. In certain circumstances, with medical monitor approval, a 3-month drug supply may be provided; however,</p>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
Section 3.7.1.3, Follow-up Period (Month 12/End of Treatment to Day 21 Post-treatment)	<p>Randomized subjects will enter the follow-up period after they complete the double-blind, randomized treatment period, or after their EoTx visit, if they discontinued IMP. The follow-up period will be for 21 days in duration.</p> <p>There will be no scheduled visits/assessments during the first week of the follow-up period. After the first week, 3 visits should be scheduled during the remaining 2 weeks of the follow-up period (between Day +7 and Day +21). The first visit should be scheduled on approximately Day +7, the second visit on approximately Day +14 and the third visit on approximately Day +21 (-2 days). These visits may be visiting nurse house calls or local laboratory visits when only blood samples will be collected, with the exception of the last visit, which will be a clinic visit.</p> <p>Assessments during the last 2 weeks of the follow-up period will include (See Table 3.7-1):</p> <p>...</p> <p>6) Collect blood for assessment of sodium levels at the first visit (see <a href="#">Section 3.7.3.2</a>)</p>	<p>initiation of the next month's supply must be directed by the site.</p> <p>For all randomized subjects, the 3-week follow-up period starts immediately after the last dose of IMP. No follow-up assessments will be taken during the first week of this period. During the last 2 weeks, Days 8 through 21, inclusive, 3 follow-up visits will be scheduled. The visits must occur at least 24 hours apart. Blood samples will be collected at each visit for serum creatinine measurements. The blood sample collected at the last follow-up visit will also include measurements of post-treatment efficacy and safety.</p> <p>These visits may be visiting nurse house calls or local laboratory visits when only blood samples will be collected, with the exception of the last visit, which will be a clinic visit. Assessments during the last 2 weeks of the follow-up period will include (See Table 3.7-1):</p> <p>...</p> <p>6) Collect blood for assessment of sodium levels at the <b>last</b> visit (see <a href="#">Section 3.7.3.2</a>)</p>
Section 3.7.3.2, Clinical Laboratory Assessments	<ul style="list-style-type: none"> <li>• during tolvaptan run-in - urinalysis (Day -1), liver function panel, creatinine, and sodium (2 times on separate days during the last 2 weeks of the period, with the last sample drawn on Day -1)</li> <li>• during the follow-up period (3 visits that begin 1 week after the Month 12/EoTx visit) - creatinine (3 visits), sodium (first visit), liver function panel and serum chemistry panel (last visit)</li> </ul>	<ul style="list-style-type: none"> <li>• during tolvaptan run-in - liver function panel (Day-8), urinalysis (Day -1), creatinine, (2 times on separate days during the last 2 weeks of the period, with the last sample drawn on Day -1), and sodium (Day -1)</li> <li>• during the 3-week follow-up period (3 visits that occur between Days 8 and 21, inclusive, after the last dose of IMP, and at least 24 hours apart) - creatinine (3 visits), sodium (first visit), liver function panel and serum chemistry panel (last visit)</li> </ul>
Section 3.7.3.5.3, DNA Blood Samples	<p>A blood sample for DNA collection will be obtained for every consenting subject at the second visit of the screening period.</p>	<p>A blood sample for DNA collection will be obtained from every consenting subject at the second visit of the screening period. Samples may be collected at a subsequent visit if subjects provide consent after the</p>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
Section 3.8.3.3, Treatment Discontinuation	<p>A subject who permanently discontinues treatment will be recorded as an IMP discontinuation on the eCRF. They will have an EoTx visit to collect vital signs, physical exam, serum creatinine assessment, clinical laboratory assessments, PK/PD samples, and biomarker urine/plasma samples. The subject will then enter the follow-up period as though they had reached the Month 12 visit. During the first week of the follow-up period, no procedures will be done. During the last two weeks of the follow-up period, the subject will have a total of 3 samples collected for serum creatinine measurements.</p>	<p>A subject who permanently discontinues treatment will be recorded as an IMP discontinuation on the eCRF. They will have an EoTx visit, which should be scheduled as soon as possible after the subject's last dose of IMP, to collect vital signs, physical exam, serum creatinine assessment, clinical laboratory assessments, PK/PD samples, and biomarker urine/plasma samples. The subject's follow-up period will be 3 weeks as though they had reached the Month 12 visit, and the follow-up period will start after the last day of treatment, which may be a different day from the EoTx visit. No follow-up assessments will be taken during the first week of this period. There will be three visits in the follow up period between Day 8 and Day 21. The first two will be for the collection of serum creatinine measurement and the third will have additional safety, efficacy, PK, and PD measurements.</p>
Section 3.13, Protocol Deviations	<p>In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, IMP dispensing or subject dosing error, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator or designee will contact the sponsor at the earliest possible time by telephone.</p>	<p>In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, IMP dispensing or subject dosing error, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator or designee will contact the <b>medical monitor</b> at the earliest possible time by telephone.</p>
Section 5.1, Definitions	<p>A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality. Additionally, in the European Union (EU), an adverse procedure-related reaction is any noxious or unintended response to a trial-related procedure and requires a</p>	<p>A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality.</p>

<b>Location</b>	<b>Old Text</b>	<b>Updated Text</b>
Section 5.3, Immediately Reportable Events	SUSAR report.  The investigator must immediately report within 24 hours after either the investigator or site personnel become aware of any SAE, new liver lab abnormality requiring special liver eCRF completion, or confirmed pregnancy, by telephone or by fax to the sponsor as outlined in Appendix 1. An IRE form must be completed and sent by fax or overnight courier to the sponsor. (Please note that the IRE form is NOT the AE eCRF.)	The investigator must immediately report within 24 hours after either the investigator or site personnel become aware of any SAE, new liver lab abnormality requiring special liver eCRF completion, or confirmed pregnancy, by telephone or by fax to <b>Quintiles drug safety services</b> as outlined in Appendix 1. An IRE form must be completed and sent by fax or overnight courier to the sponsor. (Please note that the IRE form is NOT the AE eCRF.)
Appendix 1	Global Clinical Management Laurie Debuque Sr. Manager, Global Clinical Development Otsuka Pharmaceutical Development & Commercialization, Inc. 1 University Square Drive Suite 500 Princeton, NJ 08540, USA Phone: +1-609-524-6894; Fax +1-240-514-3994	Global Clinical Management Laurie Debuque Sr. Manager, Global Clinical Development Otsuka Pharmaceutical Development & Commercialization, Inc. 506 Carnegie Center Princeton, NJ 08540, USA Phone: +1-609-524-6894; Fax +1-240-514-3994
Appendix 2	... Investigator Payments CFS Clinical 1000 Madison Ave, 1st Floor Audubon, PA 19403, USA Phone: +1-610-994-2754 Fax: +1-610-650-1895 ... DNA Sample Storage Gentris Corporation 133 Southcenter Court, Suite 400 Morrisville, NC 27560, USA Phone: +1-919-465-0100	... Investigator Payments Quintiles 5927 South Miami Blvd Morrisville, NC 27560, USA Phone: +1-214-505-6781 Mobile: +1-214-505-6781 Fax: +1-919-800-0095 ... DNA Sample Storage Cancer Genetics, Inc. 133 Southcenter Court, Suite 400 Morrisville, NC 27560, USA Phone: +1-919-465-0100

**Previous Schedule of Assessments****Table 3.7-1 Schedule of Assessments**

Assessment	Pre-randomization										Double-blind Randomized Treatment			Follow-up	
	Screening <sup>a</sup> (1-2 weeks)		Placebo run-in (1 week ± 1 day) (Days -42 to -36)		Tolvaptan titration (2 weeks ± 1 day) (Days -35 to -22)		Tolvaptan run-in (3 weeks ± 1 day) (Days -21 to -1)		(Day 0)	Visits: monthly (± 2 days)	Month 12/EoTx visit	3 weeks post-treatment			
	V1	V2	Day -43	Day -42	Day -36	Days		Days		Day 0	Months 1 to 11 <sup>b</sup>	Month 12/EoTx	Days +7 to +21 (-2 days) <sup>a</sup>		
Informed consent	X					-35	-32	-28	-24	-22	-21	-8	-1		
Inclusion/Exclusion	X														
Demographic/Medical history	X														
Vital signs <sup>c</sup>	X	X			X			X		X		(X) <sup>c</sup>	X		X
Physical examination <sup>d</sup>	X											(X) <sup>d</sup>	X		
Urine pregnancy test (WOCBP only) <sup>e</sup>	X				X							(X) <sup>e</sup>	X		X
Chemistry Blood Sample <sup>c,f</sup> :															
Serum Chemistry Panel	X												X		X
Liver Function Panel	X	X			X			X		X		X	X		X
Creatinine	X	X			X			X	X			X	X	X	X
Sodium	X	X			X			X		X		X	X		X
Hematology and coagulation	X														
PK plasma sample												(X) <sup>g</sup>	X		X
Biomarker plasma sample		X			X			X		X		(X) <sup>g</sup>	X		X

**Table 3.7-1 Schedule of Assessments**

Assessment	Pre-randomization										Double-blind Randomized Treatment			Follow-up	
	Screening <sup>a</sup> (1-2 weeks)			Placebo run-in (1 week ± 1 day) (Days -42 to -36)		Tolvaptan titration (2 weeks ± 1 day) (Days -35 to -22)			Tolvaptan run-in (3 weeks ± 1 day) (Days -21 to -1)		(Day 0)	Visits: monthly (± 2 days)	Month 12/ EoTx visit		
	V1	V2	Day -43	Day -42	Day -36	Days			Days		Day 0	Months 1 to 11 <sup>b</sup>	Month 12 /EoTx	Days +7 to +21 (-2 days) <sup>a</sup>	
DNA blood sample <sup>h</sup>		X				-35	-32	-28	-24	-22	-21	-8	-1		
Urinalysis	X	X			X							X		X	
PD and Biomarker urine sample		X			X				X			X	(X) <sup>g</sup>	X	X
Start newly dispensed IMP				X		X				X		X			
Tolerability/Dosing review					X		X	X	X	X		X		X	
Randomization											X				
Drug dispensation <sup>i</sup>			X		X				X			X			
Drug reconciliation <sup>i</sup>					X				X			X		X	
IVRS entry <sup>j</sup>	X	X	X		X	X	X	X			X		X	X	X
Exploratory PKD outcomes <sup>k</sup>		X									X		X	X	
Adverse events	X	<----->													
Concomitant medications	X	<----->													

<sup>a</sup>The screening period should be completed within 1-2 weeks before the start of the placebo run-in period. The screening period may be extended up to an additional 8 weeks for subjects who require modification of medical care specifically for this trial. Visits during the screening and follow-up periods must be scheduled at least 24 hours (1 day) apart. The Day -43 visit cannot occur until laboratory values from V2 are received. For two visits (V1, V2) during

the screening period, blood will be collected and analyzed centrally for serum creatinine concentrations, in addition to any other assessments listed. A visiting nurse house call or local laboratory visit may be substituted for visits where only blood/urine will be collected during the follow-up period. Visits during the follow-up period must be scheduled during a 2-week period that begins 1 week after the end of treatment visit.

<sup>b</sup>If IMP treatment is interrupted for  $\geq$  7 days during this period, procedures should be followed as detailed in [Section 3.8.3.2](#).

<sup>c</sup>The following visits (and all assessments required during those visits) should be performed in-clinic: screening (V1, V2, Day -43), end of placebo run-in, end of tolvaptan titration, end of tolvaptan run-in, quarterly visits during the randomized, double-blind treatment period (eg, Months 3, 6, 9), Month 12/end of treatment (EoTx) visit, and the last follow-up visit. Vital signs at each of the above visits include sitting heart rate and blood pressure. Post-void body weight should be measured at the first screening visit and the Month 12/EoTx visit only. Height should be assessed at the first screening visit only. Either height or weight may be collected as an unscheduled measurement if the planned assessment was missed. Weight may be assessed as necessary to assess changes in body weight.

<sup>d</sup>A full physical examination is required at screening (V1) and the Month 12/EoTx visit. A “directed physical examination” is performed at the quarterly visits (eg, Months 3, 6, 9) for assessment of signs or symptoms reported by the subject that might require further evaluation.

<sup>e</sup>During the trial, a pregnancy test should be completed at screening, end of placebo run-in and at the quarterly visits. On suspicion of pregnancy, unscheduled urine or serum pregnancy testing will be performed. Positive urine pregnancy tests should be confirmed with a serum pregnancy test.

<sup>f</sup>All serum creatinine samples will be analyzed by the central laboratory. The specifics and timing for all clinical laboratory samples for central and local laboratory analyses are as follows:

**All visits:** One or more tubes of blood may be collected to accommodate the needed tests.

**Screening period:** During the 1-2 weeks of the screening period, blood will be drawn 2 times on separate days (V1, V2) at least 24 hours apart. The subject's eligibility will be confirmed by the mean of eGFR calculated from the subjects' 2 pre-treatment (V1, V2), central laboratory serum creatinine assessments and entered in IVRS on Day -43.

**Placebo run-in period:** Subjects will have 1 blood draw at the end of 1 week with the sample being obtained on Day -36.

**Tolvaptan titration period:** Subjects will have 1 blood draw at the end of 2 weeks with the sample being obtained on Day -22.

**Tolvaptan run-in period:** During the last 2 weeks of this period, blood will be drawn 2 times on separate days (at least 24 hours apart) with the last sample on Day -1.

**Double-blind treatment period:** Samples will be collected for central lab analysis monthly and at the Month 12/EoTx visit. Local standard of care laboratory tests will be performed monthly per the subject's individual clinical management needs. Local liver function panel analyses will also be performed more frequently, if necessary.

**Follow-up period:** Subjects will have blood drawn on 3 visits over Days +7 to +21 post-treatment.

Full Chemistry panel will be obtained during following visit: Screening (V1), quarterly visit (M3, M6, M9, M12/EoTx, F/U period Day 21). Serum creatinine, serum sodium,: Screening (V2), end of placebo period, end of tolvaptan titration, 2 times during tolvaptan run-in, monthly during double blind treatment period, 2 times during F/U period

Liver function panel: Screening (V2), end of placebo period, end of tolvaptan titration, 2 times during tolvaptan run-in, monthly during double blind treatment period, F/U period Day 21

<sup>g</sup>During the double-blind, randomized treatment period, PK plasma samples, PD urine samples, and biomarker urine/plasma samples will be collected quarterly (eg, Months 3, 6, 9, 12/EoTx).

<sup>h</sup>DNA samples are optional.

<sup>i</sup>Drug dispensing and reconciliation will be done monthly (exceptions to allow dispensing/reconciliation at each 3-month clinic visit may be made by the medical monitor in exceptional circumstances, with instructions to take only one month's supply and start the next month only after acceptable safety lab results are confirmed by the investigator). Instructions to begin taking the next month's trial medication will be given during the time of IMP dispensation at each monthly visit or by telephone contact after the monthly LFT samples are collected. If LFT results are abnormal, the site will conduct a telephone contact with the trial subject to inform them that prompt immediate retesting (ie, within 72 hours) may be necessary (see [Section 3.7.3.4](#) for guidance) and to arrange for follow-up and adjustment of medication (as needed); if a down titration is required, the subject may need to return to the site or have new drug delivered. Subjects will be reminded of the importance of their commitment to continue participation in the trial. At the completion of the screening period, trial medication will be dispensed at Day -43 after subject eligibility is confirmed. In exceptional circumstances, trial medication may be dispensed at V2, with the instruction not to take any trial medication until eligibility is confirmed by the investigator. In these cases, confirmation of eligibility and instructions for taking trial medication will be provided by telephone on Day -43.

<sup>j</sup>If, during the titration contact, the determination is made to adjust the dose-regimen, the investigator will enter the subject's status in the IVRS and arrange for dispensation of a new IMP kit and reconciliation of returned IMP. At the end of the titration period, the subject's highest tolerated dose will be utilized for the 3-week tolvaptan run-in period.

<sup>k</sup>Exploratory PKD outcomes will be completed either monthly over the phone or in person during quarterly clinic visits.

**Revised Schedule of Assessments****Table 3.7-1 Schedule of Assessments**

Assessment	Pre-randomization											Double-blind Randomized Treatment			Follow-up					
	Screening <sup>a</sup> (1-2 weeks)		Placebo run-in (1 week ± 1 day) (Days -42 to -36)		Tolvaptan titration (2 weeks ± 1 day) (Days -35 to -22)		Tolvaptan run-in (3 weeks ± 1 day) (Days -21 to -1)		(Day 0)	Visits: monthly (± 2 days)	Month 12/ EoTx visit	3 weeks post-treatment <sup>a</sup>			Day 0	Months 1 to 11 <sup>b</sup>	Month 12 /EoTx	Days +8 to +21		
	V1	V2	Day -43	Day -42	Day -36	-35	-32	-28	-24	-22	-21	-8	-1	V1			V2	V3		
Informed consent	X																			
Inclusion/Exclusion	X																			
Demographic/Medical history	X																			
Vital signs <sup>c</sup>	X	X			X				X			X		(X) <sup>c</sup>	X				X	
Physical examination <sup>d</sup>	X													(X) <sup>d</sup>	X					
Urine pregnancy test (WOCBP only) <sup>e</sup>	X				X									(X) <sup>e</sup>	X				X	
Chemistry Blood Sample <sup>c,f</sup> :																				
Serum Chemistry Panel	X														X				X	
Liver Function Panel	X	X			X				X		X			X	X				X	
Creatinine	X	X			X				X		X	X		X	X	X	X	X	X	
Sodium	X	X			X				X			X		X	X				X	
Hematology and coagulation	X																			
PK plasma sample													X	(X) <sup>g</sup>	X				X	
Biomarker plasma sample		X			X				X			X		(X) <sup>g</sup>	X				X	

**Table 3.7-1 Schedule of Assessments**

Assessment	Pre-randomization										Double-blind Randomized Treatment			Follow-up			
	Screening <sup>a</sup> (1-2 weeks)			Placebo run-in (1 week ± 1 day) (Days -42 to -36)		Tolvaptan titration (2 weeks ± 1 day) (Days -35 to -22)			Tolvaptan run-in (3 weeks ± 1 day) (Days -21 to -1)			(Day 0)	Visits: monthly (± 2 days)	Month 12/ EoTx visit	3 weeks post-treatment <sup>a</sup>		
	V1	V2	Day -43	Day -42	Day -36	Days			Days			Day 0	Months 1 to 11 <sup>b</sup>	Month 12 /EoTx	Days +8 to +21		
	-35	-32	-28	-24	-22	-21	-8	-1							V1	V2	V3
DNA blood sample <sup>h</sup>	X																
Urinalysis	X	X			X						X			X			
PD and Biomarker urine sample		X <sup>g</sup>			X <sup>g</sup>				X <sup>g</sup>		X <sup>g</sup>		(X) <sup>g</sup>	X <sup>g</sup>			X <sup>g</sup>
Start newly dispensed IMP				X		X			X			X					
Tolerability/Dosing review					X		X	X	X	X		X		X	X		
Randomization												X					
Drug dispensation <sup>i</sup>			X		X				X			X		X			
Drug reconciliation <sup>i</sup>					X				X			X		X	X		
IVRS entry <sup>j</sup>	X		X		X				X			X		X	X		X
Exploratory PKD outcomes <sup>k</sup>		X									X		X	X			
Adverse events	X	<----->															
Concomitant medications	X	<----->															

<sup>a</sup>The screening period should be completed within 1-2 weeks before the start of the placebo run-in period. The screening period may be extended up to an additional 8 weeks for subjects who require modification of medical care specifically for this trial. Visits during the screening and follow-up periods must be scheduled at least 24 hours (1 day) apart. The Day -43 visit cannot occur until laboratory values from V2 are received. For two visits (V1, V2) during

the screening period, blood will be collected and analyzed centrally for serum creatinine concentrations, in addition to any other assessments listed. A visiting nurse house call or local laboratory visit may be substituted for visits where only blood/urine will be collected during the follow-up (F/U) period. Three visits in the F/U period should be scheduled between Day 8 and Day 21 (inclusive) after the last dose of IMP. No F/U assessments will be taken during the first week of this period. Blood samples will be drawn at each visit for serum creatinine (V1, V2) and serum creatinine and other safety, efficacy, PK and PD measurements (V3).

<sup>b</sup>If IMP treatment is interrupted for  $\geq$  7 days during this period, procedures should be followed as detailed in [Section 3.8.3.2](#).

<sup>c</sup>The following visits (and all assessments required during those visits) should be performed in-clinic: screening (V1, V2, Day -43), end of placebo run-in, end of tolvaptan titration, end of tolvaptan run-in, quarterly visits during the randomized, double-blind treatment period (eg, Months 3, 6, 9), Month 12/end of treatment (EoTx) visit, and the last follow-up visit. Vital signs at each of the above visits include sitting heart rate and blood pressure. Post-void body weight should be measured at the first screening visit and the Month 12/EoTx visit only. Height should be assessed at the first screening visit only. Either height or weight may be collected as an unscheduled measurement if the planned assessment was missed. Weight may be assessed as necessary to assess changes in body weight.

<sup>d</sup>A full physical examination is required at screening (V1) and the Month 12/EoTx visit. A “directed physical examination” is performed at the quarterly visits (eg, Months 3, 6, 9) for assessment of signs or symptoms reported by the subject that might require further evaluation.

<sup>e</sup>During the trial, a pregnancy test should be completed at screening, end of placebo run-in and at the quarterly visits. On suspicion of pregnancy, unscheduled urine or serum pregnancy testing will be performed. Positive urine pregnancy tests should be confirmed with a serum pregnancy test.

<sup>f</sup>All serum creatinine samples will be analyzed by the central laboratory. The specifics and timing for all clinical laboratory samples for central and local laboratory analyses are as follows:

**All visits:** One or more tubes of blood may be collected to accommodate the needed tests.

**Screening period:** During the 1-2 weeks of the screening period, blood will be drawn 2 times on separate days (V1, V2) at least 24 hours apart. The subject's eligibility will be confirmed by the mean of eGFR calculated from the subjects' 2 pre-treatment (V1, V2), central laboratory serum creatinine assessments and entered in IVRS on Day -43.

**Placebo run-in period:** Subjects will have 1 blood draw at the end of 1 week with the sample being obtained on Day -36.

**Tolvaptan titration period:** Subjects will have 1 blood draw at the end of 2 weeks with the sample being obtained on Day -22.

**Tolvaptan run-in period:** During the last 2 weeks of this period, blood will be drawn 2 times on separate days (at least 24 hours apart) with the last sample on Day -1.

**Double-blind treatment period:** Samples will be collected for central lab analysis monthly and at the Month 12/EoTx visit. Local standard of care laboratory tests will be performed monthly per the subject's individual clinical management needs. Local liver function panel analyses will also be performed more frequently, if necessary.

**Follow-up period:** Subjects will have blood drawn on 3 visits at least 24 hours apart during the 3-week F/U period, which starts after the last dose of IMP. Visits should be scheduled between Days 8 and 21, inclusive.

Full Chemistry panel will be obtained during the following visits: Screening (V1), quarterly visit (M3, M6, M9, M12/EoTx, F/U period (V3).

Serum creatinine, serum sodium: Screening (V2), end of placebo period, end of tolvaptan titration, 2 times during tolvaptan run-in, monthly during double-blind treatment period, 3 times for serum creatinine and 1 time for serum sodium (V3) during the F/U period. Note that the first F/U visit will occur at least 7 days (Day 8) after the last dose of IMP.

Liver function panel: Screening (V2), end of placebo period, end of tolvaptan titration, 1 time during tolvaptan run-in, monthly during double blind treatment period, F/U period (V3).

<sup>g</sup>During the double-blind, randomized treatment period, PK plasma samples, PD urine samples, and biomarker urine/plasma samples will be collected quarterly (eg, Months 3, 6, 9, 12/EoTx). Urine biomarker samples should be collected as a mid-stream, clean-catch sample during the second morning void prior to the subject eating breakfast. Where necessary, supplies for collection should be dispensed prior to the visit with instructions to collect the urine sample on the day of the visit.

<sup>h</sup>DNA samples are optional and may be collected at subsequent visits with subject's consent.

<sup>i</sup>Drug dispensing and reconciliation will be done monthly (exceptions to allow dispensing/reconciliation at each 3-month clinic visit may be made by the medical monitor in exceptional circumstances, with instructions to take only one month's supply and start the next month only after acceptable safety lab results are confirmed by the investigator). Instructions to begin taking the next month's trial medication will be given during the time of IMP dispensation at each monthly visit or by telephone contact after the monthly LFT samples are collected. If LFT results are abnormal, the site will conduct a telephone contact with the trial subject to inform them that prompt immediate retesting (ie, within 72 hours) may be necessary (see [Section 3.7.3.4](#) for guidance) and to arrange for follow-up and adjustment of medication (as needed); if a down titration is required, the subject may need to return to the site or have new drug delivered. Subjects will be reminded of the importance of their commitment to continue participation in the trial. At the completion of the screening period, trial medication will be dispensed at Day -43 after subject eligibility is confirmed. In exceptional circumstances, trial medication may be dispensed at V2, with the instruction not to take any trial medication until eligibility is confirmed by the investigator. In these cases, confirmation of eligibility and instructions for taking trial medication will be provided by telephone on Day -43.

<sup>j</sup>At the end of the titration period, the subject's highest tolerated dose will be utilized for the 3-week tolvaptan run-in period.

<sup>k</sup>Exploratory PKD outcomes will be completed either monthly over the phone or in person during quarterly clinic visits.

**ADDITIONAL RISK TO THE SUBJECT:**

There is no additional risk to the subjects.

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, [insert compound number], 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 [insert compound number] 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 sub-investigators 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 trial in a cooperative publication prior to publication of efficacy and safety results on an individual basis.

---

Principal or Coordinating Investigator Signature and Date

**Otsuka Pharmaceutical Development & Commercialization, Inc.**

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Otsuka Pharmaceutical  
Development & Commercialization, Inc.

Investigational Medicinal Product

Tolvaptan

Protocol 156-13-210  
IND No. 72,975  
EudraCT No. 2014-000226-38

A Phase 3b, Multi-center, Randomized-withdrawal, Placebo-controlled, Double-blind, Parallel-group Trial to Compare the Efficacy and Safety of Tolvaptan (45 to 120 mg/day, Split-dose) in Subjects with Chronic Kidney Disease Between Late Stage 2 to Early Stage 4 Due to Autosomal Dominant Polycystic Kidney Disease

## **Statistical Analysis Plan**

**Version: 1**

**Date: Feb. 10, 2014**

CONFIDENTIAL – PROPRIETARY INFORMATION

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## **1 Introduction**

This Statistical Analysis Plan (SAP) describes the statistical methodology and data analysis algorithms and conventions to be applied for statistical analysis and reporting of efficacy and safety data of trial 156-13-210.

## **2 Study Objectives**

### **2.1 Primary objectives**

The primary objectives of this trial are:

To compare the efficacy of tolvaptan treatment in reducing the change in eGFR from pre-treatment baseline to post-treatment follow-up, as compared with placebo, in subjects with late-stage CKD due to ADPKD who tolerate tolvaptan during an initial run-in period.

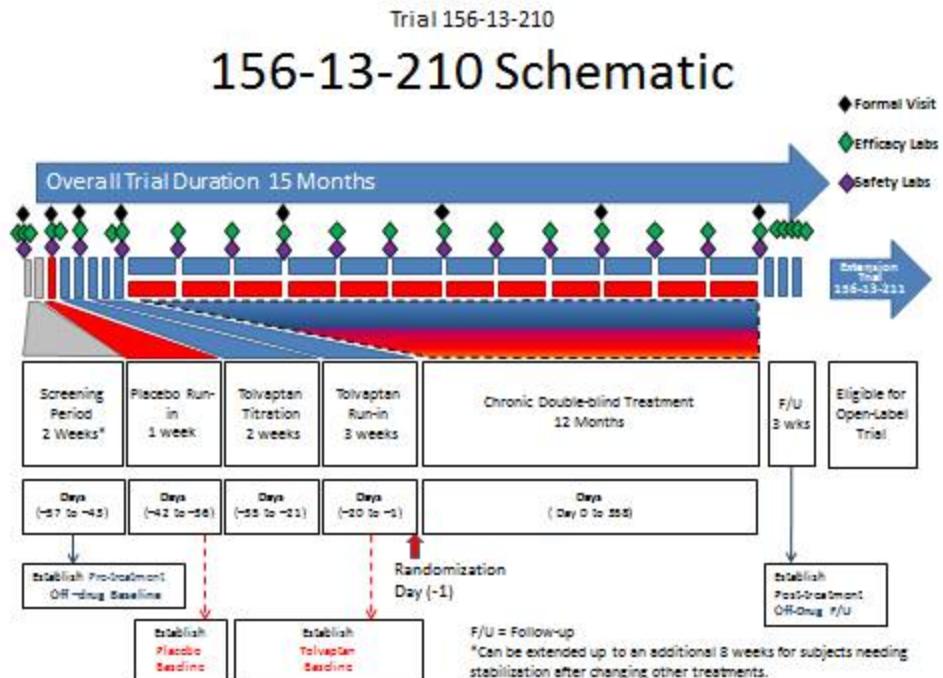
### **2.2 Secondary objectives**

The secondary objectives of this trial are:

- To compare the efficacy of tolvaptan treatment in reducing the decline of annualized eGFR slope, as compared with placebo, in subjects with late-stage CKD due to ADPKD who tolerate tolvaptan during an initial run-in period.
- To compare overall and hepatic safety of tolvaptan with that of placebo and to compare incidence of ADPKD complications (outcomes) during the trial.

## **3 Study Design**

This is a phase 3, multi-center, randomized-withdrawal, placebo-controlled, double-blind, parallel-group trial to compare the efficacy and safety of tolvaptan with placebo in subjects with ADPKD and baseline kidney function as documented by an eGFR between 25-65 mL/min/1.73m<sup>2</sup>, inclusive. The overall design is illustrated in the following figure.



## 4 Sample Size and Power Justification

### 4.1 Sample Size Estimation

In this sample size estimation, it is assumed that 4-5 observations of eGFR are observed at baseline during a 3-week interval during screening (2 weeks) and placebo run-in (1 week) and again 4-5 observations are observed after one week post-treatment follow-up during a two week interval (over a total of 3 weeks). The mean of the 4-5 eGFR observed during the screening and placebo-run periods is set as the baseline and the mean of the 4-5 eGFR observed during post-treatment follow-up period is set as the renal function measurement post-treatment. The timing of baseline and post-treatment observations are set to the median of the observation times in the two-week interval respectively. Thus, the pre-treatment baseline will be set at approximately 6 weeks prior to randomization, and the post-treatment renal function measurement will be set at approximately 2 weeks after the end of treatment.

Based on a MMRM analysis of the non-Japan CKD-3 Subjects from trial 156-04-251, the treatment difference in renal function at Month 12 based on the post-randomization baseline is 1.43 mL/min/1.73 m<sup>2</sup>. However, the US FDA has expressed a concern that the onset and offset of tolvaptan's hemodynamic effect may not be equal (Otsuka believes it is not possible to determine if the small differences observed are due to a random error). Thus, with an assumption the absolute value of the off-set eGFR increase is 25% less than the absolute onset of the decrease in eGFR, we may assume the treatment difference in renal function is 1.07 mL/min/1.73 m<sup>2</sup> in our sample size calculation. Annual reduction of GFR decline in the amount

of 1.07 mL/min/1.73 m<sup>2</sup> is clinically meaningful in the ADPKD patient population studied in this protocol (eGFR between 25 to 65 mL/min/1.73 m<sup>2</sup>), and is approximately 25% reduction for a subject with 4.5 mL/min/1.73 m<sup>2</sup> annual decline in GFR.

To investigate the reduction in intra-subject variation achieved by taking the mean of an increased number of observations at baseline and post-treatment follow-up in the sample size, we have to estimate the intra-subject error and inter-subject error.

To derive the intra-subject variance and inter-subject variance, the approach provided by Dr. Lawrence, a FDA statistician, in a FDA communication to the sponsor dated Dec. 24, 2013, is followed. For subject  $i$  randomized to the placebo group ( $i=1, \dots, n$ ), the eGFR at time  $t_j$  is assumed to be

$$Y_{i,j} = \alpha_i + \beta_i t_j + \varepsilon_{i,j} \quad (1)$$

For subject  $i$  randomized to the tolvaptan group ( $i= n+1, \dots, 2n$ ), the eGFR at time  $t_j$  is assumed to be

$$Y_{i,j} = \alpha_i + \beta_i t_j + \varepsilon_{i,j} \text{ if } j \text{ is observed at baseline} \quad (2)$$

$$Y_{i,j} = \alpha_i + \Delta + \beta_i t_j + \varepsilon_{i,j} \text{ if } j \text{ is observed at post-treatment follow-up} \quad (3)$$

$$Y_{i,j} = \alpha_i + \gamma + (\Delta + \beta_i) t_j + \varepsilon_{i,j} \text{ if } j \text{ is observed during the treatment period} \quad (4)$$

where  $\varepsilon_{i,j}$  are assumed iid  $N(0, \sigma^2)$ ,  $\beta_i$  are assumed iid  $N(\beta, \sigma_\beta^2)$ ,  $\varepsilon_{i,j}$  and  $\beta_i$  are mutual independent, and  $\Delta$  is treatment effect,  $\gamma$  is the hemodynamic onset effect. Based on this model, with baseline time is set to 0, the variance of change from baseline at a post-baseline visit is

$$\text{Var}(Y_{i,j} - Y_{i,0}) = \text{Var}(\beta_i t_j + \varepsilon_{i,j} - \varepsilon_{i,0}) = t_j^2 \sigma_\beta^2 + 2 \sigma^2 \quad (5)$$

Dr. Lawrence's derivation is based on the assumption that an observation of eGFR is made at the end of a two-week interval for  $k$  times (thus totally  $2k$  weeks) at baseline and post-treatment follow-up visit respectively. Thus, Dr. Lawrence's variance of change from baseline to post-treatment follow-up is

$$(2/k) \sigma^2 + (1 + 1/12 + k/26)^2 \sigma_\beta^2 \quad (6)$$

If we change the assumption to this one that all these  $k$  observations are observed in the two-week intervals mentioned in the first paragraph in this section, the variance would become

$$(2/k) \sigma^2 + (1 + 1/12 + 3/52)^2 \sigma_\beta^2 \quad (7)$$

And this variance formula will be used in our sample size calculation, since it matches more closely to our protocol design.

Apply the model given by (1) – (4) to the data of CKD-3 non-Japanese subjects in 156-04-251 from pre-randomization baseline to Follow-up visit #2, the  $\sigma^2$  and  $\sigma_\beta^2$  are estimated as 22.13 and 5.27 respectively as the residual variance and slope variance, which may be interpreted as intra- and inter-subject variances.

With a two-sided alpha of 0.05 and 1:1 randomization to tolvaptan and placebo, using the parameters given above and sample size formula of two-sample t-test, we have the following table

Total Sample Size with k Observations and 15% Dropout Rate						
k	1	2	3	4	5	6
85% Power	1884	1068	796	660	580	526
90% Power	2196	1246	930	770	676	612

The assumption of dropout rate of 15% is reasonable since the dropout rate was 20% in 156-04-251, and it is expected that the tolvaptan run-in will reduce the dropout rate in the double blind treatment period. From this table, it seems k = 4 would produce an acceptable sample size and without an excessive burden for enrolled subjects. Thus, with an assumption of 15% dropout rate in the trial, the total sample size (randomized subjects) would be from 660 to 770, and will be set as a range of between 700 and 1000 randomized subjects, with a goal of 800 subjects depending also on the trial's ability to enroll and the accumulated number of subjects randomized up to the end of 2014. Because this information will be helpful in guiding the treatment of ADPKD patients with more advanced stages of CKD, and because marketing approval may be granted in some participating countries by 2015, it is critical to conclude enrollment near the end of 2014 or beginning of 2015. This will help avoid missing data due to subjects wishing to leave the trial to seek commercially available treatment in those countries.

The desire for a small number of blood draws during these periods was emphasized by the trial's Steering Committee who further suggested that measures be taken to minimize the intra-subject variability by standardizing, as much as possible, the timing and conditions by which serum creatinine was assessed (in particular recommending a similar diet, avoiding variation in cooked or uncooked protein intake and exercise pattern be used during these periods). The Steering Committee also suggested that the intra-subject variance during the pre-treatment and post-treatment periods be monitored throughout the trial with a

mandatory increase in serum creatinine sample number or subject numbers (ie, from a minimum of 4 to a minimum of 5) if observed variance was greater than that used in the power assumption (assessed using only baseline eGFR data in a power re-estimation procedure). They also favored the possibility that sample numbers, but not the minimum enrollment, be lowered (ie, to a maximum of 4) if variance was significantly less due to these measures. (See Section 4.2 “Blinded Sample Size Re-estimation”)

For the sample size of the key secondary endpoint, longitudinal analysis specified in the SAP of trial 156-04-251 is applied to the eGFR data of CKD-3 non-Japan subjects using post-randomization baseline, to obtain the estimates of the variance of inter-subject eGFR<sub>CKD-EPI</sub> slope (4.39 ml/min/1.73m<sup>2</sup> per year) and the variance of intra-subject eGFR observations (22.45 ml/min/1.73m<sup>2</sup>). The power calculation using the sample size formula provided by Lefante<sup>2</sup> assumes the following: 1) placebo subjects would have an eGFR decline of 4.5 ml/min/ 1.73 m<sup>2</sup> per year; 2) tolvaptan subjects would have an eGFR decline reduced 25% compared to placebo subjects; 3) treatment duration is one year with monthly observations in eGFR. In addition, the 1:1 randomization and the alpha (0.05, two-sided) specified above in the sample size of the primary endpoint are also assumed in the sample size calculation. It is then estimated that 315 subjects per group are required for 85% power and 367 subjects per group are required for 90% power. These sample sizes are very close to the sample size calculated using FDA statistician Dr. John Lawrence’s formula, for example, sample size of 368 per group with 90% power, when the variances provided above were used. Thus, with a total sample size of from 660 to 770, the key secondary endpoint will have at least 85% to more than 90% power in detecting a slope difference in this trial.

## **4.2 Blinded Sample Size Re-estimation**

Blinded sample size re-estimation will be conducted when about half of the planned randomized subjects (350-400) have been randomized. This is expected to be conducted before the end of 2014 and thus before the availability of any post 12-month off-treatment follow-up eGFR data used for the primary analysis. The goal of this blinded sample size re-estimation is to check: 1) the differences between the observed variances and the variances used in the sample size calculation; 2) whether the approach of averaging the 4 baseline pre-treatment eGFR observation has achieved the goal of reducing the variance to the level we planned. This sample size re-estimation is necessary, especially, as recommended by our vendor, a method to analyze for serum creatinine called Rate Blanked is to be used in this protocol, while the sample size calculation is based on the data from 156-04-251, in which another method called “Enzymatic” was used to analyze for serum creatinine. Based on these

findings, the serum creatinine sample number and subject sample size of this trial may need to be adjusted.

To derive the  $\sigma^2$  and  $\sigma_\beta^2$  used in the sample size re-calculation, all post-randomization on-treatment eGFR data available at the time of sample size re-estimation will be applied to the formula (1) provided in the previous section. The formula (1) is a mixed model with intercept and slope parameters which are both fixed and random effects, with an unknown variance structure for the random effects. The variance estimates of residual and the random effect slope from this mixed model will be the estimates of the  $\sigma^2$  and  $\sigma_\beta^2$  respectively. These estimates will be used to compare with the variances used in the previous section for sample size calculation. In addition, because the month 1 observations are treated as time 0 in the mixed model analysis, the variance of average eGFR with 4 observations at -2.5 months (approximately from month 1 to end of screening) will be calculated and compared with the observed variance of pre-treatment baseline eGFR. Detailed actions in the blinded sample size re-estimation will be documented.

## **5 Patient Samples and Handling of Missing Data**

### **5.1 Patient Samples**

The following samples (populations) are defined for this trial:

Randomized Population: All subjects who were randomized in this trial.

Randomized Safety Population: All subjects who were randomized in this trial and took at least one dose of IMP after randomization. This is the primary safety population.

Treated Safety Population: All subjects who took at least one dose of IMP during the tolvaptan titration/run-in periods. This is a secondary safety population.

Efficacy Populations:

Primary Endpoint Efficacy Population: All subjects who are in the Randomized Sample, took at least one dose of IMP after randomization, and have a baseline and at least one valid post-treatment evaluation in eGFR (ie, at least one week off treatment). The primary endpoint's baseline is defined as the average of up to 5 eGFR values observed during the screening and placebo run-in periods.

Key Secondary Endpoint Efficacy Population: All subjects who are in the Randomized Sample, took at least one dose of IMP after randomization, and have a baseline and at least one post-randomization evaluation in eGFR during the double blind treatment period. This is similar to the Primary Endpoint Efficacy Sample, except that post-treatment evaluation in eGFR is

replaced by post-randomization evaluation. The baseline of the key secondary endpoint is identical to the baseline of the primary endpoint.

## **5.2 Analysis Data Sets**

The core patient population for all efficacy analyses is based on the intent-to-treat (ITT) population which consists of all randomized subjects who take at least one dose of IMP. As will be described below, in order to handle missing and restrictions imposed by different types of analyses (eg, change from baseline analysis), datasets based on modified ITT population will be used in the efficacy analyses.

The Observed Cases (OC) dataset of this protocol is defined as the data observed at study specified visits. For the primary outcome variable of this protocol, the OC dataset is consistent of the pre-treatment baseline (average of eGFR observed in screening period and the first eGFR observed in placebo run-in period) and post-treatment follow-up (average of eGFR observed in a two-week interval which is one week post the last IMP dose). For the key secondary outcome variable of this protocol, the Observed Cases (OC) dataset within treatment period is defined as the data observed at study specified visits while subjects are taking IMP or within 24 hours of the last IMP dose.

## **5.3 Handling of Missing Data**

The GFR estimated by the CKD-EPI formula is utilized as the primary efficacy assessment in this trial.

In this protocol, all data collected for the pre-treatment baseline and post-treatment follow-up periods described in section 5.2 will be used and missing data will not be imputed in deriving the pre-treatment and post-treatment eGFR observations used for the primary analysis.

For sensitivity analyses of the primary analysis, in general, missing data will be handled by analysis using mixed model methodology under the assumption of “missing at random” (MAR). However, the possibility of “missing not at random” (MNAR) data can never be ruled out. Thus, every effort will be made to follow the subjects who discontinue investigational therapy after randomization without withdrawing consent for follow-up of their eGFR assessments. When collected within the last two weeks of the 3 weeks immediately post IMP withdrawal, the data will be included in the primary analysis. Otherwise, eGFR assessments collected during or after this period will be included in sensitivity analysis. Additional sensitivity analysis will be conducted for the key secondary endpoint for all subjects who withdraw consent or who are lost to follow up, using multiple imputation methodology under appropriate assumptions. See section 8.2.4 for more details.

## **6 Study Conduct**

### **6.1 Randomization**

Central randomization will be performed through IVRS to randomize subjects to treatment group in 1:1 ratio, stratified by baseline GFR level (eGFR CKD-EPI <=45 mL/min/1.73 m<sup>2</sup> or not), age (<=55 years or not) and Total Kidney Volume (<=2000 mL or not, or unknown).

### **6.2 Treatment Compliance**

Based on the Study Medication panel of the CRF, compliance in taking tolvaptan is calculated by dividing the total dosage taken by the total dosage the patients were scheduled to take during the study period.

## **7 Baseline Characteristics**

Demographic characteristics including age, race, ethnicity, gender, weight, height and BMI will be summarized by descriptive statistics, eg, proportion, mean, median, SD, minimum and maximum values.

## **8 Efficacy Analysis**

### **8.1 Primary Outcome Analysis**

This trial's estimand is the difference in outcome improvement if all subjects tolerated and adhered to their treatment. To enrich this population, only subjects that can tolerate the tolvaptan titration and run-in periods will be randomized. This approach combines estimands #2 and #3 recommended by the 2010 National Academy of Sciences' National Research Council report on prevention and treatment of missing data<sup>1</sup>. Thus, data missing at random (MAR) is assumed in the primary analysis. Sensitivity analysis will be provided to address the concern of data missing not at random (MNAR).

This estimand focuses on the efficacy of tolvaptan in slowing renal function decline. The objective of this trial is to confirm a causal effect of tolvaptan in slowing renal function decline, consistent with the selection of an efficacy rather than effectiveness estimand.

An effectiveness estimand compares treatment policies and reasonably could include data acquired long after withdrawal from the trial (eg, when subjects discontinue tolvaptan but are followed for many weeks or months) or move to an alternate treatment regimen (eg, placebo subjects being prescribed commercial tolvaptan upon approval for ADPKD). In the absence of an approved and effective alternate treatment for ADPKD; it is premature to discuss treatment policies. Thus, while eGFR data collected in the second and third week post withdrawal are

used for analysis of the primary endpoint, data collected long after withdrawal or after a subject moves to an alternate treatment regimen will be excluded in the primary analyses of both the primary and the key secondary endpoints.

### **8.1.1 Primary Endpoint Analysis**

The primary endpoint of this trial is change from pre-treatment baseline to post-treatment follow-up, annualized (divided) by subjects' trial duration. This normalization is necessary, otherwise the treatment group having more dropouts or more earlier dropouts may assume an unfair advantage. To reduce the variation in this primary endpoint, 4 or 5 observations of eGFR are observed at baseline during a 3-week interval (screening and placebo run-in periods) and another 4 or 5 observations are observed after one week of post-treatment follow-up during a two week interval (within a total of 3-weeks post-treatment follow-up). The average of the 4-5 eGFR values observed during the baseline period is set as the baseline and the average of the 4-5 eGFR values observed during post-treatment follow-up period is set as the renal function measurement post-treatment. The timing of baseline and post-treatment observations are also set to the median of the time of these observations in the two to three-week interval respectively, and the duration is equal to the date of baseline observation minus the date of post-treatment observation plus one.

Use of the duration to annualize the change is also reasonable since it will provide an “estimate” of annualized eGFR change slope for each subject, though there is no estimate for intra-subject variation associated with it. Thus, ANCOVA with effects of treatment and randomization stratification factors and covariate baseline will be applied to the analysis of these “estimated slopes” as the primary analysis.

### **8.1.2 Sensitivity Analysis of the Primary Endpoint**

Aligned with the desire to evaluate effects free from acute hemodynamic treatment effects, a sensitivity analysis of the primary endpoint will be performed including all available placebo data. In this sensitivity analysis, in addition to the 4-5 pre-treatment baseline observations and the 4-5 post-treatment follow-up observations, all post-randomization on-treatment eGFR observations in the protocol specified visits for placebo subjects will also be included. The linear mixed effect model with effects of treatment, time (as a continuous variable), treatment time interaction, randomization stratification factors, and baseline as covariate will be used to fit the eGFR data, in which the intercept and time are both a fixed effect and a random effect. An un-structured variance covariance matrix is assumed for the random intercept and time. The time variable used in the model may start from the first observation of eGFR baseline as mentioned in section 8.1.1, and this baseline will be used in the model. Missing data will be ignored in this analysis under MAR assumption. Data acquired while taking assigned tolvaptan

cannot be used in this analysis without appropriate adjustment, but is evaluated in the key secondary efficacy endpoint of eGFR slope with a methodology which takes the acute hemodynamic drug effects of tolvaptan into account.

### **8.1.3 Sensitivity Analysis Including Data from Subjects Who Discontinue IMP**

The sensitivity analysis deviates from the MAR assumption to include the post-discontinuation follow-up data in the analysis specified in the previous section. Subjects who discontinue treatment after randomization without withdrawing consent will also be followed for additional off-treatment eGFR values up to Month 12. These post “post-treatment follow-up” eGFR data will be included to the data specified in the previous section in a sensitivity analysis using the same analytic approach specified in the previous section.

## **8.2 Secondary Outcome Analysis**

### **8.2.1 Key Secondary Endpoint Analysis**

The key secondary endpoint of the trial is the annualized rate of eGFR change, which is derived from each individual subject’s eGFR slope using the CKD-EPI formula. Slope is preferred as a practical and clinically meaningful endpoint. In this analysis, all eGFR observations from placebo run-in, tolvaptan run-in (not including tolvaptan titration), double blind treatment, and post-treatment follow-up (not including data collected in the first week after the last IMP dose) periods will be included in the analysis, with the data of tolvaptan run-in and tolvaptan subjects in the double blind treatment period are flagged (yes = 1 and no = 0) with a tolvaptan acute hemodynamic effect. The linear mixed effect model with effects of time (as a continuous variable), treatment, time-treatment interaction, acute hemodynamic effect, pre-treatment baseline (of the primary endpoint), and randomization stratification factors will be used to fit the GFR estimates, in which the intercept and time are both a fixed effect and a random effect. An un-structured variance covariance matrix is assumed for the random intercept and time. The time variable used in the model may start from the first observation of eGFR obtained from placebo run-in period.

### **8.2.2 Sensitivity Analysis of the Key Secondary Endpoint**

This sensitivity analysis of the key secondary endpoint of this trial is to compare the linear trend of eGFR between tolvaptan and placebo groups. The advantage of this sensitivity analysis is that it does not depend on the assumption of linearity and equal tolvaptan hemodynamic onset and offset effects used in section 8.2.1. The change from the pre-treatment baseline during the on-treatment visits in the double blind treatment period will be included in the analysis. Since the

hemodynamic effects of tolvaptan are believed to begin to reverse within 1-2 days, therefore on-treatment will be defined as within 24 hours of the last IMP dose.

Analysis of Mixed Model Repeated Measurement (MMRM) will be applied to the data of change from baseline in eGFR in Month 1, Month 2, ..., up to Month 12. The model will have fixed effect of treatment, visit, treatment visit interaction, randomization stratification factors, and covariate baseline and baseline visit interaction. An unstructured variance-covariance matrix is assumed for the repeated measurements. A linear contrast of the treatment differences in these 12 months will be used as the sensitivity analysis of the key secondary endpoint.

### **8.2.3 Sensitivity Analysis Including Data from Subjects Who Discontinue IMP**

This sensitivity analysis deviates from the MAR assumption to include the post-discontinuation follow-up data in the analysis of the key secondary endpoint. Subjects who discontinue treatment after randomization without withdrawing consent will be followed for additional eGFR (not including the eGFR observed in the 3 week period immediately post the last dose of IMP) up to Month 12. The data collected during this follow-up period will not be included in the key secondary endpoint analysis for the reasons given above. However, a sensitivity analysis including these follow-up data for the key secondary analysis will be performed. This analysis uses the same approach provided in the section 8.2.1 for the analysis of the key secondary endpoint.

### **8.2.4 Sensitivity Analysis Including Imputation of Missing Data**

Multiple imputation is commonly used in the analysis of MNAR data. For all randomized subjects who withdraw consent for further testing or who are lost to follow up, imputation of missing data will be applied to projected visits up to their planned end of the trial (12 months post randomization). The subjects' reasons for discontinuation will be captured and categorized to help determine the missing data pattern. Imputation will be based on the MMRM model specified in section 8.2.2. For placebo subjects, and in the absence of evidence suggesting biased missing data pattern, the imputation will follow the placebo trend.

Post-withdrawal data from the 156-04-251 trial and 156-08-271 interim analysis show that tolvaptan's eGFR benefits accumulate and are sustained after treatment discontinuation; therefore, imputation for subjects randomized to tolvaptan should reasonably begin at the value of their last eGFR. If a subject has the post-treatment follow-up in the two-week interval, imputation will be based on this post-treatment observation; if a subject does not have the post-treatment follow-up observation, imputation will be based on the last on-treatment observation and flagged with the tolvaptan acute hemodynamic effect mentioned in section 8.2.1. The

imputation of these tolvaptan withdrew consent/lost to follow-up subjects is based on the following:

These imputed data will be added to the data described in sections 8.2.1 and 8.2.3 for two sets of sensitivity analyses. In each set of sensitivity analysis, reason of discontinuation will be classified in the following order as

1. Progression of renal disease
2. Lack of efficacy
3. Other Adverse Event
4. Aquaretic AE
5. Trial too burdensome

This lists reasons for missing data due to discontinuation of trial participation in a decreasing order of their likelihood to produce data MNAR. Specifically, MNAR in the following patterns of dropout reasons will be investigated:

1. Progression of renal disease and Lack of efficacy (LOE) in tolvaptan treatment group as MNAR
2. Progression of renal disease, LOE, and other adverse events (AE) in tolvaptan treatment group as MNAR

Trial 156-04-251 and 156-08-271 data also support true disease modification and preservation of functioning kidney parenchyma through reduction of cyst growth. Therefore discontinuation of tolvaptan would not result in an immediate return to the placebo trend. Therefore eGFR decline in subjects discontinuing tolvaptan will reasonably fall somewhere between the tolvaptan trend and placebo trend. This supports a series of analyses for imputation of missing data for tolvaptan subjects, which will begin using the tolvaptan trend, and move stepwise toward the placebo trend. Therefore, the following delta adjustment imputation method will be applied:

### **Delta Adjustment Imputation Method**

This MNAR sensitivity analysis is to investigate the departure from MAR assumption by progressively decreasing the treatment differences over the missing visits in those treated subjects who fell into an assumed MNAR pattern. This progressive decrease of treatment slope difference is carried out by subtracting k times the expected treatment difference (in the absent of the hemodynamic effect) from the imputed missing data after dropout using tolvaptan slope in those treated subjects who fell into an assumed MNAR pattern, with k starts from 0%, 10%, 20%, .., and up to 100% or higher, until conclusion from the analysis of the key secondary endpoint is overturned (it is called tipping point analysis), or it becomes clinically meaningless to

go even higher. The expected treatment difference between tolvaptan and placebo at a visit may be derived from the treatment difference in slope, multiplied by the visit month number and divided by 12. Note that when 0% is used, the MI procedure would produce an analysis which is essentially MAR. When 100% is used, the MI procedure would produce an analysis which is essentially something called “copy placebo”. Specifically the MI procedure follows these steps:

- Using Monte Carlo Markov Chain (MCMC) methodology from PROC MI by treatment group to impute the intermittent missing data to a monotone missing pattern;
- Using a standard MAR-based multiple imputation approach from PROC MI to impute data from monotone missing data;
- For subjects in the treated groups who fall into a MNAR pattern specified above, a delta which equal to k times their treatment differences mentioned above will be subtracted for their imputed values after the dropout time, with k described in the above paragraph;
- Using the random coefficient regression model specified in the previous section to analyzed the completed data along with the imputed data;
- Obtaining the overall results using PROC MIANALYZE.

### **8.3 Technical Computational Details for Primary and Secondary Analysis**

(1) Two samples/aliquots of blood will be collected for serum creatinine assessments. While one blood sample will be analyzed by the central laboratory as soon as it is received and accessioned, the other one will be frozen and later batched analysis when a subject completes all his/her serum creatinine blood draws needed in the protocol. This batched assessment of serum creatinine is considered to have less intra-subject variation, and will be used for the eGFR derivations for the efficacy analysis. In case a protocol specified visit is missing for a subject in the batched assessments but available in the non-batched assessments, the missing data in the batched assessments will be filled in using the available non-batched assessments.

(2) The CKD-EPI formula is as follows:

$$\text{eGFR} = J \times A \times (\text{Scr}/B)^C \times (0.993)^{\text{Age}} \text{ where:}$$

J = 0.813 if Japanese or 1.0 if non-Japanese ethnicity

A = 166 if black female, 163 if black male, 144 if non-black female, 141 if non-black male;

B = 0.7 if female or 0.9 if male;

and

if female; C = -0.329 and serum creatinine is  $\leq 62 \text{ umol/L}$  ( $\leq 0.7 \text{ mg/dL}$ ); or -1.209 if serum creatinine  $> 62 \text{ umol/L}$  ( $> 0.7 \text{ mg/dL}$ )

Or

if male; C = -0.411 and serum creatinine is <= 80 umol/L (<=0.9 mg/dL); or -1.209 if serum creatinine > 80 umol/L (>0.9 mg/dL)

Age is expressed in years.<sup>3,4</sup>

(3) The following SAS codes will be used for the primary analyses:

```
PROC GLM;
  CLASS TREATMENT AGE_STATUS GFR_STATUS TKV_STATUS;
  MODEL ANNUALIZED_CHANGE = TREATMENT BASELINE AGE_STATUS
    GFR_STATUS TKV_STATUS;
RUN;
```

(4) The SAS code of the sensitivity analysis of the primary endpoint specified in section 8.1.2 is

```
PROC MIXED EMPRICAL;
  CLASS SUBJECT TREATMENT AGE_STATUS GFR_STATUS TKV_STATUS;
  MODEL GFR = TREATMENT TIME TREATMENT*TIME BASELINE
    AGE_STATUS GFR_STATUS TKV_STATUS;
  RANDOM INTERCEPT ITME/TYPE=UN SUB=SUBJECT G;
RUN;
```

If the model has any convergence problem, the variables of AGE\_STATUS, GFR\_STATUS, and TKV\_STATUS may be dropped out of the model.

(5) The SAS code of the analysis of the key secondary endpoint specified in section 8.2.1 is

```
PROC MIXED EMPRICAL;
  CLASS SUBJECT TREATMENT AGE_STATUS GFR_STATUS TKV_STATUS;
  MODEL GFR = TREATMENT TIME TREATMENT*TIME BASELINE
    ACUTE_HEMODYNAMIC_EFFECT AGE_STATUS GFR_STATUS
    TKV_STATUS;
  RANDOM INTERCEPT ITME/TYPE=UN SUB=SUBJECT G;
RUN;
```

If the model has any convergence problem, the variables of AGE\_STATUS, GFR\_STATUS, and TKV\_STATUS may be dropped out of the model.

(6) The on-treatment visits included in the sensitivity analysis of the key secondary endpoint mentioned in section 8.2.2 are Months 1, 2, 3, ..., 11, 12. The mean value of these visits in months is 6.5. For a new numerical axis with its original falling at 6.5 months, the 12 original time points will become -11/2, -9/2, -7/2, -5/2, -3/2, -1/2, 1/2, 3/2, 5/2, 7/2, 9/2, and 11/2 on this numerical axis. Thus the coefficients of the linear trend contrast of these 12 months are -11, -9, -7, -5, -3, -1, 1, 3, 5, 7, 9, and 11. With treatment be coded, for example, as 0 for placebo and 1 for tolvaptan, the SAS code for the analysis of the key secondary endpoint is

```
PROC MIXED;
  CLASS SUBJECT VISIT TREATMENT AGE_STATUS GFR_STATUS TKV_STATUS;
  MODEL CHANGE = TREATMENT VISIT TREATMENT*VISIT BASELINE
    BASELINE*VISIT AGE_FACTOR GFR_FACTOR TKV_FACTOR;
```

```
REPEATED VISIT/TYPE=UN SUB=SUBJECT;
LSMEANS TREATMENT*VISIT.PDIFF CL ALPHA=0.05;
ESTIMATE 'TREND DIFF' TREATMENT 0 0
          VISIT 0 0 0 0 0 0 0 0 0 0 0
          TREATMENT*VISIT 11 9 7 5 3 1 -1 -3 -5 -7 -9 -11
                           -11 -9 -7 -5 -3 -1 1 3 5 7 9 11
;
RUN;
```

If the estimate statement is not estimable, the fixed effects of AGE\_STATUS, GFR\_STATUS, and TKV\_STATUS may be dropped out of the model.

In case there is a convergence problem in the MMRM model with the unstructured variance covariance matrix, the following variance covariance matrix structures will be used in the order of 1) heterogeneous toeplitz, 2) heterogeneous autoregressive of order 1, 3) heterogeneous compound symmetry, 4) autoregressive of order 1, and 5) compound symmetry. The first (co)variance structure which does not have convergence problem will be the one used for the analysis. If a structured covariance has to be used, the “sandwich” estimator of the variance covariance matrix of the fixed effects parameters will be used in order to deal with possible model misspecification of the covariance matrix.

#### 8.4 Exploratory Analysis

Assessment of ADPKD Outcomes is specified as exploratory endpoints in this protocol. Exploratory analysis will be applied to a few frequent and clinical meaningful outcomes as well as a composite of those outcomes which are more closed related to kidney enlargement as potential events.

Events in this analysis will be defined if at least one of the PKD outcomes is checked in this CRF at a visit. The composite of these ADPKD outcomes will include kidney pain, hematuria, nephrolithiasis, urinary tract infection, anemia, and significant drop in kidney function. The frequent and clinical meaningful PKD Outcomes are Kidney Pain, Urinary Tract Infection, and Hematuria. Summary data are also provided to ADPKD outcomes and medical resource utilization collected in the PKD Outcome CRF page.

Analysis of time to multiple events, which is the analysis of the intensity model (Andersen-Gill model) using the sandwich covariance matrix estimate to derive standard errors for the Wald test<sup>5</sup>, will be applied. The analysis dataset of this analysis will be set up in this way: the data will have a counting process style of input; the timing of an event will be set to the visit when the CRF is recorded; and a subject has only one event at a visit in the analysis even if the subject has more than one PKD outcomes at the visit. This analysis will cover the double blind treatment period from randomization to Month 12. The SAS codes of the analysis will be

```
proc phreg covs(aggregate);
```

```
model (start_time, stop_time)*status(0)= treatment/rl ties=breslow;  
id subject_id;  
run;
```

## **9 Safety Analysis**

In general, baseline measurements of safety variables are defined as their last measurements prior to the randomization for the primary safety population (except for serum creatinine, which is defined similar to the baseline of eGFR assessment for the primary endpoint) and as their last measurements prior to the first dosing of study medication for the secondary safety population. Safety analysis will be conducted based on these safety populations, which are defined in section 7.1. Standard safety variables to be analyzed include AEs, clinical laboratory tests, and vital signs. In general, summarized statistics of changes from baseline will be provided for safety variables based on all available data.

### **9.1 Adverse Events**

All AEs will be coded by system organ class and Medical Dictionary for Regulatory Activities (MedDRA) preferred term. The incidence of the following events will be summarized by treatment group for the primary safety population; summary of these events will also be provided for the secondary safety population:

- a) TEAEs by severity
- b) Potentially drug-related TEAEs
- c) TEAEs with an outcome of death
- d) Serious TEAEs
- e) Discontinuations due to TEAEs

### **9.2 Clinical Laboratory Data**

Summary statistics for changes from baseline in the central clinical laboratory measurements will be provided for the primary and secondary safety populations. Potentially clinically significant results in laboratory tests identified using prospectively defined criteria will also be summarized for the primary and secondary safety populations as well. Criteria of potentially clinically significant lab test abnormalities are provided in Appendix 1.

In addition, laboratory measurements that signal the potential for Hy's Law will be reported. An incidence table and a listing will be provided for subjects who meet one or combinations of following criteria, without initial findings of cholestasis (serum alkaline phosphatase (ALP) activity >2xULN):

ALT or AST  $\geq$  3x ULN

Bilirubin  $\geq$  2x ULN

### 9.3 Physical Examination, and Vital Signs Data

By-patient listings will be provided for physical examination. Summary statistics for changes from baseline in vital signs and potentially clinically significant results in vital signs will be summarized for the primary safety population as well as the secondary safety population.

Incidence of potentially clinically significant vital sign results will also be summarized by treatment groups. Criteria of potentially clinically significant vital sign abnormalities are provided in Appendix 2.

## 10 Reference

<sup>1</sup>National Research Council. The Prevention and Treatment of Missing Data in Clinical Trials. Panel on Handling Missing Data in Clinical Trials. Committee on National Statistics, Division of Behavioral and Social Sciences and Education. Washington, DC: The Academies Press.

<sup>2</sup>Lefante JJ: The power to detect differences in average rates of change in longitudinal studies. Statistics in Medicine, 9, 437-446, 1990

<sup>3</sup>Stevens LA, Schmid CH, Greene T, Zhang Y, Beck GJ, Froissart M, Hamm LL, Lewis JB, Mauer M, Navis GJ, Steffes MW, Eggers PW, Coresh J and Levey AS. Comparative Performance of the CKD Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) Study Equations for Estimating GFR Levels Above 60 mL/min/1.73m<sup>2</sup>. Am J Kidney Dis. 2010; 56:486-495.

<sup>4</sup>Horio M, Imai E, Yasuda Y, Watanabe T and Matsuo S. Modification of the CKD Epidemiology Collaboration (CKD-EPI) Equation for Japanese: Accuracy and use for Population Estimates. Am. J. Kidney Dis. 56:32-38.

<sup>5</sup>Therneau, TM and Grambsch, PM: Modeling Survival Data: Extending the Cox Model. Springer-Verlag, New York, 2000

## 11 Appendices

### Appendix 1: Criteria of Potentially Clinically Significant Laboratory Test Abnormalities (Modified NCI Criteria)

#### Laboratory Test Abnormalities due to Test Value Increase

Test	Abnormality	Test Result Grade				
		0	1	2	3	4
APTT (sec)	Increase	ULN	>ULN - 1.5xULN	>1.5xULN - 2xULN	>2xULN	

ALT (SGPT) (IU/L)	Increase	ULN	>ULN - 3xULN	>3xULN - 5xULN	>5xULN - 20xULN	>20xULN
AST (SGOT) (IU/L)	Increase	ULN	>ULN - 3xULN	>3xULN - 5xULN	>5xULN - 20xULN	>20xULN
Bilirubin, Total (mg/dL)	Increase	ULN	>ULN - 2xULN	>2xULN - 3xULN	>3xULN - 10xULN	>10xULN
Creatinine (mg/dL)	Increase Pre-randomization	AB*	>AB - 1.5xAB	>1.5 x AB - 3 x AB	> 3 x AB - 6 x AB	> 6 x AB
Creatinine (mg/dL)	Increase Post-randomization	< 1.33 x PR*	1.33 x PR - < 2x PR	2 x PR - < 3 x PR	3 x PR - 6 x PR	>6xPR
Eosinophils, Absolute (Thous/ $\mu$ L)	Increase	$\leq$ 0.65	>0.65-1.5	>1.5-5	>5	
Glucose (mg/dL)	Increase	$\leq$ 115	>115-160	>160-250	>250-500	>500
Hemoglobin (g/dL)	Increase	ULN	>ULN-20	>20-21	>21-22.5	>22.5
Potassium (mEq/L)	Increase	ULN	>ULN-5.5	>5.5-6	>6-7	>7
INR	Increase	ULN	>ULN - 1.5xULN	>1.5xULN - 2xULN	>2xULN	
Sodium (mg/dL)	Increase	<145	146 - 150	151 - 155	156 - 160	>160
Triglycerides (mg/dL)	Increase	ULN	>ULN - 2.5xULN	>2.5xULN - 5xULN	>5xULN - 6xULN	>6xULN
Urea Nitrogen (mg/dL)	Increase	$\leq$ 22	>22-26	>26-31	>31	
White Blood Count (Thous/ $\mu$ L)	Increase	$\leq$ 10.79 9	>10.799-15	>15-20	>20-25	>25

(\* Baseline creatinine is expected to be elevated in this population. Average baseline (AB) is equal to the mean baseline value collected during screening period.

During treatment with tolvaptan, serum creatinine is expected to increase by approximately 5-10%. When these tables are generated during the double-blind conduct, the post-randomization comparisons will be made to the post-randomization (PR) value which equals the value collected post-randomization at Month 1 visit. After data-base lock, final reporting of unblinded tables and listings, APR should be changed to the highest value obtained during the run-in period matching the subject's assigned treatment, ie, either placebo or tolvaptan run-in periods.)

### Laboratory Test Abnormalities due to Test Value Decrease

Test	Abnor-mality	Test Result Grade				
		-4	-3	-2	-1	0
Glucose (mg/dL)	Decrease	<30	30-<40	40-<55	55-<65	$\geq$ 65
Hemoglobin (g/dL)	Decrease	<6.5	6.5-<8	8-<10	10-<LLN	LLN
Lymphocytes, Absolute (Thous/ $\mu$ L)	Decrease	<0.2	0.2-<0.5	0.5-<0.8	0.8-<LLN	LLN
Neutrophils, Absolute	Decrease	<0.5	0.5-<1	1-<1.5	1.5-<LLN	LLN

Test	Abnor-mality	Test Result Grade				
		-4	-3	-2	-1	0
(Thous/ $\mu$ L)						
Platelet Count (Thous/ $\mu$ L)	Decrease	<25	25-<50	50-<75	75-<LLN	LLN
Potassium (mEq/L)	Decrease	<2.5	2.5-<3		3-<LLN	LLN
Sodium (mg/dL)	Decrease	<120	120-124	125-129	130-135	$\geq$ 136
White Blood Count (Thous/ $\mu$ L)	Decrease	<1	1-<1.5	1.5-<2.5	2.5-<3.501	$\geq$ 3.501

## Appendix 2: Criteria of Potentially Clinically Significant Vital Sign Abnormalities

Test Type	Test Parameters	Unit	Sex	Criteria (meet either one will count)	
				Limit	Change from baseline
VITAL SIGNS	SBP, SITTING	mmHg	Male/Female	>=180	>=20
VITAL SIGNS	SBP, SITTING	mmHg	Male/Female	<=90	<=-20
VITAL SIGNS	DBP, SITTING	mmHg	Male/Female	>=105	>=15
VITAL SIGNS	DBP, SITTING	mmHg	Male/Female	<=50	<=-15
VITAL SIGNS	HEART RATE	bpm	Male/Female	>=120	>=15
VITAL SIGNS	HEART RATE	bpm	Male/Female	<=50	<=-15
VITAL SIGNS	TEMPERATURE	degree C	Male/Female	>=38.3	>=1.1
VITAL SIGNS	WEIGHT	kg	Male/Female		>= 7 percent

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Tolvaptan (OPC-41061)

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A Phase 3b, Multi-center, Randomized-withdrawal, Placebo-controlled, Double-blind, Parallel-group Trial to Compare the Efficacy and Safety of Tolvaptan (45 to 120 mg/day, Split-dose) in Subjects with Chronic Kidney Disease Between Late Stage 2 to Early Stage 4 Due to Autosomal Dominant Polycystic Kidney Disease

## **Statistical Analysis Plan**

**Version: 6**

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CONFIDENTIAL – PROPRIETARY INFORMATION

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## List of Abbreviations and Definition of Terms

<b><u>Abbreviation</u></b>	<b><u>Definition</u></b>
ADPKD	Autosomal dominant polycystic kidney disease
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	Aspartate aminotransferase
bpm	beats per minute
CKD	Chronic kidney disease
CRF	Case report form
eGFR	Estimated glomerular filtration rate
EudraCT	European Clinical Trial Data Base
IMP	Investigational medicinal product
ITT	intent-to-treat
LLN	lower limit of normal
LOE	Lack of efficacy
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measurements
MNAR	Missing not at random
SAP	Statistical Analysis Plan
SD	standard deviation
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States

## **1 Introduction**

This Statistical Analysis Plan (SAP) describes the statistical methodology and data analysis algorithms and conventions to be applied for statistical analysis and reporting of efficacy and safety data of trial 156-13-210.

## **2 Study Objectives**

### **2.1 Primary Objectives**

The primary objectives of this trial are:

To compare the efficacy of tolvaptan treatment in reducing the change in estimated glomerular filtration rate (eGFR) from pre-treatment baseline to post-treatment follow-up, as compared with placebo, in subjects with late-stage chronic kidney disease (CKD) due to Autosomal Dominant Polycystic Kidney Disease (ADPKD) who tolerate tolvaptan during an initial run-in period.

### **2.2 Secondary Objectives**

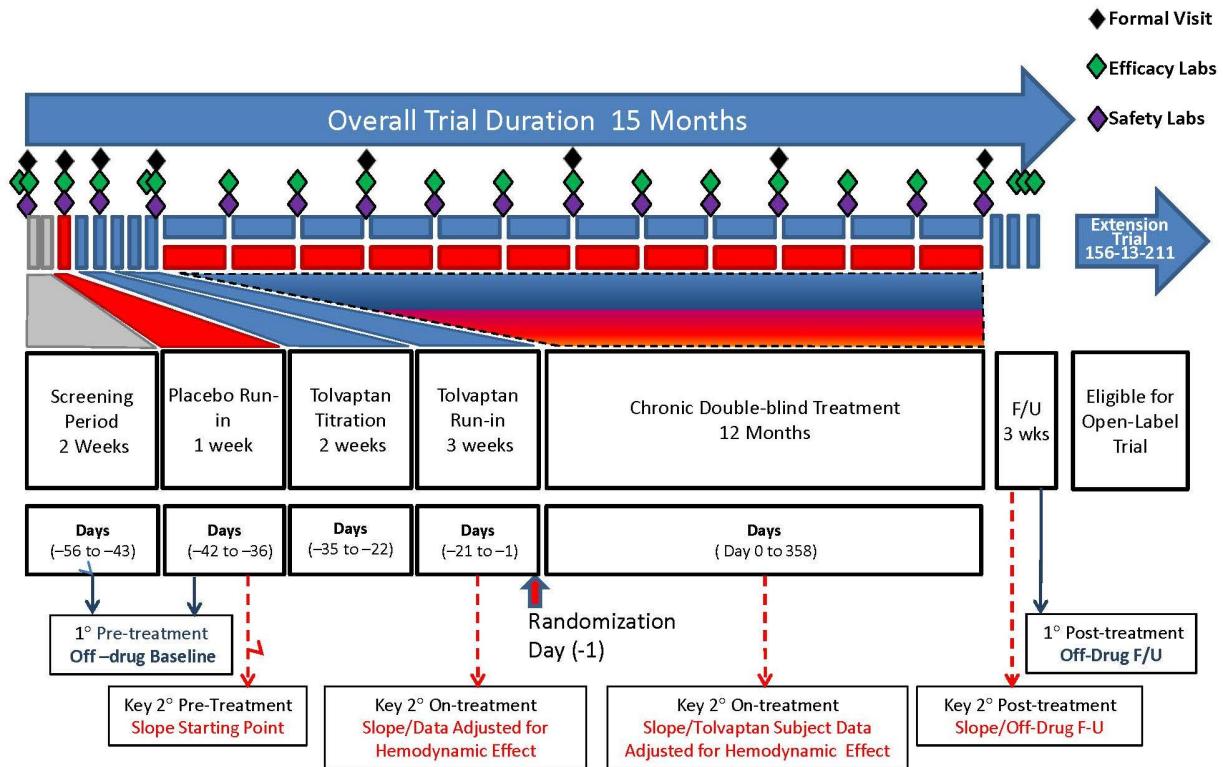
The secondary objectives of this trial are:

- To compare the efficacy of tolvaptan treatment in reducing the decline of annualized eGFR slope, as compared with placebo, in subjects with late-stage CKD due to ADPKD who tolerate tolvaptan during an initial run-in period.
- To compare overall and hepatic safety of tolvaptan with that of placebo and to compare incidence of ADPKD complications (outcomes) during the trial.

## **3 Study Design**

This is a phase 3, multi-center, randomized-withdrawal, placebo-controlled, double-blind, parallel-group trial to compare the efficacy and safety of tolvaptan with placebo in subjects with ADPKD and baseline kidney function as documented by an eGFR between 25 to 65 mL/min/1.73m<sup>2</sup>, inclusive. The overall design is illustrated in the following figure.

## Trial 156-13-210

**156-13-210 Schematic**

## 4 Sample Size and Power Justification

### 4.1 Sample Size Estimation

In this sample size estimation, it is assumed that 3 observations of eGFR are observed at baseline during a 3-week interval during screening (2 weeks) and placebo run-in (1 week) and again 3 observations are observed after one week post-treatment follow-up during a two week interval (over a total of 3 weeks). The mean of the 3 eGFR observed during the screening and placebo-run periods is set as the baseline and the mean of the 3 eGFR observed during post-treatment follow-up period is set as the renal function measurement post-treatment. The timing of baseline and post-treatment observations are set to the median of the observation times in the two-week interval respectively. Thus, the pre-treatment baseline will be set at approximately 6 weeks prior to randomization, and the post-treatment renal function measurement will be set at approximately 2 weeks after the end of treatment.

Based on a Mixed Model Repeated Measurements (MMRM) analysis of the non-Japan CKD-3 Subjects from trial 156-04-251, the treatment difference in renal function at Month 12 based on the post-randomization baseline is 1.43 mL/min/1.73 m<sup>2</sup>. However, the US FDA has expressed a concern that the onset and offset of tolvaptan's hemodynamic effect may not be equal (Otsuka believes it is not possible to determine if the small differences observed are due to a random error). Thus, with an assumption the absolute value of the off-set eGFR increase is 25% less than the absolute onset of the decrease in eGFR, we may assume the treatment difference in renal function is 1.07 mL/min/1.73 m<sup>2</sup> in our sample size calculation. Annual reduction of GFR decline in the amount of 1.07 mL/min/1.73 m<sup>2</sup> is clinically meaningful in the ADPKD patient population studied in this protocol (eGFR between 25 to 65 mL/min/1.73 m<sup>2</sup>), and is approximately 25% reduction for a subject with 4.5 mL/min/1.73 m<sup>2</sup> annual decline in GFR.

To investigate the reduction in intra-subject variation achieved by taking the mean of an increased number of observations at baseline and post-treatment follow-up in the sample size, we have to estimate the intra-subject error and inter-subject error.

One of the approaches in sample size calculation for this protocol is to use MMRM to estimate the intra- and inter-subject variances. In the ADPKD phase 3 trial 156-04-251, there were a pre-treatment baseline visit and two post-treatment follow-up visits, along with some other on-treatment visits. Assume these data follow the following model (denoted as  $j = 0$  for baseline and  $j = 37$  for follow-up, as well as  $j = 4, 8, 12, \dots, 36$ ):

$$Y_{i,0} = \alpha_i + \varepsilon_{i,0} \quad (1)$$

$$Y_{i,j} = \alpha_i + \delta_{i,j} + \varepsilon_{i,j} \quad (2)$$

where  $\delta_{i,j}$ , as a random effect of change from pre-treatment baseline for subject  $i$  at visit  $j$ . These  $\delta_{i,j}$ s are jointly follow a multivariate normal distribution with means being  $\delta_{P,j}$  for placebo subjects and  $\delta_{T,j}$  for tolvaptan subjects. Their individual variance is assumed being  $\sigma_{\delta,j}^2$ . These  $\delta_{i,j}$ s are supposed to be correlated; however, their correlations are not interested for the purpose of sample size calculation in this protocol. In addition,  $\alpha_i$ s are assumed iid normal distributed,  $\varepsilon_{i,j}$  are assumed iid  $N(0, \sigma^2)$ , and these random variables are mutually independent. Then, the change from baseline data follows this commonly used MMRM model:

$$Y_{i,j} - Y_{i,0} = \delta_{i,j} - \varepsilon_{i,0} + \varepsilon_{i,j} = \zeta_{i,j} + \varepsilon_{i,j} \quad (3)$$

where  $\zeta_{i,j} = \delta_{i,j} - \varepsilon_{i,0}$ . Note that the variance of  $\zeta_{i,j}$  (denoted by  $\sigma_{\zeta,j}^2$ ) is equal to  $\sigma_{\delta,j}^2 + \sigma^2$ . This model becomes one-way random effect model if we only consider the post-treatment follow-up visits for a treatment group. Thus, applying one-way random effect model to

the change from pre-treatment baseline to post-treatment follow-up data of placebo and tolvaptan respectively, in subjects who had both follow-up visits and baseline in 156-04-251,  $\sigma^2$  is estimated as 8.52 for placebo and 5.68 for tolvaptan. Take the average of these two estimates of  $\sigma^2$  to obtain an estimate of  $\sigma^2$  as 7.1 to be used in this sample size calculation, which is the  $\sigma^2$  for Month 12 visit of 156-04-251. Note that

$$Var(Y_{i,j} - Y_{i,0}) = \sigma_{\delta,j}^2 + 2\sigma^2 \quad (4)$$

At Month 12, the standard deviation (SD) could be assumed as 6.5, based on CKD Stage 3 non-Japan subjects in 156-04-251. Then based on (4),  $\sigma_{\delta,j}^2$  at Month 12 is estimated as 28.05 ( $= 6.5^2 - 2 \times 7.1$ ).

With k repeated measurements at pre-treatment baseline and at 12 month post-treatment follow-up in this trial, the baseline intra-subject variance and the follow-up intra-subject variance are reduced from  $\sigma^2$  to  $\sigma^2/k$  respectively. Thus, the variance of average change from average baseline at Month 12 is  $(\sigma_{\delta,12}^2 + \sigma^2/k) + \sigma^2/k$ , which is estimated as 31.6 ( $= 28.05 + 7.1/4 + 7.1/4$ ) when k = 4 and 32.8 ( $= 28.05 + 7.1/3 + 7.1/3$ ) when k = 3. Here we have the following table of sample size:

Total Sample Size with $\Delta = 1.07$ and 10% Dropout Rate (Alpha = 0.05)				
# of Blood Draws	1	2	3	4
90% Power	1722	1434	1336	1288
85% Power	1477	1230	1146	1106
80% Power	1286	1070	998	962

From the sample size table, the increase of repeated measurement at baseline and follow-up reduces the sample size significantly initially but quickly loses its effect when k is greater than 3. It seems that 3 repeated measurements may be appropriate in order to avoid patients' burden. Thus, with an assumption of 10% dropout rate in the trial, the total sample size (randomized subjects) would be approximately 1300.

The desire for a small number of blood draws during these periods was emphasized by the trial's Steering Committee who further suggested that measures be taken to minimize the intra-subject variability by standardizing, as much as possible, the timing and conditions by which serum creatinine was assessed (in particular recommending a similar diet, avoiding variation in cooked or uncooked protein intake and exercise pattern be used during these periods). The Steering Committee also suggested that the intra-subject variance during the pre-treatment and post-treatment periods be monitored throughout the trial with a mandatory increase in serum creatinine sample number (ie, from a minimum of 3 to a minimum of 4) or subject numbers if observed variance was greater than that used in the power assumption (assessed using only baseline eGFR data in a power re-estimation procedure). They also favored the possibility that sample numbers, but not the

minimum enrollment, be lowered (ie, to a maximum of 3) if variance was significantly less due to these measures. (See [Section 4.2](#) “Blinded Sample Size Re-estimation”).

For the sample size of the key secondary endpoint, longitudinal analysis specified in the SAP of trial 156-04-251 is applied to the eGFR data of CKD-3 non-Japan subjects using post-randomization baseline, to obtain the estimates of the variance of inter-subject eGFR<sub>CKD-EPI</sub> slope (4.39 ml/min/1.73m<sup>2</sup> per year) and the variance of intra-subject eGFR observations (22.45 ml/min/1.73m<sup>2</sup>). The power calculation using the sample size formula provided by Lefante<sup>1</sup> assumes the following: 1) placebo subjects would have an eGFR decline of 4.5 ml/min/ 1.73 m<sup>2</sup> per year; 2) tolvaptan subjects would have an eGFR decline reduced 25% compared to placebo subjects; 3) treatment duration is one year with monthly observations in eGFR. In addition, the 1:1 randomization and the alpha (0.05, two-sided) specified above in the sample size of the primary endpoint are also assumed in the sample size calculation. It is then estimated that 734 subjects are required for 90% power. Thus, with a total sample size of around 1300, the key secondary endpoint will have more than 90% power in detecting a slope difference in this trial.

## 4.2 Blinded Sample Size Re-estimation

Blinded sample size re-estimation will be conducted when at least a third of the planned randomized subjects (400-500) have been randomized. This is expected to be conducted before the availability of any post 12-month off-treatment follow-up eGFR data used for the primary analysis. The goal of this blinded sample size re-estimation is to check: 1) the differences between the observed variances and the variances used in the sample size calculation; 2) whether the approach of averaging the 3 eGFR observations at pre-treatment baseline and post-treatment follow-up has achieved the goal of reducing the variance to the level we planned. Based on these findings, the serum creatinine sample number and subject sample size of this trial may need to be adjusted.

To derive the variance and its components used in the sample size re-calculation, the repeated measurements at pre-treatment baseline will be analyzed using the one-way random effect model specified in (1), to derive the intra-subject variance used in the sample size calculation provided in the previous section. Comparison of this derived intra-subject variance with variance at on-treatment visits is also necessary to assess the reduction of the variance through replicated observations. In addition, review of the variance at on-treatment visits will also provide some clues to the variance at the unobserved post-treatment follow-up visits. Detailed actions in the blinded sample size re-estimation was documented in [Appendix 5](#).

## 5 Patient Samples and Handling of Missing Data

### 5.1 Patient Samples

The following samples (populations) are defined for this trial:

Randomized Population: All subjects who were randomized in this trial.

Randomized Safety Population: All subjects who were randomized in this trial and took at least one dose of investigational medicinal product (IMP) after randomization. This is the primary safety population.

Treated Safety Population: All subjects who took at least one dose of IMP during the tolvaptan titration/run-in periods. This is a secondary safety population.

Efficacy Populations:

Primary Endpoint Efficacy Population: All subjects who are in the Randomized Sample, took at least one dose of IMP after randomization, and have a baseline and at least one valid post-treatment evaluation in eGFR (ie, at least one week off-treatment). The primary endpoint's baseline is defined as the average of up to 3 eGFR values observed during the screening and placebo run-in periods.

Key Secondary Endpoint Efficacy Population: All subjects who are in the Randomized Sample, took at least one dose of IMP after randomization, and have a baseline and at least one post-randomization evaluation in eGFR during the double-blind treatment period. This is similar to the Primary Endpoint Efficacy Sample, except that post-treatment evaluation in eGFR is replaced by post-randomization evaluation. The baseline of the key secondary endpoint is identical to the baseline of the primary endpoint.

### 5.2 Analysis Data Sets

The core patient population for all efficacy analyses is based on the intent-to-treat (ITT) population which consists of all randomized subjects who take at least one dose of IMP post-randomization. As will be described below, in order to handle missing and restrictions imposed by different types of analyses (eg, change from baseline analysis), datasets based on modified ITT population will be used in the efficacy analyses.

The Observed Cases (OC) dataset of this protocol is defined as the data observed at study specified visits. For the primary outcome variable of this protocol, the OC dataset consists of the pre-treatment baseline (average of eGFR observed in screening period and the first eGFR observed in placebo run-in period) and post-treatment follow-up (average of eGFR observed in a two-week interval which is one week post the last IMP dose). For the key secondary outcome variable of this protocol, the OC dataset within treatment

period is defined as the data observed at study specified visits while subjects are taking IMP or within 24 hours of the last IMP dose.

### **5.3 Handling of Missing Data**

The GFR estimated by the CKD-EPI formula is utilized as the primary efficacy assessment in this trial.

In this protocol, all data collected for the pre-treatment baseline and post-treatment follow-up periods described in [Section 5.2](#) will be used and missing data will not be imputed in deriving the pre-treatment and post-treatment eGFR observations used for the primary analysis.

For sensitivity analyses of the primary analysis, in general, missing data will be handled by analysis using mixed model methodology under the assumption of “missing at random” (MAR). However, the possibility of “missing not at random” (MNAR) data can never be ruled out. Thus, every effort will be made to follow the subjects who discontinue investigational therapy after randomization without withdrawing consent for follow-up of their eGFR assessments. When collected within the last two weeks of the 3 weeks immediately post IMP withdrawal, the data will be included in the primary analysis. Otherwise, eGFR assessments collected during or after this period will be included in sensitivity analysis. Additional sensitivity analysis will be conducted for the key secondary endpoint for all subjects who withdraw consent or who are lost to follow up, using multiple imputation methodology under appropriate assumptions. See [Section 8.2.4](#) for more details.

## **6 Study Conduct**

### **6.1 Randomization**

Central randomization will be performed through IVRS to randomize subjects to treatment group in 1:1 ratio, stratified by baseline GFR level (eGFR CKD-EPI  $\leq 45 \text{ mL/min/1.73 m}^2$  or not), age ( $\leq 55$  years or not) and Total Kidney Volume ( $\leq 2000 \text{ mL}$  or not, or unknown).

### **6.2 Treatment Compliance**

Based on the Study Medication panel of the case report form (CRF), compliance in taking tolvaptan is calculated by dividing the total dosage taken by the total dosage the patients were scheduled to take during the study period.

## 7 Baseline Characteristics

Demographic characteristics including age, race, ethnicity, gender, weight, height and body mass index (BMI) will be summarized by descriptive statistics, eg, proportion, mean, median, SD, minimum and maximum values.

## 8 Efficacy Analysis

### 8.1 Primary Outcome Analysis

This trial's estimand is the difference in outcome improvement if all subjects tolerated and adhered to their treatment. To enrich this population, only subjects that can tolerate the tolvaptan titration and run-in periods will be randomized. This approach combines estimands #2 and #3 recommended by the 2010 National Academy of Sciences' National Research Council report on prevention and treatment of missing data.<sup>2</sup> Thus, data MAR is assumed in the primary analysis. Sensitivity analysis will be provided to address the concern of data MNAR.

This estimand focuses on the efficacy of tolvaptan in slowing renal function decline. The objective of this trial is to confirm a causal effect of tolvaptan in slowing renal function decline, consistent with the selection of an efficacy rather than effectiveness estimand.

An effectiveness estimand compares treatment policies and reasonably could include data acquired long after withdrawal from the trial (eg, when subjects discontinue tolvaptan but are followed for many weeks or months) or move to an alternate treatment regimen (eg, placebo subjects being prescribed commercial tolvaptan upon approval for ADPKD). In the absence of an approved and effective alternate treatment for ADPKD; it is premature to discuss treatment policies. Thus, while eGFR data collected in the second and third week post withdrawal are used for analysis of the primary endpoint, data collected long after withdrawal or after a subject moves to an alternate treatment regimen will be excluded in the primary analyses of both the primary and the key secondary endpoints.

Proposed tables and figures to be generated for the efficacy analysis can be found in [Appendix 3](#) and [Appendix 4](#).

#### 8.1.1 Primary Endpoint Analysis

A two-sided alpha of 0.05 will be applied to the primary analysis of the primary endpoint.

The primary endpoint of this trial is change in eGFR (CKD-EPI) from pre-treatment baseline to post-treatment follow-up, annualized (divided) by subjects' trial duration. This normalization is necessary, otherwise the treatment group having more dropouts or

more earlier dropouts may assume an unfair advantage. However, in order to reduce the impact of the outliers created by the annualized eGFR change in early dropout subjects, all annualized changes of dropout subjects that are greater (or less) than the maximum (or minimum) of the annualized eGFR change of all on-treatment completers will assume the maximum (or minimum) value as their annualized eGFR changes used in the primary analysis. This is because of the possibility that annualization of very variable short-term data (one or two months) by requiring a multiplication factor of 12 or 6 can result in an exaggerated estimate of annualized eGFR change. Early examples showed that this cannot be adequately managed by simple weighting in the analysis. Therefore, restrictions on the maximum and minimum values observed in the on-treatment completer population can further buffer the untoward effects of such outliers. In addition, the analysis based on the unadjusted annualized eGFR changes will serve as a sensitivity analysis of the primary endpoint. To reduce the variation in this primary endpoint, the last 3 observations of eGFR up to placebo run-in are observed at baseline (screening and placebo run-in periods) and another first 3 observations are observed after one week of post-treatment follow-up during a two week interval (within a total of 3-weeks post-treatment follow-up). Although it was initially designed to have subjects come back in this two week period to have their eGFR measures, it turns out that not all subjects could achieve this in our clinical operation. In order to reduce excluding subjects in the primary analysis due to failing to have follow-up data within this two week period, the window to have follow-up eGFR observations is thus set to be from 7 to 40 days post the last dose of IMP. Because the primary endpoint is annualized eGFR change, extending the follow-up window does not change placebo subjects' primary endpoint, since the duration from baseline to follow-up would be extended as well. For tolvaptan subjects, this window definition is actually conservative, since a few days of no treatment would be added to the duration of tolvaptan treatment for the annualization. The average of the 3 eGFR values observed during the baseline period is set as the baseline and the average of the 3 eGFR values observed during post-treatment follow-up period is set as the renal function measurement post-treatment. The dates of baseline and post-treatment observations are also set to the median of the dates of the (up to) three baseline and the (up to) three post-treatment follow-up observations respectively, and the duration is equal to the date of post-treatment follow-up minus the date of baseline plus one. This duration is used in the calculation of the annualized change.

Use of the duration to annualize the change is also reasonable since it will provide an "estimate" of annualized eGFR change slope for each subject, though there is no estimate for intra-subject variation associated with it. Thus, a weighted analysis of covariance (ANCOVA) with effects of treatment and randomization stratification factors and

covariate baseline will be applied to the analysis of these “estimated slopes” as the primary analysis. This weighted analysis is based on the reciprocal of the estimated variance of the “estimated slopes”, and the detailed algorithm to derive the estimated variance will be provided in [Section 8.3](#) for Computation Details of the Primary and Secondary Analyses.

### **8.1.2      Sensitivity Analysis of the Primary Endpoint**

Aligned with the desire to evaluate effects free from acute hemodynamic treatment effects, a sensitivity analysis of the primary endpoint will be performed including all available placebo data. In this sensitivity analysis, in addition to the 3 pre-treatment baseline observations and the 3 post-treatment follow-up observations, all post-randomization on-treatment eGFR observations in the protocol specified visits for placebo subjects will also be included. The linear mixed effect model with effects of treatment, time (as a continuous variable), treatment time interaction, randomization stratification factors, and baseline as covariate will be used to fit the eGFR data, in which the intercept and time are both a fixed effect and a random effect. An un-structured variance covariance matrix is assumed for the random intercept and time. The time variable used in the model may start from the first observation of eGFR baseline as mentioned in [Section 8.1.1](#), and this baseline will be used in the model. Missing data will be ignored in this analysis under MAR assumption. Data acquired while taking assigned tolvaptan cannot be used in this analysis without appropriate adjustment, but is evaluated in the key secondary efficacy endpoint of eGFR slope with a methodology which takes the acute hemodynamic drug effects of tolvaptan into account.

### **8.1.3      Sensitivity Analysis Including Data from Subjects Who Discontinue IMP**

The sensitivity analysis deviates from the MAR assumption to include the post-discontinuation follow-up data in the analysis specified in the section of the primary analysis. Subjects who discontinue treatment after randomization without withdrawing consent will also be followed for additional off-treatment eGFR values up to Month 12. These post “post-treatment follow-up” eGFR data at Month 12 will be included to replace the data observed during post-treatment follow-up for the subjects who discontinue IMP early in a sensitivity analysis using the same analytic approach specified in the section of the primary analysis.

## 8.2 Secondary Outcome Analysis

### 8.2.1 Key Secondary Endpoint Analysis

The analysis of the key secondary endpoint will be formally conducted, once the primary endpoint is significant at a two-sided alpha of 0.05. Then a two-sided alpha of 0.05 will be applied to the primary analysis of the key secondary endpoint.

The key secondary endpoint of the trial is the annualized rate of eGFR change, which is derived from each individual subject's eGFR slope using the CKD-EPI formula. Slope is preferred as a practical and clinically meaningful endpoint. In this analysis, all eGFR observations from placebo run-in, tolvaptan run-in (not including tolvaptan titration), double-blind treatment, and post-treatment follow-up (not including data collected in the first week after the last IMP dose) periods will be included in the analysis, with the data of tolvaptan run-in and tolvaptan subjects in the double-blind treatment period are flagged (yes = 1 and no = 0) with a tolvaptan acute hemodynamic effect. The linear mixed effect model with effects of time (as a continuous variable), treatment, time-treatment interaction, acute hemodynamic effect, pre-treatment baseline (of the primary endpoint), and randomization stratification factors will be used to fit the GFR estimates, in which the intercept and time are both a fixed effect and a random effect. An unstructured variance covariance matrix is assumed for the random intercept and time. The time variable used in the model may start from the first observation of eGFR obtained from placebo run-in period. The covariate "acute hemodynamic effect" in the model is the flag variable with value of 0 and 1 specified earlier in this section for the data observed during tolvaptan run-in and the data observed for tolvaptan subjects during the double-blind treatment period. The starting point of this eGFR slope analysis is the eGFR observation during the placebo run-in period.

### 8.2.2 Sensitivity Analysis of the Key Secondary Endpoint

This sensitivity analysis of the key secondary endpoint of this trial is to compare the linear trend of eGFR between tolvaptan and placebo groups. The advantage of this sensitivity analysis is that it does not depend on the assumption of linearity and equal tolvaptan hemodynamic onset and offset effects used in [Section 8.2.1](#). The change from the pre-treatment baseline during the on-treatment visits in the double-blind treatment period will be included in the analysis. Since the hemodynamic effects of tolvaptan are believed to begin to reverse within 1 to 2 days, therefore on-treatment will be defined as within 24 hours of the last IMP dose.

Analysis of MMRM will be applied to the data of change from baseline in eGFR in Month 1, Month 2, ..., up to Month 12. The model will have fixed effect of treatment,

visit, treatment visit interaction, randomization stratification factors, and covariate baseline and baseline visit interaction. An unstructured variance-covariance matrix is assumed for the repeated measurements. A linear contrast of the treatment differences in these 12 months will be used as the sensitivity analysis of the key secondary endpoint.

Another sensitivity analysis will apply MMRM analysis similar to the one provided in the previous paragraph (without deriving linear contrast) to the data of change from baseline in eGFR, from Tolvaptan Titration Visit, Tolvaptan Run-in Visits 1 and 2, and Month 1, Month 2, ..., up to Month 12, and Post-treatment Follow-up Visit (average).

### **8.2.3      Sensitivity Analysis Including Data from Subjects Who Discontinue IMP**

This sensitivity analysis deviates from the MAR assumption to include the post-discontinuation follow-up data in the analysis of the key secondary endpoint. Subjects who discontinue treatment after randomization without withdrawing consent will be followed for additional eGFR (not including the eGFR observed in the 3 week period immediately post the last dose of IMP) up to Month 12. The data collected during this follow-up period will not be included in the key secondary endpoint analysis for the reasons given above. However, a sensitivity analysis including these follow-up data for the key secondary analysis will be performed. This analysis uses the same approach provided in the [Section 8.2.1](#) for the analysis of the key secondary endpoint.

### **8.2.4      Sensitivity Analysis Including Imputation of Missing Data**

Multiple imputation is commonly used in the analysis of MNAR data. For all randomized subjects who withdraw early, imputation of missing data will be applied to projected visits up to their planned end of the trial (12 months post-randomization). The subjects' reasons for discontinuation will be captured and categorized to help determine the missing data pattern. Imputation will be based on the data used in the MMRM model specified in [Section 8.2.2](#). In order to perform the analysis of random coefficient regression model specified for the key secondary endpoint, simulated value of a missing data will be assigned a value for the time variable used in regression which is equal to the time of its previous visit plus 30.5 days. For placebo subjects, and in the absence of evidence suggesting biased missing data pattern, the imputation will follow the placebo trend.

Post-withdrawal data from the 156-04-251 trial and 156-08-271 interim analysis show that tolvaptan's eGFR benefits accumulate and are sustained after treatment discontinuation; therefore, imputation for subjects randomized to tolvaptan should reasonably begin at the value of their last on-treatment eGFR and flagged with the

tolvaptan acute hemodynamic effect mentioned in [Section 8.2.1](#). The imputation of these tolvaptan withdrew subjects is based on the following:

These imputed data will be added to the data described in [Section 8.2.1](#) and [Section 8.2.3](#) for two sets of sensitivity analyses. In each set of sensitivity analysis, reason of discontinuation will be classified in the following order as:

- 1) Progression of renal disease
- 2) Lack of efficacy
- 3) Other Adverse Event
- 4) Aquaretic AE (MedDRA preferred terms of THIRST, POLYURIA, NOCTURIA, POLLAKIURIA, POLYDIPSIA)
- 5) Trial too burdensome
- 6) Commercial tolvaptan for ADPKD available

This lists reasons for missing data due to discontinuation of trial participation in a decreasing order of their likelihood to produce data MNAR. Specifically, MNAR in the following patterns of dropout reasons will be investigated:

1. Progression of renal disease and Lack of efficacy (LOE) in tolvaptan treatment group as MNAR
2. Progression of renal disease, LOE, and other adverse events (AE) in tolvaptan treatment group as MNAR

Trial 156-04-251 and 156-08-271 data also support true disease modification and preservation of functioning kidney parenchyma through reduction of cyst growth. Therefore discontinuation of tolvaptan would not result in an immediate return to the placebo trend. Therefore eGFR decline in subjects discontinuing tolvaptan will reasonably fall somewhere between the tolvaptan trend and placebo trend. This supports a series of analyses for imputation of missing data for tolvaptan subjects, which will begin using the tolvaptan trend, and move stepwise toward the placebo trend. Therefore, the following delta adjustment imputation method will be applied:

### **Delta Adjustment Imputation Method**

This MNAR sensitivity analysis is to investigate the departure from MAR assumption by progressively decreasing the treatment differences over the missing visits in those treated subjects who fell into an assumed MNAR pattern. This progressive decrease of treatment slope difference is carried out by subtracting k times the expected treatment difference (in the absent of the hemodynamic effect) from the imputed missing data after dropout using tolvaptan slope in those treated subjects who fell into an assumed MNAR pattern, with k starts from 0%, 10%, 20%, .., and up to 100% or higher, until conclusion from the

analysis of the key secondary endpoint is overturned (it is called tipping point analysis), or it becomes clinically meaningless to go even higher. The expected treatment difference between tolvaptan and placebo at a visit may be derived from the treatment difference in slope, multiplied by the visit month number and divided by 12. Note that when 0% is used, the MI procedure would produce an analysis which is essentially MAR. When 100% is used, the MI procedure would produce an analysis which is essentially something called “copy placebo”. Specifically the MI procedure follows these steps:

- Using Monte Carlo Markov Chain (MCMC) methodology from PROC MI by treatment group to impute the intermittent missing data to a monotone missing pattern;
- Using a standard MAR-based multiple imputation approach from PROC MI to impute data from monotone missing data;
- For subjects in the treated groups who fall into a MNAR pattern specified above, a delta which equal to k times their treatment differences mentioned above will be subtracted for their imputed values after the dropout time, with k described in the above paragraph;
- Using the random coefficient regression model specified in the previous section to analyzed the completed data along with the imputed data;
- Obtaining the overall results using PROC MIANALYZE.

### **8.3 Technical Computational Details for Primary and Secondary Analysis**

(1) Two samples/aliquots of blood will be collected for serum creatinine assessments. While one blood sample will be analyzed by the central laboratory as soon as it is received and accessioned, the other one will be frozen and later batched analysis when a subject completes all his/her serum creatinine blood draws needed in the protocol. This batched assessment of serum creatinine is considered to have less intra-subject variation, and will be used for the eGFR derivations for the efficacy analysis. Since it is expected that two different methods are applied to these two sets of blood samples (enzymatic method to the batched sample and rate blank method to the first sample), these two sets of eGFR data are not interchangeable. In addition, the eGFR labeled as “Unscheduled” will be used in efficacy analysis if a subject has two eGFRs observed on the same day and same time.

(2) The CKD-EPI formula is as follows:

$$\text{eGFR} = J \times A \times (\text{Scr}/B)^C \times (0.993)^{\text{Age}} \text{ where:}$$

$J = 0.813$  if Japanese or  $1.0$  if non-Japanese ethnicity

A = 166 if black female, 163 if black male, 144 if non-black female, 141 if non-black male;

B = 0.7 if female or 0.9 if male;

and

if female; C =  $-0.329$  and serum creatinine is  $\leq 62$  umol/L ( $\leq 0.7$  mg/dL); or  $-1.209$  if serum creatinine  $> 62$  umol/L ( $> 0.7$  mg/dL)

Or

if male; C =  $-0.411$  and serum creatinine is  $\leq 80$  umol/L ( $\leq 0.9$  mg/dL); or  $-1.209$  if serum creatinine  $> 80$  umol/L ( $> 0.9$  mg/dL)

Age is expressed in years.<sup>3,4</sup>

- (3) The following SAS codes will be used for the primary analyses:

```
PROC GLM;
    CLASS TREATMENT AGE_STATUS GFR_STATUS TKV_STATUS;
    WEIGHT WEIGHT;
    MODEL ANNUALIZED_CHANGE = TREATMENT BASELINE AGE_STATUS
                                GFR_STATUS TKV_STATUS;
RUN;
```

- (4) The SAS code of the sensitivity analysis of the primary endpoint specified in Section 8.1.2 is

```
PROC MIXED EMPRICAL;
    CLASS SUBJECT TREATMENT AGE_STATUS GFR_STATUS TKV_STATUS;
    MODEL GFR = TREATMENT TIME TREATMENT*TIME BASELINE
                AGE_STATUS GFR_STATUS TKV_STATUS;
    RANDOM INTERCEPT ITME/TYPE=UN SUB=SUBJECT G;
RUN;
```

If the model has any convergence problem, the variables of AGE\_STATUS, GFR\_STATUS, and TKV\_STATUS may be dropped out of the model.

- (5) The SAS code of the analysis of the key secondary endpoint specified in Section 8.2.1 is

```
PROC MIXED EMPRICAL;
    CLASS SUBJECT TREATMENT AGE_STATUS GFR_STATUS TKV_STATUS;
    MODEL GFR = TREATMENT TIME TREATMENT*TIME BASELINE
                ACUTE_HEMODYNAMIC_EFFECT AGE_STATUS GFR_STATUS
                TKV_STATUS;
    RANDOM INTERCEPT ITME/TYPE=UN SUB=SUBJECT G;
RUN;
```

If the model has any convergence problem, the variables of AGE\_STATUS, GFR\_STATUS, and TKV\_STATUS may be dropped out of the model.

(6) The on-treatment visits included in the sensitivity analysis of the key secondary endpoint mentioned in [Section 8.2.2](#) are Months 1, 2, 3, ..., 11, 12. The mean value of these visits in months is 6.5. For a new numerical axis with its original falling at 6.5 months, the 12 original time points will become -11/2, -9/2, -7/2, -5/2, -3/2, -1/2, 1/2, 3/2, 5/2, 7/2, 9/2, and 11/2 on this numerical axis. Thus the coefficients of the linear trend contrast of these 12 months are -11, -9, -7, -5, -3, -1, 1, 3, 5, 7, 9, and 11. With treatment be coded, for example, as 0 for placebo and 1 for tolvaptan, the SAS code for the analysis of the key secondary endpoint is

```

PROC MIXED ;
  CLASS TREATMENT VISIT AGE_STATUS GFR_STATUS TKV_STATUS
  SUBJECT ;
  MODEL CHANGE = TREATMENT VISIT TREATMENT*VISIT BASELINE
    BASELINE*VISIT AGE_FACTOR GFR_FACTOR TKV_FACTOR;
  REPEATED VISIT/TYPE=UN SUB=SUBJECT;
  LSMEANS TREATMENT*VISIT/PDIFF CL ALPHA=0.05;
  ESTIMATE 'TREND DIFF' TREATMENT 0 0
    VISIT 0 0 0 0 0 0 0 0 0 0 0 0
    TREATMENT*VISIT 11 9 7 5 3 1 -1 -3 -5 -7 -9 -11
    -11 -9 -7 -5 -3 -1 1 3 5 7 9 11
    ;
RUN ;

```

If the estimate statement is not estimable, the fixed effects of AGE\_STATUS, GFR\_STATUS, and TKV\_STATUS may be dropped out of the model. In addition, 6/143 will be multiplied to the estimate of the linear trend contrast in order to provide an estimate of treatment difference in eGFR slope.

In case there is a convergence problem in the MMRM model with the unstructured variance covariance matrix, the following variance covariance matrix structures will be used in the order of 1) heterogeneous toeplitz, 2) heterogeneous autoregressive of order 1, 3) heterogeneous compound symmetry, 4) autoregressive of order 1, and 5) compound symmetry. The first (co)variance structure which does not have convergence problem will be the one used for the analysis. If a structured covariance has to be used, the “sandwich” estimator of the variance covariance matrix of the fixed effects parameters will be used in order to deal with possible model misspecification of the covariance matrix.

(7) For a tolvaptan subject who have IMP interruption during the trial, if the subject have eGFR observed during the interruption and the eGFR observation is more than one week from the last IMP dose before the interruption, the eGFR observation will be flagged (yes=1 and no = 0) with a tolvaptan hemodynamic effect and included in the key secondary analysis. If the observation is less than one week but more than 24 hours from

the last IMP dose before the interruption, the observation will be excluded from the key secondary analysis.

(8) Observations in eGFR which are 50% larger than a subject's screening eGFR observations will be excluded from the primary and second efficacy analyses.

(9) The following method to derive the weight for the primary analysis is proposed if the number of eGFR observations is kept at 3 in the pre-treatment baseline period. In order to derive the weight used in the weighted analysis, the following model is considered:

$$y_{i,0,k} = \alpha_i + e_{i,0,k} \quad \text{where } k = 1, 2, K_{i,0} \quad (1)$$

$$y_{i,j,k} = \alpha_i + \delta_{i,j} + e_{i,j,k} \quad \text{where } k = 1, 2, K_{i,j} \quad (2)$$

where  $K_{i,0}$  is the number of eGFR observations during the pre-treatment baseline period for subject  $i$ , and  $K_{i,j}$  is the number of eGFR observations during the post-treatment follow-up period for subject  $i$ , with visit  $j$  as the visit Month 12 for completers or mapped regular visits for early dropouts.  $\alpha_i$  is a random variable for the "real" eGFR baseline of subject  $i$ , and this variable will be cancelled out for change from baseline.  $\delta_{i,j}$  is a random variable for change from pre-treatment baseline for subject  $i$  to visit  $j$ . These  $\delta_{i,j}$ s are normally distributed, with means being  $\delta_{P,j}$  for placebo subjects and  $\delta_{T,j}$  for tolvaptan subjects, and variance  $\sigma_{\delta,j}^2$ . These  $\delta_{i,j}$ s are supposed to be independent from subject to subject, and each subject has only one post-baseline visit  $j$  in the primary analysis. In addition,  $\alpha_i$ s are assumed iid normally distributed,  $e_{i,j,k}$  are assumed iid  $N(0, \sigma^2)$ , and all these random variables are mutually independent. Their average over the  $K_{i,0}$  observations at baseline and the  $K_{i,j}$  observations at post-treatment follow-up will be:

$$\bar{y}_{i,0} = \alpha_i + \bar{e}_{i,0}, \quad \text{where } \bar{e}_{i,0} \sim N(0, \sigma^2/K_{i,0}) \quad (3)$$

$$\bar{y}_{i,j} = \alpha_i + \delta_{i,j} + \bar{e}_{i,j}, \quad \text{where } \bar{e}_{i,j} \sim N(0, \sigma^2/K_{i,j}) \quad (4)$$

the distribution of their difference is:

$$\bar{y}_{i,j} - \bar{y}_{i,0} = \delta_{i,j} + \bar{e}_{i,j} - \bar{e}_{i,0} \sim N(0, \sigma_{\delta,j}^2 + \sigma^2(1/K_{i,0} + 1/K_{i,j})) \quad (5)$$

where the mean of the normal distribution is  $\delta_{P,j}$  for placebo subjects and  $\delta_{T,j}$  for tolvaptan subjects.

In order to estimate the variance components given in (5), a further assumption of all  $\sigma_{\delta,j}^2$ 's are equal, ie,  $\sigma_{\delta,j}^2 = \sigma_{\delta}^2$  is made, since there may not be enough subjects withdraw to stabilized the estimate of  $\sigma_{\delta,j}^2$  at some visits. In addition, it is assumed all subjects get 3 eGFR observations at baseline. This assumption is reasonable, since usually subjects follow protocol schedules more strictly at the beginning of the trial, and could simplify

the estimation of the variance components. Then, a formula of change from baseline can be written similar to (5) for the estimation of the variance components:

$$y_{i,j,k} - \bar{y}_{i,0} = \delta_{i,j} + e_{i,j,k} - \bar{e}_{i,0} \sim N(., \sigma_\delta^2 + \sigma^2(I + 1/3)), \quad (6)$$

A mixed model with fixed effect factors of treatment nested within visit, replication (for the repeated observations at the post-treatment follow-up in eGFR) will be applied to change from baseline (as the average of the 3 pre-treatment eGFR observations) in eGFR observed at each replication. In this mixed model, replications at the post-treatment follow-up are considered as the repeated measurements, with a compound symmetric variance matrix structure. In this estimated variance-covariance matrix, the diagonal elements are the estimate of  $\sigma_\delta^2 + \sigma^2(I + 1/3)$ , and the off diagonal elements are the estimate of  $\sigma_\delta^2 + \sigma^2(I/3)$ . Solving these two equations will get the estimates of  $\sigma_\delta^2$  and  $\sigma^2$ . With these variance component estimates, the variance given in formula (5) is estimated for each subject. Dividing the estimated variance given in (5) by the subject's trial duration will provide an estimated variance for the subject's annualized change in eGFR. The inverse of this estimated variance will be the weight of the subject used in the primary analysis.

SAS code for the estimation of variance component

```
PROC MIXED ;
  CLASS SUBJECT VISIT TREATMENT REPLICATION;
  MODEL CHANGE = TREATMENT(VISIT) REPLICATION;
  REPEATED REPLICATION/TYPE=CS SUB=SUBJECT;
  RUN;
```

In this estimation of variance components, it is assumed the post-treatment follow-up eGFR observations of early withdrew subjects are mapped into scheduled visits. Since the monthly scheduled visits in this protocol, for a subject early withdrew IMP, compared to the subject's last scheduled on-treatment visit, if the first post-treatment follow-up eGFR is observed less or equal to 25 days ( $= 15 + 7 + 3$ ) after the last scheduled on treatment visit, then the subject's post-treatment follow-up eGFR observations will be mapped to the subject's last scheduled on-treatment visit; otherwise, if the first post-treatment follow-up eGFR is observed less or equal to 55.5 days ( $= 30.5 + 15 + 7 + 3$ ) after the last scheduled on treatment visit, then the subject's post-treatment follow-up eGFR observations will be mapped to one month after the subject's last scheduled on-treatment visit; etc.

(10) The following method to derive the weight for the primary analysis is proposed in case the blinded sample size re-estimation leads to a change in the number of eGFR observations in pre-treatment baseline period, so that the assumption of equal number of pre-treatment baseline eGFR observations is no longer.

In order to derive the weight used in the weighted analysis, the following model is considered:

$$y_{i,0,k} = \alpha_i + e_{i,0,k} \quad \text{where } k = 1, 2, K_{i,0} \quad (1)$$

$$y_{i,1,k} = \alpha_i + \delta_i + e_{i,1,k} \quad \text{where } k = 1, 2, K_{i,1} \quad (2)$$

where  $K_{i,0}$  is the number of eGFR observations during the pre-treatment baseline period for subject  $i$ , and  $K_{i,1}$  is the number of eGFR observations during the post-treatment follow-up period for subject  $i$ , whether subject  $i$  completes the study or not.  $\alpha_i$  is a random variable for the “real” eGFR baseline of subject  $i$ , and this effect will be cancelled out for change from baseline.  $\delta_i$  is a random variable for the “real” change from baseline to post-treatment follow-up of subject  $i$ . These  $\delta_i$ s are normally distributed, with a common variance  $\sigma^2$ , and are independent from subject to subject. In addition,  $\alpha_i$ s are assumed iid normally distributed,  $e_{i,1,k}$  are assumed iid  $N(0, \sigma^2)$ , and all these random variables are mutually independent. Their average over the  $K_{i,0}$  observations at baseline and the  $K_{i,1}$  observations at post-treatment follow-up will be:

$$\bar{y}_{i,0} = \alpha_i + \bar{e}_{i,0}, \quad \text{where } \bar{e}_{i,0} \sim N(0, \sigma^2/K_{i,0}) \quad (3)$$

$$\bar{y}_{i,1} = \alpha_i + \delta_i + \bar{e}_{i,1}, \quad \text{where } \bar{e}_{i,1} \sim N(0, \sigma^2/K_{i,1}) \quad (4)$$

the distribution of the change from baseline for subject  $i$  is:

$$\bar{y}_{i,1} - \bar{y}_{i,0} = \delta_i + \bar{e}_{i,1} - \bar{e}_{i,0} \sim N(0, \sigma^2 + \sigma^2(1/K_{i,0} + 1/K_{i,1})) \quad (5)$$

The estimation of  $\sigma^2$  is simply provided by:

$$v_e = \frac{1}{2} \{ \sum_i \sum_k (y_{i,0,k} - \bar{y}_{i,0})^2 / \sum_i (K_{i,0} - 1) + \sum_i \sum_k (y_{i,1,k} - \bar{y}_{i,1})^2 / \sum_i (K_{i,1} - 1) \} \quad (6)$$

where  $\sum_i$  sums over all subject  $i$ , and  $\sum_k$  sums over all replicate  $k$  for subject  $i$ , either at baseline visit or post-treatment follow-up visit. Let

$$d_i = (\bar{y}_{i,1} - \bar{y}_{i,0}) / t_i \sim N(0, [\sigma^2 + \sigma^2(1/K_{i,0} + 1/K_{i,1})] / t_i^2) \quad (7)$$

being the annualized change from baseline of subject  $i$  and its distribution, where  $t_i$  is the trial duration to annualize the primary endpoint for subject  $i$ , with mean  $\beta_T$  and  $\beta_P$  for tolvaptan and placebo subjects respectively. Let

$$\tau_i = [\sigma^2 + \sigma^2(1/K_{i,0} + 1/K_{i,1})] / t_i^2 \quad (8)$$

The treatment averages are:

$$\bar{d}_T = \sum_{i \text{ in TLV}} d_i / n_T \quad \text{and} \quad \bar{d}_P = \sum_{i \text{ in PLC}} d_i / n_P \quad (9)$$

where  $\Sigma_{i \text{ in } TLV}$  ( $\Sigma_{i \text{ in } PLC}$ ) sums over all tolvaptan (placebo) subjects, and  $n_T$  ( $n_P$ ) is the total number of subjects in tolvaptan (placebo). Let

$$v = \frac{1}{2} \{ \Sigma_{i \text{ in } TLV} (d_i - \bar{d}_T)^2 / (n_T - 1) + \Sigma_{i \text{ in } PLC} (d_i - \bar{d}_P)^2 / (n_P - 1) \} \quad (10)$$

Since

$$\begin{aligned} \Sigma_{i \text{ in } TLV} (d_i - \bar{d}_T)^2 &= \Sigma_{i \neq i' \text{ in } TLV} (d_i - d_{i'})^2 / 2n_T \quad \text{and} \\ \Sigma_{i \text{ in } PLC} (d_i - \bar{d}_P)^2 &= \Sigma_{i \neq i' \text{ in } PLC} (d_i - d_{i'})^2 / 2n_P \end{aligned} \quad (11)$$

formula (10) can be rewritten as:

$$v = \Sigma_{i \neq i' \text{ in } TLV} (d_i - d_{i'})^2 / [4n_T(n_T - 1)] + \Sigma_{i \neq i' \text{ in } PLC} (d_i - d_{i'})^2 / [4n_P(n_P - 1)] \quad (12)$$

and

$$\begin{aligned} E(v) &= \Sigma_{i \neq i' \text{ in } TLV} (\tau_i + \tau_{i'}) / [4n_T(n_T - 1)] + \Sigma_{i \neq i' \text{ in } PLC} (\tau_i + \tau_{i'}) / [4n_P(n_P - 1)] \\ &= \Sigma_{i \neq i' \text{ in } TLV} \{ [\sigma\delta^2 + \sigma^2(I/K_{i,0} + I/K_{i,1})] / t_i^2 + [\sigma\delta^2 + \sigma^2(I/K_{i',0} + I/K_{i',1})] / t_{i'}^2 \} / [4n_T(n_T - 1)] \\ &\quad + \Sigma_{i \neq i' \text{ in } PLC} \{ [\sigma\delta^2 + \sigma^2(I/K_{i,0} + I/K_{i,1})] / t_i^2 + [\sigma\delta^2 + \sigma^2(I/K_{i',0} + I/K_{i',1})] / t_{i'}^2 \} / [4n_P(n_P - 1)] \\ &= \Sigma_{i \text{ in } TLV} \{ [\sigma\delta^2 + \sigma^2(I/K_{i,0} + I/K_{i,1})] / t_i^2 \} / (2n_T) + \Sigma_{i \text{ in } PLC} \{ [\sigma\delta^2 + \sigma^2(I/K_{i,0} + I/K_{i,1})] / t_i^2 \} / (2n_P) \\ &= \delta^2 [\Sigma_{i \text{ in } TLV} I / (2n_T t_i^2) + \Sigma_{i \text{ in } PLC} I / (2n_P t_i^2)] \\ &\quad + \sigma^2 [\Sigma_{i \text{ in } TLV} (I/K_{i,0} + I/K_{i,1}) / (2n_T t_i^2) + \Sigma_{i \text{ in } PLC} (I/K_{i,0} + I/K_{i,1}) / (2n_P t_i^2)] \end{aligned} \quad (13)$$

where  $E(v)$  is the expectation of  $v$ . Thus, the estimate of  $\sigma\delta^2$  is:

$$\begin{aligned} v_\delta &= \{v - v_e [\Sigma_{i \text{ in } TLV} (I/K_{i,0} + I/K_{i,1}) / (2n_T t_i^2) + \Sigma_{i \text{ in } PLC} (I/K_{i,0} + I/K_{i,1}) / (2n_P t_i^2)]\} \\ &\quad / [\Sigma_{i \text{ in } TLV} I / (2n_T t_i^2) + \Sigma_{i \text{ in } PLC} I / (2n_P t_i^2)] \end{aligned} \quad (14)$$

And the estimated variance of the annualized change from baseline for subject  $i$  ( $d_i$ ) is:

$$[v_\delta + v_e (I/K_{i,0} + I/K_{i,1})] / t_i^2 \quad (15)$$

The reciprocal of (15) will be the weight for subject  $i$  used in the weighted analysis.

(11) Mapping of unscheduled visit and end of treatment visit during double-blind treatment period to nominal visits: In general, these visits will be mapped into the monthly nominal visits based on the mid-point between two monthly visits, ie, if an unscheduled visit or an end of treatment visit is within 15 days of the previous visit, it will be mapped to the previous visit; if it is greater than 15 day of the previous visit, it will be mapped to next appropriate visit, with 30.5 days (round if necessary) between each two adjacent nominal visits. If an unscheduled visit or an end of treatment visit falls into 351 (rounded from  $30.5 \times 11 + 15$ ) to 381 ( $= 366 + 15$ ) days post-randomization, it

will be mapped to visit Month 12. If an unscheduled visit or an end of treatment visit is more than 2 days post last dose, it will not be mapped to these double-blind nominal visits, but will be considered for the post-treatment follow-up visits, if it falls within 7 to 40 days from the last dose of IMP.

(12) The following reasons are collected in the CRF for subjects who discontinue IMP:

1. Discontinued based on subject decision:

1.1. IMP not tolerable (AE which is annoying or uncomfortable but not serious or hazardous)

1.2. Reason other than tolerability

1.2.1. Pregnancy

1.2.2. Trial too burdensome

1.2.3. Other reason

1.3. Taking marketed product for tolvaptan

2. Discontinued based on physician decision

2.1. Potential IMP-related safety concern or serious AR placing subject at undue hazard

2.2. Progression of disease leading to dialysis, transplantation or eGFR decline

2.3. Hepatic AE

3. Other

3.1. Subject death

3.2. Subject lost to follow-up

In [Section 8.2.4](#) for sensitivity analysis including imputation of missing data, six reasons of discontinuation of IMP were listed in the order of their likelihood to be MNAR. The mapping of the reasons of discontinuation of IMP to the reasons used in the sensitivity analysis is provided below:

- Progression of renal disease or Lack of efficacy: Item 2.2
- Other AE: Items of 1.2.3, 2.1, 2.3, 3.1 and 3.2
- Aquaretic AE: Item 1.1
- Trial too burdensome: Items of 1.2.1 and 1.2.2
- Commercial tolvaptan for ADPKD available: Item 1.3

The reason to map Items of 1.2.3 (Other reasons under Reason other than tolerability) and 3.2 (Subject lost to follow-up) to other AE is for conservativeness to consider them as a reason to be more likely MNAR.

#### **8.4 Subgroup Efficacy Analysis**

Subgroup analyses will be provided to the primary and the key secondary endpoints by region (US and non-US), gender (male and female), race (Caucasian and Other races), age ( $\leq 55$  years or not), baseline GFR level (eGFR CKD-EPI  $\leq 45$  mL/min/1.73 m<sup>2</sup> or not), and baseline Total Kidney volume ( $\leq 2000$  mL or not, or unknown), and by CKD Stage.

#### **8.5 Exploratory Analysis**

Exploratory analyses will be applied to the primary and the key secondary endpoints with tolvaptan subjects coded by their modal doses in the trial, using the same analytic approaches specified for these endpoints.

Assessment of ADPKD outcomes is specified as exploratory endpoints in this protocol. Exploratory analysis will be applied to a few frequent and clinical meaningful outcomes as well as a composite of those outcomes which are more closed related to kidney enlargement as potential events.

Events in this analysis will be defined if at least one of the PKD outcomes is checked in this CRF at a visit. The composite of these ADPKD outcomes will include kidney pain, hematuria, nephrolithiasis, urinary tract infection, anemia, and significant drop in kidney function. The frequent and clinical meaningful PKD Outcomes are Kidney Pain, Urinary Tract Infection, and Hematuria. Summary data are also provided to ADPKD outcomes and medical resource utilization collected in the PKD Outcome CRF page.

Analysis of time to multiple events, which is the analysis of the intensity model (Andersen-Gill model) using the sandwich covariance matrix estimate to derive standard errors for the Wald test<sup>5</sup> will be applied. The analysis dataset of this analysis will be set up in this way: the data will have a counting process style of input; the timing of an event will be set to the visit when the CRF is recorded; and a subject has only one event at a visit in the analysis even if the subject has more than one PKD outcomes at the visit. This analysis will cover the double-blind treatment period from randomization to Month 12. The SAS codes of the analysis will be:

```
proc phreg covs(aggregate);  
  model (start_time, stop_time)*status(0)= treatment/rl ties=breslow;  
  id subject_id;
```

## **9 Safety Analysis**

In general, baseline measurements of safety variables are defined as their last measurements prior to the randomization for the primary safety population (except for serum creatinine, which is defined similar to the baseline of eGFR assessment for the primary endpoint) and as their last measurements prior to the first dosing of study medication for the secondary safety population. Safety analysis will be conducted based on these safety populations, which are defined in [Section 5.1](#). Standard safety variables to be analyzed include AEs, clinical laboratory tests, and vital signs. In general, summarized statistics of changes from baseline will be provided for safety variables based on all available data. Proposed tables and figures to be generated for the safety analysis can be found in [Appendix 3](#) and [Appendix 4](#).

### **9.1 Adverse Events**

All AEs will be coded by system organ class and Medical Dictionary for Regulatory Activities (MedDRA) preferred term. The incidence of the following events will be summarized by treatment group for the primary safety population; summary of these events will also be provided for the secondary safety population:

- a) TEAEs by severity
- b) Potentially drug-related TEAEs
- c) TEAEs with an outcome of death
- d) Serious TEAEs
- e) Discontinuations due to TEAEs

### **9.2 Clinical Laboratory Data**

Summary statistics for changes from baseline in the central clinical laboratory measurements will be provided for the primary and secondary safety populations. Potentially clinically significant results in laboratory tests identified using prospectively defined criteria will also be summarized for the primary and secondary safety populations as well. Criteria of potentially clinically significant lab test abnormalities are provided in [Appendix 1](#).

In addition, laboratory measurements that signal the potential for Hy's Law will be reported. An incidence table and a listing will be provided for subjects who meet one or combinations of following criteria, without initial findings of cholestasis (serum alkaline phosphatase (ALP) activity  $>2\times\text{ULN}$ ):

Alanine aminotransferase (ALT) or aspartate aminotransferase (AST)  $\geq 3x$  upper limit of normal (ULN)

Bilirubin  $\geq 2x$  ULN

### **9.3 Physical Examination, and Vital Signs Data**

By-patient listings will be provided for physical examination. Summary statistics for changes from baseline in vital signs and potentially clinically significant results in vital signs will be summarized for the primary safety population as well as the secondary safety population.

Incidence of potentially clinically significant vital sign results will also be summarized by treatment groups. Criteria of potentially clinically significant vital sign abnormalities are provided in [Appendix 2](#).

## **10 Interim Analysis**

An optional interim analysis was planned but will not be conducted, because, given the rapid final enrollment, the sponsor, upon receiving recommendation from the trial's Steering Committee, deemed the analysis might only bring a few month's difference in trial conclusion. Thus, without the interim analysis, the alpha level of the final analysis will be 0.05.

## 11 Reference

- <sup>1</sup> Lefante JJ. The power to detect differences in average rates of change in longitudinal studies. *Statistics in Medicine*, 9, 437-446, 1990.
- <sup>2</sup> National Research Council (US) Panel on Handling Missing Data in Clinical Trials. *The Prevention and Treatment of Missing Data in Clinical Trials*. Washington (DC): National Academies Press (US); 2010.
- <sup>3</sup> Stevens LA, Schmid CH, Greene T, Zhang Y, Beck GJ, Froissart M, Hamm LL, Lewis JB, Mauer M, Navis GJ, Steffes MW, Eggers PW, Coresh J and Levey AS. Comparative Performance of the CKD Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) Study Equations for Estimating GFR Levels Above 60 mL/min/1.73m<sup>2</sup>. *Am J Kidney Dis*. 2010; 56:486-495.
- <sup>4</sup> Horio M, Imai E, Yasuda Y, Watanabe T and Matsuo S. Modification of the CKD Epidemiology Collaboration (CKD-EPI) Equation for Japanese: Accuracy and use for Population Estimates. *Am J Kidney Dis*. 2010;56:32-38.
- <sup>5</sup> Therneau, TM and Grambsch, PM. *Modeling Survival Data: Extending the Cox Model*. Springer-Verlag, New York. 2000.

## **Appendix 1      Criteria of Potentially Clinically Significant Laboratory Test Abnormalities (Modified NCI Criteria)**

## Laboratory Test Abnormalities due to Test Value Increase

Test	Abnormality	Test Result Grade				
		0	1	2	3	4
APTT (sec)	Increase	ULN	> ULN - 1.5xULN	> 1.5xULN - 2xULN	> 2xULN	
ALT (SGPT) (IU/L)	Increase	ULN	> ULN - 3xULN	> 3xULN - 5xULN	> 5xULN - 20xULN	> 20xULN
AST (SGOT) (IU/L)	Increase	ULN	> ULN - 3xULN	> 3xULN - 5xULN	> 5xULN - 20xULN	> 20xULN
Bilirubin, Total (mg/dL)	Increase	ULN	> ULN - 2xULN	> 2xULN - 3xULN	> 3xULN - 10xULN	> 10xULN
Creatinine (mg/dL)	Increase Pre-randomization	AB*	> AB - 1.5xAB	> 1.5 x AB - 3 x AB	> 3 x AB - 6 x AB	> 6 x AB
Creatinine (mg/dL)	Increase Post-randomization	< 1.33 x PR* PR*	1.33 x PR - < 2x PR	2 x PR - < 3 x PR	3 x PR - 6 x PR	> 6xPR
Eosinophils, Absolute (Thous/ $\mu$ L)	Increase	$\leq 0.65$	> 0.65 - 1.5	> 1.5 - 5	> 5	-
Glucose (mg/dL)	Increase	$\leq 115$	> 115 - 160	> 160 - 250	> 250 - 500	> 500
Hemoglobin (g/dL)	Increase	ULN	> ULN - 20	> 20 - 21	> 21 - 22.5	> 22.5
Potassium (mEq/L)	Increase	ULN	> ULN - 5.5	> 5.5 - 6	> 6 - 7	> 7
INR	Increase	ULN	> ULN - 1.5xULN	> 1.5xULN - 2xULN	> 2xULN	-
Sodium (mg/dL)	Increase	< 145	146 - 150	151 - 155	156 - 160	> 160
Triglycerides (mg/dL)	Increase	ULN	> ULN - 2.5xULN	> 2.5xULN - 5xULN	> 5xULN - 6xULN	> 6xULN
Urea Nitrogen (mg/dL)	Increase	$\leq 22$	> 22 - 26	> 26 - 31	> 31	-
White Blood Count (Thous/ $\mu$ L)	Increase	$\leq 10.799$	> 10.799 - 15	> 15 - 20	> 20 - 25	> 25

\* Baseline creatinine is expected to be elevated in this population. Average baseline (AB) is equal to the mean baseline value collected during screening period.

Mean baseline values collected during screening period.  
During treatment with tolvaptan, serum creatinine is expected to increase by approximately 5 to 10%.

During treatment with tolvaptan, serum creatinine is expected to increase by approximately 3% Post-randomization baseline (PR) is equal to the highest value obtained during the run-in period matching the subject's assigned treatment, ie, either placebo or tolvaptan run-in periods.

**Laboratory Test Abnormalities due to Test Value Decrease**

Test	Abnormality	Test Result Grade				
		-4	-3	-2	-1	0
Glucose (mg/dL)	Decrease	< 30	30 - < 40	40 - < 55	55 - < 65	≥ 65
Hemoglobin (g/dL)	Decrease	< 6.5	6.5 - < 8	8 - < 10	10 - < LLN	LLN
Lymphocytes, Absolute (Thous/µL)	Decrease	< 0.2	0.2 - < 0.5	0.5 - < 0.8	0.8 - < LLN	LLN
Neutrophils, Absolute (Thous/µL)	Decrease	< 0.5	0.5 - < 1	1 - < 1.5	1.5 - < LLN	LLN
Platelet Count (Thous/µL)	Decrease	< 25	25 - < 50	50 - < 75	75 - < LLN	LLN
Potassium (mEq/L)	Decrease	< 2.5	2.5 - < 3	-	3 - < LLN	LLN
Sodium (mg/dL)	Decrease	< 120	120 - 124	125 - 129	130 - 135	≥ 136
White Blood Count (Thous/µL)	Decrease	< 1	1 - < 1.5	1.5 - < 2.5	2.5 - < 3.501	≥ 3.501

**Appendix 2                      Criteria of Potentially Clinically Significant Vital Sign Abnormalities**

<b>Test Type</b>	<b>Test Parameters</b>	<b>Unit</b>	<b>Sex</b>	<b>Criteria (meet either one will count)</b>	
				<b>Limit</b>	<b>Change from baseline</b>
VITAL SIGNS	SBP, SITTING	mmHg	Male/Female	≥ 180	≥ 20
VITAL SIGNS	SBP, SITTING	mmHg	Male/Female	≤ 90	≤ -20
VITAL SIGNS	DBP, SITTING	mmHg	Male/Female	≥ 105	≥ 15
VITAL SIGNS	DBP, SITTING	mmHg	Male/Female	≤ 50	≤ -15
VITAL SIGNS	HEART RATE	bpm	Male/Female	≥ 120	≥ 15
VITAL SIGNS	HEART RATE	bpm	Male/Female	≤ 50	≤ -15
VITAL SIGNS	TEMPERATURE	degree C	Male/Female	≥ 38.3	≥ 1.1
VITAL SIGNS	WEIGHT	kg	Male/Female	-	≥ 7 percent

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Figure 4.4 Sensitivity Analysis of Key Secondary Endpoint: Multiple Imputation for Missing Data (Progression of Renal Disease, Lack of Efficacy, and Other Adverse Events in Tolvaptan Treatment Group as MNAR), Key Secondary Endpoint Efficacy Population, Including Data from Subjects Who Discontinue IMP

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Figure 5.2 Linear Mixed Effect Model of Annualized eGFR (CKD-EPI) Change Slope by Subgroup Key Secondary Endpoint Efficacy Population

Figure 6.1 Treatment Difference in Annualized Change in eGFR (CKD-EPI) from Pre-treatment Baseline to Post-treatment Follow-up by Site, Primary Endpoint Efficacy Population

Figure 6.2 Treatment Difference in Annualized Change in eGFR (CKD-EPI) from Pre-treatment Baseline to Post-treatment Follow-up by Country, Primary Endpoint Efficacy Population

Figure 7.1 Mean of Estimated Annualized eGFR Change for Subjects Completed/Discontinued from Treatment, Primary Endpoint Efficacy Population

Figure 7.2 Mean of Estimated Annualized eGFR Change by Reason for Discontinuation from Treatment, Primary Endpoint Efficacy Population

Figure 8.1 Mean Change from Baseline in eGFR (CKD-EPI) for Dropouts - Tolvaptan, Key Secondary Endpoint Population

Figure 8.2 Mean Change from Baseline in eGFR (CKD-EPI) for Dropouts - Placebo, Key Secondary Endpoint Population

Figure 9.1 Kaplan-Meier Curves of Time to Discontinuation of Study All Randomized Subjects

Figure 9.2 Kaplan-Meier Curves of Time to Discontinuation of IMP Primary Safety Population

Figure 10.1 Incidence of Treatment Emergent Adverse Events with at least 5% in any Treatment Group Primary Safety Population, Double-blind Treatment Period

Figure 10.2.1 Kaplan-Meier Curves of Time to TEAE in Liver Primary Safety Population, Double-blind Treatment Period

Figure 10.2.2 Kaplan-Meier Curves of Time to TEAE in Skin Neoplasms Primary Safety Population, Double-blind Treatment Period

Figure 11.1 Kaplan-Meier Curves of Time to ALT > 3xULN Primary Safety Population, Double-blind Treatment Period

Figure 11.2.1 Kaplan-Meier Curves of Time from Peak ALT to Normal (<1xULN) Primary Safety Population, Adjudicated Subjects

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Figure 11.2.2 Kaplan-Meier Curves of Time from Peak ALT to Normal (<1xULN)  
Based on Discontinuation Status in Tolvaptan Group Primary Safety Population,  
Adjudicated Subjects

Figure 12.1 Peak Bilirubin/ULN Ratio versus Peak ALT/ULN Ratio Primary Safety  
Population, Double-blind Treatment Period

**Appendix 5                    Biostatistics Memorandum on Sample Size Re-calculation**

Clinical Development  
**OTSUKA PHARMACEUTICAL DEVELOPMENT &  
COMMERCIALIZATION, INC.**

**Biostatistics  
MEMO**

**Compound:** OPC-41061

**Protocol:** Protocol 156-13-210

**To:** Czerwiec, Frank; Sergeyeva, Olga

**cc:** June, Li; Martinko, David; Craig, Ostroff; Debuque, Laurie

**From:** John Ouyang

**Date:** Aug. 31, 2015

**Re:** Recommendation of the Blinded Sample Size Re-estimation

---

The 156-13-210 protocol and SAP specified that “Blinded sample size re-estimation will be conducted when at least a third of the planned randomized subjects (400-500) have been randomized”. As of Aug. 19, 2015, 453 subjects had been randomized. Thus, blinded sample size re-estimation was conducted using the data transferred in August, 2015. As stated in the SAP, the goal of this blinded sample size re-estimation is to check: 1) whether the approach of averaging the 3 eGFR observations at pre-treatment baseline and post-treatment follow-up has achieved the goal of reducing the variance to the level we planned; 2) the differences between the observed variances and the variances used in the sample size calculation.

The protocol and SAP also stated that the blinded sample size re-estimation “is expected to be conducted before the availability of any post 12-month off-treatment follow-up eGFR data used for the primary analysis.” Since in this August, 2015 data transfer, there was only one subject who completed the 12-month study and had post 12-month off-treatment follow-up eGFR data, thus, this expectation on the timing of the blinded sample size re-estimation is also basically met.

Based on the goals specified for this blinded sample size re-estimation, eGFR data of repeated observations at either pre-treatment baseline or post-treatment follow-up must be used. Because the variance of eGFR observations is much larger than the variance of

eGFR change from baseline (for example, at tolvaptan titration and run-in visits, the variance of eGFR observations is about 11 but the variance of eGFR change from baseline is ranged from 4 to 4.6), we believe this blinded sample size re-estimation should be based on the data of eGFR change from baseline at the post-treatment follow-up visits, in order to provide a more relevant and accurate power estimation for this important study.

**Question 1: Whether the approach of averaging the 3 eGFR observations at pre-treatment baseline and post-treatment follow-up has achieved the goal of reducing the variance to the level we planned**

In the following Tables, the one-way ANOVA table of change from baseline to post-treatment follow-up visits of study 251 (used in the calculation of variance components for sample size calculation) and the one-way AVOVA table of change from baseline to post-treatment follow-up visits of study 210 derived from the current data transfer are provided, both based on the eGFR CKD-EPI formula (ml/min/1.73 m<sup>2</sup>):

Table 1

251 ANOVA Table of Change from Pre-titration Baseline in Renal function to FU Visits and Their Average, Non-Japan Subjects with Baseline GFR < 60 and Observation at Pre-treatment Baseline, FU Visits 1 and 2

Treatment	Source	DF	SS	MS	F-value	P-value
<hr/>						
Placebo	Between	53	10678.83	201.49	2.52	<.0001
	Within	162	12932.38	79.83		
	Corrected Total	215	23611.20			
Tolvaptan	Between	93	14568.82	156.65	3.01	<.0001
	Within	282	14654.14	51.97		
	Corrected Total	375	29222.96			

Table 2

## 210 ANOVA Table of Change from Baseline om eGFR Follow-up Observations

## Post Treatment Follow-up Visits 1, 2, and 3

Source	DF	SS	MS	F-value	P-value
<hr/>					
Between	9	1709.75	189.97	14.81	<.0001
Within	15	192.36	12.82		
Corrected Total	24	1902.10			

Because the mean sum square of within-subject error (12.82) in study 210 is only ~6.7% of the mean sum square of between-subject error (189.97), we may conclude that the increase of eGFR observations (use of more than one observation) does not reduce the variance of their average much, since increased numbers of observations only reduce the within-variance component in their average, and there is little within-subject variation to be further reduced. Notice that the 210 mean sum square of within-subject error is much less than the 251 mean sum square of within-subject error (79.83 for placebo and 51.97 for tolvaptan). Since the 210 eGFR data used for this blinded sample size re-calculation are based on Rate Blank serum creatinine and the 251 eGFR data were based on Enzymatic serum creatinine, this fact may raise the question of whether the within-subject errors of these two kinds of serum creatinine are very different or not. It is likely that Rate Blank serum creatinine is more stable with less within-subject variation. Indeed, this was considered an advantage of the Rate Blank method when our central lab vendor, Covance, recommended it to us. Thus, it is not known whether the small within-subject error in 210 is caused by Rate Blank data or is actually occurring in 210 eGFR data. Because of this, there are no grounds for making any changes to the number of eGFR observation at pre-treatment baseline and post-treatment follow-up visits, unless 210 eGFR data based on Enzymatic serum creatinine are available. Based on the current clinical operation plan, Enzymatic serum creatinine data are only available when subjects finish their 12- month visits as well as their post-treatment follow-up visits (for both completer and early withdrew subject), since batched analysis on frozen blood samples of all visits would only be done after that. Thus, more appropriate analysis to determine the number of eGFR observations at pre-treatment baseline and post-treatment follow-up visits can only be provided after more subjects complete the study.

**Question 2: The differences between the observed variances and the variances used in the sample size calculation**

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To address this question, the most straightforward way is to look at the variance of the average eGFR change from baseline at post-treatment follow-up visits, which is given in the following change from baseline by-visit table:

**Table 3**

Change from Baseline in Renal Function (CKD-EPI), Blinded

Visit	eGFR Values						Change from Baseline					
	N	Mean	Med	SD	Min	Max	N	Mean	Med	SD	Min	Max
Baseline	340	43.21	41.92	11.45	24.43	67.87						
Tolvaptan Titration	341	39.65	38.91	10.81	20.02	69.60	341	-3.65	-3.37	3.97	-24.94	13.18
Tolvaptan Run-in Day	321	39.97	38.28	11.21	20.18	74.79	321	-3.21	-3.20	4.22	-20.92	15.50
Tolvaptan run-in Day	334	39.82	38.46	10.97	18.90	82.36	334	-3.40	-3.41	4.63	-23.67	16.98
Month 1	278	40.98	39.21	11.48	21.79	84.35	278	-2.08	-2.17	4.73	-21.81	22.02
Month 2	220	40.00	39.21	11.60	20.66	81.95	220	-2.27	-2.23	4.91	-24.46	17.18
Month 3	183	40.22	37.27	12.48	21.56	75.17	183	-1.24	-1.93	5.47	-19.72	18.66
Month 4	133	39.21	36.90	11.73	21.05	74.65	133	-1.98	-2.30	4.58	-18.14	12.31
Month 5	98	38.55	36.05	12.30	20.71	73.62	98	-2.00	-2.35	5.32	-18.14	12.83
Month 6	75	39.19	38.67	11.69	20.17	72.21	75	-1.05	-1.33	5.10	-12.59	13.82
Month 7	60	40.56	38.91	12.93	23.01	93.83	60	-0.92	-1.76	5.78	-12.80	29.06
Month 8	33	39.98	37.16	14.66	20.89	93.83	33	-0.98	-2.20	6.80	-8.93	29.06
Month 9	14	39.02	35.95	16.23	20.83	78.01	14	-2.08	-2.13	7.31	-14.58	16.37
Month 10	10	39.38	39.31	12.97	23.50	61.21	10	-5.00	-4.27	4.46	-14.36	-0.41
Month 11	1	61.21	61.21		61.21	61.21	1	-0.43	-0.43		-0.43	-0.43
Month 12	1	68.68	68.68		68.68	68.68	1	7.04	7.04		7.04	7.04
End of Treatment	10	47.90	45.91	17.09	18.68	81.95	10	1.19	1.87	9.54	-15.65	17.18
Follow-up Day 7	11	46.16	36.13	17.15	29.95	81.95	11	0.55	-0.32	7.73	-8.07	17.18
Follow-up Day 14	7	45.88	38.94	17.55	32.60	81.95	7	1.06	-0.60	7.69	-5.20	17.18
Follow-up Day 21	7	51.72	46.70	21.74	29.67	94.49	7	3.30	-0.43	12.36	-8.83	29.72
Follow-up Average	11	46.16	37.12	17.19	29.95	86.13	11	0.56	-0.32	8.00	-6.74	21.36

Note that the SD of average change from baseline at Follow-up is 8.00, which is greater than the SD used in the sample size calculation (5.73, equal to the square root of 32.8). However, out of the 11 subjects in the follow-up visit, only one is a completer and the other 10 are early dropouts. Thus, the variance at the follow-up visit may be inflated by the dropout subjects. In addition, for visits with large amount of subjects, say, visits from Month 1 to Month 7, where subject numbers ranged from 60 to more than 200, the

variances of these visits are all less than 6. This raises the possibility that, when we have enough subjects in the follow-up visits so that they are not dominant by early dropouts, the SD of the average change from baseline at follow-up may also be around 6. If this is the case, the trial would be well powered. Even when the SD raised up to 6.5, the trial would still have at least 80% power. Because of this, with the limit of the current data for this blinded sample size re-calculation exercise, no conclusion can be made at this time for the comparison between the observed variances and the variances used in the sample size calculation.

Thus, this blinded sample size re-estimation failed to provide any recommendations to its objectives. The reason for failing the first question is because, when we designed the protocol, it was planned to use eGFR derived from Rate Blank serum creatinine, since this was recommended by our central lab vendor, Covance. However, in a Steering Committee meeting when the trial was under patient enrollment, the Committee Members told us they preferred the Enzymatic serum creatinine. They believed it is the golden standard in deriving eGFR. Because of this, it was decided that eGFR derived from Rate Blank serum creatinine would be used only for patient clinical monitoring, and the eGFR based on Enzymatic serum creatinine obtained from batched analysis on frozen blood samples of all visits would be used in efficacy analyses. This change in clinical operation led to the miss of the first question in this blinded sample size re-estimation exercise.

The reason for missing of the second objective in this blinded sample size re-estimation exercise is that, when we designed the protocol, we would like to make sure the sample size re-estimation would be done before half of the planned subjects were randomized. Had we specified to conduct the blinded sample size re-estimation at a time when 600 - 700 subjects were randomized to the trial, or when 40 - 50 subjects completed their 12-month post-treatment follow-up, which ever came later, we should not have problem to answer the second question.

**Otsuka Pharmaceutical Development & Commercialization, Inc.**

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## Statistical Analysis Plan Summary of Changes

### Version 1 to Version 2

Page	Old text	New Text
9	The primary endpoint's baseline is defined as the average of up to 5 eGFR values observed during the screening and placebo run-in periods.	The primary endpoint's baseline is defined as the average of up to 3 eGFR values observed during the screening and placebo run-in periods.
Page 11-12	<p>The primary endpoint of this trial is change from pre-treatment baseline to post-treatment follow-up, annualized (divided) by subjects' trial duration. This normalization is necessary, otherwise the treatment group having more dropouts or more earlier dropouts may assume an unfair advantage. To reduce the variation in this primary endpoint, 3 or 4 observations of eGFR are observed at baseline during a 3-week interval (screening and placebo run-in periods) and another 3 or 4 observations are observed after one week of post-treatment follow-up during a two week interval (within a total of 3-weeks post-treatment follow-up). The average of the 3-4 eGFR values observed during the baseline period is set as the baseline and the average of the 3-4 eGFR values observed during post-treatment follow-up period is set as the renal function measurement post-treatment.</p>	<p>The primary endpoint of this trial is change in eGFR (CKD-EPI) from pre-treatment baseline to post-treatment follow-up, annualized (divided) by subjects' trial duration. This normalization is necessary, otherwise the treatment group having more dropouts or more earlier dropouts may assume an unfair advantage. To reduce the variation in this primary endpoint, 3 observations of eGFR are observed at baseline during a 3-week interval (screening and placebo run-in periods) and another 3 observations are observed after one week of post-treatment follow-up during a two week interval (within a total of 3-weeks post-treatment follow-up). The average of the 3 eGFR values observed during the baseline period is set as the baseline and the average of the 3 eGFR values observed during post-treatment follow-up period is set as the renal function measurement post-treatment.</p>
	<p>Thus, ANCOVA with effects of treatment and randomization stratification factors and covariate baseline will be applied to the analysis of these "estimated slopes" as the primary analysis.</p> <p>8.1.2 Sensitivity Analysis of the Primary Endpoint            Aligned with the desire to evaluate effects free from acute hemodynamic treatment effects, a sensitivity analysis of the primary endpoint will be performed including all available placebo data. In this sensitivity analysis, in addition to the 3-4 pre-treatment baseline observations and the 3-4 post-treatment follow-up observations, all post-randomization on-treatment eGFR observations in the protocol specified visits for placebo subjects will also be included. The linear</p>	<p>Thus, a weighted ANCOVA with effects of treatment and randomization stratification factors and covariate baseline will be applied to the analysis of these "estimated slopes" as the primary analysis. This weighted analysis is based on the reciprocal of the estimated variance of the "estimated slopes", and the detailed algorithm to derive the estimated variance will be provided in section 8.3 for Computation Details of the Primary and Secondary Analyses.</p> <p>8.1.2 Sensitivity Analysis of the Primary Endpoint            Aligned with the desire to evaluate effects free from acute hemodynamic</p>

	<p>mixed effect model with effects of treatment, time (as a continuous variable), treatment time interaction, randomization stratification factors, and baseline as covariate will be used to fit the eGFR data, in which the intercept and time are both a fixed effect and a random effect. An un-structured variance covariance matrix is assumed for the random intercept and time. The time variable used in the model may start from the first observation of eGFR baseline as mentioned in section 8.1.1, and this baseline will be used in the model. Missing data will be ignored in this analysis under MAR assumption. Data acquired while taking assigned tolvaptan cannot be used in this analysis without appropriate adjustment, but is evaluated in the key secondary efficacy endpoint of eGFR slope with a methodology which takes the acute hemodynamic drug effects of tolvaptan into account.</p>	<p>treatment effects, a sensitivity analysis of the primary endpoint will be performed including all available placebo data. In this sensitivity analysis, in addition to the 3 pre-treatment baseline observations and the 3 post-treatment follow-up observations, all post-randomization on-treatment eGFR observations in the protocol specified visits for placebo subjects will also be included. The linear mixed effect model with effects of treatment, time (as a continuous variable), treatment time interaction, randomization stratification factors, and baseline as covariate will be used to fit the eGFR data, in which the intercept and time are both a fixed effect and a random effect. An un-structured variance covariance matrix is assumed for the random intercept and time. The time variable used in the model may start from the first observation of eGFR baseline as mentioned in section 8.1.1, and this baseline will be used in the model. Missing data will be ignored in this analysis under MAR assumption. Data acquired while taking assigned tolvaptan cannot be used in this analysis without appropriate adjustment, but is evaluated in the key secondary efficacy endpoint of eGFR slope with a methodology which takes the acute hemodynamic drug effects of tolvaptan into account.</p>
Page 13	<p>The sensitivity analysis deviates from the MAR assumption to include the post-discontinuation follow-up data in the analysis specified in the previous section.</p>	<p>The sensitivity analysis deviates from the MAR assumption to include the post-discontinuation follow-up data in the analysis specified in the section of the primary analysis.</p>
	<p>These post “post-treatment follow-up” eGFR data will be included to the data specified in the previous section in a sensitivity analysis using the same analytic approach specified in the previous section.</p>	<p>These post “post-treatment follow-up” eGFR data at Month 12 will be included to replace the data observed during post-treatment follow-up for the subjects who discontinue IMP early section in a sensitivity analysis using the same analytic approach specified in the section of the primary analysis.</p>
		<p>The covariate “acute hemodynamic effect” in the model is the flag variable</p>

		with value of 0 and 1 specified earlier in this section for the data observed during tolvaptan run-in and the data observed for tolvaptan subjects during the double blind treatment period. The starting point of this eGFR slope analysis is the eGFR observation during the placebo run-in period.
Page 17		WEIGHT WEIGHT;
Page 18		(9) The following method to derive the weight for the primary analysis is proposed if the number of eGFR observations is kept at 3 in the pre-treatment baseline period. In order to derive the weight used in the weighted analysis, the following model is considered: $y_{i,0,k} = \alpha_i + e_{i,0,k}$ where $k = 1, 2, K_{i,0}$ (1) $y_{i,j,k} = \alpha_i + \delta_{i,j} + e_{i,j,k}$ where $k = 1, 2, K_{i,j}$ (2)
Page 19		where $K_{i,0}$ is the number of eGFR observations during the pre-treatment baseline period for subject i, and $K_{i,j}$ is the number of eGFR observations during the post-treatment follow-up period for subject i, with visit j as the visit Month 12 for completers or mapped regular visits for early dropouts. $\alpha_i$ is a random variable for the “real” eGFR baseline of subject i, and this variable will be cancelled out for change from baseline. $\delta_{i,j}$ is a random variable for change from pre-treatment baseline for subject i to visit j. These $\delta_{i,j}$ s are normally distributed, with means being $\delta_{P,j}$ for placebo subjects and $\delta_{T,j}$ for tolvaptan subjects, and variance $\sigma_{\delta,j}^2$ . These $\delta_{i,j}$ s are supposed to be independent from subject to subject, and each subject has only one post-baseline visit j in the primary analysis. In addition, $\alpha_i$ s are assumed iid normally distributed, $e_{i,j,k}$ are assumed iid $N(0, \sigma^2)$ , and all these random variables are mutually independent. Their average over the $K_{i,0}$ observations at baseline and the $K_{i,j}$ observations at post-treatment follow-up will be $\bar{y}_{i,0} = \alpha_i + \bar{e}_{i,0}$ , where $\bar{e}_{i,0} \sim N(0, \sigma^2/K_{i,0})$

(3)

$$\bar{y}_{i,j} = \alpha_i + \delta_{i,j} + \bar{\epsilon}_{i,j}, \text{ where } \bar{\epsilon}_{i,j} \sim N(0, \sigma^2/K_{i,j}) \quad (4)$$

the distribution of their difference is

$$\bar{y}_{i,j} - \bar{y}_{i,0} = \delta_{i,j} + \bar{\epsilon}_{i,j} - \bar{\epsilon}_{i,0} \sim N(\cdot, \sigma^2\delta_{i,j}^2 + \sigma^2(1/K_{i,0} + 1/K_{i,j})) \quad (5)$$

where the mean of the normal distribution is  $\delta_{P,j}$  for placebo subjects and  $\delta_{T,j}$  for tolvaptan subjects.

In order to estimate the variance components given in (5), a further assumption of all  $\sigma^2\delta_{i,j}^2$ 's are equal, i.e.,  $\sigma^2\delta_{i,j}^2 = \sigma^2\delta^2$  is made, since there may not be enough subjects withdraw to stabilized the estimate of  $\sigma^2\delta_{i,j}^2$  at some visits. In addition, it is assumed all subjects get 3 eGFR observations at baseline. This assumption is reasonable, since usually subjects follow protocol schedules more strictly at the beginning of the trial, and could simplify the estimation of the variance components. Then, a formula of change from baseline can be written similar to (5) for the estimation of the variance components:

$$y_{i,j,k} - \bar{y}_{i,0} = \delta_{i,j} + \epsilon_{i,j,k} - \bar{\epsilon}_{i,0} \sim N(\cdot, \sigma^2\delta^2 + \sigma^2(1 + 1/3)) \quad (6)$$

A mixed model with fixed effect factors of treatment nested within visit, replication (for the repeated observations at the post-treatment follow-up in eGFR) will be applied to change from baseline (as the average of the 3 pre-treatment eGFR observations) in eGFR observed at each replication. In this mixed model, replications at the post-treatment follow-up are considered as the repeated measurements, with a compound symmetric variance matrix structure. In this estimated variance-covariance matrix, the diagonal elements are the estimate of  $\sigma^2\delta^2 + \sigma^2(1 + 1/3)$ , and the off diagonal elements are the estimate of  $\sigma^2\delta^2 + \sigma^2(1/3)$ . Solving these two equations will get the estimates of  $\sigma^2\delta^2$  and  $\sigma^2$ . With these variance component estimates, the variance given in formula (5) is estimated for each subject. Dividing

	<p>the estimated variance given in (5) by the subject's trial duration will provide an estimated variance for the subject's annualized change in eGFR. The inverse of this estimated variance will be the weight of the subject used in the primary analysis.</p> <p>SAS code for the estimation of variance component</p> <pre>PROC MIXED; CLASS SUBJECT VISIT TREATMENT REPLICATION; MODEL CHANGE = TREATMENT(VISIT) REPLICATION; REPEATED REPLICATION/TYPE=CS SUB=SUBJECT;</pre>
Page 20	<p>RUN;</p> <p>In this estimation of variance components, it is assumed the post-treatment follow-up eGFR observations of early withdrew subjects are mapped into scheduled visits. Since the monthly scheduled visits in this protocol, for a subject early withdrew IMP, compared to the subject's last scheduled on-treatment visit, if the first post-treatment follow-up eGFR is observed less or equal to 25 days (<math>= 15 + 7 + 3</math>) after the last scheduled on-treatment visit, then the subject's post-treatment follow-up eGFR observations will be mapped to the subject's last scheduled on-treatment visit; otherwise, if the first post-treatment follow-up eGFR is observed less or equal to 55.5 days (<math>= 30.5 + 15 + 7 + 3</math>) after the last scheduled on-treatment visit, then the subject's post-treatment follow-up eGFR observations will be mapped to one month after the subject's last scheduled on-treatment visit; etc.</p> <p>(10) The following method to derive the weight for the primary analysis is proposed in case the blinded sample size re-estimation leads to a change in the number of eGFR observations in pre-treatment baseline period, so that the assumption of equal number of pre-treatment baseline eGFR observations is</p>

	<p>no longer .</p> <p>In order to derive the weight used in the weighted analysis, the following model is considered:</p> $y_{i,0,k} = \alpha_i + e_{i,0,k} \text{ where } k = 1, 2, K_{i,0} \quad (1)$ $y_{i,1,k} = \alpha_i + \delta_i + e_{i,1,k} \text{ where } k = 1, 2, K_{i,1} \quad (2)$ <p>where <math>K_{i,0}</math> is the number of eGFR observations during the pre-treatment baseline period for subject <math>i</math>, and <math>K_{i,1}</math> is the number of eGFR observations during the post-treatment follow-up period for subject <math>i</math>, whether subject <math>i</math> completes the study or not. <math>\alpha_i</math> is a random variable for the “real” eGFR baseline of subject <math>i</math>, and this effect will be cancelled out for change from baseline. <math>\delta_i</math> is a random variable for the “real” change from baseline to post-treatment follow-up of subject <math>i</math>. These <math>\delta_i</math>s are normally distributed, with a common variance <math>\sigma^2\delta</math>, and are independent from subject to subject. In addition, <math>\alpha_i</math>s are assumed iid normally distributed, <math>e_{i,1,k}</math> are assumed iid <math>N(0, \sigma^2)</math>, and all these random variables are mutually independent. Their average over the <math>K_{i,0}</math> observations at baseline and the <math>K_{i,1}</math> observations at post-treatment follow-up will be</p> $\bar{y}_{i,0} = \alpha_i + \bar{e}_{i,0}, \text{ where } \bar{e}_{i,0} \sim N(0, \sigma^2/K_{i,0}) \quad (3)$ $\bar{y}_{i,1} = \alpha_i + \delta_i + \bar{e}_{i,1}, \text{ where } \bar{e}_{i,1} \sim N(0, \sigma^2/K_{i,1}) \quad (4)$ <p>the distribution of the change from baseline for subject <math>i</math> is</p> $\bar{y}_{i,1} - \bar{y}_{i,0} = \delta_i + \bar{e}_{i,1} - \bar{e}_{i,0} \sim N(0, \sigma^2(1/K_{i,0} + 1/K_{i,1})) \quad (5)$ <p>The estimation of <math>\sigma^2</math> is simply provided by</p> $v_e = \frac{1}{2} \left\{ \sum_i \sum_k (y_{i,0,k} - \bar{y}_{i,0})^2 / \sum_i (K_{i,0} - 1) + \sum_i \sum_k (y_{i,1,k} - \bar{y}_{i,1})^2 / \sum_i (K_{i,1} - 1) \right\} \quad (6)$ <p>where <math>\sum_i</math> sums over all subject <math>i</math>, and <math>\sum_k</math> sums over all replicate <math>k</math> for subject <math>i</math>, either at baseline visit or post-treatment follow-up visit. Let</p> $d_i = (\bar{y}_{i,1} - \bar{y}_{i,0}) / t_i \sim N(0, [\sigma^2\delta^2 + \sigma^2(1/K_{i,0} + 1/K_{i,1})] / t_i^2) \quad (7)$ <p>being the annualized change from</p>
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baseline of subject i and its distribution, where  $t_i$  is the trial duration to annualize the primary endpoint for subject i, with mean  $\beta T$  and  $\beta P$  for tolvaptan and placebo subjects respectively. Let

$$t_i = [\sigma\delta_2 + \sigma^2(1/K_{i,0} + 1/K_{i,1})]/t_{i2} \quad (8)$$

The treatment averages are

$$\bar{d}T = \sum_i \text{in TLV} \frac{d_i}{nT} \text{ and } \bar{d}P = \sum_i \text{in PLC} \frac{d_i}{nP} \quad (9)$$

where  $\sum_i \text{in TLV}$  ( $\sum_i \text{in PLC}$ ) sums over all tolvaptan (placebo) subjects, and  $nT$  ( $nP$ ) is the total number of subjects in tolvaptan (placebo). Let

$$v = \frac{1}{2} \{ \sum_i \text{in TLV} (d_i - \bar{d}T)^2 / (nT - 1) + \sum_i \text{in PLC} (d_i - \bar{d}P)^2 / (nP - 1) \} \quad (10)$$

Since

$$\sum_i \text{in TLV} (d_i - \bar{d}T)^2 = \sum_{i \neq i'} \text{in TLV} (d_i - d_{i'})^2 / 2nT \text{ and}$$

$$\sum_i \text{in PLC} (d_i - \bar{d}P)^2 = \sum_{i \neq i'} \text{in PLC} (d_i - d_{i'})^2 / 2nP \quad (11)$$

formula (10) can be rewritten as

$$v = \sum_{i \neq i'} \text{in TLV} (d_i - d_{i'})^2 / [4nT(nT - 1)] + \sum_{i \neq i'} \text{in PLC} (d_i - d_{i'})^2 / [4nP(nP - 1)] \quad (12)$$

and

$$\begin{aligned} E(v) &= \sum_{i \neq i'} \text{in TLV} (\tau_i + \tau_{i'}) / [4nT(nT - 1)] + \\ &\quad \sum_{i \neq i'} \text{in PLC} (\tau_i + \tau_{i'}) / [4nP(nP - 1)] \\ &= \sum_{i \neq i'} \text{in TLV} \{ [\sigma\delta_2 + \sigma^2(1/K_{i,0} + 1/K_{i,1})] / t_{i2} + [\sigma\delta_2 + \sigma^2(1/K'_{i,0} + 1/K'_{i,1})] / t'_{i2} \} / [4nT(nT - 1)] \\ &\quad + \sum_{i \neq i'} \text{in PLC} \{ [\sigma\delta_2 + \sigma^2(1/K_{i,0} + 1/K_{i,1})] / t_{i2} + [\sigma\delta_2 + \sigma^2(1/K'_{i,0} + 1/K'_{i,1})] / t'_{i2} \} / [4nP(nP - 1)] \\ &= \sum_i \text{in TLV} \{ [\sigma\delta_2 + \sigma^2(1/K_{i,0} + 1/K_{i,1})] / t_{i2} \} / (2nT) + \sum_i \text{in PLC} [\sigma\delta_2 + \sigma^2(1/K_{i,0} + 1/K_{i,1})] / t_{i2} \} / (2nP) \\ &= \delta_2 [\sum_i \text{in TLV} 1/(2nT t_{i2}) + \sum_i \text{in PLC} 1/(2nP t_{i2})] \\ &\quad + \sigma^2 [\sum_i \text{in TLV} (1/K_{i,0} + 1/K_{i,1}) / (2nT t_{i2}) + \sum_i \text{in PLC} (1/K_{i,0} + 1/K_{i,1}) / (2nP t_{i2})] \quad (13) \end{aligned}$$

where  $E(v)$  is the expectation of  $v$ . Thus, the estimate of  $\sigma\delta_2$  is

$$\begin{aligned} v\delta &= \{v - E(v) [\sum_i \text{in TLV} (1/K_{i,0} + 1/K_{i,1}) / (2nT t_{i2}) + \sum_i \text{in PLC} (1/K_{i,0} + 1/K_{i,1}) / (2nP t_{i2})]\} \\ &\quad / [\sum_i \text{in TLV} 1/(2nT t_{i2}) + \sum_i \text{in PLC} 1/(2nP t_{i2})] \quad (14) \end{aligned}$$

And the estimated variance of the annualized change from baseline for subject i ( $d_i$ ) is

		[vδ + ve (1/Ki,0 +1/Ki,1)] / ti2 (15) SAP Version 12 OPC41061, P156-13-210 22 The reciprocal of (15) will be the weight for subject i used in the weighted analysis.
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Version 2 to Version 3

Page	Old Text	New Text
Page 7	1288	12
Page 8	This sample size re-estimation is necessary, especially, as recommended by our vendor, a method to analyze for serum creatinine called Rate Blanked is to be used in this protocol, while the sample size calculation is based on the data from 156-04-251, in which another method called "Enzymatic" was used to analyze for serum creatinine. Based on these findings, the serum creatinine. Based on these findings, the serum creatinine sample number and subject sample size of this trial may need to be adjusted.	Based on these findings, the serum creatinine sample number and subject sample size of this trial may need to be adjusted.
Page 16	In case a protocol specified visit is missing for a subject in the batched assessments but available in the non-batched assessments, the missing data in the batched assessments will be fill in using the available non-batched assessments.	Since it is expected that two different methods are applied to these two sets of blood samples (enzymatic method to the batched sample and rate blank method to the first sample), these two sets of eGFR data are not interchangeable.
Page 27		Added Appendix 3
Page 28	a manifestation of an electronically captured signature OPC-41061 SIGNATURE PAGE SAP 156-13-210 Version 1 Final Document Name: Document Number: 0001080112 Document Version: 5.0	this blinded sample size re-estimation should be based on the data of eGFR change from baseline at the post-treatment follow-up visits, in order to provide a more relevant and accurate power estimation for this important study. Question 1: Whether the approach of averaging the 3 eGFR observations at pre-treatment baseline and post-treatment follow-up has achieved the goal of reducing the variance to the level we planned In the following Tables, the one-way ANOVA table of change from baseline to post-treatment follow-up visits of study 251 (used in the calculation of variance components for sample size calculation) and the one-way AVOVA table of change from baseline to post-treatment follow-up visits of study 210

		derived from the current data transfer are provided, both based on the eGFR CKD-EPI formula (ml/min/1.73 m <sup>2</sup> ): Table 1 251 ANOVA Table of Change from Pre-titration Baseline in Renal function to FU Visits and Their Average, Non-Japan Subjects with Baseline GFR < 60 and Observation at Pre-treatment Baseline, FU Visits 1 and 2 Treatment Source DF SS MS F-value P-value.
		Placebo Between 53 10678.83 201.49 2.52 <.0001 Within 162 12932.38 79.83 Corrected Total 215 23611.20 Tolvaptan Between 93 14568.82 156.65 3.01 <.0001 Within 282 14654.14 51.97 Corrected Total 375 29222.96 Table 2 210 ANOVA Table
Pages 36-39		Inserted

Version 3 to Version 4

Pages	Old Text	New Text
12-13		However, in order to reduce the impact of the outliers created by the annualized eGFR change in early dropout subjects, all annualized changes of dropout subjects that are greater (or less) than the maximum (or minimum) of the annualized eGFR change of all on-treatment completers will assume the maximum (or minimum) value as their annualized eGFR changes used in the primary analysis. This is because of the possibility that annualization of very variable short-term data (one or two months) by requiring a multiplication factor of 12 or 6 can result in an exaggerated estimate of annualized eGFR change. Early examples showed that this cannot be adequately managed by simple weighting in the analysis. Therefore, restrictions on the maximum and minimum values observed in the on-treatment completer population can further buffer the untoward effects of such outliers. In addition, the analysis based on the unadjusted annualized eGFR changes will serve as a sensitivity analysis of the primary endpoint.
	To reduce the variation in this primary endpoint, 3 observations of eGFR are observed at baseline during a 3-week interval (screening and placebo run-in periods) and another 3 observations are observed after one	To reduce the variation in this primary endpoint, the last 3 observations of eGFR up to placebo run-in are observed at baseline (screening and placebo run-in periods) and another first 3 observations are observed after one week of posttreatment follow-up during a two week interval (within a

	week of posttreatment follow-up during a two week interval (within a total of 3-weeks post-treatment followup).	total of 3-weeks post-treatment followup).
		Although it was initially designed to have subjects come back in this two week period to have their eGFR measures, it turns out that not all subjects could achieve this in our clinical operation. In order to reduce excluding subjects in the primary analysis due to failing to have follow-up data within this two week period, the window to have follow-up eGFR observations is thus set to be from 7 to 40 days post the last dose of IMP. Because the primary endpoint is annualized eGFR change, extending the follow-up window does not change placebo subjects' primary endpoint, since the duration from baseline to follow-up would be extended as well. For tolvaptan subjects, this window definition is actually conservative, since a few days of no treatment would be added to the duration of tolvaptan treatment for the annualization.
Page 16	4. Aquaretic AE	4. Aquaretic AE (MedDRA preferred terms of THIRST, POLYURIA, NOCTURIA, POLLAKIURIA, POLYDIPSIA)
Page 18		In addition, the eGFR labelled as "Unscheduled" will be used in efficacy analysis if a subject has two eGFRs observed on the same day and same time.
Page 19		In addition, 6/572 will be multiplied to the estimate of the linear trend contrast in order to provide an estimate of treatment difference in eGFR slope.
Page 25	This trial is to be conducted over a critical time period during which tolvaptan may be approved as therapy for ADPKD in some of the participating regions. The European Medicines Agency's (EMA) decision for a pending marketing authorization application for use of tolvaptan in treatment of ADPKD is expected in 2015. Following regulatory approval, reimbursement and commercial availability may have an impact on the ongoing ethical conduct of the trial. This may impact	An optional interim analysis was planned but not conducted, because, given the rapid final enrollment, the sponsor, upon receiving recommendation from the trial's Steering Committee, deemed the analysis might only bring a few month's difference in trial conclusion.

	<p>subjects enrolled in Europe who are continuing in the randomized, placebo-controlled treatment phase. Therefore, the IDMC for this trial will be empowered to conduct an interim analysis (IA) of the primary endpoint once approximately half of enrolled subjects (600-700) complete their planned one-year treatment. The sponsor may decide the actual timing of the IA based on the availability of commercial tolvaptan in ADPKD. This IA would use the O'Brian-Fleming spending function to apportion alpha and thus manage Type 1 error. Determination of the information time of the IA assumes total sample size in this trial to be set at 1300 if the trial is still randomizing subjects at the time of the IA. Alternatively the actual total sample size will be used if the trial has stopped enrollment. For example, if the first 650 subjects out of 1300 total sample size are included, a p-value &lt; 0.003051 is required to reject the null hypothesis, satisfy the objective of replicating efficacy, and offer a possibility for early trial completion. If a recommendation for early termination is accepted, all subjects remaining in the trial can be offered participation in a planned open-label extension trial. If the null hypothesis is not rejected at this interim analysis, the trial would continue and the alpha of the final test of the primary endpoint is 0.049002.</p>	
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Version 4 to Version 5

Page	Old Text	New Text
Page 12	The timing of baseline and post-treatment observations are also set to the median of the time of observations in the two to three-week interval respectively, and the duration is equal to the date of baseline observation minus	The dates of baseline and post-treatment observations are also set to the median of the dates of the (up to) three baseline and the (up to) three post-treatment follow-up observations respectively, and the duration is equal to the date of post-treatment follow-up minus the date of

	the date of post-treatment observation plus one.	baseline plus one. This duration is used in the calculation of the annualized change.
Page 18	CLASS SUBJECT VISIT TREATMENT AGE_STATUS GFR_STATUS TKV_STATUS; MODEL CHANGE = TREATMENT VISIT TREATMENT*VISIT BASELINE BASELINE*VISIT AGE_FACTOR GFR_FACTOR TKV_FACTOR; REPEATED VISIT/TYPE=UN SUB=SUBJECT; LSMEANS TREATMENT*VISIT./PDIFF CL ALPHA=0.05; ESTIMATE 'TREND DIFF' TREATMENT 0 0 VISIT 0 0 0 0 0 0 0 0 0 0 TREATMENT*VISIT 11 9 7 5 3 1 -1 -3 -5 -7 -9 -11 -11 -9 -7 -5 -3 -1 1 3 5 7 9 11	CLASS TREATMENT VISIT AGE_STATUS GFR_STATUS TKV_STATUS SUBJECT; MODEL CHANGE = TREATMENT VISIT TREATMENT*VISIT BASELINE BASELINE*VISIT AGE_FACTOR GFR_FACTOR TKV_FACTOR; REPEATED VISIT/TYPE=UN SUB=SUBJECT; LSMEANS TREATMENT*VISIT./PDIFF CL ALPHA=0.05; ESTIMATE 'TREND DIFF' TREATMENT 0 0 VISIT 0 0 0 0 0 0 0 0 0 0 TREATMENT*VISIT 11 9 7 5 3 1 -1 -3 -5 -7 -9 -11 -11 -9 -7 -5 -3 -1 1 3 5 7 9 11
	In addition, 6/572 will be multiplied to the estimate of the linear trend contrast in order to provide an estimate of treatment difference in eGFR slope.	In addition, 6/143 will be multiplied to the estimate of the linear trend contrast in order to provide an estimate of treatment difference in eGFR slope.
Page 24	11 An optional interim analysis was planned but not conducted, because, given the rapid final enrollment, the sponsor, upon receiving recommendation from the trial's Steering Committee, deemed the analysis might only bring a few month's difference in trial conclusion. Reference	An optional interim analysis was planned but will not be conducted, because, given the rapid final enrollment, the sponsor, upon receiving recommendation from the trial's Steering Committee, deemed the analysis might only bring a few month's difference in trial conclusion. Thus, without the interim analysis, the alpha level of the final analysis will be 0.05.

Version 5 to Version 6

Page	Old Text	New Text
Page 8	Detailed actions in the blinded sample size re-estimation will be documented.	Detailed actions in the blinded sample size re-estimation was documented in Appendix 5.
Page 11		Proposed tables and figures to be generated for the efficacy analysis can be found in Appendices 3 and 4.
Page 14		Another sensitivity analysis will apply MMRM analysis similar to the one provided in the previous paragraph (without deriving linear contrast) to the data of change from baseline in eGFR, from Tolvaptan Titration Visit, Tolvaptan Run-in Visits 1 and 2, and Month 1, Month 2,

		..., up to Month 12, and Post-treatment Follow-up Visit (average).
Page 15	<p>Multiple imputation is commonly used in the analysis of MNAR data. For all randomized subjects who withdraw consent for further testing or who are lost to follow up, imputation of missing data will be applied to projected visits up to their planned end of the trial (12 months post randomization).</p> <p>Imputation will be based on the MMRM model specified in section 8.2.2.</p>	<p>Multiple imputation is commonly used in the analysis of MNAR data. For all randomized subjects who withdraw early imputation of missing data will be applied to projected visits up to their planned end of the trial (12 months post randomization).</p> <p>Imputation will be based on the data used in the MMRM model specified in section 8.2.2.</p>
		In order to perform the analysis of random coefficient regression model specified for the key secondary endpoint, simulated value of a missing data will be assigned a value for the time variable used in regression which is equal to the time of its previous visit plus 30.5 days.
	<p>Post-withdrawal data from the 156-04-251 trial and 156-08-271 interim analysis show that tolvaptan's eGFR benefits accumulate and are sustained after treatment discontinuation; therefore, imputation for subjects randomized to tolvaptan should reasonably begin at the value of their last eGFR. If a subject has the post-treatment follow-up in the two-week interval, imputation will be based on this post-treatment observation; if a subject does not have the post-treatment follow-up observation, imputation will be based on the last on-treatment observation and flagged with the tolvaptan acute hemodynamic effect mentioned in section 8.2.1. The imputation of these tolvaptan withdrew consent/lost to follow-up subjects is based on the following:</p>	<p>Post-withdrawal data from the 156-04-251 trial and 156-08-271 interim analysis show that tolvaptan's eGFR benefits accumulate and are sustained after treatment discontinuation; therefore, imputation for subjects randomized to tolvaptan should reasonably begin at the value of their last on-treatment eGFR and flagged with the tolvaptan acute hemodynamic effect mentioned in section 8.2.1. The imputation of these tolvaptan withdrew subjects is based on the following:</p>
Page 22		(11) Mapping of unscheduled visit and End of Treatment visit during double-blind treatment period to nominal visits: In general, these visits will be mapped into the monthly nominal visits based on the mid-point between two monthly visits, ie, if an unscheduled visit or an End of Treatment visit is within 15 days of the previous visit, it will be mapped to the previous

	<p>visit; if it is greater than 15 day of the previous visit, it will be mapped to next appropriate visit, with 30.5 days (round if necessary) between each two adjacent nominal visits. If an unscheduled visit or an End of Treatment visit falls into 351 (rounded from <math>30.5 \times 11 + 15</math>) to 381 (<math>= 366 + 15</math>) days post randomization, it will be mapped to visit Month 12. If an unscheduled visit or an End of Treatment visit is more than 2 days post last dose, it will not be mapped to these double-blind nominal visits, but will be considered for the post-treatment Follow-up visits, if it falls within 7 to 40 days from the last dose of IMP.</p> <p>(12) The following reasons are collected in the CRF for subjects who discontinue IMP:</p>
Page 23	<ol style="list-style-type: none"> <li>1. Discontinued based on subject decision:             <ol style="list-style-type: none"> <li>1.1. IMP not tolerable (AE which is annoying or uncomfortable but not serious or hazardous)</li> <li>1.2. Reason other than tolerability                     <ol style="list-style-type: none"> <li>1.2.1. Pregnancy</li> <li>1.2.2. Trial too burdensome</li> <li>1.2.3. Other reason</li> </ol> </li> <li>1.3. Taking marketed product for tolvaptan</li> </ol> </li> <li>2. Discontinued based on physician decision             <ol style="list-style-type: none"> <li>2.1. Potential IMP-related safety concern or serious AR placing subject at undue hazard</li> <li>2.2. Progression of disease leading to dialysis, transplantation or eGFR decline</li> <li>2.3. Hepatic AE</li> </ol> </li> <li>3. Other             <ol style="list-style-type: none"> <li>3.1. Subject death</li> <li>3.2. Subject lost to Follow-up</li> </ol> </li> </ol> <p>In Sectin 8.2.4 for sensitivity analysis including imputation of missing data, six reasons of discontinuation of IMP were listed in the order of their likelihood to be MNAR. The mapping of the reasons of discontinuation of IMP to the reasons used in the sensitivity analysis is provided below:</p> <ul style="list-style-type: none"> <li>• Progression of renal disease or Lack of efficacy: Item 2.2</li> </ul>

		<ul style="list-style-type: none"> <li>• Other AE: Items of 1.2.3, 2.1, 2.3, 3.1 and 3.2</li> <li>• Aquaretic AE: Item 1.1</li> <li>• Trial too burdensome: Items of 1.2.1 and 1.2.2</li> <li>• Commercial tolvaptan for ADPKD available: Item 1.3</li> </ul> <p>The reason to map Items of 1.2.3 (Other reasons under Reason other than tolerability) and 3.2 (Subject lost to Follow-up) to other AE is for conservativeness to consider them as a reason to be more likely MNAR.</p>
Page 24	Subgroup analyses will be provided to the primary and the key secondary endpoints by region (US and non-US), gender (male and female), race (Caucasian and Other races), age (<= 55 years or not), baseline GFR level (eGFR CKD-EPI <= 45mL/min/1.73 m <sup>2</sup> or not), and baseline Total Kidney volume (<= 2000 mL or not, or unknown).	Subgroup analyses will be provided to the primary and the key secondary endpoints by region (US and non-US), gender (male and female), race (Caucasian and Other races), age (<= 55 years or not), baseline GFR level (eGFR CKD-EPI <= 45 mL/min/1.73 m <sup>2</sup> or not), and baseline Total Kidney volume (<= 2000 mL or not, or unknown), and by CKD Stage.
Page 25		Proposed tables and figures to be generated for the safety analysis can be found in Appendices 3 and 4.
Page 27	During treatment with tolvaptan, serum creatinine is expected to increase by approximately 5-10%. When these tables are generated during the double-blind conduct, the post-randomization comparisons will be made to the post-randomization (PR) value which equals the value collected post-randomization at Month 1 visit. After data-base lock, final reporting of unblinded tables and listings, A (PR) should be changed to the highest value obtained during the run-in period matching the subject's assigned treatment, ie, either placebo or tolvaptan run-in periods.)	During treatment with tolvaptan, serum creatinine is expected to increase by approximately 5-10%. Post-randomization baseline (PR) is equal to the highest value obtained during the run-in period matching the subject's assigned treatment, ie, either placebo or tolvaptan run-in periods.)
Page 31	CT-5.2.3 Sensitivity Analysis of Key Secondary Endpoint: Missing Data of Annualized eGFR (CKD-EPI) Change Slope (mL/min/1.73 m <sup>2</sup> /yr)	CT-5.2.3 Sensitivity Analysis of Key Secondary Endpoint: Linear Mixed Model of Annualized eGFR (CKD-EPI) Change Slope (mL/min/1.73 m <sup>2</sup> /yr)
Page 38	CT-13.2.1 Analysis of Key Secondary Endpoint by Site: Linear Mixed Effect Model	

	<p>of Annualized eGFR (CKD-EPI) Change Slope (mL/min/1.73 m<sup>2</sup>/yr) – Key Secondary Endpoint Efficacy Population</p> <p>CT-13.2.2 Analysis of Key Secondary Endpoint by Country: Linear Mixed Effect Model of Annualized eGFR (CKD-EPI) Change Slope (mL/min/1.73 m<sup>2</sup>/yr) – Key Secondary Endpoint Efficacy Population</p>	
	<p>CT-14.1 Exploratory Analysis of Primary Endpoint: Weighted ANCOVA of Annualized Change in eGFR (CKD-EPI) from Pre-treatment Baseline to Posttreatment Follow-up (mL/min/1.73 m<sup>2</sup>/yr) - Primary Endpoint Efficacy Population</p>	<p>CT-14.1 Exploratory Analysis of Primary Endpoint: Weighted ANCOVA Based on Modal Dose of Annualized Change in eGFR (CKD-EPI) from Pre-treatment Baseline to Posttreatment Follow-up (mL/min/1.73 m<sup>2</sup>/yr) - Primary Endpoint Efficacy Population</p>
	<p>CT-14.2 Exploratory Analysis of Key Secondary Endpoint: Linear Mixed Effect Model of Annualized eGFR (CKD-EPI) Change Slope (mL/min/1.73 m<sup>2</sup>/yr) –Key Secondary Endpoint Efficacy Population</p>	<p>CT-14.2 Exploratory Analysis of Key Secondary Endpoint: Linear Mixed Effect Model Based on Modal Dose of Annualized eGFR (CKD-EPI) Change Slope (mL/min/1.73 m<sup>2</sup>/yr) – Key Secondary Endpoint Efficacy Population</p>
	CT-1.1.1 - Subject Disposition	
Deleted Pages 39-44		
Page 45	<p>CT-11.3.2 - Incidence of Vital Signs with Potential Clinical Relevance - Secondary Safety Population, Single-blind Tolvaptan Treatment Period</p> <p>CT-11.3.3 - Mean Change from Baseline in Vital Signs Parameters - Secondary Safety Population, Single-blind Tolvaptan Treatment Period</p> <p>CT-12.1 - Exploratory Analysis of the Primary Endpoint of Annualized eGFR (CKD-EPI) Change Slope (mL/min/1.73 m<sup>2</sup>/yr) - ITT</p> <p>CT-12.2 - Exploratory Analysis of the Key Secondary Endpoint of Annualized rate of eGFR (CKD-EPI) Change (mL/min/1.73 m<sup>2</sup>/yr) – ITT</p> <p>CT-12.3.1 - Exploratory Analysis of Time to Multiple Events of Composite ADPKD Outcomes (Six Items) – ITT</p> <p>CT-12.3.2 - Exploratory Analysis of Time to Multiple Events of ADPKD Outcomes (Kidney Pain) – ITT</p> <p>CT-12.3.3 - Exploratory Analysis of Time to Multiple Events of ADPKD Outcomes</p>	

	(Hematuria)- ITT CT-12.3.4 - Exploratory Analysis of Time to Multiple Events of ADPKD Outcomes (UTI) – ITT	
		<p>Appendix 4: Table of Contents for Clinical Figures</p> <p>Figure 1.1 Annualized Change in eGFR (CKD-EPI) from Pre-treatment Baseline to Posttreatment</p> <p>Follow-up Primary Endpoint Efficacy Population</p> <p>Figure 1.2 Annualized Change in eGFR (CKD-EPI) from Pre-treatment Baseline to Posttreatment</p> <p>Follow-up Primary Endpoint Efficacy Population (Additional Sensitivity Analyses)</p> <p>Figure 2.1 Linear Mixed Effect Model of Annualized eGFR (CKD-EPI) Change Slope Key Secondary Endpoint Efficacy Population</p> <p>Figure 2.2.1 eGFR (CKD-EPI) Values and Their Regression Lines from Linear Mixed Effect Model Key Secondary Endpoint Efficacy Population</p> <p>Figure 2.2.2 eGFR (CKD-EPI) Values and Their Regression Lines from Linear Mixed Effect Model Key Secondary Endpoint Population, Including Data Collected During the Post-discontinuation Follow-up</p> <p>Figure 3.1 Sensitivity Analysis: Slope Comparison Based on MMRM Analysis of eGFR (CKD-EPI) Change from Baseline Key Secondary Endpoint Population</p> <p>Figure 3.2 SensitivitY Analysis: MMRM Analysis of eGFR (CKD-EPI) Change from Baseline Key Secondary Endpoint Population</p>
Page 46		<p>Figure 6.1 Treatment Difference in Annualized Change in eGFR (CKD-EPI) from Pretreatment Baseline to Post-treatment Follow-up by Site, Primary Endpoint Efficacy Population</p> <p>Figure 6.2 Treatment Difference in Annualized Change in eGFR (CKD-EPI) from Pretreatment Baseline to Post-treatment Follow-up by Country, Primary Endpoint Efficacy Population</p>
	<p>Figure 6.1 Mean of Estimated Annualized eGFR Change Slope for Subjects Completed/Discontinued from Treatment, Primary Endpoint Efficacy Population</p> <p>Figure 6.2 Mean of Estimated Annualized</p>	<p>Figure 7.1 Mean of Estimated Annualized eGFR Change for Subjects Completed/Discontinued from Treatment, Primary Endpoint Efficacy Population</p> <p>Figure 7.2 Mean of Estimated Annualized eGFR</p>

	<p>eGFR Change Slope by Reason for Discontinuation from Treatment, Primary Endpoint Efficacy Population</p> <p>Figure 7.1 Mean Change from Baseline in eGFR (CKD-EPI) for Dropouts - Tolvaptan, Key Secondary Endpoint Population</p> <p>Figure 7.2 Mean Change from Baseline in eGFR (CKD-EPI) for Dropouts - Placebo, Key Secondary Endpoint Population</p> <p>Figure 9.1 Kaplan-Meier Curves of Time to Discontinuation of Study All Randomized Subjects</p>	<p>Change by Reason for Discontinuation from Treatment, Primary Endpoint Efficacy Population</p> <p>Figure 8.1 Mean Change from Baseline in eGFR (CKD-EPI) for Dropouts - Tolvaptan, Key Secondary Endpoint Population</p> <p>Figure 8.2 Mean Change from Baseline in eGFR (CKD-EPI) for Dropouts - Placebo, Key Secondary Endpoint Population</p> <p>Figure 9.1 Kaplan-Meier Curves of Time to Discontinuation of Study All Randomized Subjects</p>
	<p>Figure 98.2 Kaplan-Meier Curves of Time to Discontinuation of IMP Primary Safety Population</p> <p>Figure 109.1 Incidence of Treatment Emergent Adverse Events with at least 5% in any Treatment Group Primary Safety Population, Double-blind Treatment Period</p> <p>Figure 109.2.1 Kaplan-Meier Curves of Time to TEAE in Liver Primary Safety Population, Double-blind Treatment Period</p> <p>Figure 109.2.2 Kaplan-Meier Curves of Time to TEAE in Skin Neoplasms Primary Safety Population, Double-blind Treatment Period</p> <p>Figure 110.1 Kaplan-Meier Curves of Time to ALT &gt; 3xULN Primary Safety Population, Double-blind Treatment Period</p>	<p>Figure 9.2 Kaplan-Meier Curves of Time to Discontinuation of IMP Primary Safety Population</p> <p>Figure 10.1 Incidence of Treatment Emergent Adverse Events with at least 5% in any Treatment Group Primary Safety Population, Double-blind Treatment Period</p> <p>Figure 10.2.1 Kaplan-Meier Curves of Time to TEAE in Liver Primary Safety Population, Double-blind Treatment Period</p> <p>Figure 10.2.2 Kaplan-Meier Curves of Time to TEAE in Skin Neoplasms Primary Safety Population, Double-blind Treatment Period</p> <p>Figure 11.1 Kaplan-Meier Curves of Time to ALT &gt; 3xULN Primary Safety Population, Double-blind Treatment Period</p>
	<p>Figure 11.1 Peak Bilirubin/ULN Ratio versus Peak ALT/ULN Ratio Primary Safety Population, Double-blind Treatment Period</p>	<p>Figure 11.2.1 Kaplan-Meier Curves of Time from Peak ALT to Normal (&lt;1xULN) Primary Safety Population, Adjudicated Subjects</p> <p>Figure 11.2.2 Kaplan-Meier Curves of Time from Peak ALT to Normal (&lt;1xULN) Based on Discontinuation Status in Tolvaptan Group Primary Safety Population, Adjudicated Subjects</p> <p>Figure 12.1 Peak Bilirubin/ULN Ratio versus Peak ALT/ULN Ratio Primary Safety Population, Double-blind Treatment Period</p>
	<p>Figure 12.1.1 Analysis of Primary Endpoint by Site: Weighted ANCOVA of Annualized Change in eGFR (CKD-EPI) from Pre-treatment Baseline to Post-treatment Follow-up (mL/min/1.73 m<sup>2</sup>/yr), Primary Endpoint Efficacy Population</p> <p>Figure 12.1.2 Analysis of Primary Endpoint by Country: Weighted ANCOVA of</p>	

	<p>Annualized Change in eGFR (CKD-EPI) from Pre-treatment Baseline to Post-treatment Follow-up (mL/min/1.73 m<sup>2</sup>/yr), Primary Endpoint Efficacy Population</p> <p>Figure 12.2.1 Analysis of Key Secondary Endpoint by Site: Linear Mixed Effect Model of Annualized eGFR (CKD-EPI) Change Slope (mL/min/1.73 m<sup>2</sup>/yr), Key Secondary Endpoint Efficacy Population</p> <p>Figure 12.2.2 Analysis of Key Secondary Endpoint by Country: Linear Mixed Effect Model of Annualized eGFR (CKD-EPI) Change Slope (mL/min/1.73 m<sup>2</sup>/yr), Key Secondary Endpoint Efficacy Population</p>
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