- **Protocol number: 156-13-211**
- **Document title: A Phase 3b, Multi-center, Open-label Trial to Evaluate the Long Term Safety of Immediate-release Tolvaptan (OPC-41061, 30 mg to 120 mg/Day, Split Dose) in Subjects With Autosomal Dominant Polycystic Kidney Disease**
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Protocol and/or Protocol Amendments
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Otsuka Pharmaceutical
Development & Commercialization, Inc.

Investigational Medicinal Product

Tolvaptan (OPC-41061)

REVISED CLINICAL PROTOCOL

A Phase 3b, Multi-center, Open-label Trial to Evaluate the Long Term Safety of Immediate-release Tolvaptan (OPC-41061, 30 mg to 120 mg/day, Split dose) in Subjects with Autosomal Dominant Polycystic Kidney Disease

Protocol No. 156-13-211
IND No. 72,975
EudraCT No. 2014-001516-19

CONFIDENTIAL – PROPRIETARY INFORMATION

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Protocol 156-13-211

Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc. Name of Investigational Medicinal Product: Tolvaptan (OPC-41061)	Protocol # 156-13-211 IND# 72,975 EudraCT# 2014-001516-19
Protocol Title:	A Phase 3b, Multi-center, Open-label Trial to Evaluate the Long Term Safety of Immediate-release Tolvaptan (OPC-41061, 30 mg to 120 mg/day, Split dose) in Subjects with Autosomal Dominant Polycystic Kidney Disease
Clinical Phase/Trial Type:	Phase 3b/Therapeutic use
Treatment Indication:	Autosomal Dominant Polycystic Kidney Disease (ADPKD)
Objective:	The primary objective of this trial is: • To evaluate and describe the long-term safety of tolvaptan.
Trial Design:	This trial is a phase 3b, multi-center, open-label extension trial. Subjects will be eligible for screening into this trial if they: • Completed and transferred from the double-blind Trial 156-13-210 (12-month period including post-treatment follow-up, regardless of whether this was on-treatment or off-treatment), or have completed all but the last follow-up visit, which will be combined with the first visit in this trial or • Completed Trial 156-08-271 or a prior tolvaptan ADPKD trial, or have completed all but the end of trial visit, which will be combined with the first visit in this trial or • Interrupted or discontinued treatment in a prior tolvaptan ADPKD trial (other than Trial 156-13-210). Subjects may be enrolled with medical monitor approval, and additional close monitoring may be required at the beginning of the trial For purposes of ensuring subject safety, all subjects will be monitored for hepatic safety monthly until they have accumulated 18 months of tolvaptan exposure. After that, and following the approval from the medical monitor, hepatic monitoring will be required every 3 months. If subjects

	approaching the 18-month threshold have had prior transaminase abnormalities (> 2 × upper limit of normal [ULN]), the investigator is responsible for contacting the medical monitor to confirm the change in frequency from monthly to every 3 months. Until their prior treatment assignment is unblinded, all Trial 156-13-210 subjects who are eligible for this trial are scheduled to have trial visits/ hepatic monitoring monthly for the first 18 months of this trial. Once unblinding occurs, it can be determined which subjects received tolvaptan in Trial 156-13-210. These subjects may have their trial visits/hepatic transaminase monitoring change to every 3 months sooner as their previous tolvaptan exposure in Trial 156-13-210 can count towards the 18-month threshold. Enrollment in this trial will be closed when the final eligible subject from Trial 156-13-210 enrolls in this trial.
Subject Population:	This trial will include approximately 2,500 subjects over the age of 18 years with ADPKD diagnosed by Pei-Ravine criteria (modified by magnetic resonance imaging [MRI]), and who have completed or participated in a prior ADPKD interventional investigational medicinal product (IMP) trial.

Inclusion/Exclusion Criteria:	<u>Main inclusion criteria:</u>
	• Male and female subjects ≥ 18 years with a confirmed diagnosis of ADPKD (during participation in prior tolvaptan trials) who have
	  • Completed and transferred from the double-blind Trial 156-13-210 (12-month period including post-treatment follow-up, regardless of whether this was on-treatment or off-treatment), or
	  • Completed Trial 156-08-271 or a prior ADPKD tolvaptan trial, or
	  • Interrupted or discontinued treatment in a prior tolvaptan ADPKD trial other than Trial 156-13-210. Subjects may be enrolled with the medical monitor approval, and additional close monitoring may be required at the beginning of the trial
	• Estimated glomerular filtration rate (eGFR) ≥ 20 mL/min/1.73m^2 within 3 months of the baseline visit. Subjects who have an eGFR

	≤ 20 mL/min/1.73m^2 may be enrolled with medical monitor and sponsor approval and increased frequency of monitoring to ensure subjects' safety. • Renal function will be assessed during screening by using historical laboratory values (within 3 months from the screening visit) for serum creatinine levels to calculate the eGFR. The eGFR values will be estimated based on the Chronic Kidney Disease - Epidemiology (CKD-EPI) formula <u>Main exclusion criteria:</u> • Need for chronic diuretic use • Hepatic impairment based on hepatic laboratory assessments (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin, total [BT]) other than that expected for ADPKD with cystic liver disease
Trial Site(s):	Approximately 220 enrolling sites including but not limited to the following regions: North America, South America, Eastern Europe, Western Europe, Russian Federation, and Australia.
Investigational Medicinal Product(s), Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration:	The dose regimens to be used in this trial are 15/15 mg, 30/15 mg, 45/15 mg, 60/30 mg, and 90/30 mg. Tolvaptan tablets (15 mg or 30 mg) will be self-administered orally as split-dose regimens, twice daily, once upon awakening and another approximately 8 to 9 hours later. Doses will be recorded as early dose/late dose (eg, 60/30 mg). Subjects will receive open-label tolvaptan for the duration of the trial. A subject's starting dose in this trial will be dependent on the trial in which they were previously enrolled: • **156-13-210**- initiated on tolvaptan at a split-dose of 45/15 mg with upward titration every 3 to 4 days to 60/30 mg or 90/30 mg per day according to tolerability • **156-08-271**- will retain the last dose level from 271 and start at the same dose in this trial • **Prior tolvaptan trials**- initiated on tolvaptan at a split-dose of 45/15 mg with upward titration every 3 to 4 days to 60/30 mg or 90/30 mg per day according to tolerability Down titration to 30/15 mg or 15/15 mg will be allowed at the

	discretion of the investigator according to individual tolerability and with medical monitor notification. Further down titration to 30 or 15 mg once daily may be allowed **only** for metabolic drug-drug interaction and requires medical monitor approval.
Trial Assessments:	Screening: Informed consent, medical history (including ADPKD updates, as required), determination of eligibility through inclusion/exclusion criteria, dietary review, vital signs, clinical laboratory assessments, physical examination, urine pregnancy test (women of child-bearing potential only [WOCBP]), concomitant medications and laboratory tests to determine eligibility. Safety: Adverse events (AEs), vital signs, directed physical examination, dietary review, self-assessed drug tolerability, serum chemistry tests (including serum transaminases, alkaline phosphatase, bilirubin, and serum sodium) and concomitant medications. CCI [redacted] CCI [redacted]
Criteria for Evaluation	Safety: • AEs • Vital signs • Clinical laboratory assessments • Serum transaminase elevations for frequency (2x, 3x, 5x and 10x ULN), time to onset, time to peak levels, time of offset (< 3x, 2x, or 1x ULN), response to de-challenge and re-challenge and frequency of progression to Hy's laboratory criteria (ALT or AST > 3x ULN and BT > 2x ULN without alkaline phosphatase ≥ 2x ULN) • Serum sodium excursions above 145, 150, or

	155 mmol/L or below 135, 130, or 125 mmol/L CCI [redacted]
Statistical Methods:	Sample size: Sample size was not determined by a formal computation to achieve a target power. No efficacy analyses are planned. It is expected that approximately 2,500 subjects may enroll from previous tolvaptan trials. Analysis datasets: • Enrolled Population: all subjects who were enrolled to this open-label trial • Safety Population: all subjects in the Enrolled Population who take at least 1 dose of IMP Safety analyses: 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 be summarized.
Trial Duration:	Trial duration is planned to continue • Until the last subject from Trial 156-13-210 completes 18 months of tolvaptan treatment in this trial • Subjects enrolling from other trials will conclude their participation once tolvaptan becomes available through routine prescription or through a CCI [redacted] or named-patient program. Trial 156-13-210 subjects may opt to conclude their participation in this trial if tolvaptan becomes available before they complete 18 months of treatment in this trial

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ADPKD	Autosomal dominant polycystic kidney disease
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AVP	Arginine vasopressin
BT	Bilirubin, total
cAMP	Cyclic adenosine monophosphate
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease - Epidemiology
CRF	Case report form
CSR	Clinical study report
DILI	Drug-induced liver injury
DILIN	Drug-induced liver injury network
CCI	[redacted]
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
eGFR CKD-EPE	Estimated glomerular filtration rate calculated by the Chronic Kidney Disease-Epidemiology (CKD-EPI) formula
EMA	European Medicines Agency
EoTx	End of treatment
ESRD	End-stage renal disease
EudraCT	European Clinical Trial Data Base
GCP	Good Clinical Practice
HAC	Hepatic adjudication committee
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
ID	Identification
IDMC	Independent data monitoring committee
IEC	Independent ethics committee
IMP	Investigational medicinal product
IND	Investigational new drug
IRB	Institutional review board
IRE	Immediately reportable event
IRT	Interactive response technology
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
OPC	Otsuka Pharmaceutical Co.
OPDC	Otsuka Pharmaceutical Development & Commercialization, Inc.
PKD	Polycystic kidney disease
SAE	Serious adverse event
SAP	Statistical Analysis Plan

SD	Standard deviation
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US or USA	United States or United States of America
WOCBP	Women of childbearing potential

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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, Republic of Korea, and Taiwan, for various forms of hyponatremia, and in Japan 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.[1] Though a rare genetic disease, it ranks as the 6th leading cause of ESRD in the US (2.3% of the new ESRD cases).[2] An estimated 45% to 70% of patients with ADPKD progress to ESRD by age 65.[3] 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 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.[4 5] Refer to the Tolvaptan Investigator's Brochure (IB) for more information.[4]

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.[6 7] 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_2 receptor. For information on nonclinical toxicology and absorption, distribution and metabolism data on tolvaptan please refer to the most current version of the IB.[4]

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.[8] 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).[9] 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.

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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 $eGFR_{CKD-EPI}$ ($mL/min/1.73m^2$)		N (Tolvaptan/ Placebo)	eGFR Slope Tolvaptan	eGFR Slope Placebo	Effect Size	Relative Effect Size
Stage 1 (≥ 90)		330/173	-1.93	-2.86	0.94[a]	33%
Stage 2 (60-90)		465/224	-2.64	-3.85	1.21[a]	31%
Stage 3[b] (30-60)	3a (45-60)	135/70	-3.51	-5.23	1.72	33%
	3b (30-45)	28/14	-3.92	-5.99	2.07	35%

eGFR CKD-EPE = estimated glomerular filtration rate calculated by the Chronic Kidney Disease-Epidemiology (CKD-EPI) formula

[a] All $p < 0.005$

[b] CKD-Stage 3: relative effect size (33%); N (tolvaptan/placebo; 163/84)

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

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1.3 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.

As of 31 Mar 2013, pooled exposure data are available from 82 trials, involving 6,794 subjects worldwide comprising 3,115 subjects in trials for with heart failure, 425 subjects in trials for hyponatremia, 961 subjects in a long-term trial for ADPKD, 137 subjects in a short-term trial for ADPKD or renal impairment, 217 subjects in trials for cardiac edema, 855 subjects in trials for hepatic edema, 37 subjects with renal impairment in a phase 1 trial, and 1,047 healthy subjects in clinical pharmacokinetic

trials. Overall, subjects were exposed to oral doses of tolvaptan ranging from 3.75 to 480 mg. The median exposure for all doses of oral formulations combined was 29 days, with a mean exposure of 228 days (± 346 days).

Pooled safety data from 80 trials indicate that the most commonly reported (> 3%) treatment-emergent adverse events (TEAEs) for tolvaptan-treated subjects were thirst (25.8%), dry mouth (10.8%) and pollakiuria (9.9%).

The most notable safety issue associated with chronic tolvaptan use, which was newly identified in Trial 156-04-251, was 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, combined from Trials 156-04-251 and 156-08-271) with laboratory and clinical evidence of potentially serious drug-induced liver injury (DILI).[10] Based on the available data from the afore-mentioned trials, the sponsor proposes that appropriate subject monitoring and management be implemented to mitigate this potential risk in the ADPKD population.

In this extension trial, subjects enrolling from the double-blind Trial 156-13-210 will have monthly visits and transaminase level assessments for the first 18 months while the treatment code from Trial 156-10-210 remains blinded, to ensure that all subjects have adequate safety monitoring during this period of susceptibility. Once unblinding occurs, it can be determined which subjects received tolvaptan in Trial 156-13-210. These subjects may have their trial visits/hepatic transaminase monitoring change to every 3 months sooner as their previous tolvaptan exposure in Trial 156-13-210 can count towards the 18-month threshold. If subjects approaching the 18-month threshold have had prior transaminase abnormalities (> 2 × upper limit of normal [ULN]), the investigator is responsible for contacting the medical monitor to confirm the change in frequency from monthly to every 3 months. Subjects enrolling from the open-label Trial 156-08-271 will have transaminase assessments conducted every 3 months, since they will have already received tolvaptan for at least 18 months. The current IB lists all of the tolvaptan trials. Subjects enrolling in this trial who were in a previous ADPKD tolvaptan trial other than Trials 156-13-210 and 156-08-271 will have monthly visits and alanine aminotransferase (ALT) level assessments for the first 18 months.

2 Trial Rationale and Objectives

2.1 Trial Rationale

Evidence from previous studies suggests that during the first 18 months of long-term treatment in subjects with ADPKD, ALT and/or aspartate aminotransferase (AST) elevations and evidence of idiosyncratic DILI occurs at a greater frequency in tolvaptan treated subjects. However, the rate of new transaminase elevations beyond 18 months and up to 4.5 years was similar between tolvaptan treatment and placebo subjects.

Over the 3 years of placebo-controlled treatment, ALT was elevated to a greater than three times the upper limit of normal (> 3 × ULN) in 4.4% of tolvaptan subjects compared with 1% of placebo subjects. To date, 3 tolvaptan subjects' transaminases and bilirubin levels reached Hy's laboratory criteria (> 3 × and > 2 × ULN, respectively). Upon discontinuation, all subjects' liver tests showed reversibility of the elevation within approximately 4 months after tolvaptan was discontinued. Nevertheless, without adequate monitoring and management, it is estimated that a 1:4,000 risk for irreversible liver injury may exist.

Through more frequent (eg, monthly) monitoring of liver transaminases, 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.

CCI

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This trial will extend our understanding of tolvaptan's long-term safety in ADPKD patients.

2.2 Dosing Rationale

In animal models of cystic disease, successful treatment of disease progression as indicated by kidney size appeared to require early, constant inhibition of the vasopressin V_2 receptor. The clinical formulation of tolvaptan requires 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 an interruption of sleep.

2.3 Trial Objectives

The primary objective of this trial is:

- To evaluate and describe the long-term safety of tolvaptan.

3 Trial Design

3.1 Type/Design of Trial

This trial is a phase 3b, multi-center, open-label trial.

Eligible subjects will have an opportunity to enroll into Trial 156-13-211 following completion of the follow-up visit(s) of the previous trial. Eligible subjects from Trials 156-08-271 and 156-13-210 can have the last visit assessments from their previous respective protocols (end of trial visit for 156-08-271 subjects and last follow-up visit for 156-13-210 subjects) overlap the first visit in this trial. These last visit assessments can be combined with the screening and baseline visits for this trial, with all required assessments from each visit performed only once, so long as the time between the last visit assessments from the previous trial and the screening visit for this trial is within 30 days. If the first visit in this trial combines the last visit from a previous trial with both the screening and the baseline visits in this trial, the results from laboratory assessments performed at this combined visit will not be immediately available. Should any laboratory abnormalities be identified, the investigator will need to notify the subject

and provide instructions regarding dosing or returning to the site for additional assessments.

Medical monitor approval is needed for enrollment of subjects whose completion of the preceding trial prior to entry in this trial exceeds 3 months, and these subjects will be required to undergo all screening and baseline assessments.

After consenting, subjects will be assigned a new screening number. Subjects who are found to be eligible will retain the same subject number they had been assigned in their previous trial. For purposes of ensuring subject safety, tolvaptan exposure of at least 18 months is required for all subjects. While Trial 156-13-210 remains blinded, subjects enrolling from any prior trial besides Trial 156-08-271 are scheduled to have monthly hepatic monitoring for the first 18 months of this trial. After that, following the approval of the medical monitor, hepatic monitoring will take place every 3 months. Subjects enrolling from Trial 156-08-271 will have hepatic monitoring every 3 months. All Trial 156-13-210 subjects who are eligible for this trial will initially be scheduled to have trial visits and hepatic monitoring monthly for the first 18 months, then every 3 months thereafter, because their tolvaptan exposure cannot be determined since Trial 156-13-210 is a double blind trial. Once unblinding occurs, it can be determined which subjects received tolvaptan in Trial 156-13-210. These subjects may have their trial visits/hepatic transaminase monitoring changed to every 3 months sooner as their previous tolvaptan exposure in Trial 156-13-210 can count towards the 18-month threshold. Subjects from prior tolvaptan trials other than Trial 156-08-271 will have monthly trial visits/ALT level assessments for the first 18 months. After that, the trial visits/ALT monitoring will be conducted every 3 months after the change in frequency is confirmed with the medical monitor.

Enrollment in this trial will be closed when the last eligible subject from Trial 156-13-210 enrolls in this trial.

The duration of this trial is planned to continue

- Until the last subject from Trial 156-13-210 completes 18 months of tolvaptan treatment in this trial
- Subjects enrolling from other trials will conclude their participation once tolvaptan becomes available through routine prescription or through a CCI Trial 156-13-210 subjects may opt to conclude their participation in this trial if tolvaptan becomes available before they complete 18 months of treatment in this trial

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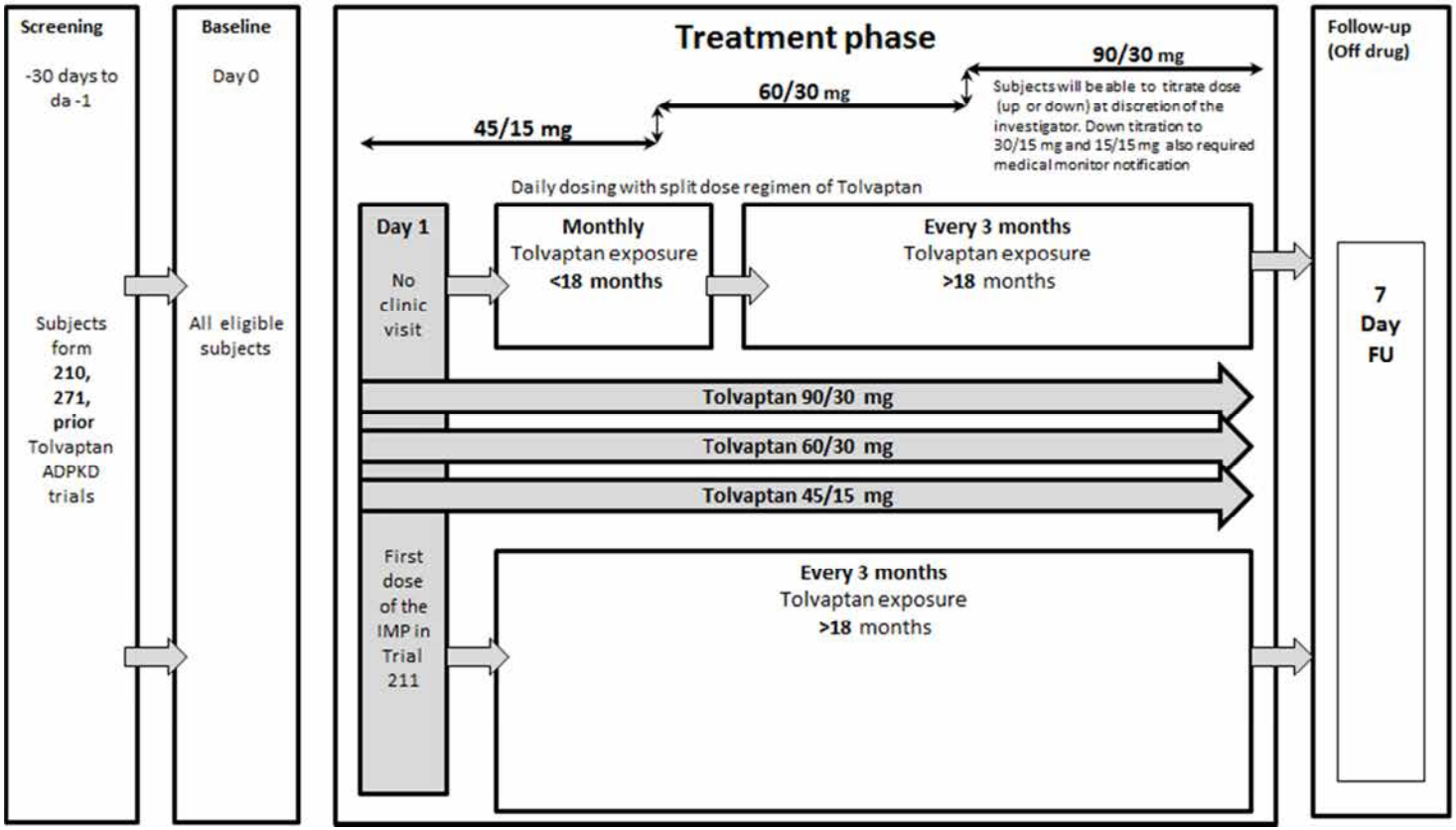

Figure 3.1-1 Trial Design Schematic

3.2 Treatments

The dose regimens to be used in this trial are 15/15 mg, 30/15 mg, 45/15 mg, 60/30 mg, and 90/30 mg.

Following consent, and once subjects have satisfied all of the inclusion criteria and none of the exclusion criteria, subjects will retain the subject number assigned from their previous trial. Subjects will receive open-label tolvaptan for the duration of the trial. All subjects will be administered tolvaptan tablets in a daily split-dose, once upon awakening and another approximately 8 to 9 hours later (twice daily dosing). The exact time 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 recorded as early dose/late dose (eg, 60/30 mg).

A subject's starting dose in this trial will be dependent on the trial in which they were previously enrolled:

- **156-13-210**- initiated on tolvaptan at a split-dose of 45/15 mg with upward titration every 3 to 4 days to 60/30 mg or 90/30 mg per day according to tolerability
- **156-08-271**- will retain the last dose level from 271 and start at the same dose in this trial
- **Prior tolvaptan trials**- initiated on tolvaptan at a split-dose of 45/15 mg with upward titration every 3 to 4 days to 60/30 mg or 90/30 mg per day according to tolerability

Down titration to 30/15 mg and 15/15 mg is also permitted at the discretion of the investigator according to subject tolerability with medical monitor notification. Further down titration to 30 or15 mg once daily may be allowed only for metabolic drug-drug interaction and requires medical monitor approval.

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Table 3.2-1 Trial Treatments		
Trial Day	**Time**	**Dose**
Day 1 to last on-treatment visit	8:00 am	1 to 6 tolvaptan tablets (15 mg or 30 mg each)
	4:00 to 5:00 pm	1 to 2 tolvaptan tablets (15 mg or 30 mg each) Allowed doses are 45/15 mg, 60/30 mg, 90/30 mg. Down titration to 30/15 mg and 15/15 mg will be allowed after discussion with the medical monitor. Further down titration to 30 or 15 mg once daily may be allowed only for metabolic drug-drug interaction and requires medical monitor approval.

For subjects moving from the 156-13-210 trial and requiring tolvaptan titration, it will be conducted in the following way: subjects will be instructed to take tolvaptan starting at a split dose of 45/15 mg (as 3 tablets upon waking and 1 tablet approximately 8 to 9 hours later) and to titrate up every 3 to 4 days; first to 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. 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?" Subjects will continue in the trial with the regimen to which tolerability was established.

While taking tolvaptan, 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 Dosing with CYP3A4 Potent Inhibitors

Tolvaptan is a sensitive CYP3A4 substrate with 4-fold or higher increases in exposure following administration with potent CYP3A4 inhibitors.[4]

For subjects requiring treatment with a potent CYP3A4 inhibitor and on a total daily tolvaptan dose of 90 or 120 mg, tolvaptan treatment should be reduced to 30 mg once daily. The dose may be reduced to 15 mg once daily for tolerability. For subjects on a total daily dose of 60 mg, tolvaptan treatment should be reduced to 15 mg once daily. For subjects on lower total daily doses, tolvaptan interruption should be considered if no alternative medications can be used.

3.2.2 Dosing with CYP3A4 Moderate Inhibitors

For subjects who require dosing with a moderate inhibitor, initial tolvaptan reductions as shown below should be tried, with further dose reductions or interruption as necessary for tolerability.

- 90/30 mg to 45/15 mg
- 60/30 mg to 30/15 mg
- 45/15 mg to 15/15 mg
- 30/15 mg to 15 mg once daily
- 15/15 mg to 15 mg once daily

A partial list of strong and moderate CYP3A4 inhibitors can be found in Section 4.1.

3.3 Trial Population

This trial will include approximately 2,500 subjects over the age of 18 years with ADPKD diagnosed by Pei-Ravine criteria[11 12] (modified by magnetic resonance imaging [MRI]) who completed or participated in a prior tolvaptan trial.

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 informed consent form (ICF) that shall be approved by the same institutional review board/independent ethics committee (IRB/IEC) responsible for approval of this protocol. Each ICF will comply with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guideline[14] 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 sponsor approval of any written ICF used in the trial prior to submission to the IRB/IEC.

Investigators may discuss trial availability and the possibility for entry with a potential subject without first obtaining consent. However, informed consent will be obtained from all subjects (or their guardian or legal representative) 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).

Once appropriate essential information has been provided and fully explained in layman's language to the subject by the investigator (or a qualified designee), the IRB/IEC-approved written ICF will be signed and dated by both the subject and the person obtaining consent (investigator or designee), as well as by any other parties required by the IRB/IEC. The subject will receive a copy of the signed ICF; the original shall be kept on file by the investigator.

CCI [redacted]

3.4.2 Inclusion Criteria

Subjects are required to meet the following inclusion criteria in Table 3.4.2-1.

Table 3.4.2-1 Inclusion Criteria

1.	Male and female subjects aged ≥ 18 years with confirmed diagnosis of ADPKD (during participation in prior tolvaptan trials) who have • Completed and transferred from the double-blind Trial 156-13-210 (12-month period including post-treatment follow-up, regardless of whether this was on-treatment or off-treatment), or • Completed Trial 156-08-271 or a prior tolvaptan trial, or • Interrupted or discontinued treatment in a tolvaptan trial other than Trial 156-13-210. Subjects may be enrolled with the medical monitor approval, and additional close monitoring may be required at the beginning of the trial • Renal function will be assessed during screening by using historical laboratory values (in the last 3 months) for serum creatinine levels to calculate the eGFR. The eGFR values will be estimated based on the CKD-EPI formula. (Levey AS et al. Ann Intern Med. 2009; 150:604–612)
2.	Estimated glomerular filtration rate ≥ 20 mL/min/1.73 m^2 (calculated using the CKD-EPI formula) within 3 months prior to the baseline visit. Subjects who have an eGFR ≤ 20 mL/min/1.73 m^2 may be permitted to enter the trial with medical monitor and sponsor approval and increased frequency of monitoring to ensure safety of subjects.

eGFR=estimated glomerular filtration rate; CKD-EPI= Chronic Kidney Disease - Epidemiology

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3.4.3 Exclusion Criteria

Subjects will be excluded if they meet any of the exclusion criteria in Table 3.4.3-1.

Table 3.4.3-1 Exclusion Criteria

1.	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 based on liver function abnormalities other than that expected for ADPKD with cystic liver disease during screening based on recent historical laboratory values (in the last 3 months).
5.	Subjects with contraindications to required trial assessments (contraindications to optional assessments, eg, MRI are not a limitation).
6.	Subjects who, in the opinion of the investigator or medical monitor, have a medical history or medical finding inconsistent with safety or trial compliance. This includes prior evidence of significant hepatic injury deemed to be related to tolvaptan use.

WOCBP=women of childbearing potential; IMP=investigational medicinal product

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

3.5 Trial Endpoints

3.5.1 Safety Endpoints

This trial will have no formal endpoints. Safety variables will be summarized by descriptive statistics, (eg, proportion, mean, median, standard deviation [SD], minimum, and maximum values). In general, summary statistics, including changes from baseline, will be provided for safety variables based on all available data. Safety endpoints will be as follows:

- Adverse events
- Vital signs

- Clinical laboratory assessments
- Serum transaminase elevations for frequency (2x, 3x, 5x and 10x ULN), time to onset, time to peak levels, time of offset (< 3x, 2x, or 1x ULN), response to de-challenge and re-challenge and frequency of progression to Hy's laboratory criteria (ALT or AST > 3x ULN and bilirubin, total (BT), > 2x ULN without alkaline phosphatase ≥ 2x ULN)
- Serum sodium excursions above 145, 150, or 155 mmol/L or below 135, 130, or 125 mmol/L

3.6 Measures to Minimize/Avoid Bias

This is an open-label trial. For subjects entering from placebo-controlled trials, prior therapy (placebo or tolvaptan), will not be known (by trial site, investigator, or sponsor) at the time of entry into this trial.

All blood and urine chemistry will be analyzed and reported by a central laboratory.

3.7 Trial Procedures

Trial assessment time points are summarized in Table 3.7-1.

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Table 3.7-1 Schedule of Assessments

	Screening (-30 to -1 days prior to Baseline)[a]	Baseline/ Day 0	Monthly[b] (± 7 days)	Every 3 months[b] (± 14 days)	Early Termination/End of Treatment (+ 7 days)	Titration Contact (phone contact)	Follow-up 7 days post-treatment (+ 7 days)
Informed consent	X						
Inclusion/Exclusion	X	X					
Demographics, Medical/ADPKD history[c]	X						
Dietary review	X	X	X	X	X		
CCI [redacted]							
Vital signs[d]	X	X	X	X	X		X
Chemistry Blood Samples[e]							
Serum Chemistry Panel	X[f]				X		
Liver Function tests[g]	X		X	X	X		X
Sodium	X		X	X	X		
Creatinine	X		X	X	X		X
Hematology and coagulation	X				X		
Urinalysis	X		X	X	X		
Urine osmolality[h]	X		X	X	X		
Urine specific gravity	X		X	X	X		
Urine pregnancy test (WOCBP only)[i]	X		X	X	X		X
Urine at-home pregnancy test kits dispensed[j]		X	X	X			
Physical examination [k]	X	X	X	X	X		
Tolerability/Dosing Review		X	X	X	X	X	
Interactive Response Technology Entry	X	X	X	X	X	X[l]	X
Drug dispensation		X	X	X		X[l]	
Drug reconciliation			X	X	X	X[l]	
CCI [redacted]							
[redacted]							
[redacted]							

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	Screening (-30 to -1 days prior to Baseline)[a]	Baseline/ Day 0	Monthly[b] (± 7 days)	Every 3 months[b] (± 14 days)	Early Termination/End of Treatment (+ 7 days)	Titration Contact (phone contact)	Follow-up 7 days post-treatment (+ 7 days)
Adverse events	X^n	←----------	----------	----------	----------	----------	----------→
Concomitant medications[o]		←----------	----------	----------	----------	----------	----------→

[a]The last visit assessments from the previous trial can be combined with the screening and baseline visits for this trial, with all required assessments from each visit performed only once.

[b]Monthly visits are for subjects < 18 months on tolvaptan, and every 3 month visits are for subjects > 18 months on tolvaptan.

[c]Includes prior trial identifiers (screening identification [ID], subject ID, site ID, prior tolvaptan ADPKD trial protocol number).

[d]Vital signs at each visit include seated heart rate, calibrated blood pressure and post void body weight. Height should be performed only at screening.

[e]Central laboratory non-fasting serum laboratory tests will be performed. All subjects must be monitored for hepatic safety monthly until they have known tolvaptan exposure data of at least 18 months. After that, and following the approval of the medical monitor, hepatic monitoring will take place every 3 months. Trial 156-13-210 subjects who are eligible for this trial will have trial visits/hepatic monitoring monthly for the first 18 months of this trial then every 3 months thereafter, because their tolvaptan exposure will be unknown. Once unblinding occurs, it can be determined which subjects received tolvaptan in Trial 156-13-210. These subjects may have their trial visits/hepatic transaminase monitoring changed to every 3 months sooner as their previous tolvaptan exposure in Trial 156-13-210 can count towards the 18 month threshold. Subjects who enroll from other ADPKD tolvaptan trials will be monitored for hepatic safely monthly for their first 18 months they are in this trial.

[f]Hepatitis testing at screening will be optional. If hepatitis testing is performed, then both pre- and post-counseling activities relating to hepatitis testing are to be carried out based on local requirements and best practices. Upon request, if clinically indicated and approved by the medical monitor, subjects may have the following evaluations in addition to the protocol-specified chemistry panel: serum calcium, phosphorous, parathyroid hormone, vitamin D, and bicarbonate levels.

[g]A full liver function panel (AST, ALT, alkaline phosphatase, BT) will be done at screening. All other liver function tests at subsequent visits are for ALT only, unless otherwise clinically indicated. An ALT elevation > 2 × ULN should trigger prompt testing of hepatic function within 72 hours. Any transaminase or bilirubin values which exceed 2 × ULN should 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, and every 3 months as indicated by the results. Local liver function panel analyses will also be performed more frequently, if necessary.

[h]Urine osmolality is optional.

[i]A urine pregnancy test for pregnancy for women of childbearing potential (WOCBP) will be performed at screening, at every 3 months visits, at the End of Treatment (EoTx) visit, and at the follow-up visit. On suspicion of pregnancy, an unscheduled urine or serum pregnancy testing will be performed. Positive urine pregnancy tests should be confirmed with a serum pregnancy test.

[j]At-home urine pregnancy test kits will be dispensed to WOCBP to be used if a menstrual period is missed between visits. Kits will be dispensed as needed throughout the trial.

[k]A full physical examination is required at screening. At other visits, an optional "directed" physical examination may be performed to focus on PKD-related signs and symptoms.

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[l]If during the titration contact the determination is made to adjust the dose regimen, dose adjustments will be made using dispensed supply, and dose instructions will be provided by the investigator. The subject's current dose will be entered into the interactive response technology (IRT) at each visit. Drug dispensation/reconciliation will be conducted on a monthly basis for subjects who have monthly trial visits and once every 3 months for subjects who have trial visits every 3 months. If additional drug supply is required for titration purposes, the site will arrange a subject visit for dispensation.

CCI [redacted]

[n]At screening, AEs reported as ongoing or resolved at the end of the prior trial will be assessed to determine entry as either medical history or ongoing event for this trial.

[o]Only concomitant medications ongoing at the baseline visit and throughout the trial will be recorded. This would occur at the screening visit only if the screening visit occurs simultaneously with the last visit from a previous tolvaptan trial.

3.7.1 Schedule of Assessments

3.7.1.1 Screening (-30 days to 1 day prior to Baseline)

Screening for eligibility is required for all subjects. The screening and baseline visit may be combined with the last visit from either Trials 156-08-271 or 156-13-210 with all required assessments from each visit performed only once. Therefore, in some cases, if a subject enrolls in this trial from a prior tolvaptan trial, the end of trial or last follow-up visit for that trial and the screening and baseline visit for this one may occur simultaneously. Required assessments for the screening visit are as follows:

1. Obtain subject consent.
2. Obtain subject's new screening identification (ID) assigned by interactive response technology (IRT).
3. Determine subject eligibility through inclusion/exclusion criteria
4. Record demographic information and prior trial identifiers (screening ID, subject ID, site ID, prior tolvaptan ADPKD trial protocol number).
5. Record medical/ADPKD history using prior trial data.
6. Review dietary recommendations and compliance
7. Record vital signs (post-void weight and seated heart rate) and in-clinic calibrated blood pressure (BP) measurement. Record height.
8. Collect blood for serum chemistry, liver function panel (ALT, AST, BT, bilirubin [direct], and alkaline phosphatase), serum sodium, serum creatinine, and hematology and coagulation. Hepatitis testing is optional. If hepatitis testing is performed, then both pre- and post-counseling activities relating to hepatitis testing are to be carried out based on local requirements and best practices.
9. Collect urine for urinalysis, urine osmolality (optional), and urine specific gravity.
10. Perform urine pregnancy test on women of childbearing potential (WOCBP). If positive, a follow-up serum test will be performed.
11. Conduct full physical examination.
12. Enter subject into interactive response technology (IRT) including prior trial identifier/information (protocol number, subject ID), confirmed dose regimen, and scheduled date of next visit.
13. Assess AEs reported as ongoing or resolved from prior trial to determine entry as medical history or ongoing event for this trial.
14. Record ongoing concomitant medications. (This will happen only if the screening visit occurs simultaneously with the last visit from a previous tolvaptan trial).

3.7.1.2 Baseline (Day 0)

The baseline visit is the beginning of the treatment period in this trial. At the baseline visit, subjects will retain the subject number assigned in the previous tolvaptan trial, and the following assessments and procedures will be performed:

1. Review inclusion/exclusion criteria.
2. Review dietary recommendations and compliance.
3. CCI [redacted]
4. Record vital signs (post-void weight, seated heart rate, and calibrated blood pressure measurement).
5. Dispense at-home urine pregnancy test kits to WOCBP to be used if a menstrual period is missed before the next visit.
6. An optional directed physical examination may be performed to focus on PKD-related signs and symptoms.
7. Assess tolerability/dosing review of investigational medicinal product (IMP).
8. Enroll subject into trial through IRT and obtain IMP.
9. Dispense IMP (sufficient for 1 month or 3 months of dosing based on the subject's required visit schedule for hepatic evaluation as either monthly or every 3 months).
10. Provide subject with dosing instructions to begin on the following day.
11. Record ongoing concomitant medications
12. Assess AEs.

3.7.1.3 Monthly Visit (± 7 days)

The following subjects will return for a monthly visit to assess safety and tolerability of IMP and to monitor liver function.

- Subjects enrolling from the double-blind Trial 156-13-210 will have monthly trial visits/ALT level assessments for the first 18 months while treatment code from Trial 156-13-210 remains blinded, to ensure that they have adequate safety monitoring during this period of susceptibility. Once unblinding occurs, it can be determined which subjects received tolvaptan in Trial 156-13-210. These subjects may have their trial visits/hepatic transaminase monitoring change to every 3 months sooner as their previous tolvaptan exposure in Trial 156-13-210

can count towards the 18-month threshold. The investigator will need to discuss the change in frequency with the medical monitor before instituting the change.

- Subjects from prior tolvaptan trials other than Trial 156-08-271 will have monthly trial visits/ALT level assessments for the first 18 months. After that, the trial visits/ALT monitoring will be conducted every 3 months after the change in frequency is confirmed with the medical monitor.
- Subjects enrolling from the open-label Trial 156-08-271 who have greater than 18 months of exposure to tolvaptan will have trial visits/ALT monitoring conducted every 3 months.

The following will be assessments will be completed:

1. Review dietary recommendations and compliance.
2. CCI [redacted]
3. Record vital signs (post-void weight, seated heart rate, and calibrated blood pressure measurement).
4. Collect blood for central laboratory assessments for serum sodium, serum creatinine, and ALT (see Section 3.7.2.4).
5. CCI [redacted]
6. CCI [redacted]
7. Urinalysis, urine osmolality (optional), urine specific gravity.
8. Perform urine pregnancy test on WOCBP (every 3 months). If positive, a follow-up serum test will be performed.
9. Dispense at-home urine pregnancy test kits to WOCBP, as required.
10. An optional directed physical examination may be performed to focus on PKD-related signs and symptoms.
11. Assess tolerability/dosing review of IMP.
12. Enter subject status in IRT, including any dose regimen changes and obtain IMP assignment.
13. Collect and reconcile returned IMP, assess compliance.
14. Dispense IMP based on subject's required visit schedule, and provide subject with dosing instructions.
15. Update concomitant medications.
16. Assess AEs.

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3.7.1.4 Every 3 Months (± 14 days)

1. Review dietary recommendations and compliance.
2. CCI [redacted]
3. Record vital signs (post-void weight, seated heart rate, and calibrated blood pressure measurement).
4. Collect blood for central laboratory assessments serum sodium, serum creatinine, ALT (see Section 3.7.2.4).
5. CCI [redacted]
6. Urinalysis, urine osmolality (optional), urine specific gravity.
7. Perform urine pregnancy test on WOCBP. If positive, a follow-up serum test will be performed.
8. Dispense at-home urine pregnancy test kits to WOCBP, as required.
9. CCI [redacted]
10. An optional directed physical examination may be performed to focus on PKD-related signs and symptoms.
11. Assess tolerability/dosing review of IMP.
12. Enter subject status in IRT, including any dose-regimen changes and obtain IMP assignment.
13. Collect and reconcile returned IMP; assess compliance.
14. Enter subject status in IRT, including any dose-regimen changes.
15. Dispense IMP based on subject's visit schedule, and provide subject with dosing instructions.
16. Update concomitant medications.
17. Assess AEs.

3.7.1.5 Early Termination/End of Treatment (+ 7 days)

At the early termination/end of treatment (EoTx) visit the following will be assessed:

1. Review dietary recommendations and compliance.
2. CCI [redacted]

3. Record vital signs (post-void weight, seated heart rate, and calibrated blood pressure measurement).
4. Collect blood for serum chemistry, serum creatinine, ALT, serum sodium and hematology and coagulation.
5. CCI [redacted]
6. CCI [redacted]
7. Collect urine for urinalysis, urine osmolality (optional), urine specific gravity.
8. Perform urine pregnancy test on WOCBP. If positive, a follow-up serum test will be performed.
9. An optional directed physical examination may be performed to focus on PKD-related signs and symptoms.
10. Assess tolerability/dosing review of IMP.
11. Enter subject status in IRT, including any dose-regimen changes since the previous entry.
12. Collect and reconcile returned IMP; assess compliance.
13. Update concomitant medications.
14. Assess AEs.

3.7.1.6 7-day Follow-up Visit (+ 7 days)

1. Record vital signs (post-void weight, seated heart rate, and calibrated blood pressure measurement).
2. Collect blood for serum creatinine and ALT.
3. CCI [redacted]
4. Perform urine pregnancy test on WOCBP. If positive, a follow-up serum test will be performed.
5. Enter subject status in IRT.
6. Update concomitant medications.
7. Assess AEs.

3.7.2 Safety Assessments

3.7.2.1 Adverse Events

Refer to Section 5, Reporting of Adverse Events.

3.7.2.2 Clinical Laboratory Assessments

Central laboratory non-fasting serum laboratory tests will be performed. 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 in order to reduce variability in the samples over time.

CCI [redacted]

A list of the specific clinical laboratory assessments is presented in Table 3.7.2.2-1.

Clinical laboratory samples will be collected and sent to the central laboratory at the following time points:

Screening: Hematology and coagulation panel, serum chemistry panel, liver function panel (AST, ALT, alkaline phosphatase, bilirubin direct [BT]) serum sodium, serum creatinine, urinalysis panel, urine osmolality (optional), urine specific gravity, urine pregnancy test (WOCBP) and hepatitis (optional).

Monthly visits (± 7 days): ALT (for the first 18 months for subjects enrolled from other tolvaptan ADPKD trials and Trial 156-13-210 while trial remains blinded), serum sodium, and serum creatinine (all subjects), urinalysis, urine osmolality (optional), urine specific gravity, and urine pregnancy test (every 3 months in WOCBP). CCI [redacted]

Every 3 months: (± 14 days): ALT (after 18 months of treatment for subjects enrolled from other ADPKD tolvaptan trials, or from Trial 156-13-210 after the trial is unblinded, and for subjects enrolled from Trial 156-08-271), serum sodium and serum creatinine,

urinalysis panel, urine pregnancy test (WOCBP), urine osmolality (optional), and urine specific gravity. P[CCI redacted]

Early Termination/EoTx (+ 7 days): Serum chemistry panel, hematology and coagulation panel, ALT, serum sodium and serum creatinine, [CCI redacted], urinalysis panel, urine pregnancy test (WOCBP), urine osmolality (optional), and urine specific gravity.

7-day Follow-up visit (+ 7 days): ALT, serum creatinine, and urine pregnancy test (WOCBP).

Table 3.7.2.2-1 Clinical Laboratory Assessments

Hematology and Coagulation Panel: Hemoglobin Platelet count Mean corpuscular hemoglobin concentration (MCHC) Mean corpuscular volume (MCV) Red blood cell (RBC) count White blood cell (WBC) count with differential Prothrombin time (PT) as international normalized ratio (INR) Activated partial thromboplastin time (aPTT) Urinalysis Panel: Appearance Color Blood Glucose Microscopic analysis, WBC/RBC counts per high power field pH Protein Urine Chemistry Osmolality (optional) Specific gravity Additional Tests: Urine (or serum) pregnancy for WOCBP Hepatitis (optional)	Serum Chemistry Panel: Albumin Blood urea nitrogen (BUN) Serum calcium Carbon dioxide Serum chloride Gamma-glutamyl transpeptidase Cholesterol, total Glucose Lactate dehydrogenase (LDH) Phosphorus Potassium Protein, total Uric acid Liver Function Panel: Alkaline phosphatase (ALP) Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Bilirubin, total (BT) Bilirubin, direct
Creatinine	**Sodium**

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. Blood testing for hepatitis will be optional for all subjects. Urine pregnancy testing will be performed

with commercially available, high-sensitivity kits supplied to the subject by the site (acquired by the sponsor).

3.7.2.3 Physical Examination and Vital Signs

A full physical examination will be performed and documented at the screening visit although this may be combined with the last visit from the previous trial. At other visits, an optional 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.

Height will be measured only at screening. 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 Food and Drug Administration (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, height, and weight will be taken at the visits identified in the Schedule of Assessments (Table 3.7-1).

3.7.2.4 Assessment of Liver Symptoms, Signs or Test Abnormalities

Testing for hepatic transaminase (ALT/AST), alkaline phosphatase, bilirubin direct, and BT will be performed during screening. Subjects enrolling from the double-blind Trial 156-13-210 will have monthly ALT assessments for the first 18 months while the treatment code from Trial 156-13-210 remains blinded to ensure that all subjects have adequate safety monitoring during this period of susceptibility. Once unblinding occurs, it can be determined which subjects received tolvaptan in Trial 156-13-210. These subjects may have their trial visits/hepatic transaminase monitoring changed to every 3 months sooner as their previous tolvaptan exposure in Trial 156-13-210 can count towards the 18-month threshold.

Following the first 18 months, ALT assessments will be made every 3 months for Trial 156-13-210 subjects and for subjects from other tolvaptan ADPKD trials besides Trial 156-08-271.

Subjects enrolling from the open-label Trial 156-08-271 who have tolvaptan exposure greater than 18 months will continue with ALT monitoring every 3 months.

Subjects enrolling from prior tolvaptan trials besides Trial 156-08-271 will have monthly ALT assessments for the first 18 months. Upon reaching 18 months of exposure and after confirmation from the medical monitor, the frequency of ALT monitoring for these subjects will occur every 3 months.

ALT will also be assessed at the Early Termination/EoTx visit and at the 7-day Follow-up visit.

Management of liver abnormalities is discussed in the paragraphs below.

3.7.2.4.1 Liver Test Abnormalities and Interruption/Discontinuation of Investigational Medicinal Product

An ALT elevation 2 × ULN or 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 × 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, or every three months as indicated by the results.

Liver transaminase or bilirubin levels reaching or exceeding 2 × ULN that have an uncertain or rapidly increasing trajectory should prompt at least temporary IMP interruption. Tolvaptan 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 tolvaptan if they have:

- transaminase levels rise above 8 × ULN,
- transaminase levels are > 5 × ULN for more than 2 weeks, or
- concurrent elevations of transaminase > 3 × ULN and BT > 2 × 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)[10] by an independent hepatic adjudication committee (HAC) 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.

3.7.2.4.2 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 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).[10] 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. Has normal screening levels and develops ALT or AST levels ≥ 3x ULN,
4. Has normal screening levels and develops BT levels ≥ 2x ULN, or
5. Has an abnormal screening level and develops abnormalities in that test that are > 2x the upper limit of their highest screening value.

CCI [redacted] 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.

CCI [redacted]

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CCI [redacted]

3.7.5 Treatment Interruption and Discontinuation

In this trial, it is expected that subjects may possibly have one or more planned or unplanned treatment interruptions. If a subject's IMP treatment must be interrupted for medical or surgical reasons, liver test abnormalities, use of a prohibited 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 investigator should be notified as soon as possible and the reason for treatment interruption must be documented in the source documents and case report form (CRF). If permissible, the subject's IMP may be resumed following approval by the medical monitor.

If IMP treatment is permanently discontinued, the reason for discontinuation must be recorded appropriately in the source document and in the CRF.

A subject who permanently discontinues IMP treatment ends trial participation and the early termination visit should be completed.

3.7.6 End of Trial

The End of Trial date is defined as the last date of contact or the date of final contact attempt from the post-treatment Follow-up CRF page for the last subject completing or withdrawing from the trial.

3.7.7 Independent Data Monitoring Committee

For this trial, an Independent Data Monitoring Committee (IDMC), also known as a Data Safety and Monitoring Committee, 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

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

If a subject discontinues the trial prematurely, the reason must be fully evaluated and recorded appropriately in source documents and the CRF. If the subject is being withdrawn because of an AE, that AE should be indicated as the reason for withdrawal.

All subjects have the right to withdraw at any time during treatment without prejudice. The investigator can discontinue a subject's participation in the trial at any time if medically necessary. It is preferred that subjects who permanently discontinue IMP will have the option to continue participation off IMP with regular scheduled visits or with a modified (ie, less frequent) schedule. If subjects are unable or unwilling to complete the visits and procedures off IMP, the early termination/EoTx visit should be completed. The investigator may continue to contact those who discontinue IMP through to the final completion date of the trial or thereafter if needed to determine outcomes ie, vital status.

In addition, subjects meeting the following criteria must be withdrawn from the trial:

a) Occurrence of any AE, intercurrent illness, or abnormality in a laboratory assessment which, in the opinion of the investigator, warrants the subject's permanent withdrawal from the trial;

b) Subject noncompliance, defined as refusal or inability to adhere to the trial schedule or procedures (see Section 3.12);

c) At the request of the subject, investigator, sponsor, or regulatory authority;

d) Subject is lost to follow-up.

The investigator will notify the sponsor promptly when a subject is withdrawn.

3.9 Screen Failures

A screen failure subject is one from whom informed consent is obtained and is documented in writing (ie, subject signs an ICF), but who is not started on treatment.

3.10 Definition of Completed Subjects

For purposes of this trial, subjects who complete the EoTx visit will be defined as trial completers.

3.11 Definition of Subjects Lost to Follow-up

Subjects, or the subject's parent/guardian who cannot be contacted on or before their final visit prior to the trial termination date, who do not have a known reason for discontinuation (eg, withdrew consent or AE) and for whom a current health status at the end of the trial cannot be determined will be classified as "lost to follow-up" as the reason for discontinuation. Current health status can be determined from a variety of sources, either by obtaining acceptable documentation for death (ie, death certificate, medical records, public records, or statement by a family member or primary care physician) or acceptable documentation for life (ie, direct contact with the subject, medical records, successful telephone contact with the subject, statement by a family member or primary care physician, or public records). It is expected that 3 documented attempts will be made to determine a subject's current health status before assigning a "lost to follow-up" status.

3.12 Subject Compliance

Subject compliance will be monitored by pill counts as IMP is returned. Any subject who, without the instruction of the investigator, discontinues tolvaptan investigational product, discontinues tolvaptan for 30 consecutive days or misses > 30% of the doses intended for a period between visits (whichever is greater) will be deemed noncompliant. Depending on the circumstances leading to noncompliance, the subject may be withdrawn from the trial or discontinued from investigational product administration by the investigator and/or sponsor. It is preferred that subjects who discontinue tolvaptan, or are withdrawn by the investigator for reasons other than noncompliance or lost to follow-up, will continue with regularly scheduled visits completing all procedures as provided in the protocol.

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3.13 Protocol Deviations

This trial is to be conducted as described in this protocol. In the event of a significant deviation from the protocol due to an emergency, accident or mistake (eg, violation of informed consent process, IMP dispensing or subject dosing error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator or designee must contact the sponsor at the earliest possible time. This will allow an early joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator and the sponsor, and reviewed by the 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 therapies, vasopressin antagonists other than tolvaptan, (eg, OPC-31260 (mozavaptan), Vaprisol (conivaptan), 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 tolvaptan metabolism (see Section 3.2.1 and Section 3.2.2).

A partial list of strong and moderate CYP3A4 inhibitors can be found in Table 4.1-1 below:

Table 4.1-1 Strong and Moderate CYP3A Inhibitors (partial list)

amprenavir	atorvastin	aprepitant	chloramphenicol (if used orally)
cimetidine	clarithromycin	clotrimazole (if used orally)	danazol
delavirdine	diltiazem	erythromycin	fluconazole
fluvoxamine	indinavir	isoniazid	itraconzazole
josamycin	ketoconazole (if used orally)	nelfinavir	nefazadone
quinupristin/ dalfopristin	ritonavir	saquinavir	troleandomycin
verapamil	Seville orange products	grapefruit products	

Pharmacodynamic interactions are a consideration for the use of diuretics, which may be only used intermittently, and 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 and is an exclusionary criterion for this 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 list would include: non-steroidal anti-inflammatory drugs like aspirin or ibuprofen, chemotherapy drugs, cephalosporin, the combination of elvitegravir, cobicistat, emtricitabine, and tenofovir (Stribild™), dolutegravir, dronedarone, ranolazine, metformin, and trimethoprim.

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, dietary salt < 5g/day, dietary cooked meat protein < 1 g/kg/day and a limit on caffeinated drinks/foods should also be given (no more than 2 coffee equivalents per day). A history of alcohol and smoking intake will be collected at screening. Alcohol and tobacco consumption should be avoided or minimized as much as possible.

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 ingest at least 2 to 3 liters of fluid (including in solid, semi-solid, and liquid foods) per day, unless otherwise directed by their trial 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 the IMP.

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.

Medical follow up is expected for AEs which lead to discontinuation which are serious, or which are of special interest (eg, liver abnormalities, skin neoplasms, glaucoma).

ADPKD is a progressive disorder involving the kidney, liver and occasionally other organ systems. A number of AEs may be associated with this disorder 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 and investigational new drug [IND] safety reports).

5.1 Definitions

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

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

A serious adverse event (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 inpatient 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.

Nonserious 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 nonserious) that necessitates discontinuation of IMP.
- Any subject with a new liver test abnormality meeting the AE (whether serious or nonserious) 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 CRF. The intensity of an adverse experience is defined as follows:

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

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

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

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

Related: There is a reasonable probability or possibility of a temporal and causal relationship between the IMP and the AE.

Not Related: There is no temporal or causal 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 nonserious) reported by the subject must be recorded on the source documents and eCRFs provided by the sponsor.

In addition, Quintiles (drug safety service) 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 laboratory abnormality requiring special liver eCRF completion, or confirmed pregnancy, by telephone or by fax to Quintiles (drug safety service) as outlined in Appendix 1. An IRE form must be completed and sent by fax, email or overnight courier to the sponsor. (Please note that the IRE form is NOT the AE eCRF).

Nonserious 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, email, 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.

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 an 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 ICF 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 IMP administration, the IMP administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the IMP and must not be enrolled in the trial. If pregnancy is suspected while the subject is taking IMP, the IMP must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy is known. If pregnancy is confirmed, the 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.

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

5.5 Follow-up of Adverse Events

For this trial, AEs will be followed up for 7 days after the last dose of tolvaptan 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.

5.5.1 Follow-up of Nonserious Adverse Events

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

5.5.2 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.

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5.5.3 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 serious related AEs identified after the last scheduled contact until the events are resolved, or the subject is lost to follow-up. The investigator should continue to report any significant follow-up information to OPDC up to the point the event has been resolved.

6 [redacted]

7 Statistical Analysis

7.1 Sample Size

Sample size was not determined by a formal computation to achieve a target power. No efficacy analyses are planned. It is expected that approximately 2,500 subjects may enroll from previous tolvaptan trials.

7.2 Dataset for Analysis

The following datasets are defined for this trial:

- Enrolled Population: all subjects who were enrolled to this open-label trial.
- Safety Population: all subjects in the Enrolled Sample who take at least one dose of IMP

7.3 Handling of Missing Data

No missing data will be imputed under the assumption of missing at random.

7.4 Interim Analysis

No interim analysis for this trial is planned.

7.5 Trial Outcome Analyses

7.5.1 Analysis of Demographic and Baseline Characteristics

Demographic characteristics, disease severity, and medical history at (pretreatment) baseline will be summarized by descriptive statistics, eg, proportion, mean, median, SD, minimum and maximum values.

7.5.2 Safety Analysis

Safety analysis will be conducted based on the Safety Population, which is defined as all subjects in the Enrolled Population who take at least one dose of IMP. Safety variables to be analyzed include clinical laboratory tests, vital signs, and AEs. CCI [redacted]

In general, baseline measurements of safety variables are defined as the last measurements prior to the first dose of IMP in Trial 156-13-211. Safety variables will be summarized by descriptive statistics, (eg, proportion, mean, median, SD, minimum, and maximum values). Summary statistics, including changes from baseline, will be provided for safety variables based on all available data.

7.5.2.1 Adverse Events

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

a) TEAEs by severity
b) TEAEs potentially causally related to tolvaptan
c) TEAEs with an outcome of death
d) Serious TEAEs
e) Discontinuations due to TEAEs

7.5.2.2 Vital Signs

Summary statistics for changes from baseline in vital signs and potentially clinically significant results in vital signs will be summarized.

7.5.2.3 Clinical Laboratory Assessments

Summary statistics for changes from baseline in clinical laboratory measurements will be provided for the Safety Population. Potentially clinically significant results in laboratory

tests identified using prospectively defined criteria, including criteria for liver enzyme elevations, will also be summarized for the Safety Population. 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 × ULN):

- ALT or AST ≥ 3 × ULN
- Bilirubin ≥ 2 × ULN

7.5.2.4 Serum Sodium

The following will be summarized:

- Serum sodium excursions above 145, 150, or 155 mmol/L or below 135, 130, or 125 mmol/L
- Interruptions of protocol-specified therapies for hypernatremia or hyponatremia.

7.5.3 CCI

[redacted]

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CCI

[redacted]

8 Management of Investigational Medicinal Product

8.1 Packaging and Labeling

Tolvaptan will be provided to the investigator(s) by the sponsor or designated agent as tablets of 15 or 30 mg tolvaptan (OPC-41061). Each bottle will be labeled to clearly disclose the subject 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 IMP is to be used.

8.2 Storage

Tolvaptan 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 tolvaptan to any subject not participating in this protocol.

Tolvaptan will be stored at the conditions specified in the IMP label. The clinical site staff will maintain a temperature log in the IMP 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 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 initialed 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 three periods:

- A period of at least 2 years following the date on which approval to market the IMP 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 IMP 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 CRFs, the investigator, sub-investigator and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject number and subject ID 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 be 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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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 IMP) to:

Quintiles
Clinical Safety and Pharmacovigilance
5927 South Miami Blvd
Morrisville, NC 27560, USA
Phone: PPD
Fax: PPD
Email: PPD

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

Global Project Leaders
Global Clinical Director/
Medical Director
(Program Lead)

PPD
PPD
Otsuka Pharmaceutical Development & Commercialization, Inc.
2440 Research Blvd.
Rockville, MD 20850, USA
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Appendix 2 Institutions Concerned With the Trial

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Appendix 3 CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

Protocol 156-13-211

CCI

[redacted]

Protocol 156-13-211

CCI [redacted]

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Appendix 5 Protocol Amendments and Administrative Changes

Amendment Number: 1

Issue Date: 14 July 2014

PURPOSE:

The purpose of this amendment was to revise protocol procedures to accommodate the treatment and monitoring of subjects with ADPKD enrolling into the protocol from additional tolvaptan trials. Consequently, sample size was increased, the inclusion criteria were slightly modified, schedules for initiation of treatment and liver function testing were further defined, CCI [redacted] Down titration for metabolic drug-drug interactions was added to the synopsis and additionally it was required that medical monitor approval is needed. A table of strong and moderate CYP3A4 inhibitors was added to the text. The list of vendors and study personnel was updated. Minor linguistic changes were made for clarity and typographical errors were corrected.

BACKGROUND:

It was decided to allow subjects from additional tolvaptan trials entry into this safety trial for an increased understanding of tolvaptan's long-term safety in ADPKD patients and provide expanded access to tolvaptan for those subjects who would like to continue treatment after completing their previous trial.

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Other Revisions

Figure 3.1-1 - Trial Design Schematic

Table 3.2-1 - Trial Treatments

Table 3.4.2-1 - Inclusion Criteria

Table 3.7-1 - Schedule of Assessments

Sectional Revisions

Location	Old Text	Updated Text
Synopsis, Trial Design	Subjects will be eligible for screening into this trial if they:	Subjects will be eligible for screening into this trial if they:

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Location	Old Text	Updated Text
	• Participated in the double-blind Trial 156-13-210 (only upon successful completion of their randomized 12-month period including post-treatment follow-up,regardless of whether this was on-treatment or off-treatment),or • Participated in the open-label Trial 156-08-271. After consenting and screening, eligible subjects will be assigned a new subject number and administered tolvaptan at a split-dose of 45/15 mg. Subjects will have the opportunity for either up or down-titration to a maximum split tolvaptan dose of 90/30 mg or a minimum split dose of 15/15 mg at the discretion of the investigator according to individual tolerability. Subjects entering the trial from Trial 156-08-271 may receive up to 33 months of open-label tolvaptan therapy, and subjects entering the trial from Trial 156-13-210 may receive up to 15 to 21 months of open-label tolvaptan therapy.	• **Completed and transferred from the double-blind Trial 156-13-210 (12-month period including post-treatment follow-up, regardless of whether this was on-treatment or off-treatment), or** • **Completed Trial 156-08-271 or a prior tolvaptan ADPKD trial, or** • **Interrupted or discontinued treatment in a prior tolvaptan ADPKD trial (other than Trial 156-13-210). Subjects may be enrolled with the medical monitor approval, and additional close monitoring may be required at the beginning of the trial** **For purposes of ensuring subject safety, all subjects will be monitored for hepatic safety monthly until 18 months of tolvaptan exposure has been collected.. After that, and following the approval from the medical monitor, hepatic monitoring will be required every 3 months. Until their prior treatment assignment is unblinded, all Trial 156-13-210 subjects who are eligible for this trial are scheduled to have trial visits/ hepatic monitoring monthly for the first 18 months of this trial. Once unblinding occurs, it can be determined which subjects received tolvaptan in Trial 156-13-210. These subjects may have their trial visits/hepatic transaminase monitoring change to every 3 months sooner as their previous tolvaptan exposure in Trial 156-13-210 can count towards the 18-month threshold.**

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Location	Old Text	Updated Text
		Enrollment in this trial will be closed when the final eligible subject from Trial 156-13-210 enrolls in this trial.
Synopsis, Subject Population	This trial will include up to 2,450 subjects over the age of 18 years with ADPKD diagnosed by Pei-Ravine criteria (modified by magnetic resonance imaging [MRI]). Renal function will be assessed during screening by using historical laboratory values for serum creatinine levels to calculate the estimated glomerular filtration rate (eGFR). The eGFR values will be estimated based on the Chronic Kidney Disease - Epidemiology (CKD-EPI) formula.	This trial will include **approximately 2,500** subjects over the age of 18 years with ADPKD diagnosed by Pei-Ravine criteria (modified by magnetic resonance imaging [MRI])**, and who have completed or participated in a prior tolvaptan ADPKD interventional investigational medicinal product (IMP) trial.**

Synopsis, Inclusion/Exclusion Criteria	Main inclusion criteria:
	• Male and female subjects ≥ 18 years with ADPKD who have completed either Trial 156-13-210 or Trial 156-08-271
	• Diagnosis of ADPKD by modified Pei-Ravine criteria
	• eGFR ≥ 20 mL/min/1.73m^2 within 45 days of the baseline visit. Subjects who have an eGFR between 15 and 19 mL/min/1.73m^2 may be enrolled with medical monitor approval
	
	<u>Main exclusion criteria:</u>
	• Need for chronic diuretic use
	• Hepatic impairment based on liver function assessments other than that expected for ADPKD with cystic liver disease
		Main inclusion criteria:
		• Male and female subjects ≥ 18 years with **confirmed diagnosis of ADPKD (during participation in prior tolvaptan trials) who have**
		  • **Completed and transferred from the double-blind Trial 156-13-210 (12-month period including post-treatment follow-up, regardless of whether this was on-treatment or off-treatment), or**
		  • **Completed Trial 156-08-271 or a prior ADPKD tolvaptan trial, or**
		  • **Interrupted or discontinued treatment in a prior tolvaptan ADPKD trial other than Trial 156-13-210. Subjects may be enrolled with the medical monitor approval, and additional close monitoring may be required at the beginning of the trial**

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Location	Old Text	Updated Text
		• **Estimated glomerular filtration rate (**eGFR**)** ≥ 20 mL/min/1.73m^2 within 45 days of the baseline visit. Subjects who have an eGFR between 15 and 19 mL/min/1.73m^2 may be enrolled with medical monitor approval • **Renal function will be assessed during screening by using historical laboratory values (in the last 30 days) for serum creatinine levels to calculate the eGFR. the eGFR values will be estimated based on the Chronic Kidney Disease - Epidemiology (CKD-EPI) formula** <u>Main exclusion criteria:</u> • Need for chronic diuretic use • Hepatic impairment based on **hepatic laboratory** assessments **(alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin, total [BT])** other than that expected for ADPKD with cystic liver disease
Synopsis, Trial Site(s)	Up to 220 sites which may include North America, South America, Russian Federation and Australia.	**Approximately** 220 **enrolling** sites **including but not limited to the following regions:** North America, South America, **Eastern Europe, Western Europe,** Russian Federation, and Australia.
Synopsis, Investigational Medicinal Product(s), Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration	Tolvaptan tablets (15 mg or 30 mg) 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). Allowed doses are 15/15 mg, 30/15 mg, 45/15 mg, 60/30 mg and 90/30 mg. All subjects will be started at a split-dose of tolvaptan 45/15 mg and titrated according to tolerability. The dose range permitted will be a	**The dose regimens to be used in this trial are 15/15 mg, 30/15 mg, 45/15 mg, 60/30 mg, and 90/30 mg.** Tolvaptan tablets (15 mg or 30 mg) will be self-administered orally as split-dose regimens, **twice daily,** once upon awakening and another approximately 8 to 9 hours later. Doses will be **recorded** as early dose/late dose (eg, 60/30 mg). **Subjects will receive open-label tolvaptan for the duration of the trial.**

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Location	Old Text	Updated Text
	maximum of 90/30 mg and a minimum of 15/15 mg.	**A subject's starting dose in this trial will be dependent on the trial in which they were previously enrolled:** • **156-13-210- initiated on tolvaptan at a split-dose of 45/15 mg with upward titration every 3 to 4 days to 60/30 mg or 90/30 mg per day according to tolerability** • **156-08-271- will retain the last dose level from 271 and start at the same dose in this trial** • **Prior tolvaptan trials- initiated on tolvaptan at a split-dose of 45/15 mg with upward titration every 3 to 4 days to 60/30 mg or 90/30 mg per day according to tolerability** **Down titration to 30/15 mg or 15/15 mg daily will be allowed at the discretion of the investigator according to individual tolerability and with medical monitor notification. Further down titration to 30 or 15 mg once daily may be allowed only for metabolic drug-drug interaction and requires medical monitor approval.**
Synopsis, Trial Assessments	… Screening: Informed consent, medical history (including ADPKD updates, as required), determination of eligibility through inclusion/exclusion criteria, dietary review, vital signs, clinical laboratory assessments, complete physical examination, urine pregnancy test (women of child-bearing potential only [WOCBP]), concomitant medications and laboratory tests to determine eligibility. ...	… Screening: Informed consent, medical history (including ADPKD updates, as required), determination of eligibility through inclusion/exclusion criteria, dietary review, vital signs, clinical laboratory assessments, physical examination, urine pregnancy test (women of child-bearing potential only [WOCBP]), concomitant medications and laboratory tests to determine eligibility. ... CCI [redacted]

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Location	Old Text	Updated Text
Synopsis, Criteria for Evaluation	Safety: • AEs • Vital signs • Clinical laboratory assessments • Serum transaminase elevations for frequency (2x, 3x, 5x and 10x upper limit normal [ULN]), time to onset, time to peak levels, time of offset (< 3x, 2x, or 1x ULN), response to de-challenge and re-challenge and frequency of progression to Hy's laboratory criteria (alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3x ULN and bilirubin, total (BT) > 2x ULN without alkaline phosphatase ≥ 2x ULN) • Serum sodium excursions above 145, 150 or 155 mmol/L or below 135, 130 or 125 mmol/L • Interruptions of protocol specified therapies for hypernatremia or hyponatremia	Safety: • AEs • Vital signs • Clinical laboratory assessments • Serum transaminase elevations for frequency (2x, 3x, 5x and 10x ULN), time to onset, time to peak levels, time of offset (< 3x, 2x, or 1x ULN), response to de-challenge and re-challenge and frequency of progression to Hy's laboratory criteria (ALT or AST > 3x ULN and BT > 2x ULN without alkaline phosphatase ≥ 2x ULN) • Serum sodium excursions above 145, 150, or 155 mmol/L or below 135, 130, or 125 mmol/L
Synopsis, Statistical Methods	Sample size: Sample size was not determined by a formal computation to achieve a target power. No efficacy analyses are planned. It is expected that approximately 2,450 subjects may enroll from previous tolvaptan trials.	Sample size: Sample size was not determined by a formal computation to achieve a target power. No efficacy analyses are planned. It is expected that approximately **2,500** subjects may enroll from previous tolvaptan trials.

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Location	Old Text	Updated Text
	Analysis datasets: • Enrolled Population: all subjects who were enrolled to this open-label trial. • Safety Population: all subjects in the Enrolled Population who take at least 1 dose of investigational medicinal product (IMP).	Analysis datasets: • Enrolled Population: all subjects who were enrolled to this open-label trial. • Safety Population: all subjects in the Enrolled Population who take at least 1 dose of IMP.
Synopsis, Trial Duration	This trial is planned to be continued until one of the following has occurred: 1) All subjects entering from Trial 156-13-210 will be eligible for up to 15 months in Trial 156-13-211 2) After up to 15 months participation for subjects from Trial 156-13-210, and for all subjects entering from Trial 156-08-271, participation may continue until the first of: • the trial concludes (last subject from Trial 156-13-210 reaches at least 10 months participation, or 31 July 2017), or • tolvaptan is approved for use in ADPKD in their region, or • CCI [redacted]	**Trial duration is planned to continue** • **Until the last subject from Trial 156-13-210 completes 18 months of tolvaptan treatment in this trial** • **Subjects enrolling from other trials will conclude their participation once tolvaptan becomes available through routine prescription or through a** CCI [redacted] **Trial 156-13-210 subjects may opt to conclude their participation in this trial if tolvaptan becomes available before they complete 18 months of treatment in this trial**
Section 1.2, Clinical Data	N/A.	CCI [redacted]

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Location	Old Text	Updated Text
		.
Section 1.3, Known and Potential Risks and Benefits	In this extension trial, subjects enrolling from the double-blind Trial 156-13-210 will have monthly transaminase level assessments for the first 18 months while the treatment code from Trial 156-10-210 remains blinded, to ensure that all subjects have adequate safety monitoring during this period of susceptibility. Monitoring will be quarterly for these subjects following the first 18 months of known exposure to tolvaptan. Subjects enrolling from the open-label Trial 156-08-271 will have quarterly transaminase assessments conducted, since they will have already received tolvaptan for 2 years or more.	In this extension trial, subjects enrolling from the double-blind Trial 156-13-210 will have monthly **visits and** transaminase level assessments for the first 18 months while the treatment code from Trial 156-10-210 remains blinded, to ensure that all subjects have adequate safety monitoring during this period of susceptibility. **Once unblinding occurs, it can be determined which subjects received tolvaptan in Trial 156-13-210. These subjects may have their trial visits/hepatic transaminase monitoring changed to every 3 months sooner as their previous tolvaptan exposure in Trial 156-13-210 can count towards the 18-month threshold. If subjects approaching the 18-month threshold have had prior transaminase abnormalities (> 2 × upper limit of normal [ULN]), the investigator is responsible for contacting the medical monitor to confirm the change in frequency from monthly to every 3 months.** Subjects enrolling from the open-label Trial 156-08-271 will have transaminase assessments conducted **every 3 months**, since they will have already received tolvaptan for **at least 18 months**. **The current IB lists all of the tolvaptan trials. Subjects enrolling in this trial who were in a previous ADPKD trial other than Trials 156-13-210 and 156-08-271 will have monthly visits and transaminase level assessments for the first 18 months.**
Section 2.1, Trial Rationale	... Over the 3 years of placebo-controlled treatment, ALT was elevated to a greater than three times the upper limit of normal (> 3 × ULN) in 4.4% of tolvaptan subjects compared with 1% of placebo subjects. To date, 3 tolvaptan	… Over the 3 years of placebo-controlled treatment, ALT was elevated to a greater than three times the upper limit of normal (> 3 × ULN) in 4.4% of tolvaptan subjects compared with 1% of placebo

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Location	Old Text	Updated Text
	subjects' transaminases and bilirubin levels reached Hy's laboratory criteria (> 3 × and > 2 × ULN, respectively). Upon discontinuation, all subjects' liver tests showed reversibility of the elevation within approximately 4 months after tolvaptan was discontinued. Nevertheless, without adequate monitoring and management, it is estimated that a 1:3,000 risk for irreversible liver injury may exist	subjects. To date, 3 tolvaptan subjects' transaminases and bilirubin levels reached Hy's laboratory criteria (> 3 × and > 2 × ULN, respectively). Upon discontinuation, all subjects' liver tests showed reversibility of the elevation within approximately 4 months after tolvaptan was discontinued. Nevertheless, without adequate monitoring and management, it is estimated that a 1:**4**,000 risk for irreversible liver injury may exist
Section 3.1, Type/Design of Trial	This trial is a phase 3b, multi-center, open-label trial. Subjects will be eligible for screening into this trial if they: • Participated in the double-blind Trial 156-13-210 (only upon successful completion of their randomized 12-month period including post-treatment follow-up, regardless of whether this was on-treatment or off-treatment), or • Participated in the open-label Trial 156-08-271 Upon the successful completion of Trial 156-13-210 or Trial 156-08-271, subjects will have an opportunity to enroll into Trial 156-13-211 immediately following completion of the follow-up visit(s) of the previous trial. The last follow-up visit assessments can be utilized for screening into this trial. However, for subjects who require a longer period between completion of the preceding trial and entry into this trial, this may be allowed at the discretion of the medical monitor. After consenting and screening, eligible subjects will be assigned a new subject number and administered tolvaptan at a split-dose of 45/15 mg. Subjects will have the opportunity for	This trial is a phase 3b, multi-center, open-label trial. **Eligible subjects** will have an opportunity to enroll into Trial 156-13-211 immediately following completion of the follow-up visit(s) of the previous trial. The last visit assessments **from the previous protocol can be combined with the screening visit for this trial, with all required assessments from each visit only performed once, as long as the time between the last follow-up visit assessments from the previous trial and the screening visit for this trial is within 30 days.** **Medical monitor approval is needed for enrollment of subjects whose completion of the preceding trial prior to entry in this trial exceeds 3 months, and these subjects will be required to undergo all screening and baseline assessments.** **After consenting, subjects will be assigned a new screening number. Subjects who are found to be eligible will retain the same subject number they had been assigned in their previous trial.. For purposes of ensuring subject safety, tolvaptan exposure of at least 18 months is required for all**

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	either up or down-titration to a maximum tolvaptan split dose of 90/30 mg, or a minimum split dose of 15/15 mg at the discretion of the investigator according to individual tolerability. Subjects entering the trial from Trial 156-08-271 may receive up to 33 months of open-label tolvaptan therapy, and subjects entering the trial from Trial 156-13-210 may receive up to 15 to 21 months of open-label tolvaptan therapy. This trial is planned to continue until one of the following has occurred: 1) All subjects entering from Trial 156-13-210 will be eligible for up to 15 months in Trial 156-13-211 2) After up to 15 months participation for subjects from Trial 156-13-210, and for all subjects entering from Trial 156-08-271, participation may continue until the first of: • the trial concludes (last subject from Trial 156-13-210 reaches at least 10 months, or 31 July 2017), or • tolvaptan is approved for use in ADPKD in their region, or • CCI [redacted]	**subjects. While Trial 156-13-210 remains blinded, subjects enrolling from any prior trial besides Trial 156-08-271 are scheduled to have monthly hepatic monitoring for the first 18 months of this trial. After that, following the approval of the medical monitor, hepatic monitoring will take place every 3 months. Subjects enrolling from Trial 156-08-271 will have hepatic monitoring every 3 months. All Trial 156-13-210 subjects who are eligible for this trial will initially be scheduled to have trial visits and hepatic monitoring monthly for the first 18 months, then every 3 months thereafter, because their tolvaptan exposure cannot be determined since Trial 156-13-210 is a double blind trial. Once unblinding occurs, it can be determined which subjects received tolvaptan in Trial 156-13-210. These subjects may have their trial visits/hepatic transaminase monitoring changed to every 3 months sooner as their previous tolvaptan exposure in Trial 156-13-210 can count towards the 18-month threshold.** **Enrollment in this trial will be closed when the last eligible subject from Trial 156-13-210 enrolls in this trial.** The **duration of this** trial is planned to continue • **Until the last subject** from Trial 156-13-210 **completes 18 months of tolvaptan treatment in this trial** • **Subjects enrolling from other trials will conclude their participation in this trial once tolvaptan becomes available through routine prescription or through a** CCI [redacted]

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Location	Old Text	Updated Text
		Trial 156-13-210 subjects may opt to conclude their participation in this trial if tolvaptan becomes available before they complete 18 months of treatment in this trial
Section 3.1.1, Figure 3.1-1	See previous Figure at the end of Appendix 5.	See previous Figure at the end of Appendix 5
Section 3.2 Treatments	Following consent, and once subjects have satisfied all of the inclusion criteria and none of the exclusion criteria, subjects will be assigned a new subject number and administered tolvaptan at a split-dose of 45/15 mg. Subjects will be titrated up to 60/30 mg and 90/30 mg according to subject tolerability. Down titration to 30/15 mg and 15/15 mg is also permitted at the discretion of the medical monitor and individual subject tolerability. All subjects will be administered tolvaptan tablets in a daily split-dose, once upon awakening and another approximately 8 to 9 hours later. The exact time 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). While taking tolvaptan, 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.	**The dose regimens to be used in this trial are 15/15 mg, 30/15 mg, 45/15 mg, 60/30 mg, and 90/30 mg.** Following consent, and once subjects have satisfied all of the inclusion criteria and none of the exclusion criteria, subjects will **retain their subject number assigned from their previous trial. Subjects will receive open-label tolvaptan for the duration of the trial.** All subjects will be administered tolvaptan tablets in a daily split-dose, once upon awakening and another approximately 8 to 9 hours later (twice daily dosing). The exact time 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 **recorded** as early dose/late dose (eg, 60/30 mg). **A subject's starting dose in this trial will be dependent on the trial in which they were previously enrolled:** • **156-13-210- initiated on tolvaptan at a split-dose of 45/15 mg with upward titration every 3 to 4 days to 60/30 mg or 90/30 mg per day according to tolerability** • **156-08-271- will retain the last dose level from 271 and start at the same dose in this trial**

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Location	Old Text	Updated Text
		• **Prior tolvaptan trials- initiated on tolvaptan at a split-dose of 45/15 mg with upward titration every 3 to 4 days to 60/30 mg or 90/30 mg per day according to tolerability** Down titration to 30/15 mg and 15/15 mg is also permitted at the discretion of the **investigator according to subject tolerability with** medical monitor **notification**. **Further down titration to 30 or 15 mg once daily may be allowed only for metabolic drug-drug interaction and requires medical monitor approval.** **For subjects moving from the 156-13-210 trial and requiring tolvaptan titration itwill be conducted in the following way: Subjects will be instructed to take tolvaptan starting at a split dose of 45/15 mg (as 3 tablets upon waking and 1 tablet approximately 8 to 9 hours later) and to titrate up every 3 to 4 days; first to 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. 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?" Subjects will continue in the trial with the regimen to which tolerability was established.** While taking tolvaptan, 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.

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Location	Old Text	Updated Text
Table 3.2-1, Trial Treatments	Previous Table is at the end of Appendix 5	Updated Table with tracked changes is at the end of Appendix 5
Section 3.2.2 Dosing with CYP3A4 Moderate Inhibitors	For subjects who require dosing with a moderate inhibitor, initial tolvaptan reductions as shown below should be tried, with further dose reductions or interruption as necessary for tolerability. • 90/30 mg to 45/15 mg • 60/30 mg to 30/15 mg • 45/15 mg to 15/15 mg • 30/15 mg to 15 mg once daily • 15/15 mg to 15 mg once daily	For subjects who require dosing with a moderate inhibitor, initial tolvaptan reductions as shown below should be tried, with further dose reductions or interruption as necessary for tolerability. • 90/30 mg to 45/15 mg • 60/30 mg to 30/15 mg • 45/15 mg to 15/15 mg • 30/15 mg to 15 mg once daily • 15/15 mg to 15 mg once daily **A partial list of strong and moderate CYP3A4 inhibitors can be found in Section 4.1.**
Section 3.3, Trial Population	This trial will include up to 2,450 subjects over the age of 18 years with ADPKD diagnosed by Pei-Ravine criteria[11 12] (modified by magnetic resonance imaging [MRI]). Renal function will be assessed during screening using historical laboratory values for serum creatinine levels to calculate the estimated glomerular filtration rate (eGFR). The eGFR values will be estimated based on the Chronic Kidney Disease – Epidemiology (CKD-EPI) formula.[13]	This trial will include **approximately 2,500** subjects over the age of 18 years with ADPKD diagnosed by Pei-Ravine criteria[11 12] (modified by magnetic resonance imaging [MRI]) **who completed or participated in a prior tolvaptan trial.**
Table 3.4.2-1, Inclusion Criteria	Previous Table is at the end of Appendix 5	Updated Table with tracked changes is at the end of Appendix 5
Section 3.5.1, Safety Endpoints	Interruption of protocol-specified therapies for hypernatremia or hyponatremia	Endpoint deleted
CCI [redacted]	[redacted]	CCI [redacted]
Section 3.5.3, Exploratory Endpoints	CCI [redacted]	[redacted]

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Location	Old Text	Updated Text
	CCI [redacted]	[redacted]
Section 3.6, Measures to Minimize/Avoid Bias (old text section number was 3.5.3)	All blood and urine chemistry will be analyzed and reported by a local laboratory.	All blood and urine chemistry will be analyzed and reported by a **central** laboratory.
Section 3.7, Table 3.7-1, Schedule of Assessments	See previous table at the end of Appendix 5	See revised Table at the end of Appendix 5. The changes made include: Screening changed from -6 to -30 days Language outlining assessments based on subjects' previous trial expanded; Central rather than local laboratory will be used; CCI [redacted] Hepatitis testing wording added
Section 3.7.1.1, Screening (old text Section 3.6.1.1)	Screening (-6 days to 0 days prior to Baseline) Screening for eligibility is required for all subjects. The screening and baseline visits may be combined with the EoTx visit from the previous protocol with all required assessments from each visit only performed once. Required assessments are as follows: 1. Obtain subject consent 2. Determine subject eligibility through inclusion/exclusion criteria 3. Record demographic information and prior trial identifiers (screening	Screening (**-30** days to **-1** day prior to Baseline) Screening for eligibility is required for all subjects. The screening and baseline visits may be combined with the **last** visit from the previous protocol with all required assessments from each visit only performed once. **In some cases, if a subject enrolls in this trial from a prior tolvaptan trial, the end of trial visit for that trial and the screening visit for this one may occur simultaneously.** Required assessments are as follows: 1. Obtain subject consent. 2. Determine subject eligibility through

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Location	Old Text	Updated Text
	identification [ID], subject ID, site ID) 4. Record medical/ADPKD history using prior trial data 5. Review dietary recommendations and compliance 6. Record vital signs (post-void weight and seated heart rate) and in-clinic calibrated blood pressure (BP) measurement. Record height 7. Collect blood for serum chemistry, liver function panel (ALT, AST, bilirubin, total (BT), bilirubin (direct), and alkaline phosphatase), serum sodium, creatinine and hematology and coagulation. Hepatitis testing is optional 8. Collect urine for urinalysis, urine osmolality (optional), and urine specific gravity 9. Perform urine pregnancy test on women of childbearing potential (WOCBP). If positive, a follow-up serum test will be performed 10. Conduct full physical examination 11. Enter subject into interactive response technology (IRT) including prior trial identifier/information (protocol number, subject ID), confirmed dose regimen and scheduled date of next visit 12. Assess AEs reported as ongoing or resolved from	inclusion/exclusion criteria. 3. Record demographic information and prior trial identifiers (screening identification [ID], subject ID, site ID)**, prior tolvaptan ADPKD trial protocol number).** 4. Record medical/ADPKD history using prior trial data. 5. Review dietary recommendations and compliance. 6. Record vital signs (post-void weight and seated heart rate) and in-clinic calibrated blood pressure (BP) measurement. Record height. 7. Collect blood for serum chemistry, liver function panel (ALT, AST, bilirubin, total [BT], bilirubin [direct], and alkaline phosphatase), serum sodium, creatinine, and hematology and coagulation. Hepatitis testing is optional. **If hepatitis testing is performed, then both pre- and post-counseling activities relating to hepatitis testing are to be carried out based on local requirements and best practices.** 8. Collect urine for urinalysis, urine osmolality (optional), and urine specific gravity. 9. Perform urine pregnancy

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Location	Old Text	Updated Text
	prior trial to determine entry as medical history or ongoing event for this trial	test on women of childbearing potential (WOCBP). If positive, a follow-up serum test will be performed. 10. Conduct full physical examination. 11. Enter subject into interactive response technology (IRT) including prior trial identifier/information (protocol number, subject ID), confirmed dose regimen, and scheduled date of next visit. 12. Assess AEs reported as ongoing or resolved from prior trial to determine entry as medical history or ongoing event for this trial. 13. **Record ongoing concomitant medications. (This may be done if the screening visit occurs simultaneously with the last visit from a previous tolvaptan trial).**
Section 3.7.1.2, Baseline (old text Section 3.6.1.2)	The baseline visit is the beginning of the treatment period in this trial. At the baseline visit, subjects will be assigned a new subject number and the following assessments and procedures will be performed: 1. Review inclusion/exclusion criteria 2. Review dietary recommendations and compliance 3. CCI [redacted]	The baseline visit is the beginning of the treatment period in this trial. At the baseline visit, subjects will **retain the** subject number **assigned in the previous tolvaptan trial,** and the following assessments and procedures will be performed: 1. Review inclusion/exclusion criteria. 2. Review dietary recommendations and compliance. 3. CCI [redacted]

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	4. Record vital signs (post-void weight, seated heart rate, and calibrated blood pressure measurement) 5. Dispense at-home urine pregnancy test kits to WOCBP to be used if a menstrual period is missed before the next visit 6. An optional directed physical examination may be performed to focus on PKD-related signs and symptoms 7. Assess tolerability/dosing review of IMP 8. Enroll subject into trial through IRT and obtain IMP 9. Dispense IMP (sufficient for 1 month of dosing) 10. Provide subject with dosing instructions to begin on the following day 11. Record ongoing concomitant medications 12. Assess AEs .	CCI 4. Record vital signs (post-void weight, seated heart rate, and calibrated blood pressure measurement). 5. Dispense at-home urine pregnancy test kits to WOCBP to be used if a menstrual period is missed before the next visit. 6. An optional directed physical examination may be performed to focus on PKD-related signs and symptoms. 7. Assess tolerability/dosing review of IMP. 8. Enroll subject into trial through IRT and obtain IMP. 9. Dispense IMP (sufficient for 1 month **or 3 months** of dosing **based on subject's required visit schedule for hepatic evaluation as either monthly or every 3 months**). 10. Provide subject with dosing instructions to begin on the following day. 11. Record ongoing concomitant medications. 12. Assess AEs.
Section 3.7.1.3, Monthly Visit (old text Section 3.6.1.3)	Monthly Visit (± 4 days) Subjects will return for a monthly visit to assess safety and tolerability of IMP and to monitor liver function. Subjects enrolling from the double-blind Trial 156-13-210 will have monthly ALT level assessments for the first 18 months while treatment code from Trial 156-13-210 remains	Monthly Visit (± **7** days) **The following s**ubjects will return for a monthly visit to assess safety and tolerability of IMP and to monitor liver function. • Subjects enrolling from the double-blind Trial 156-13-210 will have monthly **trial**

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	blinded, to ensure that they have adequate safety monitoring during this period of susceptibility. The following will be assessed: 1. Collect blood for sodium and creatinine 2. Collect blood for ALT (for the first 18 months of tolvaptan treatment in subjects enrolling from Trial 156-13-210). If at any time within the first 18 months of tolvaptan treatment the ALT elevates to > 1x ULN to < 3x ULN, ALT will be monitored monthly for an additional 6 months beyond the date of elevation, to ensure that the level is stable and does not exceed this threshold. If at any time the ALT elevates ≥ 3x ULN, a full liver function panel is required (ALT, AST, BT and alkaline phosphatase) within 72 hours of the site being aware of this result. CCI [redacted] 3. An optional directed physical examination may be performed to focus on PKD-related signs and symptoms 4. Assess tolerability/dosing review of IMP 5. Enter subject status in IRT, including any dose-regimen	**visits**/ALT level assessments for the first 18 months while treatment code from Trial 156-13-210 remains blinded, to ensure that they have adequate safety monitoring during this period of susceptibility. **Once unblinding occurs, it can be determined which subjects received tolvaptan in Trial 156-13-210. These subjects may have their trial visits/hepatic transaminase monitoring change to every 3 months sooner as their previous tolvaptan exposure in Trial 156-13-210 can count towards the 18-month threshold. The investigator will need to discuss the change in frequency with the medical monitor before instituting the change.** • **Subjects from prior tolvaptan trials other than Trial 156-08-271 will have monthly trial visits/ALT level assessments for the first 18 months. After that, the trial visits/ALT monitoring will be conducted every 3 months after the change in frequency is confirmed with the medical monitor** • **Subjects enrolling from the open-label Trial 156-08-271 who**

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	changes and obtain IMP assignment 6. Collect and reconcile returned IMP 7. Dispense IMP 8. Update concomitant medications 9. Assess AEs	**have greater than 18 months of cumulative exposure to tolvaptan will have trial visits/ALT monitoring conducted every 3 months.** The following **assessments** will be **completed**: **1. Review dietary recommendations and compliance.** **2.** CCI [redacted] **3. Record vital signs (post-void weight, seated heart rate, and calibrated blood pressure measurement).** 4. Collect blood **for central laboratory assessments** for **serum** sodium, **serum** creatinine, **and ALT (see Section 3.7.2.4).** 5. CCI [redacted] **7. Urinalysis, urine osmolality (optional), urine specific gravity.** **8. Perform urine pregnancy test on WOCBP (every 3**

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		months). If positive, a follow-up serum test will be performed. **9. Dispense at-home urine pregnancy test kits to WOCBP, as required** 10. An optional directed physical examination may be performed to focus on PKD-related signs and symptoms. 11. Assess tolerability/dosing review of IMP. 12. Enter subject status in IRT, including any dose-regimen changes and obtain IMP assignment. 13. Collect and reconcile returned IMP**, assess compliance.** 14. Dispense IMP **based on subject's required visit schedule and provide.subject with dosing instructions.** 15. Update concomitant medications. 16. Assess AEs.
Section 3.7.1.4, Every 3 Months	Every 3 Months (±4 days) 1. Review dietary recommendations and compliance 2. CCI [redacted] 3. Record vital signs (post-void weight, seated heart rate, and calibrated blood pressure measurement) 4. Collect blood for local standard of care laboratory assessments	Every 3 Months (±**14** days) 1. Review dietary recommendations and compliance. 2. CCI [redacted] 3. Record vital signs (post-void weight, seated heart rate, and calibrated blood pressure measurement). 4. Collect blood for **central** laboratory assessments **serum sodium, serum**

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Location	Old Text	Updated Text
	5. Urinalysis, urine osmolality (optional), urine specific gravity 6. Perform urine pregnancy test on WOCBP. If positive, a follow-up serum test will be performed 7. Dispense at-home urine pregnancy test kits to WOCBP, as required 8. Collect blood for ALT. If at any time the ALT elevates to > 1x ULN to < 3x ULN, ALT will be monitored monthly for an additional 6 months beyond the date of elevation, to ensure that the level is stable and does not exceed this threshold. If at any time the ALT elevates ≥ 3x ULN, a full liver function panel is required (ALT, AST, BT and alkaline phosphatase) within 72 hours of the site being aware of this result. CCI [redacted] 9. Update concomitant medications 10. Assess AEs	**creatinine, ALT (see Section 3.7.2.4).** 5. CCI [redacted] 6. Urinalysis, urine osmolality (optional), urine specific gravity. 7. Perform urine pregnancy test on WOCBP. If positive, a follow-up serum test will be performed. 8. Dispense at-home urine pregnancy test kits to WOCBP, as required. 9. CCI [redacted] **10. An optional directed physical examination may be performed to focus on PKD-related signs and symptoms.** **11. Assess tolerability/dosing review of IMP.** **12. Enter subject status in IRT, including any dose-regimen changes and obtain IMP assignment.** **13. Collect and reconcile returned IMP; assess compliance.** **14. Enter subject status in IRT, including any dose-regimen changes.** **15. Dispense IMP based on**

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		subject's visit schedule and provide subject with dosing instructions. 16. Update concomitant medications. 17. Assess AEs.
Section 3.7.1.5, Early Termination/End of Treatment (old text Section 3.6.1.5)	Early Termination/End of Treatment (+ 3 months) At the early termination/end of treatment visit the following will be assessed: 1. Review dietary recommendations and compliance 2. CCI [redacted] 3. Record vital signs (post-void weight, seated heart rate, and calibrated blood pressure measurement) 4. Collect blood for serum chemistry, creatinine, serum sodium and hematology and coagulation 5. Collect blood for ALT. If the ALT elevates ≥ 3x ULN, a full liver function panel is required (ALT, AST, BT and alkaline phosphatase) within 72 hours of the site being aware of this result. CCI [redacted] 6. Collect urine for urinalysis, urine osmolality (optional), urine specific gravity	Early Termination/End of Treatment (**+ 7 days**) At the early termination/end of treatment visit the following will be assessed: 1. Review dietary recommendations and compliance. 2. CCI [redacted] 3. Record vital signs (post-void weight, seated heart rate, and calibrated blood pressure measurement). 4. Collect blood for serum chemistry, **serum** creatinine, **ALT,** serum sodium and hematology and coagulation. 5. CCI [redacted] **6.** CCI [redacted] 7. Collect urine for urinalysis, urine osmolality (optional), urine specific gravity. 8. Perform urine pregnancy test on WOCBP. If

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Location	Old Text	Updated Text
	7. Perform urine pregnancy test on WOCBP. If positive, a follow-up serum test will be performed 8. An optional directed physical examination may be performed to focus on PKD-related signs and symptoms 9. Assess tolerability/dosing review of IMP 10. Enter subject status in IRT, including any dose-regimen changes since the previous entry 11. Collect and reconcile returned IMP 12. Update concomitant medications 13. Assess AEs	positive, a follow-up serum test will be performed. 9. An optional directed physical examination may be performed to focus on PKD-related signs and symptoms. 10. Assess tolerability/dosing review of IMP. 11. Enter subject status in IRT, including any dose-regimen changes since the previous entry. 12. Collect and reconcile returned IMP**; assess compliance.** 13. Update concomitant medications. 14. Assess AEs.
Section 3.7.1.6, Follow-up Visit	Follow-up Visit 7 Days (+ 7 days)	**7-day** Follow-up Visit (+ 7 days)
Section 3.7.1.6, Follow-up Visit (old text Section 3.6.1.6)	1. Record vital signs (post-void weight, seated heart rate, and calibrated blood pressure measurement) 2. Collect blood for creatinine 3. Collect blood for ALT. If the ALT elevates ≥ 3x ULN, a full liver function panel is required (ALT, AST, BT and alkaline phosphatase) within 72 hours of the site being aware of this result. CCI [redacted] 4. Perform urine pregnancy test	1. Record vital signs (post-void weight, seated heart rate, and calibrated blood pressure measurement). 2. Collect blood for **serum** creatinine **and ALT.** 3. CCI [redacted] 4. Perform urine pregnancy test on WOCBP. If positive, a follow-up serum test will be performed. **5. Enter subject status in IRT.**

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	on WOCBP. If positive, a follow-up serum test will be performed 5. Update concomitant medications 6. Assess AEs	6. Update concomitant medications. 7. Assess AEs.
Section 3.7.2.2, Clinical Laboratory Assessments (old text Section 3.6.2.2)	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 in order to reduce variability in the samples over time. While serum creatinine is being collected primarily for safety reporting purposes, it is a key measure in the management of patients with ADPKD CCI [redacted] Therefore, great care should be taken in ensuring these measurements are collected and analyzed in as uniform a manner as possible (preferably using isotope dilution mass spectroscopy (IDMS)-traceable methodologies). Clinical laboratory samples will be collected at the following time points: Screening: Hematology and coagulation panel, serum chemistry panel, liver function panel (AST, ALT, alkaline phosphatase, bilirubin direct [BT]) serum sodium, urinalysis panel, urine osmolality (optional), urine specific gravity, urine pregnancy test (WOCBP) and hepatitis (optional). Monthly visits (± 4 days): ALT (for the first 18 months in subjects	**Central laboratory non-fasting serum laboratory tests will be performed.** 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 in order to reduce variability in the samples over time. While serum creatinine is being collected primarily for safety reporting purposes, it is a key measure in the management of patients with ADPKD CCI [redacted]. **The eGFR values will be calculated by CKD-EPI from the central-laboratory serum creatinine concentrations taken during every trial visit.** Clinical laboratory samples will be collected **and sent to the central laboratory** at the following time points: Screening: Hematology and coagulation panel, serum chemistry panel, liver function panel (AST, ALT, alkaline phosphatase, bilirubin direct [BT]) serum sodium, **serum**

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	enrolled from Trial 156-13-210), and serum sodium, creatinine (all subjects). Every 3 months: (± 4 days): ALT (after 18 months of treatment in subjects enrolled from Trial 156-13-210 and for all subjects enrolled from Trial 156-08-271), standard of care laboratory assessments, urinalysis panel, urine pregnancy test (WOCBP), urine osmolality (optional), and urine specific gravity. Early Termination/End of Treatment (+ 3 months): Serum chemistry panel, hematology and coagulation panel, ALT, creatinine, serum sodium, urinalysis panel, urine pregnancy test (WOCBP), urine osmolality (optional), and urine specific gravity. Follow-up visit (+ 7 days): ALT, creatinine, and urine pregnancy test (WOCBP). … 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).	**creatinine,** urinalysis panel, urine osmolality (optional), urine specific gravity, urine pregnancy test (WOCBP) and hepatitis (optional). Monthly visits (± 7 days): ALT (for the first 18 months **for** subjects enrolled f**rom other tolvaptan ADPKD trials and** Trial 156-13-210 **while trial remains blinded**), serum sodium, **and serum** creatinine (all subjects), **urinalysis, urine osmolality (optional), urine specific gravity, and urine pregnancy test (every 3 months in WOCBP).** CCI [redacted] Every 3 months: (± **1**4 days): ALT (after 18 months of treatment **for** subjects enrolled from **other ADPKD tolvaptan trials, or from** Trial 156-13-210 **after the trial is unblinded,** and for subjects enrolled from Trial 156-08-271**), serum sodium and serum creatinine,** urinalysis panel, urine pregnancy test (WOCBP), urine osmolality (optional), and urine specific gravity. CCI [redacted] Early Termination/End of Treatment (+ **7 days**): Serum chemistry panel, hematology and coagulation panel, ALT, **serum sodium and serum** creatinine, [redacted] urinalysis panel, urine pregnancy test (WOCBP), urine osmolality (optional), and urine specific gravity. **7-day**Follow-up visit (+ 7 days): ALT, **serum** creatinine, and urine pregnancy test (WOCBP). … 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. **Blood testing for hepatitis will be**

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		optional for all subjects. Urine pregnancy testing will be performed with commercially available, high-sensitivity kits supplied to the subject by the site (acquired by the sponsor).
Table 3.7.2.2-, Clinical Laboratory Assessments	Please see original table at the end of Appendix 5,	Please see revised table at the end of Appendix 5,
Section 3.7.2.3, Physical Examination and Vital Signs (old text, Section 3.6.2.3)	A full physical examination will be performed and documented at the screening visit although this may be combined with the EoTx visit from the previous trial. At other visits, an optional 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. ...	A full physical examination will be performed and documented at the screening visit although this may be combined with the **last** visit from the previous trial. At other visits, an optional 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. **Height will be measured only at screening.** 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. ...
Section 3.7.2.4, Assessment of Liver Symptoms, Signs or Test Abnormalities (old text, Section 3.6.2.4)	Testing for hepatic transaminase (ALT/AST), alkaline phosphatase, bilirubin direct, and BT will be performed during screening. Subjects enrolling from the double-blind Trial 156-13-210 will have monthly ALT assessments for the first 18 months while the treatment code from Trial 156-13-210 remains blinded to ensure that all subjects have adequate safety monitoring during this period of susceptibility. Following the first 18 months, ALT assessments will be made quarterly for these subjects. Subjects enrolling from the open-	Testing for hepatic transaminase (ALT/AST), alkaline phosphatase, bilirubin direct, and BT will be performed during screening. Subjects enrolling from the double-blind Trial 156-13-210 will have monthly ALT assessments for the first 18 months while the treatment code from Trial 156-13-210 remains blinded to ensure that all subjects have adequate safety monitoring during this period of susceptibility. **Once unblinding occurs, it can be determined which subjects received tolvaptan in Trial 156-13-**

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	label Trial 156-08-271 will have quarterly ALT assessments since they will have already received tolvaptan for 2 years or more. Management of liver abnormalities is discussed in the paragraphs below.	**210. These subjects may have their trial visits/hepatic transaminase monitoring changed to every 3 months sooner as their previous tolvaptan exposure in Trial 156-13-210 can count towards the 18-month threshold.** Following the first 18 months, ALT assessments will be made **every 3 months** for **Trial 156-13-210 subjects and for subjects from other tolvaptan ADPKD trials besides Trial 156-08-271** . Subjects enrolling from the open-label Trial 156-08-271 **who have tolvaptan exposure greater than 18 months will continue with ALT monitoring every 3 months.** **Subjects enrolling from prior tolvaptan trials besides Trial 156-08-271 will have monthly ALT assessments for the first 18 months. Upon reaching 18 months of exposure and after confirmation from the medical monitor, the frequency of ALT monitoring for these subjects will occur every 3 months.** **ALT will also be assessed at the Early Termination/End of Treatment visit and at the 7-day Follow-up visit.** Management of liver abnormalities is discussed in the paragraphs below.
Section 3.7.2.4.1, Liver Test Abnormalities and Interruption/ Discontinuation of Investigational Medicinal Product (old text Section 3.6.2.4.1)	The appearance of any suspicious symptom or sign should trigger prompt testing of hepatic function (ie, within 72 hours). Liver transaminase or bilirubin levels ≥ 2 × ULN should prompt immediate retesting within 72 hours and tolvaptan should be temporarily interrupted. Tolvaptan should not be resumed until monitoring indicates abnormalities have resolved, are stable or are not	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 × ULN should also prompt immediate retesting within 72 hours. While values remain in an abnormal**

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	increasing, and then only with an increased frequency of monitoring. Subjects would not typically be allowed to resume treatment with tolvaptan if they have: • transaminase levels rise above 8 × ULN, • transaminase levels are > 5 × ULN for more than 2 weeks, or • concurrent elevations of transaminase > 3 × ULN and BT > 2 × ULN.	**range, testing frequency should be increased to at least weekly for the first month, gradually returning to monthly, or every three months as indicated by the results.** **Liver transaminase or bilirubin levels reaching or exceeding 2 × ULN that have an uncertain or rapidly increasing trajectory should prompt at least temporary IMP interruption.** Tolvaptan 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 tolvaptan if they have: • transaminase levels rise above 8 × ULN, • transaminase levels are > 5 × ULN for more than 2 weeks, or • concurrent elevations of transaminase > 3 × ULN and BT > 2 × ULN.
CCI [redacted]	N/A	CCI [redacted]

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Section 3.7.5, Treatment Interruption and Discontinuation	N/A	In this trial, it is expected that subjects may possibly have one or more planned or unplanned treatment interruptions. If a subject's IMP treatment must be interrupted for medical or surgical reasons, liver test abnormalities, use of a prohibited 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 investigator should be notified as soon as possible and the reason for treatment interruption must be documented in the source documents and CRF. If permissible, the subject's IMP may be resumed following approval by the medical monitor. If IMP treatment is permanently discontinued, the reason for discontinuation must be recorded appropriately in the source document and in the CRF. A subject who permanently discontinues IMP treatment may have the option to end trial participation (complete the early termination visit) or to continue participation off IMP and complete ongoing trial assessments as per protocol or with a modified (ie, less frequent) schedule as outlined in Section 3.8.3.
Section 3.8.1	3.7.1 Entire Trial or Treatment Arm(s)	3.8.1 Entire Trial
Section 3.8.3, Individual Subject	... All subjects have the right to withdraw at any time during treatment without prejudice. The investigator can discontinue a subject's participation in the trial at any time if medically necessary. In addition, subjects meeting the following criteria must be withdrawn from the trial: a) Occurrence of any AE, intercurrent	... All subjects have the right to withdraw at any time during treatment without prejudice. The investigator can discontinue a subject's participation in the trial at any time if medically necessary. **It is preferred that subjects who permanently discontinue IMP will have the option to continue participation off IMP with regular**

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	illness, or abnormality in a laboratory assessment which, in the opinion of the investigator, warrants the subject's permanent withdrawal from the trial; b) Treatment with a prohibited concomitant medication other than the use of appropriate medications for the treatment of AEs under direction of the investigator; c) Subject noncompliance, defined as refusal or inability to adhere to the trial schedule or procedures (see Section 3.12); d) At the request of the subject, investigator, sponsor, or regulatory authority; e) Subject becomes pregnant; or f) Subject is lost to follow-up. The investigator will notify the sponsor promptly when a subject is withdrawn.	**scheduled visits or with a modified (ie, less frequent) schedule. If subjects are unable or unwilling to complete the visits and procedures off IMP, the early termination/EoTx visit should be completed. The investigator may continue to contact those who discontinue IMP through to the final completion date of the trial or thereafter if needed to determine outcomes ie, vital status.** In addition, subjects meeting the following criteria must be withdrawn from the trial: a) Occurrence of any AE, intercurrent illness, or abnormality in a laboratory assessment which, in the opinion of the investigator, warrants the subject's permanent withdrawal from the trial; **b**) Subject noncompliance, defined as refusal or inability to adhere to the trial schedule or procedures (see Section 3.11); **c**) At the request of the subject, investigator, sponsor, or regulatory authority; **d**) Subject is lost to follow-up. The investigator will notify the sponsor promptly when a subject is withdrawn.
Section 3.12, Subject Compliance	Subject compliance will be monitored by pill counts as IMP is returned. Any subject who, without the instruction of the investigator, discontinues tolvaptan investigational product without the instruction of the investigator, discontinues tolvaptan for 30 consecutive days or misses > 30% of the doses intended for a period between visits (whichever is greater) will be deemed noncompliant. ...	Subject compliance will be monitored by pill counts as IMP is returned. Any subject who, without the instruction of the investigator, discontinues tolvaptan investigational product, discontinues tolvaptan for 30 consecutive days or misses > 30% of the doses intended for a period between visits (whichever is greater) will be deemed noncompliant. ...
Section 3.13, Protocol Deviations	This trial is to be conducted as described in this protocol. In the event of a significant deviation from the protocol due to an emergency,	This trial is to be conducted as described in this protocol. In the event of a significant deviation from the protocol due to an emergency,

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	accident or mistake, the investigator or designee must contact the sponsor at the earliest possible time. This will allow an early joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator and the sponsor, and reviewed by the monitor.	accident or mistake **(eg, violation of informed consent process, IMP dispensing or subject dosing error, subject enrolled in violation of eligibility criteria or concomitant medication criteria)**, the investigator or designee must contact the sponsor at the earliest possible time. This will allow an early joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator and the sponsor, and reviewed by the **site** monitor.
Section 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 therapies, tolvaptan, and other vasopressin antagonists, (eg, OPC-31260 (mozavaptan), Vaprisol (conivaptan), 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 tolvaptan metabolism (see Section 3.2.1 and Section 3.2.2). ... 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 list would include: cimetidine, non-steroidal anti-inflammatory drugs like aspirin or ibuprofen, chemotherapy drugs, cephalosporin, the combination of elvitegravir, cobicistat, emtricitabine, and tenofovir (Stribild™), dolutegravir, dronedarone, ranolazine, metformin,	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 therapies, vasopressin antagonists **other than tolvaptan**, (eg, OPC-31260 (mozavaptan), Vaprisol (conivaptan), 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 tolvaptan metabolism (see Section 3.2.1 and Section 3.2.2). **A partial list of strong and moderate CYP3A4 inhibitors can be found in Table 4.1-1 below:** ... 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 list would include: non-steroidal anti-inflammatory drugs like aspirin or ibuprofen, chemotherapy drugs,

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	and trimethoprim.	cephalosporin, the combination of elvitegravir, cobicistat, emtricitabine, and tenofovir (Stribild™), dolutegravir, dronedarone, ranolazine, metformin, and trimethoprim.
Table 4.1-1	N/A	Please see end of Appendix 5 for this new table.
Section 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, dietary salt < 5g/day, dietary cooked meat protein < 1 g/kg/day and a limit on caffeinated drinks/foods should also be given (no more than 2 coffee equivalents per day).	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, dietary salt < 5g/day, dietary cooked meat protein < 1 g/kg/day and a limit on caffeinated drinks/foods should also be given (no more than 2 coffee equivalents per day). **A history of alcohol and smoking intake will be collected at screening. Alcohol and tobacco consumption should be avoided or minimized as much as possible.**
Section 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.	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. **Medical follow up is expected for AEs which lead to discontinuation which are serious, or which are of special interest (eg, liver abnormalities, skin neoplasms, glaucoma).**
Section 5.5, Follow-up of Adverse Events	For this trial, AEs will be followed up for 21 days after the last dose of tolvaptan 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	For this trial, AEs will be followed up for 7 days after the last dose of tolvaptan 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

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	to normal, or have otherwise been explained. For subjects who have discontinued tolvaptan but have not withdrawn from the trial, vital status, AEs, concomitant medications, and scheduled laboratory data (including serum creatinine data) are planned to be collected regardless of tolvaptan discontinuation until the scheduled end of the trial.	to normal, or have otherwise been explained.
CCI [redacted]	[redacted]	CCI [redacted]
Section 7.1, Sample Size	Sample size was not determined by a formal computation to achieve a target power. No efficacy analyses are planned. It is expected that approximately 2,450 subjects may enroll from previous tolvaptan trials.	Sample size was not determined by a formal computation to achieve a target power. No efficacy analyses are planned. It is expected that approximately **2,500** subjects may enroll from previous tolvaptan trials.
Appendix 1, Name of Sponsor Personnel	PPD PPD PPD PPD PPD USA Phone: PPD	PPD PPD PPD PPD PPD USA Phone: PPD
Appendix 2, Institutions Concerned With the Trial	Traveling Coordinator Assistant Princeton Medical 349 Route 206 south Hillsborough, NJ 0884, USA Phone: PPD Fax: PPD Central Laboratory Service Covance Central Laboratory Services 8211 SciCor Dr. Indianapolis, IN 46214, USA Phone: PPD Toll-free: PPD Fax: PPD	Traveling Coordinator Assistant row deleted; Central Laboratory Services Covance Central Laboratory Services 8211 SciCor Dr. Indianapolis, IN 46214, USA Phone: PPD Toll-free: PPD Fax: PPD **Covance Asia Pte. Ltd.** **Central Laboratory Services-Singapore** **1 International Business Park, #05-13** **The Synergy, Singapore 609917**

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Location	Old Text	Updated Text
		Phone: PPD **Covance Central Laboratory Services-Sydney** **95 Epping Rd., North Ryde** **NSW 2113 Australia** **Phone:** PPD **Covance Central Laboratory Services-Geneva** **Rue Moise-Marcinhes 7** **1217 Meyrin/Geneva- CH** **Switzerland** **Phone :** PPD CCI **Phone:** PPD
CCI		

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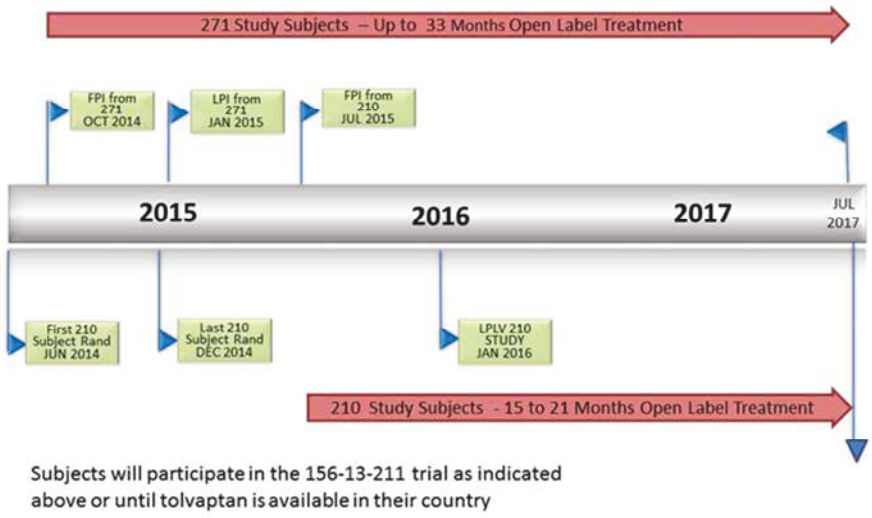
Location	Old Text	Updated Text
		CCI [redacted]
Appendix 5, Protocol Amendment	N/A	

Previous Figure 3.1-1 - Trial Design Schematic:



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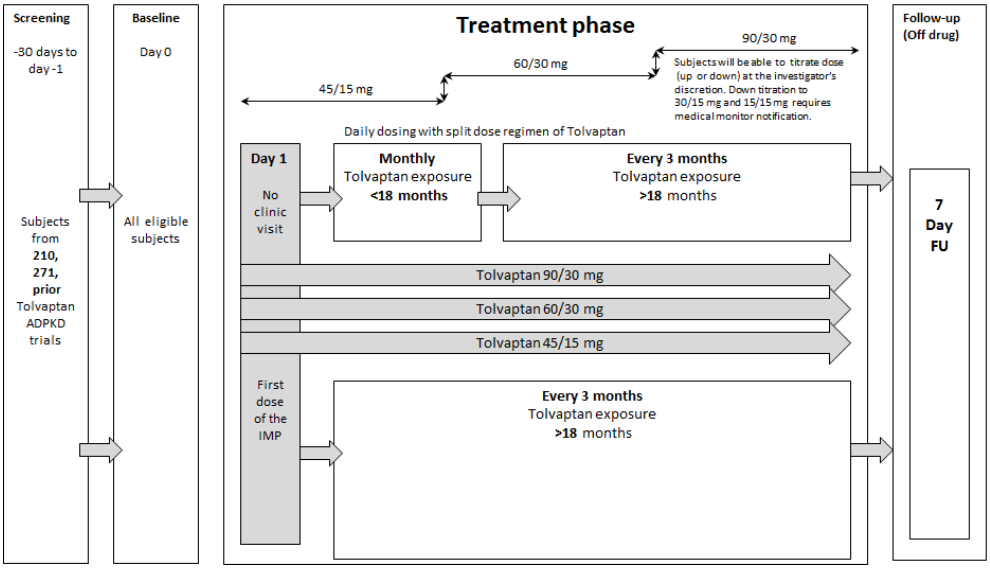
Revised Figure 3.1-1 - Trial Design Schematic:



Previous Table 3.2-1 - Trial Treatments:

Table 3.2-1 Trial Treatments		
Trial Day	**Time**	**Dose**
Day 1 to last on-treatment visit	8:00 am	1 to 6 tolvaptan tablets (15 mg or 30 mg each)
	4:00 to 5:00 pm	1 to 2 tolvaptan tablets (15 mg or 30 mg each) Allowed doses are 45/15 mg, 60/30 mg, 90/30 mg. Down titration to 30/15 mg and 15/15 mg will be allowed after discussion with the medical monitor.

Revised Table 3.2-1 - Trial Treatments:

Table 3.2-1 Trial Treatments		
Trial Day	**Time**	**Dose**
Day 1 to last on-treatment visit	8:00 am	1 to 6 tolvaptan tablets (15 mg or 30 mg each)
	4:00 to 5:00 pm	1 to 2 tolvaptan tablets (15 mg or 30 mg each) Allowed doses are 45/15 mg, 60/30 mg, 90/30 mg. Down titration to 30/15 mg and 15/15 mg will be allowed after discussion

		with the medical monitor. **Further down titration to 30 or 15 mg once daily may be allowed only for metabolic drug-drug interaction and requires medical monitor approval.**

Previous Table 3.4.2-1 – Inclusion Criteria:

Table 3.4.2-1 Inclusion Criteria	
1.	Male and female subjects aged ≥ 18 years with ADPKD who have completed either trial 156-13-210 or trial 156-08-271
2.	Diagnosis of ADPKD by modified Pei-Ravine criteria: • With family history: several cysts per kidney (3 if by sonography, 5 if by computed tomography or MRI). • 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. • Distribution and number of cysts consistent with the observed level of renal function deficit.
3.	Estimated glomerular filtration rate ≥ 20 mL/min/1.73 m^2 (calculated using the CKD-EPI formula) within 45 days prior to the baseline visit. Subjects who have an eGFR between 15 and 19 mL/min/1.73 m^2 may be permitted with documented medical monitor approval prior to enrollment.

Revised Table 3.4.2-1 – Inclusion Criteria:

Table 3.4.2-1 Inclusion Criteria	
1.	Male and female subjects aged ≥ 18 years with **confirmed diagnosis of ADPKD (during participation in prior tolvaptan trials) who have** • **Completed and transferred from the double-blind Trial 156-13-210 (12-month period including post-treatment follow-up, regardless of whether this was on-treatment or off-treatment), or** • **Completed Trial 156-08-271 or a prior tolvaptan trial, or** • **Interrupted or discontinued treatment in a tolvaptan trial other than Trial 156-13-210. Subjects may be enrolled with the medical monitor approval, and additional close monitoring may be required at the beginning of the trial** • **Renal function will be assessed during screening using historical laboratory values (in the last 30 days) for serum creatinine levels to calculate the estimated glomerular filtration rate (eGFR). The eGFR values will be estimated based on the Chronic Kidney Disease - Epidemiology (CKD-EPI) formula. (Levey AS et al. Ann Intern Med. 2009; 150:604–612)**
2.	Estimated glomerular filtration rate ≥ 20 mL/min/1.73 m^2 (calculated using the CKD-EPI formula) within 45 days prior to the baseline visit. Subjects who have an eGFR between 15 and 19 mL/min/1.73 m^2 may be permitted with documented medical monitor approval prior to enrollment.

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Previous Table 3.6-1 – Schedule of Assessments

Table 3.6-1 Schedule of Assessments

	Screening (-6 to 0 days prior to Baseline)[a]	Baseline/ Day 0	Monthly (± 4 days)	Every 3 months (± 4 days)	Early Termination/End of Trial Visit (+ 3 months)	Titration Contact (phone contact)	Follow-up 7 days post-treatment (+ 7 days)
Informed consent	X						
Inclusion/Exclusion	X	X					
Demographics, Medical/ADPKD history[b]	X						
Dietary review	X	X		X	X		
CCI [redacted]		[redacted]		[redacted]	[redacted]		
Vital signs[c]	X	X		X	X		X
Chemistry Blood Samples[d]							
Serum Chemistry Panel	X			X[e]	X		
Liver Function tests	X[f]		X[f]	X[f]	X[f]		X[f]
Sodium	X		X		X		
Creatinine	X		X		X		X
Hematology and coagulation	X				X		
Urinalysis	X			X	X		
Urine osmolality[g]	X			X	X		
Urine specific gravity	X			X	X		
Urine pregnancy test (WOCBP only)[h]	X			X	X		X
Urine at-home pregnancy test kits dispensed[i]		X		X			
Physical examination [j]	X	X	X		X		
Tolerability/Dosing Review		X	X		X	X	
Interactive Response Technology Entry	X	X	X		X	X[k]	
Drug dispensation		X	X			X[k]	
Drug reconciliation			X		X	X[k]	
Adverse events	X[l]	←----------	----------	----------	----------	----------	----------→
Concomitant medications[m]		←----------	----------	----------	----------	----------	----------→

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[a]The screening and baseline visits may be combined with the end of treatment (EoTx) visit from the previous protocol with all required assessments from each visit only performed once.
[b]Includes prior trial identifiers (screening identification [ID], subject ID, site ID).
[c]Vital signs at each visit include seated heart rate, calibrated blood pressure and post void body weight. Height should be performed only at screening and ET/EoTx visits.
[d]Local non fasting serum laboratory tests will be performed:

- Full chemistry panel including serum sodium, and serum creatinine at baseline and early termination/end of treatment (ET/EoTx)
- Hepatitis testing at screening will be optional.
- Upon request, if clinically indicated and approved by the medical monitor, subjects may have the following evaluations in addition to the protocol-specified chemistry panel: serum calcium, phosphorous, parathyroid hormone, vitamin D, and bicarbonate levels.

[e]Local Standard of Care laboratory assessments will be performed every 3 months per subject's individual clinical management needs.
[f]Liver function tests will be conducted as follows:

- At baseline, a full liver function panel will be assessed (ALT, AST, bilirubin total and direct, alkaline phosphatase)
- For subjects enrolling from the double-blind Trial 156-13-210. ALT levels will be assessed monthly for the first 18 months, quarterly (every 3 months) after 18 months of treatment, at the ET/EoTx and at the follow-up 7 Day visit.
- For subjects enrolling from the open-label Trial 156-08-271, ALT levels will be assessed quarterly (every 3 months), at the ET/EoTx and at the follow-up 7 Day visit.

Any subject with an ALT elevation > 1x ULN and < 3x ULN will be monitored monthly for an additional 6 months beyond the date of elevation, to establish that this level is stable and that further elevation does not occur. Any ALT level ≥ 3x ULN will require the addition of full liver function panel (ALT, AST, bilirubin total and direct, alkaline phosphatase) within 72 hours of the site being aware of this result. CCI [redacted]

[g]Urine osmolality is optional
[h]A urine pregnancy test for pregnancy for women of child bearing potential (WOCBP) will be performed at screening, at the quarterly visits, at the EoTx visit and at the follow-up visit. On suspicion of pregnancy, an unscheduled urine or serum pregnancy testing will be performed. Positive urine pregnancy tests should be confirmed with a serum pregnancy test
[i]At-home urine pregnancy test kits will be dispensed to WOCBP to be used if a menstrual period is missed between visits. Kits will be dispensed as needed throughout the trial at each quarterly visit.
[j]A full physical examination is required at screening, this may be combined with the EoTx visit from the previous trial. At other visits, an optional directed physical examination may be performed to focus on PKD-related signs and symptoms
[k]If during the titration contact the determination is made to adjust the dose-regimen, the subject status will be entered into the interactive response technology (IRT) and arrangements made for dispensation of a new IMP kit and reconciliation of returned IMP.
[l]At screening, AEs reported as ongoing or resolved at the end of the prior trial will be assessed to determine entry as either medical history or ongoing event for this trial.
[m]Only concomitant medications ongoing at the baseline visit and throughout the trial will be recorded.

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Revised Table 3.7-1 – Schedule of Assessments

Table 3.7-1 Schedule of Assessments

	Screening (-30 to -1 days prior to Baseline)[a]	Baseline/ Day 0	Monthly[b] (± 7 days)	Every 3 months[b] (± 14 days)	Early Termination/End of Treatment (+ 7 days)	Titration Contact (phone contact)	Follow-up 7 days post-treatment (+ 7 days)
Informed consent	X						
Inclusion/Exclusion	X	X					
Demographics, Medical/ADPKD history[c]	X						
Dietary review	X	X	X	X	X		
CCI [redacted]		[redacted]	[redacted]	[redacted]	[redacted]		
Vital signs[d]	X	X	X	X	X		X
Chemistry Blood Samples[e]							
Serum Chemistry Panel	X[f]				X		
Liver Function tests[g]	X		X	X	X		X
Sodium	X		X	X	X		
Creatinine	X		X	X	X		X
Hematology and coagulation	X				X		
Urinalysis	X		X	X	X		
Urine osmolality[h]	X		X	X	X		
Urine specific gravity	X		X	X	X		
Urine pregnancy test (WOCBP only)[i]	X		X	X	X		X
Urine at-home pregnancy test kits dispensed[j]		X	X	X			
Physical examination [k]	X	X	X	X	X		
Tolerability/Dosing Review		X	X	X	X	X	
Interactive Response Technology Entry	X	X	X	X	X	X[l]	X
Drug dispensation		X	X	X		X[l]	
Drug reconciliation			X	X	X	X[l]	
[redacted] CCI			[redacted]	[redacted]	[redacted]		

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	Screening (-30 to -1 days prior to Baseline)[a]	Baseline/ Day 0	Monthly[b] (± 7 days)	Every 3 months[b] (± 14 days)	Early Termination/End of Treatment (+ 7 days)	Titration Contact (phone contact)	Follow-up 7 days post-treatment (+ 7 days)
CCI [redacted]			[redacted]	[redacted]	[redacted]		
[redacted]			[redacted]	[redacted]	[redacted]		
Adverse events	X^n	←----------	----------	----------	----------→		
Concomitant medications[o]		←----------	----------	----------	----------→		

[a]The last visit assessments from the previous protocol can be combined with the screening visit for this trial, with all required assessments from each visit performed only once.

[b]Monthly visits are for subjects < 18 months on tolvaptan, and every 3 month visits are for subjects > 18 months on tolvaptan.

[c] Includes prior trial identifiers (screening identification [ID], subject ID, site ID, prior tolvaptan ADPKD trial protocol number).

[d]Vital signs at each visit include seated heart rate, calibrated blood pressure and post void body weight. Height should be performed only at screening.

[e] Central laboratory non-fasting serum laboratory tests will be performed. All subjects must be monitored for hepatic safety monthly until they have known tolvaptan exposure data of at least 18 months. After that, and following the approval of the medical monitor, hepatic monitoring will take place every 3 months. Trial 156-13-210 subjects who are eligible for this trial will have trial visits/hepatic monitoring monthly for the first 18 months of this trial then every 3 months thereafter, because their tolvaptan exposure will be unknown. Once unblinding occurs, it can be determined which subjects received tolvaptan in Trial 156-13-210. These subjects may have their trial visits/hepatic transaminase monitoring changed to every 3 months sooner as their previous tolvaptan exposure in Trial 156-13-210 can count towards the 18 month threshold. Subjects who enroll from other ADPKD tolvaptan trials will be monitored for hepatic safely monthly for their first 18 months they are in this trial.

[f] Hepatitis testing at screening will be optional. If hepatitis testing is performed, then both pre- and post-counseling activities relating to hepatitis testing are to be carried out based on local requirements and best practices. Upon request, if clinically indicated and approved by the medical monitor, subjects may have the following evaluations in addition to the protocol-specified chemistry panel: serum calcium, phosphorous, parathyroid hormone, vitamin D, and bicarbonate levels.

[g]A full liver function panel (AST, ALT, alkaline phosphatase, BT) will be done at screening. All other liver function tests at subsequent visits are for ALT only, unless otherwise clinically indicated. Any transaminase or bilirubin values which exceed 2 × ULN should 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, and every 3 months as indicated by the results. Local liver function panel analyses will also be performed more frequently, if necessary.

[h]Urine osmolality is optional.

[i] A urine pregnancy test for pregnancy for women of childbearing potential (WOCBP) will be performed at screening, at every 3 months visits, at the End of Treatment (EoTx) visit, and at the follow-up visit. On suspicion of pregnancy, an unscheduled urine or serum pregnancy testing will be performed. Positive urine pregnancy tests should be confirmed with a serum pregnancy test.

[j] At-home urine pregnancy test kits will be dispensed to WOCBP to be used if a menstrual period is missed between visits. Kits will be dispensed as needed throughout the trial.

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[k]A full physical examination is required at screening. At other visits, an optional "directed" physical examination may be performed to focus on PKD-related signs and symptoms.
[l] If during the titration contact the determination is made to adjust the dose regimen, dose adjustments will be made using dispensed supply, and dose instructions will be provided by the investigator. The subject's current dose will be entered into the interactive response technology (IRT) at each visit. Drug dispensation/reconciliation will be conducted on a monthly basis for subjects who have monthly trial visits and once every 3 months for subjects who have trial visits every 3 months.
CCI [redacted]
At screening, AEs reported as ongoing or resolved at the end of the prior trial will be assessed to determine entry as either medical history or ongoing event for this trial.
[o]Only concomitant medications ongoing at the baseline visit and throughout the trial will be recorded. This would occur at the screening visit only if the screening visit occurs simultaneously with the last visit from a previous tolvaptan trial.

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Previous Table 3.7.2.2-1 - Clinical Laboratory Assessments:

Table 3.7.2.2-1 Clinical Laboratory Assessments

Hematology and Coagulation Panel: Hemoglobin Mean corpuscular hemoglobin concentration (MCHC) Mean corpuscular volume (MCV) Red blood cell (RBC) count White blood cell (WBC) count with differential Prothrombin time (PT) as international normalized ratio (INR) Activated partial thromboplastin time (aPTT) Urinalysis Panel: Appearance Color Blood Glucose Microscopic analysis, WBC/RBC counts per high power field pH Protein Urine Chemistry Osmolality Specific gravity Additional Tests: Urine (or serum) pregnancy for WOCBP Hepatitis (optional)	Serum Chemistry Panel: Albumin Blood urea nitrogen (BUN) Serum calcium Carbon dioxide Serum chloride Gamma-glutamyl transpeptidase Cholesterol, total Glucose Lactate dehydrogenase (LDH) Phosphorus Potassium Protein, total Uric acid Liver Function Panel: Alkaline phosphatase (ALP) Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Bilirubin, total (BT) Bilirubin, direct CCI [redacted]
Creatinine	**Sodium**

WOCBP=women of childbearing potential.

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Revised Table 3.7.2.2-1 - Clinical Laboratory Assessments:

Table 3.7.2.2-1 Clinical Laboratory Assessments	
Hematology and Coagulation Panel: Hemoglobin **Platelet count** Mean corpuscular hemoglobin concentration (MCHC) Mean corpuscular volume (MCV) Red blood cell (RBC) count White blood cell (WBC) count with differential Prothrombin time (PT) as international normalized ratio (INR) Activated partial thromboplastin time (aPTT) Urinalysis Panel: Appearance Color Blood Glucose Microscopic analysis, WBC/RBC counts per high power field pH Protein Urine Chemistry Osmolality **(optional)** Specific gravity Additional Tests: Urine (or serum) pregnancy for WOCBP Hepatitis (optional)	Serum Chemistry Panel: Albumin Blood urea nitrogen (BUN) Serum calcium Carbon dioxide Serum chloride Gamma-glutamyl transpeptidase Cholesterol, total Glucose Lactate dehydrogenase (LDH) Phosphorus Potassium Protein, total Uric acid Liver Function Panel: Alkaline phosphatase (ALP) Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Bilirubin, total (BT) Bilirubin, direct
Creatinine	**Sodium**

WOCBP=women of childbearing potential.

New Table 4.1-1 Moderate and Strong CYP3A4 Inhibitors (partial list):

Table 4.1-1 Moderate and Strong CYP3A Inhibitors (partial list)

amprenavir	atorvastin	aprepitant	chloramphenicol (if used orally)
cimetidine	clarithromycin	clotrimazole (if used orally)	danazol
delavirdine	diltiazem	erythromycin	fluconazole
fluvoxamine	indinavir	isoniazid	itraconzazole
josamycin	ketoconazole (if used orally)	nelfinavir	nefazadone
quinupristin/ dalfopristin	ritonavir	saquinavir	troleandomycin
verapamil	Seville orange products	grapefruit products	

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

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Administrative Change Number: 1

Issue Date: 05 September 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 safety endpoints between the synopsis and Section 3.5.1, and to clarify the timeline for when IRE forms must be completed and submitted to the sponsor. In addition, a statement at the beginning of Section 3.5.1 explaining that the trial would have no formal endpoints had been inadvertently deleted in an earlier draft.

BACKGROUND:

While reviewing the protocol before proceeding with the clinicaltrial.gov posting, a few inconsistencies were found. It was decided that fixing the inconsistencies would provide better clarity.

Sectional Revisions

Location	Old Text	Updated Text
Section 3.5.1 Safety Endpoints	Safety endpoints will be as follows: • Adverse events • Vital signs • Clinical laboratory assessments • Serum transaminase elevations for frequency (2x, 3x, 5x and 10x ULN), time to onset, time to peak levels, time of offset (< 3x, 2x, or 1x ULN), response to de-challenge and re-challenge and frequency of progression to Hy's laboratory criteria (ALT or AST > 3x ULN and bilirubin, total (BT), > 2x ULN without alkaline phosphatase ≥ 2x ULN) • Serum sodium excursions above 145, 150, or 155 mmol/L or below 135,	This trial will have no formal endpoints. Safety variables will be summarized by descriptive statistics, (eg, proportion, mean, median, standard deviation [SD], minimum, and maximum values). In general, summary statistics, including changes from baseline, will be provided for safety variables based on all available data. Safety endpoints will be as follows: • Adverse events • Vital signs • Clinical laboratory assessments • Serum transaminase elevations for frequency (2x, 3x, 5x and 10x ULN), time to onset, time to peak levels, time of offset (< 3x, 2x, or 1x ULN), response to de-challenge and re-challenge and frequency of

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Location	Old Text	Updated Text
	130, or 125 mmol/L • Interruptions of protocol-specifed therapies for hypernatremia or hyponatremia	progression to Hy's laboratory criteria (ALT or AST > 3x ULN and bilirubin, total (BT), > 2x ULN without alkaline phosphatase ≥ 2x ULN) • Serum sodium excursions above 145, 150, or 155 mmol/L or below 135, 130, or 125 mmol/L
Section 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, an AE that necessitates IMP discontinuation, any new liver result meeting the AE laboratory threshold criteria, any AE of special interest or a 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, email 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 laboratory 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, email, or overnight courier to the sponsor. (Please note that the IRE form is NOT the AE eCRF).
Appendix 5, Title change	Protocol Amendment	Protocol Amendments and Administrative Changes

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

Protocol 156-13-211

Amendment Number: 2

Issue Date: 06 Mar 2015

PURPOSE:

The purpose of this amendment was to increase the window from 30 days to up to 3 months to allow use of historical laboratory values for screening, to add flexibility and allow combining of screening and baseline visits in the trial, and to provide clarification on trial discontinuation. The list of vendors was updated. Minor linguistic changes were made for clarity and typographical errors were corrected.

BACKGROUND:

Eligible subjects enrolling from Trials 156-08-271 or 156-13-210 can enroll before they complete the last visit in their respective trials, and the last visit as well as the screening and baseline visit in this trial can be combined into one visit with all required assessments from each visit performed only once, so long as the time between the last visit assessments from the previous trial and the screening visit for this trial is within 30 days.

Other Revisions

Figure 3.1-1 - Trial Design Schematic

Table 3.4.2-1 - Inclusion Criteria

Table 3.4.3-1 - Exclusion Criteria

Table 3.7-1 - Schedule of Assessments footnotes

Sectional Revisions

Location	Old Text	Updated Text
Title page	Clinical Protocol A Phase 3b, Multi-center, Open-label Trial to Evaluate the Long Term Safety of Titrated Immediate-release Tolvaptan (OPC 41061, 30 mg to 120 mg/day, Split dose) in Subjects with Autosomal Dominant Polycystic Kidney Disease	Revised Clinical Protocol A Phase 3b, Multi-center, Open-label Trial to Evaluate the Long Term Safety of Immediate-release Tolvaptan (OPC 41061, 30 mg to 120 mg/day, Split dose) in Subjects with Autosomal Dominant Polycystic Kidney Disease
Synopsis, Protocol Title	A Phase 3b, Multi-center, Open-label Trial to Evaluate the Long Term Safety of Titrated Immediate-release	A Phase 3b, Multi-center, Open-label Trial to Evaluate the Long Term Safety of Immediate-release

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Location	Old Text	Updated Text
	Tolvaptan (OPC 41061, 30 mg to 120 mg/day, Split dose) in Subjects with Autosomal Dominant Polycystic Kidney Disease	Tolvaptan (OPC 41061, 30 mg to 120 mg/day, Split dose) in Subjects with Autosomal Dominant Polycystic Kidney Disease
Synopsis, Trial Design	Subjects will be eligible for screening into this trial if they: • Completed and transferred from the double-blind Trial 156-13-210 (12-month period including post treatment follow-up, regardless of whether this was on-treatment or off-treatment), or • Completed Trial 156-08-271 or a prior tolvaptan ADPKD trial, or • Interrupted or discontinued treatment in a prior tolvaptan ADPKD trial (other than Trial 156-13-210). Subjects may be enrolled with medical monitor approval, and additional close monitoring may be required at the beginning of the trial	Subjects will be eligible for screening into this trial if they: • Completed and transferred from the double-blind Trial 156-13-210 (12-month period including post treatment follow-up, regardless of whether this was on-treatment or off-treatment), or have completed all but the last follow-up visit, which will be combined with the first visit in this trial or • Completed Trial 156-08-271 or a prior tolvaptan ADPKD trial, or have completed all but the end of trial visit, which will be combined with the first visit in this trial or • Interrupted or discontinued treatment in a prior tolvaptan ADPKD trial (other than Trial 156-13-210). Subjects may be enrolled with medical monitor approval, and additional close monitoring may be required at the beginning of the trial
Synopsis, Inclusion and Exclusion Criteria	• Estimated glomerular filtration rate (eGFR) $\geq$ 20 mL/min/1.73m^2 within 45 days of the baseline visit. Subjects who have an eGFR between 15 and 19 mL/min/1.73m^2 may be enrolled with medical monitor approval • Renal function will be assessed during screening by using historical values (in the last 30 days) for serum creatinine levels to calculate the eGFR. The eGFT values will be estimated based on the Chronic Kidney Disease – Epidemiology (CKD-EPI) formula.	• Estimated glomerular filtration rate (eGFR) $\geq$ 20 mL/min/1.73m^2 within **3 months** of the baseline visit. Subjects who have an eGFR $\leq$ 20 mL/min/1.73m^2 may be enrolled with medical monitor and sponsor approval and increased frequency of monitoring to ensure subjects' safety. • Renal function will be assessed during screening by using historical values (within **3 months** from the screening visit) for serum creatinine levels to calculate the eGFR. The eGFR values will be estimated

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Location	Old Text	Updated Text
		based on the Chronic Kidney Disease – Epidemiology (CKD-EPI) formula.
Section 1.3, Known and Potential Risks and Benefits	... ...Subjects enrolling in this trial who were in a previous ADPKD tolvaptan trial other than Trials 156-13-210 and 156-08-271 will have monthly visits and transaminase level assessments for the first 18 months.	... ...Subjects enrolling in this trial who were in a previous ADPKD tolvaptan trial other than Trials 156-13-210 and 156-08-271 will have monthly visits and **alanine aminotransferase (ALT)** level assessments for the first 18 months.
Section 2.1, Trial Rationale	Evidence from previous studies suggests that during the first 18 months of long-term treatment in subjects with ADPKD, alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations and evidence of idiosyncratic DILI occurs at a greater frequency in tolvaptan treated subjects. ...	Evidence from previous studies suggests that during the first 18 months of long-term treatment in subjects with ADPKD, ALT and/or aspartate aminotransferase (AST) elevations and evidence of idiosyncratic DILI occurs at a greater frequency in tolvaptan treated subjects. ...
Section 3.1, Type/Design of Trial	... Eligible subjects will have an opportunity to enroll into Trial 156-13-211 immediately following completion of the follow-up visit(s) of the previous trial. The last visit assessments from the previous protocol can be combined with the screening visit for this trial, with all required assessments from each visit only performed once, as long as the time between the last follow-up visit assessments from the previous trial and the screening visit for this trial is within 30 days. ... These subjects may have their trial visits/hepatic transaminase monitoring changed to every 3 months sooner as their previous tolvaptan exposure in Trial 156-13-210 can count towards the 18-month threshold.	... Eligible subjects will have an opportunity to enroll into Trial 156-13-211 following completion of the follow-up visit(s) of the previous trial. Eligible subjects from Trials 156-08-271 and 156-13-210 can have the last visit assessments from their previous respective protocols (end of trial visit for 156-08-271 subjects and last follow-up visit for 156-13-210 subjects) overlap the first visit in this trial. These last visit assessments can be combined with the screening and baseline visits for this trial, with all required assessments from each visit performed only once, so long as the time between the last visit assessments from the previous trial and the screening visit for this trial is within 30 days. If the first visit in this trial combines the last visit from a previous trial with both the screening and the baseline visits in this trial, the results from laboratory assessments performed at this combined visit will not be immediately available. Should any

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Location	Old Text	Updated Text
		laboratory abnormalities be identified, the investigator will need to notify the subject and provide instructions regarding dosing or returning to the site for additional assessments. ... These subjects may have their trial visits/hepatic transaminase monitoring changed to every 3 months sooner as their previous tolvaptan exposure in Trial 156-13-210 can count towards the 18-month threshold. Subjects from prior tolvaptan trials other than Trial 156-08-271 will have monthly trial visits/ALT level assessments for the first 18 months. After that, the trial visits/ALT monitoring will be conducted every 3 months after the change in frequency is confirmed with the medical monitor.
Figure 3.1-1	Day 1 No clinic visit First dose of the IMP	Day 1 No clinic visit First dose of the IMP in Trial 211
Table 3.4.2-1, Inclusion Criteria	1. Male and female subjects aged ≥ 18 years with confirmed diagnosis of ADPKD (during participation in prior tolvaptan trials) who have • Completed and transferred from the double-blind Trial 156-13-210 (12-month period including post-treatment follow-up, regardless of whether this was on-treatment or off-treatment), or • Completed Trial 156-08-271 or a prior tolvaptan trial, or • Interrupted or discontinued treatment in a tolvaptan trial other than Trial 156-13-210. Subjects may be enrolled with the medical monitor approval, and additional close monitoring may be required at the beginning of the trial • Renal function will be assessed during screening by using historical laboratory values (in the last 30 days) for serum	Male and female subjects aged ≥ 18 years with confirmed diagnosis of ADPKD (during participation in prior tolvaptan trials) who have • Completed and transferred from the double-blind Trial 156-13-210 (12-month period including post-treatment follow-up, regardless of whether this was on-treatment or off-treatment), or • Completed Trial 156-08-271 or a prior tolvaptan trial, or • Interrupted or discontinued treatment in a tolvaptan trial other than Trial 156-13-210. Subjects may be enrolled with the medical monitor approval, and additional close monitoring may be required at the beginning of the trial • Renal function will be assessed during screening by using historical laboratory values (in the last **3 months**) for serum

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Location	Old Text	Updated Text
	creatinine levels to calculate the estimated glomerular filtration rate (eGFR). The eGFR values will be estimated based on the Chronic Kidney Disease - Epidemiology (CKD-EPI) formula. (Levey AS et al. Ann Intern Med. 2009; 150:604–612) 2. Estimated glomerular filtration rate ≥ 20 mL/min/1.73 m^2 (calculated using the CKD-EPI formula) within 45 days prior to the baseline visit. Subjects who have an eGFR between 15 and 19 mL/min/1.73 m^2 may be permitted with documented medical monitor approval prior to enrollment	creatinine levels to calculate the estimated glomerular filtration rate (eGFR). The eGFR values will be estimated based on the CKD-EPI formula. (Levey AS et al. Ann Intern Med. 2009; 150:604–612) 2. Estimated glomerular filtration rate ≥ 20 mL/min/1.73 m^2 (calculated using the CKD-EPI formula) within **3 months** prior to the baseline visit. Subjects who have an eGFR **≤ 20** mL/min/1.73 m^2 may be permitted to enter the trial with medical monitor and sponsor approval and increased frequency of monitoring to ensure safety of subjects. At end of table, abbreviations added: eGFR=estimated glomerular filtration rate; CKD-EPI= Chronic Kidney Disease - Epidemiology
Table 3.4.3-1, Exclusion Criteria	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. … 4. Hepatic impairment based on liver function abnormalities other than that expected for ADPKD with cystic liver disease during screening.	1. 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. … 4. Hepatic impairment based on liver function abnormalities other than that expected for ADPKD with cystic liver disease during screening based on recent historical laboratory values (in the last 3 months).
Section 3.7, Trial Procedures, Table 3.7-1	Footnote a: [a]The last visit assessments from the previous protocol can be combined with the screening visit for this trial, with all required assessments from each visit performed only once. ... Footnote g:	Footnote a: [a]The last visit assessments from the previous **trial** can be combined with the screening **and baseline** visits for this trial, with all required assessments from each visit performed only once. ...

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	[g]A full liver function panel (AST, ALT, alkaline phosphatase, BT) will be done at screening. All other liver function tests at subsequent visits are for ALT only, unless otherwise clinically indicated. Any transaminase or bilirubin values which exceed 2 × ULN should 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, and every 3 months as indicated by the results. Local liver function panel analyses will also be performed more frequently, if necessary. ... Footnote l: [l]If during the titration contact the determination is made to adjust the dose regimen, dose adjustments will be made using dispensed supply, and dose instructions will be provided by the investigator. The subject's current dose will be entered into the interactive response technology (IRT) at each visit. Drug dispensation/reconciliation will be conducted on a monthly basis for subjects who have monthly trial visits and once every 3 months for subjects who have trial visits every 3 months. ...	Footnote g: [g]A full liver function panel (AST, ALT, alkaline phosphatase, BT) will be done at screening. All other liver function tests at subsequent visits are for ALT only, unless otherwise clinically indicated. An ALT elevation > 2 × ULN should trigger prompt testing of hepatic function within 72 hours. Any transaminase or bilirubin values which exceed 2 × ULN should 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, and every 3 months as indicated by the results. Local liver function panel analyses will also be performed more frequently, if necessary. ... Footnote l: [l]If during the titration contact the determination is made to adjust the dose regimen, dose adjustments will be made using dispensed supply, and dose instructions will be provided by the investigator. The subject's current dose will be entered into the interactive response technology (IRT) at each visit. Drug dispensation/reconciliation will be conducted on a monthly basis for subjects who have monthly trial visits and once every 3 months for subjects who have trial visits every 3 months. If additional drug supply is required for titration purposes, the site will arrange a subject visit for dispensation. ...
Section 3.7.1.1, Screening (-30 days to 1 day prior to Baseline)	Screening for eligibility is required for all subjects. The screening visit may be combined with the last visit from the previous protocol with all required assessments from each visit only performed once. In some cases, if a subject enrolls in this trial from a prior tolvaptan trial, the end of trial visit for that trial and the screening visit for this one may occur	Screening for eligibility is required for all subjects. The screening **and baseline** visit may be combined with the last visit from either the 156-08-271 or 156-13-210 protocol with all required assessments from each visit performed only once. **Therefore,** in some cases, if a subject enrolls in this trial from a prior tolvaptan trial, the end of trial

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	simultaneously. Required assessments are as follows: 1. Obtain subject consent. 2. Determine subject eligibility through inclusion/exclusion criteria. 3. Record demographic information and prior trial identifiers (screening identification [ID], subject ID, site ID, prior tolvaptan ADPKD trial protocol number). 4. Record medical/ADPKD history using prior trial data. 5. Review dietary recommendations and compliance ….	or last follow-up visit for that trial and the screening **and baseline** visit for this one may occur simultaneously. Required assessments for the screening visit are as follows: 1. Obtain subject consent. 2. **Obtain subject's new screening identification (ID) assigned by interactive response technology (IRT).** 3. Determine subject eligibility through inclusion/exclusion criteria. 4. Record demographic information and prior trial identifiers (screening ID, subject ID, prior tolvaptan ADPKD trial protocol number). 5. Record medical/ADPKD history using prior trial data. 6. Review dietary recommendations and compliance …
Section 3.7.2.4.1 Liver Test Abnormalities and Interruption/Discontinuation of Investigational Medical Product	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.	An ALT elevation > 2 × ULN or 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.
Section 3.7.5, Treatment Interruption and Discontinuation	... A subject who permanently discontinues IMP treatment may have the option to end trial participation (complete the early termination visit) or to continue participation off IMP and complete ongoing trial assessments as per protocol or with a modified (ie, less frequent) schedule as outlined in Section 3.8.3.	... A subject who permanently discontinues IMP treatment ends trial participation and the early termination visit should be completed.
Section 5.2, Eliciting and Reporting Adverse Events	… 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. …	… In addition, Quintiles (drug safety service) must be notified immediately by telephone or fax of any immediately reportable events according to the procedure outlined

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Location	Old Text	Updated Text
		below in Section 5.3. …
Section 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 laboratory abnormality requiring special liver eCRF completion, or confirmed pregnancy, by telephone or by fax to the sponsor as outlined in Appendix 1. ...	The investigator must immediately report within 24 hours after either the investigator or site personnel become aware of any SAE, new liver laboratory abnormality requiring special liver eCRF completion, or confirmed pregnancy, by telephone or by fax to **Quintiles (drug safety service)** as outlined in Appendix 1. ...
Appendix 2	Safety Reporting Quintiles 5927 South Miami Blvd Morrisville, NC 27560, USA Phone: PPD Fax: PPD … Investigator Payments CFS Clinical 1000 Madison Ave, 1st Floor Audubon, PA 19403, USA Phone: PPD Fax: PPD … CCI PPD	Safety Reporting Quintiles (Drug Safety Service) 5927 South Miami Blvd Morrisville, NC 27560, USA Phone: PPD Fax: PPD … Investigator Payments Quintiles, Inc. Investigator Payment Administration Department 10188 Telesis Court., Suite 400 San Diego, CA 92121, USA PPD … CCI PPD

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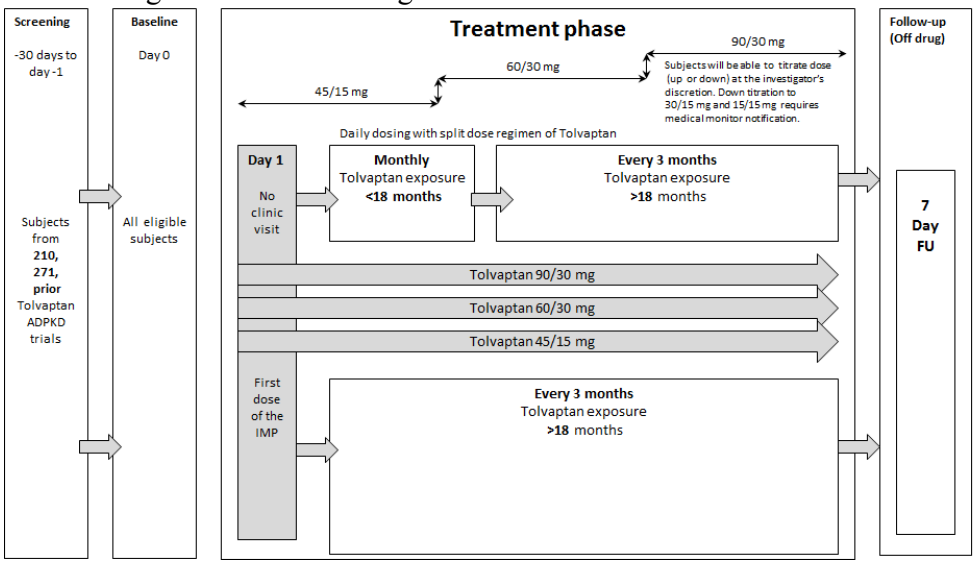
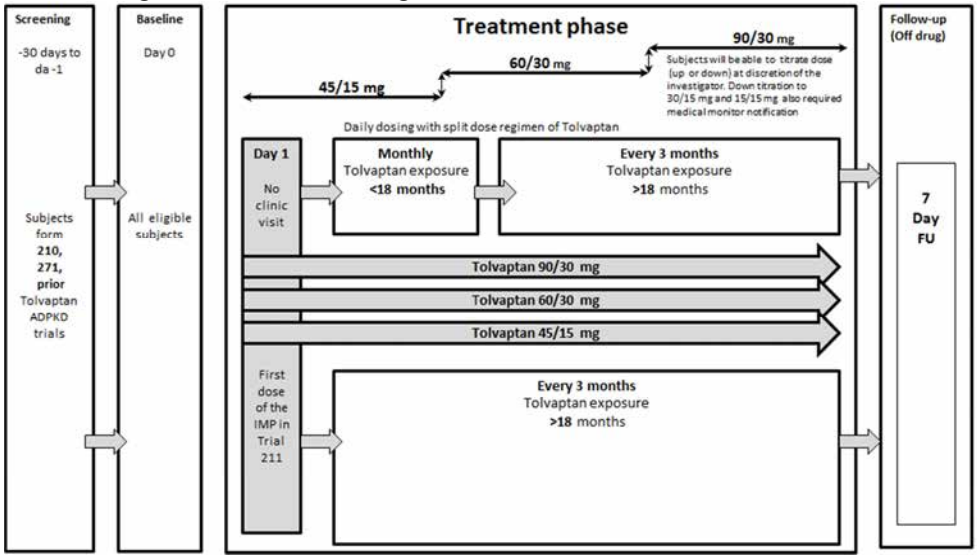
Previous Figure 3..-1 Trial Design Schematic



Revised Figure 3.1-1 Trial Design Schematic



ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

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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 trail 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.
This page is a manifestation of an electronically captured signature

OPC-41061

SIGNATURE PAGE

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Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
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	Clinical Approval	09-Mar-2015 13:17 GMT+00
	Biostatistics Approval	10-Mar-2015 15:24 GMT+00

Otsuka Pharmaceutical
Development & Commercialization, Inc.

Investigational Medicinal Product

Tolvaptan (OPC-41061)

REVISED CLINICAL PROTOCOL

A Phase 3b, Multi-center, Open-label Trial to Evaluate the Long Term Safety of Immediate-release Tolvaptan (OPC-41061, 30 mg to 120 mg/day, Split dose) in Subjects with Autosomal Dominant Polycystic Kidney Disease

Protocol No. 156-13-211
IND No. 72,975
EudraCT No. 2014-001516-19

CONFIDENTIAL – PROPRIETARY INFORMATION

Clinical Development Phase:	3b
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Boulevard Rockville, Maryland 20850, USA
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Immediately Reportable Event	Clinical Safety and Pharmacovigilance Phone: PPD Fax: PPD
Issue Date:	20 May 2014
Date of Amendment 1	14 July 2014
Date of Administrative Change 1	05 September 2014
Date of Amendment 2, UK	25 February 2015
Date of Amendment 3, UK	06 March 2015

Protocol 156-13-211

Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc. Name of Investigational Medicinal Product: Tolvaptan (OPC-41061)	Protocol # 156-13-211 IND# 72,975 EudraCT# 2014-001516-19
Protocol Title:	A Phase 3b, Multi-center, Open-label Trial to Evaluate the Long Term Safety of Immediate-release Tolvaptan (OPC-41061, 30 mg to 120 mg/day, Split dose) in Subjects with Autosomal Dominant Polycystic Kidney Disease
Clinical Phase/Trial Type:	Phase 3b/Therapeutic use
Treatment Indication:	Autosomal Dominant Polycystic Kidney Disease (ADPKD)
Objective:	The primary objective of this trial is: • To evaluate and describe the long-term safety of tolvaptan.
Trial Design:	This trial is a phase 3b, multi-center, open-label extension trial. Subjects will be eligible for screening into this trial if they: • Completed and transferred from the double-blind Trial 156-13-210 (12-month period including post-treatment follow-up, regardless of whether this was on-treatment or off-treatment), or have completed all but the last follow-up visit, which will be combined with the first visit in this trial or • Completed Trial 156-08-271 or a prior tolvaptan ADPKD trial, or have completed all but the end of trial visit, which will be combined with the first visit in this trial or • Interrupted or discontinued treatment in a prior tolvaptan ADPKD trial (other than Trial 156-13-210). Subjects may be enrolled with medical monitor approval, and additional close monitoring may be required at the beginning of the trial For purposes of ensuring subject safety, all subjects will be monitored for hepatic safety monthly until they have accumulated 18 months of tolvaptan exposure. After that, and following the approval from the medical monitor, hepatic monitoring will be required every 3 months. If subjects

	approaching the 18-month threshold have had prior transaminase abnormalities (> 2 × upper limit of normal [ULN]), the investigator is responsible for contacting the medical monitor to confirm the change in frequency from monthly to every 3 months. Until their prior treatment assignment is unblinded, all Trial 156-13-210 subjects who are eligible for this trial are scheduled to have trial visits/ hepatic monitoring monthly for the first 18 months of this trial. Once unblinding occurs, it can be determined which subjects received tolvaptan in Trial 156-13-210. These subjects may have their trial visits/hepatic transaminase monitoring change to every 3 months sooner as their previous tolvaptan exposure in Trial 156-13-210 can count towards the 18-month threshold. Enrollment in this trial will be closed when the final eligible subject from Trial 156-13-210 enrolls in this trial.
Subject Population:	This trial will include approximately 2,500 subjects over the age of 18 years with ADPKD diagnosed by Pei-Ravine criteria (modified by magnetic resonance imaging [MRI]), and who have completed or participated in a prior ADPKD interventional investigational medicinal product (IMP) trial.

Inclusion/Exclusion Criteria:	<u>Main inclusion criteria:</u>
	• Male and female subjects ≥ 18 years with a confirmed diagnosis of ADPKD (during participation in prior tolvaptan trials) who have
	  • Completed and transferred from the double-blind Trial 156-13-210 (12-month period including post-treatment follow-up, regardless of whether this was on-treatment or off-treatment), or
	  • Completed Trial 156-08-271 or a prior ADPKD tolvaptan trial, or
	  • Interrupted or discontinued treatment in a prior tolvaptan ADPKD trial other than Trial 156-13-210. Subjects may be enrolled with the medical monitor approval, and additional close monitoring may be required at the beginning of the trial
	• Estimated glomerular filtration rate (eGFR) ≥ 20 mL/min/1.73m^2 within 3 months of the baseline visit. Subjects who have an eGFR

	≤ 20 mL/min/1.73m^2 may be enrolled with medical monitor and sponsor approval and increased frequency of monitoring to ensure subjects' safety • Renal function will be assessed during screening by using historical laboratory values (within 3 months from the screening visit) for serum creatinine levels to calculate the eGFR. The eGFR values will be estimated based on the Chronic Kidney Disease - Epidemiology (CKD-EPI) formula <u>Main exclusion criteria:</u> • Need for chronic diuretic use • Hepatic impairment based on hepatic laboratory assessments (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin, total [BT]) other than that expected for ADPKD with cystic liver disease
Trial Site(s):	Approximately 220 enrolling sites including but not limited to the following regions: North America, South America, Eastern Europe, Western Europe, Russian Federation, and Australia.

Investigational Medicinal Product(s), Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration:	The dose regimens to be used in this trial are 15/15 mg, 30/15 mg, 45/15 mg, 60/30 mg, and 90/30 mg. Tolvaptan tablets (15 mg or 30 mg) will be self-administered orally as split-dose regimens, twice daily, once upon awakening and another approximately 8 to 9 hours later. Doses will be recorded as early dose/late dose (eg, 60/30 mg). Subjects will receive open-label tolvaptan for the duration of the trial. A subject's starting dose in this trial will be dependent on the trial in which they were previously enrolled: • **156-13-210**- initiated on tolvaptan at a split-dose of 45/15 mg with upward titration every 3 to 4 days to 60/30 mg or 90/30 mg per day according to tolerability • **156-08-271**- will retain the last dose level from 271 and start at the same dose in this trial • **Prior tolvaptan trials**- initiated on tolvaptan at a split-dose of 45/15 mg with upward titration every 3 to 4 days to 60/30 mg or 90/30 mg per day according to tolerability Down titration to 30/15 mg or 15/15 mg will be allowed at the discretion of the investigator according to individual tolerability and with medical monitor notification. Further down titration to 30 or 15 mg once daily may be allowed **only** for metabolic drug-drug interaction and requires medical monitor approval.
Trial Assessments:	Screening: Informed consent, medical history (including ADPKD updates, as required), determination of eligibility through inclusion/exclusion criteria, dietary review, vital signs, clinical laboratory assessments, physical examination, urine pregnancy test (women of child-bearing potential only [WOCBP]), concomitant medications and laboratory tests to determine eligibility. Safety: Adverse events (AEs), vital signs, directed physical examination, dietary review, self-assessed drug tolerability, serum chemistry tests (including serum transaminases, alkaline phosphatase, bilirubin, and serum sodium) and concomitant medications.

	CCI [redacted] CCI [redacted]
Criteria for Evaluation	Safety: • AEs • Vital signs • Clinical laboratory assessments • Serum transaminase elevations for frequency (2x, 3x, 5x and 10x ULN), time to onset, time to peak levels, time of offset (< 3x, 2x, or 1x ULN), response to de-challenge and re-challenge and frequency of progression to Hy's laboratory criteria (ALT or AST > 3x ULN and BT > 2x ULN without alkaline phosphatase ≥ 2x ULN) • Serum sodium excursions above 145, 150, or 155 mmol/L or below 135, 130, or 125 mmol/L CCI [redacted]
Statistical Methods:	Sample size: Sample size was not determined by a formal computation to achieve a target power. No efficacy analyses are planned. It is expected that approximately 2,500 subjects may enroll from previous tolvaptan trials. Analysis datasets: • Enrolled Population: all subjects who were enrolled to this open-label trial • Safety Population: all subjects in the Enrolled Population who take at least 1 dose of IMP

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	Safety analyses: 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 be summarized.
Trial Duration:	Trial duration is planned to continue • Until the last subject from Trial 156-13-210 completes 18 months of tolvaptan treatment in this trial • All subjects will receive at least 18 months of tolvaptan treatment in the extension study. Trial 156-13-210 subjects or subjects enrolling from other trials may opt to conclude their participation in this trial if tolvaptan becomes available before they complete 18 months of treatment in this trial

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List of Appendices

List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ADPKD	Autosomal dominant polycystic kidney disease
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AVP	Arginine vasopressin
BT	Bilirubin, total
cAMP	cyclic adenosine monophosphate
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease - Epidemiology
CRF	Case report form
CSR	Clinical study report
DILI	Drug-induced liver injury
DILIN	Drug-induced liver injury network
CCI	[redacted]
eCRF	Electronic case report form
eGFR	estimated glomerular filtration rate
eGFR CKD-EPE	Estimated glomerular filtration rate calculated by the Chronic Kidney Disease-Epidemiology (CKD-EPI) formula
EMA	European Medicines Agency
EoTx	End of treatment
ESRD	End-stage renal disease
EudraCT	European Clinical Trial Data Base
GCP	Good Clinical Practice
HAC	Hepatic adjudication committee
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
ID	Identification
IDMC	Independent data monitoring committee
IEC	Independent ethics committee
IMP	Investigational medicinal product
IND	Investigational new drug
IRB	Institutional review board
IRE	Immediately reportable event
IRT	Interactive response technology
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic resonance imaging
OPC	Otsuka Pharmaceutical Co.
OPDC	Otsuka Pharmaceutical Development & Commercialization, Inc.
PKD	Polycystic kidney disease
SAE	Serious adverse event

SAP	Statistical Analysis Plan
SD	Standard deviation
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
UK	United Kingdom
US or USA	United States or United States of America
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, Republic of Korea, and Taiwan, for various forms of hyponatremia, and in Japan 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.[1] Though a rare genetic disease, it ranks as the 6th leading cause of ESRD in the US (2.3% of the new ESRD cases).[2] An estimated 45% to 70% of patients with ADPKD progress to ESRD by age 65.[3] 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 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.[4 5] Refer to the Tolvaptan Investigator's Brochure (IB) for more information.[4]

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.[6 7] 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_2 receptor. For information on nonclinical toxicology and absorption, distribution and metabolism data on tolvaptan please refer to the most current version of the IB.[4]

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.[8] 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).[9] 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.

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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 $eGFR_{CKD-EPI}$ ($mL/min/1.73m^2$)		N (Tolvaptan/ Placebo)	eGFR Slope Tolvaptan	eGFR Slope Placebo	Effect Size	Relative Effect Size
Stage 1 (≥ 90)		330/173	-1.93	-2.86	0.94[a]	33%
Stage 2 (60-90)		465/224	-2.64	-3.85	1.21[a]	31%
Stage 3[b] (30-60)	3a (45-60)	135/70	-3.51	-5.23	1.72	33%
	3b (30-45)	28/14	-3.92	-5.99	2.07	35%

eGFR CKD-EPE = estimated glomerular filtration rate calculated by the Chronic Kidney Disease-Epidemiology (CKD-EPI) formula

[a] All $p < 0.005$

[b] CKD-Stage 3: relative effect size (33%); N (tolvaptan/placebo; 163/84)

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

CCI [redacted]

1.3 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.

As of 31 Mar 2013, pooled exposure data are available from 82 trials, involving 6,794 subjects worldwide comprising 3,115 subjects in trials for with heart failure, 425 subjects in trials for hyponatremia, 961 subjects in a long-term trial for ADPKD, 137 subjects in a short-term trial for ADPKD or renal impairment, 217 subjects in trials for cardiac edema, 855 subjects in trials for hepatic edema, 37 subjects with renal impairment in a phase 1 trial, and 1,047 healthy subjects in clinical pharmacokinetic

trials. Overall, subjects were exposed to oral doses of tolvaptan ranging from 3.75 to 480 mg. The median exposure for all doses of oral formulations combined was 29 days, with a mean exposure of 228 days (± 346 days).

Pooled safety data from 80 trials indicate that the most commonly reported (> 3%) treatment-emergent adverse events (TEAEs) for tolvaptan-treated subjects were thirst (25.8%), dry mouth (10.8%) and pollakiuria (9.9%).

The most notable safety issue associated with chronic tolvaptan use, which was newly identified in Trial 156-04-251, was 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, combined from Trials 156-04-251 and 156-08-271) with laboratory and clinical evidence of potentially serious drug-induced liver injury (DILI).[10] Based on the available data from the afore-mentioned trials, the sponsor proposes that appropriate subject monitoring and management be implemented to mitigate this potential risk in the ADPKD population.

In this extension trial, subjects enrolling from the double-blind Trial 156-13-210 will have monthly visits and transaminase level assessments for the first 18 months while the treatment code from Trial 156-10-210 remains blinded, to ensure that all subjects have adequate safety monitoring during this period of susceptibility. Once unblinding occurs, it can be determined which subjects received tolvaptan in Trial 156-13-210. These subjects may have their trial visits/hepatic transaminase monitoring change to every 3 months sooner as their previous tolvaptan exposure in Trial 156-13-210 can count towards the 18-month threshold. If subjects approaching the 18-month threshold have had prior transaminase abnormalities (> 2 × upper limit of normal [ULN]), the investigator is responsible for contacting the medical monitor to confirm the change in frequency from monthly to every 3 months. Subjects enrolling from the open-label Trial 156-08-271 will have transaminase assessments conducted every 3 months, since they will have already received tolvaptan for at least 18 months. The current IB lists all of the tolvaptan trials. Subjects enrolling in this trial who were in a previous ADPKD tolvaptan trial other than Trials 156-13-210 and 156-08-271 will have monthly visits and alanine aminotransferase (ALT) level assessments for the first 18 months.

2 Trial Rationale and Objectives

2.1 Trial Rationale

Evidence from previous studies suggests that during the first 18 months of long-term treatment in subjects with ADPKD, ALT and/or aspartate aminotransferase (AST) elevations and evidence of idiosyncratic DILI occurs at a greater frequency in tolvaptan treated subjects. However, the rate of new transaminase elevations beyond 18 months and up to 4.5 years was similar between tolvaptan treatment and placebo subjects.

Over the 3 years of placebo-controlled treatment, ALT was elevated to a greater than three times the upper limit of normal (> 3 × ULN) in 4.4% of tolvaptan subjects compared with 1% of placebo subjects. To date, 3 tolvaptan subjects' transaminases and bilirubin levels reached Hy's laboratory criteria (> 3 × and > 2 × ULN, respectively). Upon discontinuation, all subjects' liver tests showed reversibility of the elevation within approximately 4 months after tolvaptan was discontinued. Nevertheless, without adequate monitoring and management, it is estimated that a 1:4,000 risk for irreversible liver injury may exist.

Through more frequent (eg, monthly) monitoring of liver transaminases, 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.

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This trial will extend our understanding of tolvaptan's long-term safety in ADPKD patients.

2.2 Dosing Rationale

In animal models of cystic disease, successful treatment of disease progression as indicated by kidney size appeared to require early, constant inhibition of the vasopressin V_2 receptor. The clinical formulation of tolvaptan requires 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 an interruption of sleep.

2.3 Trial Objectives

The primary objective of this trial is:

- To evaluate and describe the long-term safety of tolvaptan.

3 Trial Design

3.1 Type/Design of Trial

This trial is a phase 3b, multi-center, open-label trial.

Eligible subjects will have an opportunity to enroll into Trial 156-13-211 following completion of the follow-up visit(s) of the previous trial. Eligible subjects from Trials 156-08-271 and 156-13-210 can have the last visit assessments from their previous respective protocols (end of trial visit for 156-08-271 subjects and last follow-up visit for 156-13-210 subjects) overlap the first visit in this trial. These last visit assessments can be combined with the screening and baseline visits for this trial, with all required assessments from each visit performed only once, so long as the time between the last visit assessments from the previous trial and the screening visit for this trial is within 30 days. If the first visit in this trial combines the last visit from a previous trial with both the screening and the baseline visits in this trial, the results from laboratory assessments performed at this combined visit will not be immediately available. Should any laboratory abnormalities be identified, the investigator will need to notify the subject and provide instructions regarding dosing or returning to the site for additional assessments.

Medical monitor approval is needed for enrollment of subjects whose completion of the preceding trial prior to entry in this trial exceeds 3 months, and these subjects will be required to undergo all screening and baseline assessments.

After consenting, subjects will be assigned a new screening number. Subjects who are found to be eligible will retain the same subject number they had been assigned in their previous trial. For purposes of ensuring subject safety, tolvaptan exposure of at least 18 months is required for all subjects. While Trial 156-13-210 remains blinded, subjects enrolling from any prior trial besides Trial 156-08-271 are scheduled to have monthly hepatic monitoring for the first 18 months of this trial. After that, following the approval of the medical monitor, hepatic monitoring will take place every 3 months. Subjects enrolling from Trial 156-08-271 will have hepatic monitoring every 3 months. All Trial 156-13-210 subjects who are eligible for this trial will initially be scheduled to have trial visits and hepatic monitoring monthly for the first 18 months, then every 3 months thereafter, because their tolvaptan exposure cannot be determined since Trial 156-13-210 is a double blind trial. Once unblinding occurs, it can be determined which subjects received tolvaptan in Trial 156-13-210. These subjects may have their trial visits/hepatic transaminase monitoring changed to every 3 months sooner as their previous tolvaptan exposure in Trial 156-13-210 can count towards the 18-month threshold. Subjects from prior tolvaptan trials other than Trial 156-08-271 will have monthly trial visits/ALT level assessments for the first 18 months. After that, the trial visits/ALT monitoring will be conducted every 3 months after the change in frequency is confirmed with the medical monitor.

Enrollment in this trial will be closed when the last eligible subject from Trial 156-13-210 enrolls in this trial.

The duration of this trial is planned to continue

- Until the last subject from Trial 156-13-210 completes 18 months of tolvaptan treatment in this trial
- All subjects will receive at least 18 months of tolvaptan treatment in the extension study. Trial 156-13-210 subjects or subjects enrolling from other trials may opt to conclude their participation in this trial if tolvaptan becomes available before they complete 18 months of treatment in this trial

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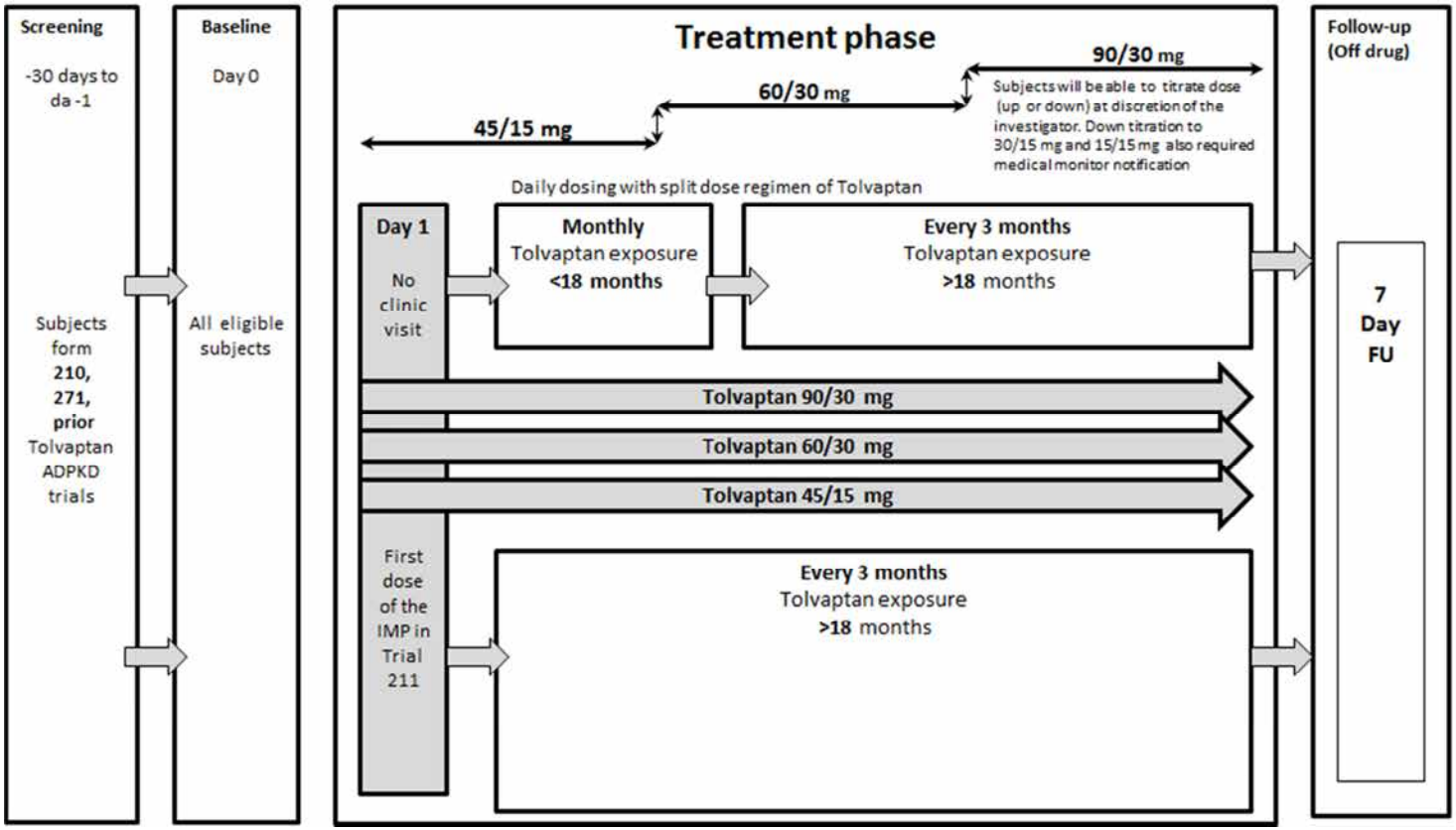

Figure 3.1-1 Trial Design Schematic

3.2 Treatments

The dose regimens to be used in this trial are 15/15 mg, 30/15 mg, 45/15 mg, 60/30 mg, and 90/30 mg.

Following consent, and once subjects have satisfied all of the inclusion criteria and none of the exclusion criteria, subjects will retain the subject number assigned from their previous trial. Subjects will receive open-label tolvaptan for the duration of the trial. All subjects will be administered tolvaptan tablets in a daily split-dose, once upon awakening and another approximately 8 to 9 hours later (twice daily dosing). The exact time 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 recorded as early dose/late dose (eg, 60/30 mg).

A subject's starting dose in this trial will be dependent on the trial in which they were previously enrolled:

- **156-13-210**- initiated on tolvaptan at a split-dose of 45/15 mg with upward titration every 3 to 4 days to 60/30 mg or 90/30 mg per day according to tolerability
- **156-08-271**- will retain the last dose level from 271 and start at the same dose in this trial
- **Prior tolvaptan trials**- initiated on tolvaptan at a split-dose of 45/15 mg with upward titration every 3 to 4 days to 60/30 mg or 90/30 mg per day according to tolerability

Down titration to 30/15 mg and 15/15 mg is also permitted at the discretion of the investigator according to subject tolerability with medical monitor notification. Further down titration to 30 or15 mg once daily may be allowed only for metabolic drug-drug interaction and requires medical monitor approval.

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Table 3.2-1 Trial Treatments		
Trial Day	**Time**	**Dose**
Day 1 to last on-treatment visit	8:00 am	1 to 6 tolvaptan tablets (15 mg or 30 mg each)
	4:00 to 5:00 pm	1 to 2 tolvaptan tablets (15 mg or 30 mg each) Allowed doses are 45/15 mg, 60/30 mg, 90/30 mg. Down titration to 30/15 mg and 15/15 mg will be allowed after discussion with the medical monitor. Further down titration to 30 or 15 mg once daily may be allowed only for metabolic drug-drug interaction and requires medical monitor approval.

For subjects moving from the 156-13-210 trial and requiring tolvaptan titration, it will be conducted in the following way: subjects will be instructed to take tolvaptan starting at a split dose of 45/15 mg (as 3 tablets upon waking and 1 tablet approximately 8 to 9 hours later) and to titrate up every 3 to 4 days; first to 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. 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?" Subjects will continue in the trial with the regimen to which tolerability was established.

While taking tolvaptan, 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 Dosing with CYP3A4 Potent Inhibitors

Tolvaptan is a sensitive CYP3A4 substrate with 4-fold or higher increases in exposure following administration with potent CYP3A4 inhibitors.[4]

For subjects requiring treatment with a potent CYP3A4 inhibitor and on a total daily tolvaptan dose of 90 or 120 mg, tolvaptan treatment should be reduced to 30 mg once daily. The dose may be reduced to 15 mg once daily for tolerability. For subjects on a total daily dose of 60 mg, tolvaptan treatment should be reduced to 15 mg once daily. For subjects on lower total daily doses, tolvaptan interruption should be considered if no alternative medications can be used.

3.2.2 Dosing with CYP3A4 Moderate Inhibitors

For subjects who require dosing with a moderate inhibitor, initial tolvaptan reductions as shown below should be tried, with further dose reductions or interruption as necessary for tolerability.

- 90/30 mg to 45/15 mg
- 60/30 mg to 30/15 mg
- 45/15 mg to 15/15 mg
- 30/15 mg to 15 mg once daily
- 15/15 mg to 15 mg once daily

A partial list of strong and moderate CYP3A4 inhibitors can be found in Section 4.1.

3.3 Trial Population

This trial will include approximately 2,500 subjects over the age of 18 years with ADPKD diagnosed by Pei-Ravine criteria[11 12] (modified by magnetic resonance imaging [MRI]) who completed or participated in a prior tolvaptan trial.

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 informed consent form (ICF) that shall be approved by the same institutional review board/independent ethics committee (IRB/IEC) responsible for approval of this protocol. Each ICF will comply with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guideline[14] 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 sponsor approval of any written ICF used in the trial prior to submission to the IRB/IEC.

Investigators may discuss trial availability and the possibility for entry with a potential subject without first obtaining consent. However, informed consent will be obtained from all subjects (or their guardian or legal representative) 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).

Once appropriate essential information has been provided and fully explained in layman's language to the subject by the investigator (or a qualified designee), the IRB/IEC-approved written ICF will be signed and dated by both the subject and the person obtaining consent (investigator or designee), as well as by any other parties required by the IRB/IEC. The subject will receive a copy of the signed ICF; the original shall be kept on file by the investigator.

CCI [redacted]

3.4.2 Inclusion Criteria

Subjects are required to meet the following inclusion criteria in Table 3.4.2-1.

Table 3.4.2-1 Inclusion Criteria

1.	Male and female subjects aged ≥ 18 years with confirmed diagnosis of ADPKD (during participation in prior tolvaptan trials) who have • Completed and transferred from the double-blind Trial 156-13-210 (12-month period including post-treatment follow-up, regardless of whether this was on-treatment or off-treatment), or • Completed Trial 156-08-271 or a prior tolvaptan trial, or • Interrupted or discontinued treatment in a tolvaptan trial other than Trial 156-13-210. Subjects may be enrolled with the medical monitor approval, and additional close monitoring may be required at the beginning of the trial • Renal function will be assessed during screening by using historical laboratory values (in the last 3 months) for serum creatinine levels to calculate the eGFR. The eGFR values will be estimated based on the CKD-EPI formula. (Levey AS et al. Ann Intern Med. 2009; 150:604–612)
2.	Estimated glomerular filtration rate ≥ 20 mL/min/1.73 m^2 (calculated using the CKD-EPI formula) within 3 months prior to the baseline visit. Subjects who have an eGFR ≤ 20 mL/min/1.73 m^2 may be permitted to enter the trial with medical monitor and sponsor approval and increased frequency of monitoring to ensure safety of participants.

eGFR=estimated glomerular filtration rate; CKD-EPI= Chronic Kidney Disease - Epidemiology

3.4.3 Exclusion Criteria

Subjects will be excluded if they meet any of the exclusion criteria in Table 3.4.3-1.

Table 3.4.3-1 Exclusion Criteria	
1.	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 based on liver function abnormalities other than that expected for ADPKD with cystic liver disease during screening based on recent historical laboratory values (in the last 3 months).
5.	Subjects with contraindications to required trial assessments (contraindications to optional assessments, eg, MRI are not a limitation).
6.	Subjects who, in the opinion of the investigator or medical monitor, have a medical history or medical finding inconsistent with safety or trial compliance. This includes prior evidence of significant hepatic injury deemed to be related to tolvaptan use.

WOCBP=women of childbearing potential; IMP=investigational medicinal product

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

3.5 Trial Endpoints

3.5.1 Safety Endpoints

This trial will have no formal endpoints. Safety variables will be summarized by descriptive statistics, (eg, proportion, mean, median, standard deviation [SD], minimum, and maximum values). In general, summary statistics, including changes from baseline, will be provided for safety variables based on all available data. Safety endpoints will be as follows:

- Adverse events
- Vital signs
- Clinical laboratory assessments
- Serum transaminase elevations for frequency (2x, 3x, 5x and 10x ULN), time to onset, time to peak levels, time of offset (< 3x, 2x, or 1x ULN), response to

de-challenge and re-challenge and frequency of progression to Hy's laboratory criteria (ALT or AST > 3x ULN and bilirubin, total (BT), > 2x ULN without alkaline phosphatase ≥ 2x ULN)

- Serum sodium excursions above 145, 150, or 155 mmol/L or below 135, 130, or 125 mmol/L

3.5.2 CCI [redacted]

[redacted]

3.5.3 CCI [redacted]

[redacted]

3.6 Measures to Minimize/Avoid Bias

This is an open-label trial. For subjects entering from placebo-controlled trials, prior therapy (placebo or tolvaptan), will not be known (by trial site, investigator, or sponsor) at the time of entry into this trial.

All blood and urine chemistry will be analyzed and reported by a central laboratory.

3.7 Trial Procedures

Trial assessment time points are summarized in Table 3.7-1.

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Table 3.7-1 Schedule of Assessments

	Screening (-30 to -1 days prior to Baseline)[a]	Baseline/ Day 0	Monthly[b] (± 7 days)	Every 3 months[b] (± 14 days)	Early Termination/End of Treatment (+ 7 days)	Titration Contact (phone contact)	Follow-up 7 days post-treatment (+ 7 days)
Informed consent	X						
Inclusion/Exclusion	X	X					
Demographics, Medical/ADPKD history[c]	X						
Dietary review	X	X	X	X	X		
CCI [redacted]							
Vital signs[d]	X	X	X	X	X		X
Chemistry Blood Samples[e]							
Serum Chemistry Panel	X[f]				X		
Liver Function tests[g]	X		X	X	X		X
Sodium	X		X	X	X		
Creatinine	X		X	X	X		X
Hematology and coagulation	X				X		
Urinalysis	X		X	X	X		
Urine osmolality[h]	X		X	X	X		
Urine specific gravity	X		X	X	X		
Urine pregnancy test (WOCBP only)[i]	X		X	X	X		X
Urine at-home pregnancy test kits dispensed[j]		X	X	X			
Physical examination [k]	X	X	X	X	X		
Tolerability/Dosing Review		X	X	X	X	X	
Interactive Response Technology Entry	X	X	X	X	X	X[l]	X
Drug dispensation		X	X	X		X[l]	
Drug reconciliation			X	X	X	X[l]	
CCI [redacted]							
[redacted]							
[redacted]							

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	Screening (-30 to -1 days prior to Baseline)[a]	Baseline/ Day 0	Monthly[b] (± 7 days)	Every 3 months[b] (± 14 days)	Early Termination/End of Treatment (+ 7 days)	Titration Contact (phone contact)	Follow-up 7 days post-treatment (+ 7 days)
Adverse events	X[n]	←----------	----------	----------	----------	----------	----------→
Concomitant medications[o]		←----------	----------	----------	----------	----------	----------→

[a]The last visit assessments from the previous trial can be combined with the screening and baseline visits for this trial, with all required assessments from each visit performed only once.

[b]Monthly visits are for subjects < 18 months on tolvaptan, and every 3 month visits are for subjects > 18 months on tolvaptan.

[c] Includes prior trial identifiers (screening identification [ID], subject ID, site ID, prior tolvaptan ADPKD trial protocol number).

[d]Vital signs at each visit include seated heart rate, calibrated blood pressure and post void body weight. Height should be performed only at screening.

[e] Central laboratory non-fasting serum laboratory tests will be performed. All subjects must be monitored for hepatic safety monthly until they have known tolvaptan exposure data of at least 18 months. After that, and following the approval of the medical monitor, hepatic monitoring will take place every 3 months. Trial 156-13-210 subjects who are eligible for this trial will have trial visits/hepatic monitoring monthly for the first 18 months of this trial then every 3 months thereafter, because their tolvaptan exposure will be unknown. Once unblinding occurs, it can be determined which subjects received tolvaptan in Trial 156-13-210. These subjects may have their trial visits/hepatic transaminase monitoring changed to every 3 months sooner as their previous tolvaptan exposure in Trial 156-13-210 can count towards the 18 month threshold. Subjects who enroll from other ADPKD tolvaptan trials will be monitored for hepatic safely monthly for their first 18 months they are in this trial.

[f] Hepatitis testing at screening will be optional. If hepatitis testing is performed, then both pre- and post-counseling activities relating to hepatitis testing are to be carried out based on local requirements and best practices. Upon request, if clinically indicated and approved by the medical monitor, subjects may have the following evaluations in addition to the protocol-specified chemistry panel: serum calcium, phosphorous, parathyroid hormone, vitamin D, and bicarbonate levels.

[g]A full liver function panel (AST, ALT, alkaline phosphatase, BT) will be done at screening. All other liver function tests at subsequent visits are for ALT only, unless otherwise clinically indicated. An ALT elevation > 2 × ULN should trigger prompt testing of hepatic function within 72 hours. Any transaminase values which exceed 2 × ULN should 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, and every 3 months as indicated by the results. Local liver function panel analyses will also be performed more frequently, if necessary.

[h]Urine osmolality is optional.

[i] A urine pregnancy test for pregnancy for women of childbearing potential (WOCBP) will be performed at screening, at every 3 months visits, at the End of Treatment (EoTx) visit, and at the follow-up visit. On suspicion of pregnancy, an unscheduled urine or serum pregnancy testing will be performed. Positive urine pregnancy tests should be confirmed with a serum pregnancy test.

[j] At-home urine pregnancy test kits will be dispensed to WOCBP to be used if a menstrual period is missed between visits. Kits will be dispensed as needed throughout the trial.

[k]A full physical examination is required at screening. At other visits, an optional "directed" physical examination may be performed to focus on PKD-related signs and symptoms.

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[l] If during the titration contact the determination is made to adjust the dose regimen, dose adjustments will be made using dispensed supply, and dose instructions will be provided by the investigator. The subject's current dose will be entered into the interactive response technology (IRT) at each visit. Drug dispensation/reconciliation will be conducted on a monthly basis for subjects who have monthly trial visits and once every 3 months for subjects who have trial visits every 3 months. If additional drug supply is required for titration purposes, the site will arrange a subject visit for dispensation.

CCI [redacted]

[n] At screening, AEs reported as ongoing or resolved at the end of the prior trial will be assessed to determine entry as either medical history or ongoing event for this trial.

[o] Only concomitant medications ongoing at the baseline visit and throughout the trial will be recorded. This would occur at the screening visit only if the screening visit occurs simultaneously with the last visit from a previous tolvaptan trial.

3.7.1 Schedule of Assessments

3.7.1.1 Screening (-30 days to 1 day prior to Baseline)

Screening for eligibility is required for all subjects. The screening and baseline visits may be combined with the last visit from either Trials 156-08-271 or 156-13-210 with all required assessments from each visit performed only once. Therefore, in some cases, if a subject enrolls in this trial from a prior tolvaptan trial, the end of trial or last follow-up visit for that trial and the screening and baseline visit for this one may occur simultaneously. Required assessments for the screening visit are as follows:

1. Obtain subject consent.
2. Obtain subject's new screening identification (ID) assigned by interactive response technology (IRT)
3. Determine subject eligibility through inclusion/exclusion criteria.
4. Record demographic information and prior trial identifiers (screening ID, subject ID, site ID, prior tolvaptan ADPKD trial protocol number).
5. Record medical/ADPKD history using prior trial data.
6. Review dietary recommendations and compliance
7. Record vital signs (post-void weight and seated heart rate) and in-clinic calibrated blood pressure (BP) measurement. Record height.
8. Collect blood for serum chemistry, liver function panel (ALT, AST, BT, bilirubin [direct], and alkaline phosphatase), serum sodium, serum creatinine, and hematology and coagulation. Hepatitis testing is optional. If hepatitis testing is performed, then both pre- and post-counseling activities relating to hepatitis testing are to be carried out based on local requirements and best practices.
9. Collect urine for urinalysis, urine osmolality (optional), and urine specific gravity.
10. Perform urine pregnancy test on women of childbearing potential (WOCBP). If positive, a follow-up serum test will be performed.
11. Conduct full physical examination.
12. Enter subject into IRT including prior trial identifier/information (protocol number, subject ID), confirmed dose regimen, and scheduled date of next visit.
13. Assess AEs reported as ongoing or resolved from prior trial to determine entry as medical history or ongoing event for this trial.
14. Record ongoing concomitant medications. (This will happen only if the screening visit occurs simultaneously with the last visit from a previous tolvaptan trial).

3.7.1.2 Baseline (Day 0)

The baseline visit is the beginning of the treatment period in this trial. At the baseline visit, subjects will retain the subject number assigned in the previous tolvaptan trial, and the following assessments and procedures will be performed:

1. Review inclusion/exclusion criteria.
2. Review dietary recommendations and compliance.
3. CCI [redacted]
4. Record vital signs (post-void weight, seated heart rate, and calibrated blood pressure measurement).
5. Dispense at-home urine pregnancy test kits to WOCBP to be used if a menstrual period is missed before the next visit.
6. An optional directed physical examination may be performed to focus on PKD-related signs and symptoms.
7. Assess tolerability/dosing review of investigational medicinal product (IMP).
8. Enroll subject into trial through IRT and obtain IMP.
9. Dispense IMP (sufficient for 1 month or 3 months of dosing based on the subject's required visit schedule for hepatic evaluation as either monthly or every 3 months).
10. Provide subject with dosing instructions to begin on the following day.
11. Record ongoing concomitant medications
12. Assess AEs.

3.7.1.3 Monthly Visit (± 7 days)

The following subjects will return for a monthly visit to assess safety and tolerability of IMP and to monitor liver function.

- Subjects enrolling from the double-blind Trial 156-13-210 will have monthly trial visits/ALT level assessments for the first 18 months while treatment code from Trial 156-13-210 remains blinded, to ensure that they have adequate safety monitoring during this period of susceptibility. Once unblinding occurs, it can be determined which subjects received tolvaptan in Trial 156-13-210. These subjects may have their trial visits/hepatic transaminase monitoring change to every 3 months sooner as their previous tolvaptan exposure in Trial 156-13-210 can count towards the 18-month threshold. The investigator will need to discuss the change in frequency with the medical monitor before instituting the change.

- Subjects from prior tolvaptan trials other than Trial 156-08-271 will have monthly trial visits/ALT level assessments for the first 18 months. After that, the trial visits/ALT monitoring will be conducted every 3 months after the change in frequency is confirmed with the medical monitor.
- Subjects enrolling from the open-label Trial 156-08-271 who have greater than 18 months of exposure to tolvaptan will have trial visits/ALT monitoring conducted every 3 months.

The following will be assessments will be completed:

1. Review dietary recommendations and compliance.
2. CCI [redacted]
3. Record vital signs (post-void weight, seated heart rate, and calibrated blood pressure measurement).
4. Collect blood for central laboratory assessments for serum sodium, serum creatinine, and ALT (see Section 3.7.2.4).
5. CCI [redacted]
6. CCI [redacted]
7. Urinalysis, urine osmolality (optional), urine specific gravity.
8. Perform urine pregnancy test on WOCBP (every 3 months). If positive, a follow-up serum test will be performed.
9. Dispense at-home urine pregnancy test kits to WOCBP, as required.
10. An optional directed physical examination may be performed to focus on PKD-related signs and symptoms.
11. Assess tolerability/dosing review of IMP.
12. Enter subject status in IRT, including any dose regimen changes and obtain IMP assignment.
13. Collect and reconcile returned IMP, assess compliance.
14. Dispense IMP based on subject's required visit schedule, and provide subject with dosing instructions.
15. Update concomitant medications.
16. Assess AEs.

3.7.1.4 Every 3 Months (± 14 days)

1. Review dietary recommendations and compliance.

2. CCI [redacted]
3. Record vital signs (post-void weight, seated heart rate, and calibrated blood pressure measurement).
4. Collect blood for central laboratory assessments serum sodium, serum creatinine, ALT (see Section 3.7.2.4).
5. CCI [redacted]
6. Urinalysis, urine osmolality (optional), urine specific gravity.
7. Perform urine pregnancy test on WOCBP. If positive, a follow-up serum test will be performed.
8. Dispense at-home urine pregnancy test kits to WOCBP, as required.
9. CCI [redacted]
10. An optional directed physical examination may be performed to focus on PKD-related signs and symptoms.
11. Assess tolerability/dosing review of IMP.
12. Enter subject status in IRT, including any dose-regimen changes and obtain IMP assignment.
13. Collect and reconcile returned IMP; assess compliance.
14. Enter subject status in IRT, including any dose-regimen changes.
15. Dispense IMP based on subject's visit schedule, and provide subject with dosing instructions.
16. Update concomitant medications.
17. Assess AEs.

3.7.1.5 Early Termination/End of Treatment (+ 7 days)

At the early termination/end of treatment (EoTx) visit the following will be assessed:

1. Review dietary recommendations and compliance.
2. CCI [redacted]
3. Record vital signs (post-void weight, seated heart rate, and calibrated blood pressure measurement).
4. Collect blood for serum chemistry, serum creatinine, ALT, serum sodium and hematology and coagulation.

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5. CCI [redacted]
6. CCI [redacted]
7. Collect urine for urinalysis, urine osmolality (optional), urine specific gravity.
8. Perform urine pregnancy test on WOCBP. If positive, a follow-up serum test will be performed.
9. An optional directed physical examination may be performed to focus on PKD-related signs and symptoms.
10. Assess tolerability/dosing review of IMP.
11. Enter subject status in IRT, including any dose-regimen changes since the previous entry.
12. Collect and reconcile returned IMP; assess compliance.
13. Update concomitant medications.
14. Assess AEs.

3.7.1.6 7-day Follow-up Visit (+ 7 days)

1. Record vital signs (post-void weight, seated heart rate, and calibrated blood pressure measurement).
2. Collect blood for serum creatinine and ALT.
3. CCI [redacted]
4. Perform urine pregnancy test on WOCBP. If positive, a follow-up serum test will be performed.
5. Enter subject status in IRT.
6. Update concomitant medications.
7. Assess AEs.

3.7.2 Safety Assessments

3.7.2.1 Adverse Events

Refer to Section 5, Reporting of Adverse Events.

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CCI [redacted]

CCI [redacted]

A list of the specific clinical laboratory assessments is presented in Table 3.7.2.2-1.

Clinical laboratory samples will be collected and sent to the central laboratory at the following time points:

Screening: Hematology and coagulation panel, serum chemistry panel, liver function panel (AST, ALT, alkaline phosphatase, bilirubin direct [BT]) serum sodium, serum creatinine, urinalysis panel, urine osmolality (optional), urine specific gravity, urine pregnancy test (WOCBP) and hepatitis (optional).

Monthly visits (± 7 days): ALT (for the first 18 months for subjects enrolled from other tolvaptan ADPKD trials and Trial 156-13-210 while trial remains blinded), serum sodium, and serum creatinine (all subjects), urinalysis, urine osmolality (optional), urine specific gravity, and urine pregnancy test (every 3 months in WOCBP). CCI [redacted]

Every 3 months: (± 14 days): ALT (after 18 months of treatment for subjects enrolled from other ADPKD tolvaptan trials, or from Trial 156-13-210 after the trial is unblinded, and for subjects enrolled from Trial 156-08-271), serum sodium and serum creatinine, urinalysis panel, urine pregnancy test (WOCBP), urine osmolality (optional), and urine specific gravity. CCI [redacted]

Early Termination/EoTx (+ 7 days): Serum chemistry panel, hematology and coagulation panel, ALT, serum sodium and serum creatinine, CCI [redacted] urinalysis

panel, urine pregnancy test (WOCBP), urine osmolality (optional), and urine specific gravity.

7-day Follow-up visit (+ 7 days): ALT, serum creatinine, and urine pregnancy test (WOCBP).

Table 3.7.2.2-1 Clinical Laboratory Assessments

Hematology and Coagulation Panel: Hemoglobin Platelet count Mean corpuscular hemoglobin concentration (MCHC) Mean corpuscular volume (MCV) Red blood cell (RBC) count White blood cell (WBC) count with differential Prothrombin time (PT) as international normalized ratio (INR) Activated partial thromboplastin time (aPTT) Urinalysis Panel: Appearance Color Blood Glucose Microscopic analysis, WBC/RBC counts per high power field pH Protein Urine Chemistry Osmolality (optional) Specific gravity Additional Tests: Urine (or serum) pregnancy for WOCBP Hepatitis (optional)	Serum Chemistry Panel: Albumin Blood urea nitrogen (BUN) Serum calcium Carbon dioxide Serum chloride Gamma-glutamyl transpeptidase Cholesterol, total Glucose Lactate dehydrogenase (LDH) Phosphorus Potassium Protein, total Uric acid Liver Function Panel: Alkaline phosphatase (ALP) Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Bilirubin, total (BT) Bilirubin, direct
Creatinine	**Sodium**

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. Blood testing for hepatitis will be optional for all subjects. Urine pregnancy testing will be performed with commercially available, high-sensitivity kits supplied to the subject by the site (acquired by the sponsor).

3.7.2.3 Physical Examination and Vital Signs

A full physical examination will be performed and documented at the screening visit although this may be combined with the last visit from the previous trial. At other visits,

an optional 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.

Height will be measured only at screening. 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 Food and Drug Administration (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, height, and weight will be taken at the visits identified in the Schedule of Assessments (Table 3.7-1).

3.7.2.4 Assessment of Liver Symptoms, Signs or Test Abnormalities

Testing for hepatic transaminase (ALT/AST), alkaline phosphatase, bilirubin direct, and BT will be performed during screening. Subjects enrolling from the double-blind Trial 156-13-210 will have monthly ALT assessments for the first 18 months while the treatment code from Trial 156-13-210 remains blinded to ensure that all subjects have adequate safety monitoring during this period of susceptibility. Once unblinding occurs, it can be determined which subjects received tolvaptan in Trial 156-13-210. These subjects may have their trial visits/hepatic transaminase monitoring changed to every 3 months sooner as their previous tolvaptan exposure in Trial 156-13-210 can count towards the 18-month threshold.

Following the first 18 months, ALT assessments will be made every 3 months for Trial 156-13-210 subjects and for subjects from other tolvaptan ADPKD trials besides Trial 156-08-271.

Subjects enrolling from the open-label Trial 156-08-271 who have tolvaptan exposure greater than 18 months will continue with ALT monitoring every 3 months.

Subjects enrolling from prior tolvaptan trials besides Trial 156-08-271 will have monthly ALT assessments for the first 18 months. Upon reaching 18 months of exposure and after confirmation from the medical monitor, the frequency of ALT monitoring for these subjects will occur every 3 months.

ALT will also be assessed at the Early Termination/EoTx visit and at the 7-day Follow-up visit.

Management of liver abnormalities is discussed in the paragraphs below.

3.7.2.4.1 Liver Test Abnormalities and Interruption/Discontinuation of Investigational Medicinal Product

An ALT elevation 2 × ULN or 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 × 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, or every three months as indicated by the results.

Liver transaminase levels reaching or exceeding 2 × ULN that have an uncertain or rapidly increasing trajectory should prompt at least temporary IMP interruption. Tolvaptan 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 tolvaptan if they have:

- transaminase levels rise above 8 × ULN,
- transaminase levels are > 5 × ULN for more than 2 weeks, or
- concurrent elevations of transaminase > 3 × ULN and BT > 2 × 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)[10] by an independent hepatic adjudication committee (HAC) 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.

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3.7.2.4.2 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 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).[10] 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. Has normal screening levels and develops ALT or AST levels ≥ 3x ULN,
4. Has normal screening levels and develops BT levels ≥ 2x ULN, or
5. Has an abnormal screening level and develops abnormalities in that test that are > 2x the upper limit of their highest screening value.

CCI [redacted] 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 CCI [redacted]

[redacted]

3.7.4 CCI

[redacted]

3.7.5 Treatment Interruption and Discontinuation

In this trial, it is expected that subjects may possibly have one or more planned or unplanned treatment interruptions. If a subject's IMP treatment must be interrupted for medical or surgical reasons, liver test abnormalities, use of a prohibited 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 investigator should be notified as soon as possible and the reason for treatment interruption must be documented in the source documents and case report form (CRF). If permissible, the subject's IMP may be resumed following approval by the medical monitor.

If IMP treatment is permanently discontinued, the reason for discontinuation must be recorded appropriately in the source document and in the CRF.

A subject who permanently discontinues IMP treatment ends trial participation and the early termination visit should be completed.

3.7.6 End of Trial

The End of Trial date is defined as the last date of contact or the date of final contact attempt from the post-treatment Follow-up CRF page for the last subject completing or withdrawing from the trial.

3.7.7 Independent Data Monitoring Committee

For this trial, an Independent Data Monitoring Committee (IDMC), also known as a Data Safety and Monitoring Committee, 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

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

If a subject discontinues the trial prematurely, the reason must be fully evaluated and recorded appropriately in source documents and the CRF. If the subject is being withdrawn because of an AE, that AE should be indicated as the reason for withdrawal.

All subjects have the right to withdraw at any time during treatment without prejudice. The investigator can discontinue a subject's participation in the trial at any time if medically necessary. It is preferred that subjects who permanently discontinue IMP will have the option to continue participation off IMP with regular scheduled visits or with a modified (ie, less frequent) schedule. If subjects are unable or unwilling to complete the visits and procedures off IMP, the early termination/EoTx visit should be completed. The investigator may continue to contact those who discontinue IMP through to the final completion date of the trial or thereafter if needed to determine outcomes ie, vital status.

In addition, subjects meeting the following criteria must be withdrawn from the trial:

a) Occurrence of any AE, intercurrent illness, or abnormality in a laboratory assessment which, in the opinion of the investigator, warrants the subject's permanent withdrawal from the trial;

b) Subject noncompliance, defined as refusal or inability to adhere to the trial schedule or procedures (see Section 3.12);

c) At the request of the subject, investigator, sponsor, or regulatory authority;

d) Subject is lost to follow-up.

The investigator will notify the sponsor promptly when a subject is withdrawn.

3.9 Screen Failures

A screen failure subject is one from whom informed consent is obtained and is documented in writing (ie, subject signs an ICF), but who is not started on treatment.

3.10 Definition of Completed Subjects

For purposes of this trial, subjects who complete the EoTx visit will be defined as trial completers.

3.11 Definition of Subjects Lost to Follow-up

Subjects, or the subject's parent/guardian who cannot be contacted on or before their final visit prior to the trial termination date, who do not have a known reason for discontinuation (eg, withdrew consent or AE) and for whom a current health status at the end of the trial cannot be determined will be classified as "lost to follow-up" as the reason for discontinuation. Current health status can be determined from a variety of sources, either by obtaining acceptable documentation for death (ie, death certificate, medical records, public records, or statement by a family member or primary care physician) or acceptable documentation for life (ie, direct contact with the subject, medical records, successful telephone contact with the subject, statement by a family member or primary care physician, or public records). It is expected that 3 documented attempts will be made to determine a subject's current health status before assigning a "lost to follow-up" status.

3.12 Subject Compliance

Subject compliance will be monitored by pill counts as IMP is returned. Any subject who, without the instruction of the investigator, discontinues tolvaptan investigational product, discontinues tolvaptan for 30 consecutive days or misses > 30% of the doses intended for a period between visits (whichever is greater) will be deemed noncompliant. Depending on the circumstances leading to noncompliance, the subject may be withdrawn from the trial or discontinued from investigational product administration by the investigator and/or sponsor. It is preferred that subjects who discontinue tolvaptan, or are withdrawn by the investigator for reasons other than noncompliance or lost to follow-up, will continue with regularly scheduled visits completing all procedures as provided in the protocol.

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3.13 Protocol Deviations

This trial is to be conducted as described in this protocol. In the event of a significant deviation from the protocol due to an emergency, accident or mistake (eg, violation of informed consent process, IMP dispensing or subject dosing error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator or designee must contact the sponsor at the earliest possible time. This will allow an early joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator and the sponsor, and reviewed by the 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 therapies, vasopressin antagonists other than tolvaptan, (eg, OPC-31260 (mozavaptan), Vaprisol (conivaptan), 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 tolvaptan metabolism (see Section 3.2.1 and Section 3.2.2).

A partial list of strong and moderate CYP3A4 inhibitors can be found in Table 4.1-1 below:

Table 4.1-1 Strong and Moderate CYP3A Inhibitors (partial list)

amprenavir	atorvastin	aprepitant	chloramphenicol (if used orally)
cimetidine	clarithromycin	clotrimazole (if used orally)	danazol
delavirdine	diltiazem	erythromycin	fluconazole
fluvoxamine	indinavir	isoniazid	itraconzazole
josamycin	ketoconazole (if used orally)	nelfinavir	nefazadone
quinupristin/ dalfopristin	ritonavir	saquinavir	troleandomycin
verapamil	Seville orange products	grapefruit products	

Pharmacodynamic interactions are a consideration for the use of diuretics, which may be only used intermittently, and 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 and is an exclusionary criterion for this 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 list would include: non-steroidal anti-inflammatory drugs like aspirin or ibuprofen, chemotherapy drugs, cephalosporin, the combination of elvitegravir, cobicistat, emtricitabine, and tenofovir (Stribild™), dolutegravir, dronedarone, ranolazine, metformin, and trimethoprim.

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, dietary salt < 5g/day, dietary cooked meat protein < 1 g/kg/day and a limit on caffeinated drinks/foods should also be given (no more than 2 coffee equivalents per day). A history of alcohol and smoking intake will be collected at screening. Alcohol and tobacco consumption should be avoided or minimized as much as possible.

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 ingest at least 2 to 3 liters of fluid (including in solid, semi-solid, and liquid foods) per day, unless otherwise directed by their trial 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 the IMP.

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.

Medical follow up is expected for AEs which lead to discontinuation which are serious, or which are of special interest (eg, liver abnormalities, skin neoplasms, glaucoma).

ADPKD is a progressive disorder involving the kidney, liver and occasionally other organ systems. A number of AEs may be associated with this disorder 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 and investigational new drug [IND] safety reports).

5.1 Definitions

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

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

A serious adverse event (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 inpatient 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.

Nonserious 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 nonserious) that necessitates discontinuation of IMP.
- Any subject with a new liver test abnormality meeting the AE (whether serious or nonserious) 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 CRF. The intensity of an adverse experience is defined as follows:

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

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

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

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

Related: There is a reasonable probability or possibility of a temporal and causal relationship between the IMP and the AE.

Not Related: There is no temporal or causal 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 nonserious) reported by the subject must be recorded on the source documents and eCRFs provided by the sponsor.

In addition, Quintiles (drug safety service) 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 laboratory abnormality requiring special liver eCRF completion, or confirmed pregnancy, by telephone or by fax to Quintiles (drug safety service) as outlined in Appendix 1. An IRE form must be completed and sent by fax, email or overnight courier to the sponsor. (Please note that the IRE form is NOT the AE eCRF).

Nonserious 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, email, 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.

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 an 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. Abstinence is only acceptable when part of the preferred and usual lifestyle of the subject; should that lifestyle change, double barrier contraceptive methods should be employed.

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 ICF 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 IMP administration, the IMP administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the IMP and must not be enrolled in the trial. If pregnancy is suspected while the subject is taking IMP, the IMP must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy is known. If pregnancy is confirmed, the 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.

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

5.5 Follow-up of Adverse Events

For this trial, AEs will be followed up for 7 days after the last dose of tolvaptan 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.

5.5.1 Follow-up of Nonserious Adverse Events

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

5.5.2 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.

5.5.3 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 serious related AEs identified after the last scheduled contact until the events are resolved, or the subject is lost to follow-up. The investigator should continue to report any significant follow-up information to OPDC up to the point the event has been resolved.

6 CCI [redacted]

[redacted]

7 Statistical Analysis

7.1 Sample Size

Sample size was not determined by a formal computation to achieve a target power. No efficacy analyses are planned. It is expected that approximately 2,500 subjects may enroll from previous tolvaptan trials.

7.2 Dataset for Analysis

The following datasets are defined for this trial:

- Enrolled Population: all subjects who were enrolled to this open-label trial.
- Safety Population: all subjects in the Enrolled Sample who take at least one dose of IMP

7.3 Handling of Missing Data

No missing data will be imputed under the assumption of missing at random.

7.4 Interim Analysis

No interim analysis for this trial is planned.

7.5 Trial Outcome Analyses

7.5.1 Analysis of Demographic and Baseline Characteristics

Demographic characteristics, disease severity, and medical history at (pretreatment) baseline will be summarized by descriptive statistics, eg, proportion, mean, median, SD, minimum and maximum values.

7.5.2 Safety Analysis

Safety analysis will be conducted based on the Safety Population, which is defined as all subjects in the Enrolled Population who take at least one dose of IMP. Safety variables to be analyzed include clinical laboratory tests, vital signs, and AEs. CCI [redacted]

In general, baseline measurements of safety variables are defined as the last measurements prior to the first dose of IMP in Trial 156-13-211. Safety variables will be summarized by descriptive statistics, (eg, proportion, mean, median, SD, minimum, and maximum values). Summary statistics, including changes from baseline, will be provided for safety variables based on all available data.

7.5.2.1 Adverse Events

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

a) TEAEs by severity
b) TEAEs potentially causally related to tolvaptan
c) TEAEs with an outcome of death
d) Serious TEAEs
e) Discontinuations due to TEAEs

7.5.2.2 Vital Signs

Summary statistics for changes from baseline in vital signs and potentially clinically significant results in vital signs will be summarized.

7.5.2.3 Clinical Laboratory Assessments

Summary statistics for changes from baseline in clinical laboratory measurements will be provided for the Safety Population. Potentially clinically significant results in laboratory

tests identified using prospectively defined criteria, including criteria for liver enzyme elevations, will also be summarized for the Safety Population. 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 × ULN):

- ALT or AST ≥ 3 × ULN
- Bilirubin ≥ 2 × ULN

7.5.2.4 Serum Sodium

The following will be summarized:

- Serum sodium excursions above 145, 150, or 155 mmol/L or below 135, 130, or 125 mmol/L
- Interruptions of protocol-specified therapies for hypernatremia or hyponatremia.

7.5.3 CCI

[redacted]

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CCI

8 Management of Investigational Medicinal Product

8.1 Packaging and Labeling

Tolvaptan will be provided to the investigator(s) by the sponsor or designated agent as tablets of 15 or 30 mg tolvaptan (OPC-41061). Each bottle will be labeled to clearly disclose the subject 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 IMP is to be used.

8.2 Storage

Tolvaptan 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 tolvaptan to any subject not participating in this protocol.

Tolvaptan will be stored at the conditions specified in the IMP label. The clinical site staff will maintain a temperature log in the IMP 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 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 initialed 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 three periods:

- A period of at least 2 years following the date on which approval to market the IMP 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 IMP 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 CRFs, the investigator, sub-investigator and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject number and subject ID 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 be 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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2 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

3 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.

4 OPC-41061 Investigator's Brochure. Rockville (MD): Otsuka Pharmaceutical Development & Commercialization, Inc.; Edition 19 Otsuka Report, issued 11 July 2013.

5 OPC-41061 Common Technical Document. Rockville (MD): Otsuka Pharmaceutical Development & Commercialization, Inc.; Section 2.5: Clinical Overview; 2013.

6 Wang X, Gattone V 2nd, Harris PC, Torres VE. Effectiveness of vasopressin V2 receptor antagonists OPC-31260 and OPC-41061 on polycystic kidney disease development in the PCK rat. J Am Soc Nephrol. 2005 Apr;16(4):846-51.

7 Reif GA, Yamaguchi T, Nivens E, Fujiki H, Pinto CS, Wallace DP. Tolvaptan inhibits ERK-dependent cell proliferation, Cl- secretion, and in vitro cyst growth of human ADPKD cells stimulated by vasopressin. Amer J Physiol Renal Physiol. 2011 Nov;301(5):F1005-13.

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11 Pei Y, Obaji J, Dupuis A, et al. Unified criteria for ultrasonographic diagnosis of ADPKD. J Am Soc Nephrol 2010 20: 205-212.

[12] Ravine D, Gibson RN, Walker RG, et al. Evaluation of ultrasonographic diagnostic criteria for autosomal dominant polycystic kidney disease 1. Lancet 1994; 343:824-827.

[13] Levey AS, Stevens LA, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009; 150:604-612.

[14] International Conference on Harmonisation; Good Clinical Practice: Consolidated Guideline; Notice of Availability, 62 C.F.R. Sect. 90 (1997).

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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 IMP) to:

Quintiles
Clinical Safety and Pharmacovigilance
5927 South Miami Blvd
Morrisville, NC 27560, USA
Phone: PPD
Fax: PPD
Email: PPD

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

Global Project Leaders
Global Clinical Director/
Medical Director
(Program Lead)

PPD
PPD
Otsuka Pharmaceutical Development & Commercialization, Inc.
2440 Research Blvd.
Rockville, MD 20850, USA
Phone: PPD Fax PPD

Global Clinical Director/
Medical Director
(Project Lead)

PPD
PPD
Otsuka Pharmaceutical Development & Commercialization, Inc.
506 Carnegie Center Drive
Suite 200
Princeton, NJ 08540, USA
Phone: PPD Fax PPD

Global Clinical Management
Global Clinical Management

PPD
USA
Phone: PPD

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Appendix 2 Institutions Concerned With the Trial

Lead Principal (Communicating) Investigator/Steering Committee Chair	PPD PPD USA Phone: PPD
Independent Data Monitoring Committee Chair	PPD PPD Phone: PPD
Hepatic Adjudication Committee Chair	PPD PPD Phone: PPD Fax: PPD
Global Medical Monitoring	Quintiles 5927 South Miami Blvd Morrisville, NC 27560, USA Phone: PPD Mobile: PPD Fax: PPD
Trial Management	Quintiles 5927 South Miami Blvd Morrisville, NC 27560, USA Office: PPD Mobile: PPD Fax: PPD
Safety Reporting	Quintiles (Drug Safety Service) 5927 South Miami Blvd Morrisville, NC 27560, USA Phone: PPD Fax: PPD
Investigational Materials	Almac 25 Fretz Rd Souderton, PA 18964, USA Phone: PPD
Budget and Contract Negotiation	INC Research, LLC 3201 Beechleaf Ct., #600 Raleigh, NC 27604, USA Phone: PPD
Investigator Payments	Quintiles, Inc. Investigator Payment Administration Department 10188 Telesis Court., Suite 400 San Diego, CA 92121, USA Phone: PPD

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Electronic Data Capture	MediData Solutions 79 Fifth Avenue, 8th Floor New York, NY 10003, USA Phone: PPD Fax: PPD
IRT Systems	Almac Clinical Technologies 25 Fretz Road Souderton, PA 18964, USA US Tel: PPD RoW Tel: PPD
Central Laboratory Services	Covance Central Laboratory Services 8211 SciCor Dr. Indianapolis, IN 46214, USA Phone: PPD Toll-free: PPD Fax: PPD Covance Asia Pte. Ltd. Central Laboratory Services-Singapore 1 International Business Park, #05-13 The Synergy, Singapore 609917 Phone: PPD Covance Central Laboratory Services-Sydney 95 Epping Rd., North Ryde NSW 2113 Australia Phone: PPD Covance Central Laboratory Services-Geneva Rue Moise-Marcinhes 7 1217 Meyrin/Geneva- CH Switzerland Phone : PPD
CCI	[redacted] PPD
CCI	[redacted] Phone: PPD

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Appendix 3

[redacted]

Protocol 156-13-211

CCI

[redacted]

Protocol 156-13-211

Appendix 4

CCI

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Appendix 5 Protocol Amendments and Administrative Changes

Amendment Number: 1

Issue Date: 14 July 2014

PURPOSE:

The purpose of this amendment was to revise protocol procedures to accommodate the treatment and monitoring of subjects with ADPKD enrolling into the protocol from additional tolvaptan trials. Consequently, sample size was increased, the inclusion criteria were slightly modified, schedules for initiation of treatment and liver function testing were further defined, CCI [redacted] Down titration for metabolic drug-drug interactions was added to the synopsis and additionally it was required that medical monitor approval is needed. A table of strong and moderate CYP3A4 inhibitors was added to the text. The list of vendors and study personnel was updated. Minor linguistic changes were made for clarity and typographical errors were corrected.

BACKGROUND:

It was decided to allow subjects from additional tolvaptan trials entry into this safety trial for an increased understanding of tolvaptan's long-term safety in ADPKD patients and provide expanded access to tolvaptan for those subjects who would like to continue treatment after completing their previous trial.

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Other Revisions

Figure 3.1-1 - Trial Design Schematic

Table 3.2-1 - Trial Treatments

Table 3.4.2-1 - Inclusion Criteria

Table 3.7-1 - Schedule of Assessments

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Sectional Revisions

Location	Old Text	Updated Text
Synopsis, Trial Design	Subjects will be eligible for screening into this trial if they: • Participated in the double-blind Trial 156-13-210 (only upon successful completion of their randomized 12-month period including post-treatment follow-up,regardless of whether this was on-treatment or off-treatment),or • Participated in the open-label Trial 156-08-271. After consenting and screening, eligible subjects will be assigned a new subject number and administered tolvaptan at a split-dose of 45/15 mg. Subjects will have the opportunity for either up or down-titration to a maximum split tolvaptan dose of 90/30 mg or a minimum split dose of 15/15 mg at the discretion of the investigator according to individual tolerability. Subjects entering the trial from Trial 156-08-271 may receive up to 33 months of open-label tolvaptan therapy, and subjects entering the trial from Trial 156-13-210 may receive up to 15 to 21 months of open-label tolvaptan therapy.	Subjects will be eligible for screening into this trial if they: • **Completed and transferred from the double-blind Trial 156-13-210 (12-month period including post-treatment follow-up, regardless of whether this was on-treatment or off-treatment), or** • **Completed Trial 156-08-271 or a prior tolvaptan ADPKD trial, or** • **Interrupted or discontinued treatment in a prior tolvaptan ADPKD trial (other than Trial 156-13-210). Subjects may be enrolled with the medical monitor approval, and additional close monitoring may be required at the beginning of the trial** **For purposes of ensuring subject safety, all subjects will be monitored for hepatic safety monthly until 18 months of tolvaptan exposure has been collected.. After that, and following the approval from the medical monitor, hepatic monitoring will be required every 3 months. Until their prior treatment assignment is unblinded, all Trial 156-13-210 subjects who are eligible for this trial are scheduled to have trial visits/ hepatic monitoring monthly for the first 18 months of this trial. Once unblinding occurs, it can be determined which subjects received tolvaptan in Trial 156-13-210. These subjects may have their trial visits/hepatic**

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Location	Old Text	Updated Text
		transaminase monitoring change to every 3 months sooner as their previous tolvaptan exposure in Trial 156-13-210 can count towards the 18-month threshold. Enrollment in this trial will be closed when the final eligible subject from Trial 156-13-210 enrolls in this trial.
Synopsis, Subject Population	This trial will include up to 2,450 subjects over the age of 18 years with ADPKD diagnosed by Pei-Ravine criteria (modified by magnetic resonance imaging [MRI]). Renal function will be assessed during screening by using historical laboratory values for serum creatinine levels to calculate the estimated glomerular filtration rate (eGFR). The eGFR values will be estimated based on the Chronic Kidney Disease - Epidemiology (CKD-EPI) formula.	This trial will include **approximately 2,500** subjects over the age of 18 years with ADPKD diagnosed by Pei-Ravine criteria (modified by magnetic resonance imaging [MRI])**, and who have completed or participated in a prior tolvaptan ADPKD interventional investigational medicinal product (IMP) trial.**

Synopsis, Inclusion/Exclusion Criteria	Main inclusion criteria:
	• Male and female subjects ≥ 18 years with ADPKD who have completed either Trial 156-13-210 or Trial 156-08-271
	• Diagnosis of ADPKD by modified Pei-Ravine criteria
	• eGFR ≥ 20 mL/min/1.73m^2 within 45 days of the baseline visit. Subjects who have an eGFR between 15 and 19 mL/min/1.73m^2 may be enrolled with medical monitor approval
	
	<u>Main exclusion criteria:</u>
	• Need for chronic diuretic use
	• Hepatic impairment based on liver function assessments other than that expected for ADPKD with cystic liver disease
		Main inclusion criteria:
		• Male and female subjects ≥ 18 years with **confirmed diagnosis of ADPKD (during participation in prior tolvaptan trials) who have**
		  • **Completed and transferred from the double-blind Trial 156-13-210 (12-month period including post-treatment follow-up, regardless of whether this was on-treatment or off-treatment), or**
		  • **Completed Trial 156-08-271 or a prior ADPKD tolvaptan trial, or**
		  • **Interrupted or discontinued treatment in a prior tolvaptan ADPKD trial other than Trial 156-13-210. Subjects may be enrolled**

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Location	Old Text	Updated Text
		with the medical monitor approval, and additional close monitoring may be required at the beginning of the trial • **Estimated glomerular filtration rate (**eGFR**)** ≥ 20 mL/min/1.73m^2 within 45 days of the baseline visit. Subjects who have an eGFR between 15 and 19 mL/min/1.73m^2 may be enrolled with medical monitor approval • **Renal function will be assessed during screening by using historical laboratory values (in the last 30 days) for serum creatinine levels to calculate the eGFR. the eGFR values will be estimated based on the Chronic Kidney Disease - Epidemiology (CKD-EPI) formula** Main exclusion criteria: • Need for chronic diuretic use • Hepatic impairment based on **hepatic laboratory** assessments **(alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin, total [BT])** other than that expected for ADPKD with cystic liver disease
Synopsis, Trial Site(s)	Up to 220 sites which may include North America, South America, Russian Federation and Australia.	**Approximately** 220 **enrolling** sites **including but not limited to the following regions:** North America, South America, **Eastern Europe, Western Europe,** Russian Federation, and Australia.
Synopsis, Investigational Medicinal Product(s), Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration	Tolvaptan tablets (15 mg or 30 mg) 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). Allowed doses are 15/15 mg, 30/15 mg, 45/15 mg,	**The dose regimens to be used in this trial are 15/15 mg, 30/15 mg, 45/15 mg, 60/30 mg, and 90/30 mg.** Tolvaptan tablets (15 mg or 30 mg) will be self-administered orally as split-dose regimens, **twice daily,** once upon awakening and another

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Location	Old Text	Updated Text
	60/30 mg and 90/30 mg. All subjects will be started at a split-dose of tolvaptan 45/15 mg and titrated according to tolerability. The dose range permitted will be a maximum of 90/30 mg and a minimum of 15/15 mg.	approximately 8 to 9 hours later. Doses will be **recorded** as early dose/late dose (eg, 60/30 mg). **Subjects will receive open-label tolvaptan for the duration of the trial.** **A subject's starting dose in this trial will be dependent on the trial in which they were previously enrolled:** • **156-13-210- initiated on tolvaptan at a split-dose of 45/15 mg with upward titration every 3 to 4 days to 60/30 mg or 90/30 mg per day according to tolerability** • **156-08-271- will retain the last dose level from 271 and start at the same dose in this trial** • **Prior tolvaptan trials- initiated on tolvaptan at a split-dose of 45/15 mg with upward titration every 3 to 4 days to 60/30 mg or 90/30 mg per day according to tolerability** **Down titration to 30/15 mg or 15/15 mg daily will be allowed at the discretion of the investigator according to individual tolerability and with medical monitor notification. Further down titration to 30 or 15 mg once daily may be allowed only for metabolic drug-drug interaction and requires medical monitor approval.**
Synopsis, Trial Assessments	… Screening: Informed consent, medical history (including ADPKD updates, as required), determination of eligibility through inclusion/exclusion criteria, dietary review, vital signs, clinical laboratory assessments, complete physical examination, urine pregnancy test (women of child-bearing potential only [WOCBP]), concomitant medications and laboratory tests to determine eligibility. ...	… Screening: Informed consent, medical history (including ADPKD updates, as required), determination of eligibility through inclusion/exclusion criteria, dietary review, vital signs, clinical laboratory assessments, physical examination, urine pregnancy test (women of child-bearing potential only [WOCBP]), concomitant medications and laboratory tests to determine eligibility. ...

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Location	Old Text	Updated Text
		CCI [redacted]
Synopsis, Criteria for Evaluation	Safety: • AEs • Vital signs • Clinical laboratory assessments • Serum transaminase elevations for frequency (2x, 3x, 5x and 10x upper limit normal [ULN]), time to onset, time to peak levels, time of offset (< 3x, 2x, or 1x ULN), response to de-challenge and re-challenge and frequency of progression to Hy's laboratory criteria (alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3x ULN and bilirubin, total (BT) > 2x ULN without alkaline phosphatase ≥ 2x ULN) • Serum sodium excursions above 145, 150 or 155 mmol/L or below 135, 130 or 125 mmol/L • Interruptions of protocol specified therapies for hypernatremia or hyponatremia	Safety: • AEs • Vital signs • Clinical laboratory assessments • Serum transaminase elevations for frequency (2x, 3x, 5x and 10x ULN), time to onset, time to peak levels, time of offset (< 3x, 2x, or 1x ULN), response to de-challenge and re-challenge and frequency of progression to Hy's laboratory criteria (ALT or AST > 3x ULN and BT > 2x ULN without alkaline phosphatase ≥ 2x ULN) • Serum sodium excursions above 145, 150, or 155 mmol/L or below 135, 130, or 125 mmol/L
Synopsis, Statistical Methods	Sample size: Sample size was not determined by a formal computation to achieve a target power. No	Sample size: Sample size was not determined by a formal computation to achieve a target power. No

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Location	Old Text	Updated Text
	efficacy analyses are planned. It is expected that approximately 2,450 subjects may enroll from previous tolvaptan trials. Analysis datasets: • Enrolled Population: all subjects who were enrolled to this open-label trial. • Safety Population: all subjects in the Enrolled Population who take at least 1 dose of investigational medicinal product (IMP).	efficacy analyses are planned. It is expected that approximately **2,500** subjects may enroll from previous tolvaptan trials. Analysis datasets: • Enrolled Population: all subjects who were enrolled to this open-label trial. • Safety Population: all subjects in the Enrolled Population who take at least 1 dose of IMP.
Synopsis, Trial Duration	This trial is planned to be continued until one of the following has occurred: 1) All subjects entering from Trial 156-13-210 will be eligible for up to 15 months in Trial 156-13-211 2) After up to 15 months participation for subjects from Trial 156-13-210, and for all subjects entering from Trial 156-08-271, participation may continue until the first of: • the trial concludes (last subject from Trial 156-13-210 reaches at least 10 months participation, or 31 July 2017), or • tolvaptan is approved for use in ADPKD in their region, or • CCI [redacted]	**Trial duration is planned to continue** • **Until the last subject from Trial 156-13-210 completes 18 months of tolvaptan treatment in this trial** • **Subjects enrolling from other trials will conclude their participation once tolvaptan becomes available through routine prescription or through a** CCI [redacted] **Trial 156-13-210 subjects may opt to conclude their participation in this trial if tolvaptan becomes available before they complete 18 months of treatment in this trial**
Section 1.2, Clinical Data	N/A.	CCI [redacted]

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Location	Old Text	Updated Text
		CCI [redacted] .
Section 1.3, Known and Potential Risks and Benefits	In this extension trial, subjects enrolling from the double-blind Trial 156-13-210 will have monthly transaminase level assessments for the first 18 months while the treatment code from Trial 156-10-210 remains blinded, to ensure that all subjects have adequate safety monitoring during this period of susceptibility. Monitoring will be quarterly for these subjects following the first 18 months of known exposure to tolvaptan. Subjects enrolling from the open-label Trial 156-08-271 will have quarterly transaminase assessments conducted, since they will have already received tolvaptan for 2 years or more.	In this extension trial, subjects enrolling from the double-blind Trial 156-13-210 will have monthly **visits and** transaminase level assessments for the first 18 months while the treatment code from Trial 156-10-210 remains blinded, to ensure that all subjects have adequate safety monitoring during this period of susceptibility. **Once unblinding occurs, it can be determined which subjects received tolvaptan in Trial 156-13-210. These subjects may have their trial visits/hepatic transaminase monitoring changed to every 3 months sooner as their previous tolvaptan exposure in Trial 156-13-210 can count towards the 18-month threshold. If subjects approaching the 18-month threshold have had prior transaminase abnormalities (> 2 × upper limit of normal [ULN]), the investigator is responsible for contacting the medical monitor to confirm the change in frequency from monthly to every 3 months.** Subjects enrolling from the open-label Trial 156-08-271 will have transaminase assessments conducted **every 3 months**, since they will have already received tolvaptan for **at least 18 months**. **The current IB lists all of the tolvaptan trials. Subjects enrolling in this trial who were in a previous ADPKD trial other than Trials 156-13-210 and 156-08-271 will have monthly visits and transaminase level assessments for the first 18 months.**

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Location	Old Text	Updated Text
Section 2.1, Trial Rationale	... Over the 3 years of placebo-controlled treatment, ALT was elevated to a greater than three times the upper limit of normal (> 3 × ULN) in 4.4% of tolvaptan subjects compared with 1% of placebo subjects. To date, 3 tolvaptan subjects' transaminases and bilirubin levels reached Hy's laboratory criteria (> 3 × and > 2 × ULN, respectively). Upon discontinuation, all subjects' liver tests showed reversibility of the elevation within approximately 4 months after tolvaptan was discontinued. Nevertheless, without adequate monitoring and management, it is estimated that a 1:3,000 risk for irreversible liver injury may exist	… Over the 3 years of placebo-controlled treatment, ALT was elevated to a greater than three times the upper limit of normal (> 3 × ULN) in 4.4% of tolvaptan subjects compared with 1% of placebo subjects. To date, 3 tolvaptan subjects' transaminases and bilirubin levels reached Hy's laboratory criteria (> 3 × and > 2 × ULN, respectively). Upon discontinuation, all subjects' liver tests showed reversibility of the elevation within approximately 4 months after tolvaptan was discontinued. Nevertheless, without adequate monitoring and management, it is estimated that a 1:**4**,000 risk for irreversible liver injury may exist
Section 3.1, Type/Design of Trial	This trial is a phase 3b, multi-center, open-label trial. Subjects will be eligible for screening into this trial if they: • Participated in the double-blind Trial 156-13-210 (only upon successful completion of their randomized 12-month period including post-treatment follow-up, regardless of whether this was on-treatment or off-treatment), or • Participated in the open-label Trial 156-08-271 Upon the successful completion of Trial 156-13-210 or Trial 156-08-271, subjects will have an opportunity to enroll into Trial 156-13-211 immediately following completion of the follow-up visit(s) of the previous trial. The last follow-up visit assessments can be utilized for screening into this trial. However, for subjects who require a longer period between completion of the preceding trial and entry into this trial, this may	This trial is a phase 3b, multi-center, open-label trial. **Eligible subjects** will have an opportunity to enroll into Trial 156-13-211 immediately following completion of the follow-up visit(s) of the previous trial. The last visit assessments **from the previous protocol can be combined with the screening visit for this trial, with all required assessments from each visit only performed once, as long as the time between the last follow-up visit assessments from the previous trial and the screening visit for this trial is within 30 days.** **Medical monitor approval is needed for enrollment of subjects whose completion of the preceding trial prior to entry in this trial exceeds 3 months, and these subjects will be required to undergo all screening and baseline assessments.** **After consenting, subjects will be**

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Location	Old Text	Updated Text
	be allowed at the discretion of the medical monitor. After consenting and screening, eligible subjects will be assigned a new subject number and administered tolvaptan at a split-dose of 45/15 mg. Subjects will have the opportunity for either up or down-titration to a maximum tolvaptan split dose of 90/30 mg, or a minimum split dose of 15/15 mg at the discretion of the investigator according to individual tolerability. Subjects entering the trial from Trial 156-08-271 may receive up to 33 months of open-label tolvaptan therapy, and subjects entering the trial from Trial 156-13-210 may receive up to 15 to 21 months of open-label tolvaptan therapy. This trial is planned to continue until one of the following has occurred: 1) All subjects entering from Trial 156-13-210 will be eligible for up to 15 months in Trial 156-13-211 2) After up to 15 months participation for subjects from Trial 156-13-210, and for all subjects entering from Trial 156-08-271, participation may continue until the first of: • the trial concludes (last subject from Trial 156-13-210 reaches at least 10 months, or 31 July 2017), or • tolvaptan is approved for use in ADPKD in their region, or [redacted]	**assigned a new screening number. Subjects who are found to be eligible will retain the same subject number they had been assigned in their previous trial.. For purposes of ensuring subject safety, tolvaptan exposure of at least 18 months is required for all subjects. While Trial 156-13-210 remains blinded, subjects enrolling from any prior trial besides Trial 156-08-271 are scheduled to have monthly hepatic monitoring for the first 18 months of this trial. After that, following the approval of the medical monitor, hepatic monitoring will take place every 3 months. Subjects enrolling from Trial 156-08-271 will have hepatic monitoring every 3 months. All Trial 156-13-210 subjects who are eligible for this trial will initially be scheduled to have trial visits and hepatic monitoring monthly for the first 18 months, then every 3 months thereafter, because their tolvaptan exposure cannot be determined since Trial 156-13-210 is a double blind trial. Once unblinding occurs, it can be determined which subjects received tolvaptan in Trial 156-13-210. These subjects may have their trial visits/hepatic transaminase monitoring changed to every 3 months sooner as their previous tolvaptan exposure in Trial 156-13-210 can count towards the 18-month threshold.** **Enrollment in this trial will be closed when the last eligible subject from Trial 156-13-210 enrolls in this trial.** The **duration of this** trial is planned to continue • **Until the last subject** from Trial 156-13-210 **completes 18 months of tolvaptan treatment in this trial** • **Subjects enrolling from**

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Location	Old Text	Updated Text
		other trials will conclude their participation in this trial once tolvaptan becomes available through routine prescription or through a [redacted] **Trial 156-13-210 subjects may opt to conclude their participation in this trial if tolvaptan becomes available before they complete 18 months of treatment in this trial**
Section 3.1.1, Figure 3.1-1	See previous Figure at the end of Appendix 5.	See previous Figure at the end of Appendix 5
Section 3.2 Treatments	Following consent, and once subjects have satisfied all of the inclusion criteria and none of the exclusion criteria, subjects will be assigned a new subject number and administered tolvaptan at a split-dose of 45/15 mg. Subjects will be titrated up to 60/30 mg and 90/30 mg according to subject tolerability. Down titration to 30/15 mg and 15/15 mg is also permitted at the discretion of the medical monitor and individual subject tolerability. All subjects will be administered tolvaptan tablets in a daily split-dose, once upon awakening and another approximately 8 to 9 hours later. The exact time 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). While taking tolvaptan, all subjects should be instructed to ingest fluids in anticipation of, or at the first sign of thirst in order to avoid excessive	**The dose regimens to be used in this trial are 15/15 mg, 30/15 mg, 45/15 mg, 60/30 mg, and 90/30 mg.** Following consent, and once subjects have satisfied all of the inclusion criteria and none of the exclusion criteria, subjects will **retain their subject number assigned from their previous trial. Subjects will receive open-label tolvaptan for the duration of the trial.** All subjects will be administered tolvaptan tablets in a daily split-dose, once upon awakening and another approximately 8 to 9 hours later (twice daily dosing). The exact time 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 **recorded** as early dose/late dose (eg, 60/30 mg). **A subject's starting dose in this trial will be dependent on the trial in which they were previously enrolled:** • **156-13-210- initiated on**

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	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.	**tolvaptan at a split-dose of 45/15 mg with upward titration every 3 to 4 days to 60/30 mg or 90/30 mg per day according to tolerability** • **156-08-271- will retain the last dose level from 271 and start at the same dose in this trial** • **Prior tolvaptan trials- initiated on tolvaptan at a split-dose of 45/15 mg with upward titration every 3 to 4 days to 60/30 mg or 90/30 mg per day according to tolerability** Down titration to 30/15 mg and 15/15 mg is also permitted at the discretion of the **investigator according to subject tolerability with** medical monitor **notification**. **Further down titration to 30 or 15 mg once daily may be allowed only for metabolic drug-drug interaction and requires medical monitor approval.** **For subjects moving from the 156-13-210 trial and requiring tolvaptan titration it will be conducted in the following way: Subjects will be instructed to take tolvaptan starting at a split dose of 45/15 mg (as 3 tablets upon waking and 1 tablet approximately 8 to 9 hours later) and to titrate up every 3 to 4 days; first to 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. 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?" Subjects will continue in the trial with the regimen to which tolerability was established.** While taking tolvaptan, all subjects should be instructed to ingest fluids

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		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.
Table 3.2-1, Trial Treatments	Previous Table is at the end of Appendix 5	Updated Table with tracked changes is at the end of Appendix 5
Section 3.2.2 Dosing with CYP3A4 Moderate Inhibitors	For subjects who require dosing with a moderate inhibitor, initial tolvaptan reductions as shown below should be tried, with further dose reductions or interruption as necessary for tolerability. • 90/30 mg to 45/15 mg • 60/30 mg to 30/15 mg • 45/15 mg to 15/15 mg • 30/15 mg to 15 mg once daily • 15/15 mg to 15 mg once daily	For subjects who require dosing with a moderate inhibitor, initial tolvaptan reductions as shown below should be tried, with further dose reductions or interruption as necessary for tolerability. • 90/30 mg to 45/15 mg • 60/30 mg to 30/15 mg • 45/15 mg to 15/15 mg • 30/15 mg to 15 mg once daily • 15/15 mg to 15 mg once daily **A partial list of strong and moderate CYP3A4 inhibitors can be found in Section 4.1.**
Section 3.3, Trial Population	This trial will include up to 2,450 subjects over the age of 18 years with ADPKD diagnosed by Pei-Ravine criteria[11 12] (modified by magnetic resonance imaging [MRI]). Renal function will be assessed during screening using historical laboratory values for serum creatinine levels to calculate the estimated glomerular filtration rate (eGFR). The eGFR values will be estimated based on the Chronic Kidney Disease – Epidemiology (CKD-EPI) formula.[13]	This trial will include **approximately 2,500** subjects over the age of 18 years with ADPKD diagnosed by Pei-Ravine criteria[11 12] (modified by magnetic resonance imaging [MRI]) **who completed or participated in a prior tolvaptan trial.**
Table 3.4.2-1, Inclusion Criteria	Previous Table is at the end of Appendix 5	Updated Table with tracked changes is at the end of Appendix 5
Section 3.5.1, Safety Endpoints	Interruption of protocol-specified therapies for hypernatremia or hyponatremia	Endpoint deleted
CCI [redacted]	[redacted]	CCI [redacted]
Section 3.5.3, Exploratory Endpoints	CCI [redacted]	[redacted]

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Location	Old Text	Updated Text
	CCI [redacted]	[redacted]
Section 3.6, Measures to Minimize/Avoid Bias (old text section number was 3.5.3)	All blood and urine chemistry will be analyzed and reported by a local laboratory.	All blood and urine chemistry will be analyzed and reported by a **central** laboratory.
Section 3.7, Table 3.7-1, Schedule of Assessments	See previous table at the end of Appendix 5	See revised Table at the end of Appendix 5. The changes made include: Screening changed from -6 to -30 days Language outlining assessments based on subjects' previous trial expanded; Central rather than local laboratory will be used; CCI [redacted] Hepatitis testing wording added
Section 3.7.1.1, Screening (old text Section 3.6.1.1)	Screening (-6 days to 0 days prior to Baseline) Screening for eligibility is required for all subjects. The screening and baseline visits may be combined with the EoTx visit from the previous protocol with all required assessments from each visit only performed once. Required assessments are as follows: 1. Obtain subject consent	Screening (**-30** days to **-1** day prior to Baseline) Screening for eligibility is required for all subjects. The screening and baseline visits may be combined with the **last** visit from the previous protocol with all required assessments from each visit only performed once. **In some cases, if a subject enrolls in this trial from a prior tolvaptan trial, the end of trial visit for that trial and the**

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Location	Old Text	Updated Text
	2. Determine subject eligibility through inclusion/exclusion criteria 3. Record demographic information and prior trial identifiers (screening identification [ID], subject ID, site ID) 4. Record medical/ADPKD history using prior trial data 5. Review dietary recommendations and compliance 6. Record vital signs (post-void weight and seated heart rate) and in-clinic calibrated blood pressure (BP) measurement. Record height 7. Collect blood for serum chemistry, liver function panel (ALT, AST, bilirubin, total (BT), bilirubin (direct), and alkaline phosphatase), serum sodium, creatinine and hematology and coagulation. Hepatitis testing is optional 8. Collect urine for urinalysis, urine osmolality (optional), and urine specific gravity 9. Perform urine pregnancy test on women of childbearing potential (WOCBP). If positive, a follow-up serum test will be performed 10. Conduct full physical examination 11. Enter subject into interactive response technology (IRT) including prior trial identifier/information	**screening visit for this one may occur simultaneously.** Required assessments are as follows: 1. Obtain subject consent. 2. Determine subject eligibility through inclusion/exclusion criteria. 3. Record demographic information and prior trial identifiers (screening identification [ID], subject ID, site ID)**, prior tolvaptan ADPKD trial protocol number).** 4. Record medical/ADPKD history using prior trial data. 5. Review dietary recommendations and compliance. 6. Record vital signs (post-void weight and seated heart rate) and in-clinic calibrated blood pressure (BP) measurement. Record height. 7. Collect blood for serum chemistry, liver function panel (ALT, AST, bilirubin, total [BT], bilirubin [direct], and alkaline phosphatase), serum sodium, creatinine, and hematology and coagulation. Hepatitis testing is optional. **If hepatitis testing is performed, then both pre- and post-counseling activities relating to hepatitis testing are to be carried out based on local**

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	(protocol number, subject ID), confirmed dose regimen and scheduled date of next visit 12. Assess AEs reported as ongoing or resolved from prior trial to determine entry as medical history or ongoing event for this trial	**requirements and best practices.** 8. Collect urine for urinalysis, urine osmolality (optional), and urine specific gravity. 9. Perform urine pregnancy test on women of childbearing potential (WOCBP). If positive, a follow-up serum test will be performed. 10. Conduct full physical examination. 11. Enter subject into interactive response technology (IRT) including prior trial identifier/information (protocol number, subject ID), confirmed dose regimen, and scheduled date of next visit. 12. Assess AEs reported as ongoing or resolved from prior trial to determine entry as medical history or ongoing event for this trial. 13. **Record ongoing concomitant medications. (This may be done if the screening visit occurs simultaneously with the last visit from a previous tolvaptan trial).**
Section 3.7.1.2, Baseline (old text Section 3.6.1.2)	The baseline visit is the beginning of the treatment period in this trial. At the baseline visit, subjects will be assigned a new subject number and the following assessments and procedures will be performed: 1. Review inclusion/exclusion	The baseline visit is the beginning of the treatment period in this trial. At the baseline visit, subjects will **retain the** subject number **assigned in the previous tolvaptan trial,** and the following assessments and procedures will be performed:

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Location	Old Text	Updated Text
	criteria 2. Review dietary recommendations and compliance 3. CCI [redacted] 4. Record vital signs (post-void weight, seated heart rate, and calibrated blood pressure measurement) 5. Dispense at-home urine pregnancy test kits to WOCBP to be used if a menstrual period is missed before the next visit 6. An optional directed physical examination may be performed to focus on PKD-related signs and symptoms 7. Assess tolerability/dosing review of IMP 8. Enroll subject into trial through IRT and obtain IMP 9. Dispense IMP (sufficient for 1 month of dosing) 10. Provide subject with dosing instructions to begin on the following day 11. Record ongoing concomitant medications 12. Assess AEs .	1. Review inclusion/exclusion criteria. 2. Review dietary recommendations and compliance. 3. CCI [redacted] 4. Record vital signs (post-void weight, seated heart rate, and calibrated blood pressure measurement). 5. Dispense at-home urine pregnancy test kits to WOCBP to be used if a menstrual period is missed before the next visit. 6. An optional directed physical examination may be performed to focus on PKD-related signs and symptoms. 7. Assess tolerability/dosing review of IMP. 8. Enroll subject into trial through IRT and obtain IMP. 9. Dispense IMP (sufficient for 1 month **or 3 months** of dosing **based on subject's required visit schedule for hepatic evaluation as either monthly or every 3 months**). 10. Provide subject with dosing instructions to begin on the following day. 11. Record ongoing concomitant medications. 12. Assess AEs.
Section 3.7.1.3, Monthly Visit (old text Section 3.6.1.3)	Monthly Visit (± 4 days) Subjects will return for a monthly	Monthly Visit (± **7** days) **The following s**ubjects will return

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	visit to assess safety and tolerability of IMP and to monitor liver function. Subjects enrolling from the double-blind Trial 156-13-210 will have monthly ALT level assessments for the first 18 months while treatment code from Trial 156-13-210 remains blinded, to ensure that they have adequate safety monitoring during this period of susceptibility. The following will be assessed: 1. Collect blood for sodium and creatinine 2. Collect blood for ALT (for the first 18 months of tolvaptan treatment in subjects enrolling from Trial 156-13-210). If at any time within the first 18 months of tolvaptan treatment the ALT elevates to > 1x ULN to < 3x ULN, ALT will be monitored monthly for an additional 6 months beyond the date of elevation, to ensure that the level is stable and does not exceed this threshold. If at any time the ALT elevates ≥ 3x ULN, a full liver function panel is required (ALT, AST, BT and alkaline phosphatase) within 72 hours of the site being aware of this result. CCI [redacted] 3. An optional directed physical examination may be performed to focus on PKD-	for a monthly visit to assess safety and tolerability of IMP and to monitor liver function. • Subjects enrolling from the double-blind Trial 156-13-210 will have monthly **trial visits**/ALT level assessments for the first 18 months while treatment code from Trial 156-13-210 remains blinded, to ensure that they have adequate safety monitoring during this period of susceptibility. **Once unblinding occurs, it can be determined which subjects received tolvaptan in Trial 156-13-210. These subjects may have their trial visits/hepatic transaminase monitoring change to every 3 months sooner as their previous tolvaptan exposure in Trial 156-13-210 can count towards the 18-month threshold. The investigator will need to discuss the change in frequency with the medical monitor before instituting the change.** • **Subjects from prior tolvaptan trials other than Trial 156-08-271 will have monthly trial visits/ALT level assessments for the first 18 months. After that, the trial visits/ALT monitoring will be conducted every 3 months after the change in**

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	related signs and symptoms 4. Assess tolerability/dosing review of IMP 5. Enter subject status in IRT, including any dose-regimen changes and obtain IMP assignment 6. Collect and reconcile returned IMP 7. Dispense IMP 8. Update concomitant medications 9. Assess AEs	**frequency is confirmed with the medical monitor** • **Subjects enrolling from the open-label Trial 156-08-271 who have greater than 18 months of cumulative exposure to tolvaptan will have trial visits/ALT monitoring conducted every 3 months.** The following **assessments** will be **completed**: **1. Review dietary recommendations and compliance.** **2.** CCI [redacted] **3. Record vital signs (post-void weight, seated heart rate, and calibrated blood pressure measurement).** 4. Collect blood **for central laboratory assessments** for **serum** sodium, **serum** creatinine, **and ALT (see Section 3.7.2.4).** 5. CCI [redacted]

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		7. Urinalysis, urine osmolality (optional), urine specific gravity. **8. Perform urine pregnancy test on WOCBP (every 3 months). If positive, a follow-up serum test will be performed.** **9. Dispense at-home urine pregnancy test kits to WOCBP, as required** 10. An optional directed physical examination may be performed to focus on PKD-related signs and symptoms. 11. Assess tolerability/dosing review of IMP. 12. Enter subject status in IRT, including any dose-regimen changes and obtain IMP assignment. 13. Collect and reconcile returned IMP**, assess compliance.** 14. Dispense IMP **based on subject's required visit schedule and provide.subject with dosing instructions.** 15. Update concomitant medications. 16. Assess AEs.
Section 3.7.1.4, Every 3 Months	Every 3 Months (±4 days) 1. Review dietary recommendations and compliance 2. CCI [redacted] 3. Record vital signs (post-void weight, seated heart rate, and	Every 3 Months (±**14** days) 1. Review dietary recommendations and compliance. 2. CCI [redacted]. 3. Record vital signs (post-void weight, seated heart

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Location	Old Text	Updated Text
	calibrated blood pressure measurement) 4. Collect blood for local standard of care laboratory assessments 5. Urinalysis, urine osmolality (optional), urine specific gravity 6. Perform urine pregnancy test on WOCBP. If positive, a follow-up serum test will be performed 7. Dispense at-home urine pregnancy test kits to WOCBP, as required 8. Collect blood for ALT. If at any time the ALT elevates to > 1x ULN to < 3x ULN, ALT will be monitored monthly for an additional 6 months beyond the date of elevation, to ensure that the level is stable and does not exceed this threshold. If at any time the ALT elevates ≥ 3x ULN, a full liver function panel is required (ALT, AST, BT and alkaline phosphatase) within 72 hours of the site being aware of this result. CCI [redacted] 9. Update concomitant medications 10. Assess AEs	rate, and calibrated blood pressure measurement). 4. Collect blood for **central** laboratory assessments **serum sodium, serum creatinine, ALT (see Section 3.7.2.4).** 5. CCI [redacted] 6. Urinalysis, urine osmolality (optional), urine specific gravity. 7. Perform urine pregnancy test on WOCBP. If positive, a follow-up serum test will be performed. 8. Dispense at-home urine pregnancy test kits to WOCBP, as required. 9. CCI [redacted] **10. An optional directed physical examination may be performed to focus on PKD-related signs and symptoms.** **11. Assess tolerability/dosing review of IMP.** **12. Enter subject status in IRT, including any dose-regimen changes and obtain IMP assignment.** **13. Collect and reconcile returned IMP; assess**

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Location	Old Text	Updated Text
		compliance. **14. Enter subject status in IRT, including any dose-regimen changes.** **15. Dispense IMP based on subject's visit schedule and provide subject with dosing instructions.** 16. Update concomitant medications. 17. Assess AEs.
Section 3.7.1.5, Early Termination/End of Treatment (old text Section 3.6.1.5)	Early Termination/End of Treatment (+ 3 months) At the early termination/end of treatment visit the following will be assessed: 1. Review dietary recommendations and compliance 2. CCI [redacted] 3. Record vital signs (post-void weight, seated heart rate, and calibrated blood pressure measurement) 4. Collect blood for serum chemistry, creatinine, serum sodium and hematology and coagulation 5. Collect blood for ALT. If the ALT elevates ≥ 3x ULN, a full liver function panel is required (ALT, AST, BT and alkaline phosphatase) within 72 hours of the site being aware of this result. CCI [redacted]	Early Termination/End of Treatment **(+ 7 days)** At the early termination/end of treatment visit the following will be assessed: 1. Review dietary recommendations and compliance. 2. CCI [redacted]. 3. Record vital signs (post-void weight, seated heart rate, and calibrated blood pressure measurement). 4. Collect blood for serum chemistry, **serum** creatinine, **ALT,** serum sodium and hematology and coagulation. 5. CCI [redacted]

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Location	Old Text	Updated Text
	CCI [redacted] 6. Collect urine for urinalysis, urine osmolality (optional), urine specific gravity 7. Perform urine pregnancy test on WOCBP. If positive, a follow-up serum test will be performed 8. An optional directed physical examination may be performed to focus on PKD-related signs and symptoms 9. Assess tolerability/dosing review of IMP 10. Enter subject status in IRT, including any dose-regimen changes since the previous entry 11. Collect and reconcile returned IMP 12. Update concomitant medications 13. Assess AEs	7. Collect urine for urinalysis, urine osmolality (optional), urine specific gravity. 8. Perform urine pregnancy test on WOCBP. If positive, a follow-up serum test will be performed. 9. An optional directed physical examination may be performed to focus on PKD-related signs and symptoms. 10. Assess tolerability/dosing review of IMP. 11. Enter subject status in IRT, including any dose-regimen changes since the previous entry. 12. Collect and reconcile returned IMP**; assess compliance.** 13. Update concomitant medications. 14. Assess AEs.
Section 3.7.1.6, Follow-up Visit	Follow-up Visit 7 Days (+ 7 days)	**7-day** Follow-up Visit (+ 7 days)
Section 3.7.1.6, Follow-up Visit (old text Section 3.6.1.6)	1. Record vital signs (post-void weight, seated heart rate, and calibrated blood pressure measurement) 2. Collect blood for creatinine 3. Collect blood for ALT. If the ALT elevates ≥ 3x ULN, a full liver function panel is required (ALT, AST, BT and alkaline phosphatase) within 72 hours of the site being aware of this result. CCI [redacted]	1. Record vital signs (post-void weight, seated heart rate, and calibrated blood pressure measurement). 2. Collect blood for **serum** creatinine **and ALT.** 3. CCI [redacted] 4. Perform urine pregnancy

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Location	Old Text	Updated Text
	CCI [redacted] 4. Perform urine pregnancy test on WOCBP. If positive, a follow-up serum test will be performed 5. Update concomitant medications 6. Assess AEs	test on WOCBP. If positive, a follow-up serum test will be performed. **5. Enter subject status in IRT.** 6. Update concomitant medications. 7. Assess AEs.
Section 3.7.2.2, Clinical Laboratory Assessments (old text Section 3.6.2.2)	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 in order to reduce variability in the samples over time. While serum creatinine is being collected primarily for safety reporting purposes, it is a key measure in the management of patients with ADPKD CCI [redacted] Therefore, great care should be taken in ensuring these measurements are collected and analyzed in as uniform a manner as possible (preferably using isotope dilution mass spectroscopy (IDMS)-traceable methodologies). Clinical laboratory samples will be collected at the following time points: <u>Screening:</u> Hematology and coagulation panel, serum chemistry panel, liver function panel (AST, ALT, alkaline phosphatase, bilirubin direct [BT]) serum sodium, urinalysis panel, urine osmolality (optional), urine specific gravity, urine	**Central laboratory non-fasting serum laboratory tests will be performed.** 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 in order to reduce variability in the samples over time. While serum creatinine is being collected primarily for safety reporting purposes, it is a key measure in the management of patients with ADPKD CCI [redacted] **The eGFR values will be calculated by CKD-EPI from the central-laboratory serum creatinine concentrations taken during every trial visit.** Clinical laboratory samples will be collected **and sent to the central laboratory** at the following time points:

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	pregnancy test (WOCBP) and hepatitis (optional). Monthly visits (± 4 days): ALT (for the first 18 months in subjects enrolled from Trial 156-13-210), and serum sodium, creatinine (all subjects). Every 3 months: (± 4 days): ALT (after 18 months of treatment in subjects enrolled from Trial 156-13-210 and for all subjects enrolled from Trial 156-08-271), standard of care laboratory assessments, urinalysis panel, urine pregnancy test (WOCBP), urine osmolality (optional), and urine specific gravity. Early Termination/End of Treatment (+ 3 months): Serum chemistry panel, hematology and coagulation panel, ALT, creatinine, serum sodium, urinalysis panel, urine pregnancy test (WOCBP), urine osmolality (optional), and urine specific gravity. Follow-up visit (+ 7 days): ALT, creatinine, and urine pregnancy test (WOCBP). … 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).	Screening: Hematology and coagulation panel, serum chemistry panel, liver function panel (AST, ALT, alkaline phosphatase, bilirubin direct [BT]) serum sodium, **serum creatinine,** urinalysis panel, urine osmolality (optional), urine specific gravity, urine pregnancy test (WOCBP) and hepatitis (optional). Monthly visits (± 7 days): ALT (for the first 18 months **for** subjects enrolled f**rom other tolvaptan ADPKD trials and** Trial 156-13-210 **while trial remains blinded**), serum sodium, **and serum** creatinine (all subjects), **urinalysis, urine osmolality (optional), urine specific gravity, and urine pregnancy test (every 3 months in WOCBP).** CCI [redacted] Every 3 months: (± **1**4 days): ALT (after 18 months of treatment **for** subjects enrolled from **other ADPKD tolvaptan trials, or from** Trial 156-13-210 **after the trial is unblinded,** and for subjects enrolled from Trial 156-08-271**), serum sodium and serum creatinine,** urinalysis panel, urine pregnancy test (WOCBP), urine osmolality (optional), and urine specific gravity. CCI [redacted] Early Termination/End of Treatment (+ **7 days**): Serum chemistry panel, hematology and coagulation panel, ALT, **serum sodium and serum** creatinine, CCI [redacted] urinalysis panel, urine pregnancy test (WOCBP), urine osmolality (optional), and urine specific gravity. **7-day**Follow-up visit (+ 7 days): ALT, **serum** creatinine, and urine pregnancy test (WOCBP). …

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Location	Old Text	Updated Text
		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. **Blood testing for hepatitis will be optional for all subjects.** Urine pregnancy testing will be performed with commercially available, high-sensitivity kits supplied to the subject by the site (acquired by the sponsor).
Table 3.7.2.2-, Clinical Laboratory Assessments	Please see original table at the end of Appendix 5,	Please see revised table at the end of Appendix 5,
Section 3.7.2.3, Physical Examination and Vital Signs (old text, Section 3.6.2.3)	A full physical examination will be performed and documented at the screening visit although this may be combined with the EoTx visit from the previous trial. At other visits, an optional 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. ...	A full physical examination will be performed and documented at the screening visit although this may be combined with the **last** visit from the previous trial. At other visits, an optional 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. **Height will be measured only at screening.** 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. ...
Section 3.7.2.4, Assessment of Liver Symptoms, Signs or Test Abnormalities (old text, Section 3.6.2.4)	Testing for hepatic transaminase (ALT/AST), alkaline phosphatase, bilirubin direct, and BT will be performed during screening. Subjects enrolling from the double-blind Trial 156-13-210 will have monthly ALT assessments for the first 18 months while the treatment code from Trial 156-13-210 remains blinded to ensure	Testing for hepatic transaminase (ALT/AST), alkaline phosphatase, bilirubin direct, and BT will be performed during screening. Subjects enrolling from the double-blind Trial 156-13-210 will have monthly ALT assessments for the first 18 months while the treatment code from Trial 156-13-210 remains

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	that all subjects have adequate safety monitoring during this period of susceptibility. Following the first 18 months, ALT assessments will be made quarterly for these subjects. Subjects enrolling from the open-label Trial 156-08-271 will have quarterly ALT assessments since they will have already received tolvaptan for 2 years or more. Management of liver abnormalities is discussed in the paragraphs below.	blinded to ensure that all subjects have adequate safety monitoring during this period of susceptibility. **Once unblinding occurs, it can be determined which subjects received tolvaptan in Trial 156-13-210. These subjects may have their trial visits/hepatic transaminase monitoring changed to every 3 months sooner as their previous tolvaptan exposure in Trial 156-13-210 can count towards the 18-month threshold.** Following the first 18 months, ALT assessments will be made **every 3 months** for **Trial 156-13-210 subjects and for subjects from other tolvaptan ADPKD trials besides Trial 156-08-271** . Subjects enrolling from the open-label Trial 156-08-271 **who have tolvaptan exposure greater than 18 months will continue with ALT monitoring every 3 months.** **Subjects enrolling from prior tolvaptan trials besides Trial 156-08-271 will have monthly ALT assessments for the first 18 months. Upon reaching 18 months of exposure and after confirmation from the medical monitor, the frequency of ALT monitoring for these subjects will occur every 3 months.** **ALT will also be assessed at the Early Termination/End of Treatment visit and at the 7-day Follow-up visit.** Management of liver abnormalities is discussed in the paragraphs below.
Section 3.7.2.4.1, Liver Test Abnormalities and Interruption/ Discontinuation of Investigational Medicinal Product (old text Section 3.6.2.4.1)	The appearance of any suspicious symptom or sign should trigger prompt testing of hepatic function (ie, within 72 hours). Liver transaminase or bilirubin levels ≥ 2 × ULN should prompt immediate retesting within	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.**

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	72 hours and tolvaptan should be temporarily interrupted. Tolvaptan should not be resumed until monitoring indicates abnormalities have resolved, are stable or are not increasing, and then only with an increased frequency of monitoring. Subjects would not typically be allowed to resume treatment with tolvaptan if they have: • transaminase levels rise above 8 × ULN, • transaminase levels are > 5 × ULN for more than 2 weeks, or • concurrent elevations of transaminase > 3 × ULN and BT > 2 × ULN.	**Any transaminase or bilirubin values which exceed 2 × 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, or every three months as indicated by the results.** **Liver transaminase or bilirubin levels reaching or exceeding 2 × ULN that have an uncertain or rapidly increasing trajectory should prompt at least temporary IMP interruption.** Tolvaptan 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 tolvaptan if they have: • transaminase levels rise above 8 × ULN, • transaminase levels are > 5 × ULN for more than 2 weeks, or • concurrent elevations of transaminase > 3 × ULN and BT > 2 × ULN.
CCI [redacted]	[redacted]	CCI [redacted]

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		CCI [redacted]
Section 3.7.5, Treatment Interruption and Discontinuation	N/A	In this trial, it is expected that subjects may possibly have one or more planned or unplanned treatment interruptions. If a subject's IMP treatment must be interrupted for medical or surgical reasons, liver test abnormalities, use of a prohibited 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 investigator should be notified as soon as possible and the reason for treatment interruption must be documented in the source documents and CRF. If permissible, the subject's IMP may be resumed following approval by the medical monitor. If IMP treatment is permanently discontinued, the reason for discontinuation must be recorded appropriately in the source document and in the CRF. A subject who permanently discontinues IMP treatment may have the option to end trial participation (complete the early termination visit) or to continue participation off IMP and complete ongoing trial assessments as per protocol or with a modified (ie, less frequent) schedule as outlined in Section 3.8.3.
Section 3.8.1	3.7.1 Entire Trial or Treatment Arm(s)	3.8.1 Entire Trial

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Section 3.8.3, Individual Subject	... All subjects have the right to withdraw at any time during treatment without prejudice. The investigator can discontinue a subject's participation in the trial at any time if medically necessary. In addition, subjects meeting the following criteria must be withdrawn from the trial: a) Occurrence of any AE, intercurrent illness, or abnormality in a laboratory assessment which, in the opinion of the investigator, warrants the subject's permanent withdrawal from the trial; b) Treatment with a prohibited concomitant medication other than the use of appropriate medications for the treatment of AEs under direction of the investigator; c) Subject noncompliance, defined as refusal or inability to adhere to the trial schedule or procedures (see Section 3.12); d) At the request of the subject, investigator, sponsor, or regulatory authority; e) Subject becomes pregnant; or f) Subject is lost to follow-up. The investigator will notify the sponsor promptly when a subject is withdrawn.	... All subjects have the right to withdraw at any time during treatment without prejudice. The investigator can discontinue a subject's participation in the trial at any time if medically necessary. **It is preferred that subjects who permanently discontinue IMP will have the option to continue participation off IMP with regular scheduled visits or with a modified (ie, less frequent) schedule. If subjects are unable or unwilling to complete the visits and procedures off IMP, the early termination/EoTx visit should be completed. The investigator may continue to contact those who discontinue IMP through to the final completion date of the trial or thereafter if needed to determine outcomes ie, vital status.** In addition, subjects meeting the following criteria must be withdrawn from the trial: a) Occurrence of any AE, intercurrent illness, or abnormality in a laboratory assessment which, in the opinion of the investigator, warrants the subject's permanent withdrawal from the trial; **b**) Subject noncompliance, defined as refusal or inability to adhere to the trial schedule or procedures (see Section 3.11); **c**) At the request of the subject, investigator, sponsor, or regulatory authority; **d**) Subject is lost to follow-up. The investigator will notify the sponsor promptly when a subject is withdrawn.
Section 3.12, Subject Compliance	Subject compliance will be monitored by pill counts as IMP is returned. Any subject who, without the instruction of the investigator, discontinues tolvaptan investigational	Subject compliance will be monitored by pill counts as IMP is returned. Any subject who, without the instruction of the investigator, discontinues tolvaptan

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	product without the instruction of the investigator, discontinues tolvaptan for 30 consecutive days or misses > 30% of the doses intended for a period between visits (whichever is greater) will be deemed noncompliant. ...	investigational product, discontinues tolvaptan for 30 consecutive days or misses > 30% of the doses intended for a period between visits (whichever is greater) will be deemed noncompliant. ...
Section 3.13, Protocol Deviations	This trial is to be conducted as described in this protocol. In the event of a significant deviation from the protocol due to an emergency, accident or mistake, the investigator or designee must contact the sponsor at the earliest possible time. This will allow an early joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator and the sponsor, and reviewed by the monitor.	This trial is to be conducted as described in this protocol. In the event of a significant deviation from the protocol due to an emergency, accident or mistake **(eg, violation of informed consent process, IMP dispensing or subject dosing error, subject enrolled in violation of eligibility criteria or concomitant medication criteria)**, the investigator or designee must contact the sponsor at the earliest possible time. This will allow an early joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator and the sponsor, and reviewed by the **site** monitor.
Section 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 therapies, tolvaptan, and other vasopressin antagonists, (eg, OPC-31260 (mozavaptan), Vaprisol (conivaptan), 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 tolvaptan metabolism (see Section 3.2.1 and Section 3.2.2). ... 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	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 therapies, vasopressin antagonists **other than tolvaptan**, (eg, OPC-31260 (mozavaptan), Vaprisol (conivaptan), 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 tolvaptan metabolism (see Section 3.2.1 and Section 3.2.2). **A partial list of strong and moderate CYP3A4 inhibitors can be found in Table 4.1-1 below:**

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	consideration when considering changes in their prescribed or over-the-counter medications. A list would include: cimetidine, non-steroidal anti-inflammatory drugs like aspirin or ibuprofen, chemotherapy drugs, cephalosporin, the combination of elvitegravir, cobicistat, emtricitabine, and tenofovir (Stribild™), dolutegravir, dronedarone, ranolazine, metformin, and trimethoprim.	... 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 list would include: non-steroidal anti-inflammatory drugs like aspirin or ibuprofen, chemotherapy drugs, cephalosporin, the combination of elvitegravir, cobicistat, emtricitabine, and tenofovir (Stribild™), dolutegravir, dronedarone, ranolazine, metformin, and trimethoprim.
Table 4.1-1	N/A	Please see end of Appendix 5 for this new table.
Section 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, dietary salt < 5g/day, dietary cooked meat protein < 1 g/kg/day and a limit on caffeinated drinks/foods should also be given (no more than 2 coffee equivalents per day).	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, dietary salt < 5g/day, dietary cooked meat protein < 1 g/kg/day and a limit on caffeinated drinks/foods should also be given (no more than 2 coffee equivalents per day). **A history of alcohol and smoking intake will be collected at screening. Alcohol and tobacco consumption should be avoided or minimized as much as possible.**
Section 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.	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. **Medical follow up is expected for AEs which lead to discontinuation which are serious, or which are of**

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		special interest (eg, liver abnormalities, skin neoplasms, glaucoma).
Section 5.5, Follow-up of Adverse Events	For this trial, AEs will be followed up for 21 days after the last dose of tolvaptan 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 tolvaptan but have not withdrawn from the trial, vital status, AEs, concomitant medications, and scheduled laboratory data (including serum creatinine data) are planned to be collected regardless of tolvaptan discontinuation until the scheduled end of the trial.	For this trial, AEs will be followed up for 7 days after the last dose of tolvaptan 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.
CCI [redacted]	[redacted]	CCI [redacted]
Section 7.1, Sample Size	Sample size was not determined by a formal computation to achieve a target power. No efficacy analyses are planned. It is expected that approximately 2,450 subjects may enroll from previous tolvaptan trials.	Sample size was not determined by a formal computation to achieve a target power. No efficacy analyses are planned. It is expected that approximately **2,500** subjects may enroll from previous tolvaptan trials.
Appendix 1, Name of Sponsor Personnel	PPD PPD PPD PPD PPD USA Phone: PPD	PPD PPD PPD PPD PPD USA Phone: PPD
Appendix 2, Institutions Concerned With the Trial	Traveling Coordinator Assistant Princeton Medical 349 Route 206 south Hillsborough, NJ 0884, USA Phone: PPD Fax: PPD	Traveling Coordinator Assistant row deleted; Central Laboratory Services Covance Central Laboratory Services

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	Central Laboratory Service Covance Central Laboratory Services 8211 SciCor Dr. Indianapolis, IN 46214, USA Phone: PPD Toll-free: PPD Fax: PPD	8211 SciCor Dr. Indianapolis, IN 46214, USA Phone: PPD Toll-free: PPD Fax: PPD **Covance Asia Pte. Ltd.** **Central Laboratory Services-Singapore** **1 International Business Park, #05-13** **The Synergy, Singapore 609917** **Phone:** PPD **Covance Central Laboratory Services-Sydney** **95 Epping Rd., North Ryde** **NSW 2113 Australia** **Phone:** PPD **Covance Central Laboratory Services-Geneva** **Rue Moise-Marcinhes 7** **1217 Meyrin/Geneva- CH** **Switzerland** **Phone :** PPD CCI [redacted] **Phone:** PPD
CCI [redacted]	[redacted]	[redacted]

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		CCI [redacted]
Appendix 5, Protocol Amendment	N/A	

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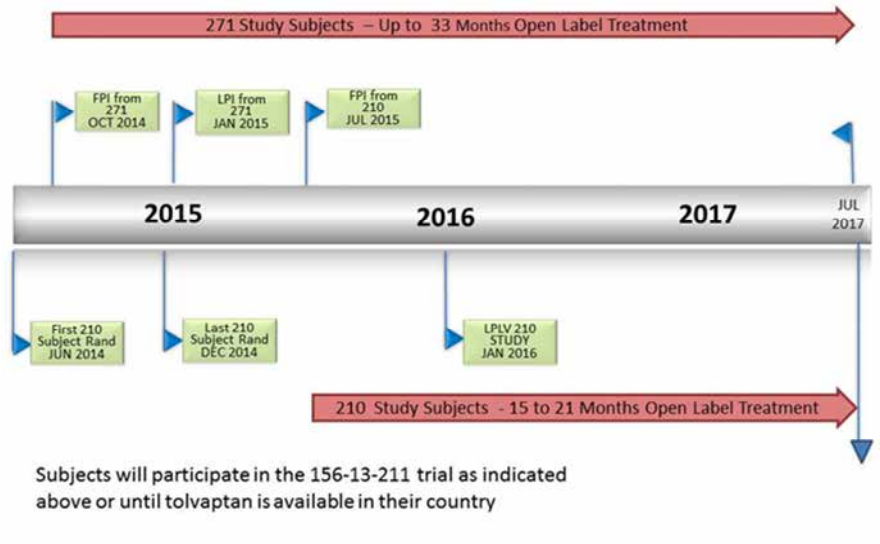
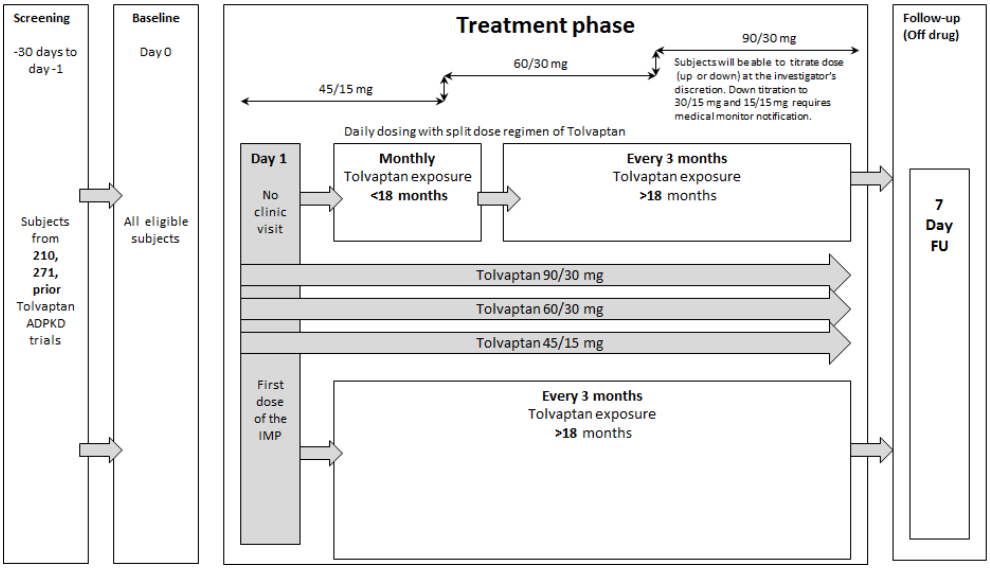
Previous Figure 3.1-1 - Trial Design Schematic:



Revised Figure 3.1-1 - Trial Design Schematic:



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Previous Table 3.2-1 - Trial Treatments:

Table 3.2-1 Trial Treatments		
Trial Day	**Time**	**Dose**
Day 1 to last on-treatment visit	8:00 am	1 to 6 tolvaptan tablets (15 mg or 30 mg each)
	4:00 to 5:00 pm	1 to 2 tolvaptan tablets (15 mg or 30 mg each) Allowed doses are 45/15 mg, 60/30 mg, 90/30 mg. Down titration to 30/15 mg and 15/15 mg will be allowed after discussion with the medical monitor.

Revised Table 3.2-1 - Trial Treatments:

Table 3.2-1 Trial Treatments		
Trial Day	**Time**	**Dose**
Day 1 to last on-treatment visit	8:00 am	1 to 6 tolvaptan tablets (15 mg or 30 mg each)
	4:00 to 5:00 pm	1 to 2 tolvaptan tablets (15 mg or 30 mg each) Allowed doses are 45/15 mg, 60/30 mg, 90/30 mg. Down titration to 30/15 mg and 15/15 mg will be allowed after discussion with the medical monitor. **Further down titration to 30 or 15 mg once daily may be allowed only for metabolic drug-drug interaction and requires medical monitor approval.**

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Previous Table 3.4.2-1 – Inclusion Criteria:

Table 3.4.2-1 Inclusion Criteria	
1.	Male and female subjects aged ≥ 18 years with ADPKD who have completed either trial 156-13-210 or trial 156-08-271
2.	Diagnosis of ADPKD by modified Pei-Ravine criteria: • With family history: several cysts per kidney (3 if by sonography, 5 if by computed tomography or MRI). • 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. • Distribution and number of cysts consistent with the observed level of renal function deficit.
3.	Estimated glomerular filtration rate ≥ 20 mL/min/1.73 m^2 (calculated using the CKD-EPI formula) within 45 days prior to the baseline visit. Subjects who have an eGFR between 15 and 19 mL/min/1.73 m^2 may be permitted with documented medical monitor approval prior to enrollment.

Revised Table 3.4.2-1 – Inclusion Criteria:

Table 3.4.2-1 Inclusion Criteria	
1.	Male and female subjects aged ≥ 18 years with **confirmed diagnosis of ADPKD (during participation in prior tolvaptan trials) who have** • **Completed and transferred from the double-blind Trial 156-13-210 (12-month period including post-treatment follow-up, regardless of whether this was on-treatment or off-treatment), or** • **Completed Trial 156-08-271 or a prior tolvaptan trial, or** • **Interrupted or discontinued treatment in a tolvaptan trial other than Trial 156-13-210. Subjects may be enrolled with the medical monitor approval, and additional close monitoring may be required at the beginning of the trial** • **Renal function will be assessed during screening using historical laboratory values (in the last 30 days) for serum creatinine levels to calculate the estimated glomerular filtration rate (eGFR). The eGFR values will be estimated based on the Chronic Kidney Disease - Epidemiology (CKD-EPI) formula. (Levey AS et al. Ann Intern Med. 2009; 150:604–612)**
2.	Estimated glomerular filtration rate ≥ 20 mL/min/1.73 m^2 (calculated using the CKD-EPI formula) within 45 days prior to the baseline visit. Subjects who have an eGFR between 15 and 19 mL/min/1.73 m^2 may be permitted with documented medical monitor approval prior to enrollment.

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Previous Table 3.6-1 – Schedule of Assessments

Table 3.6-1 Schedule of Assessments

	Screening (-6 to 0 days prior to Baseline)[a]	Baseline/ Day 0	Monthly (± 4 days)	Every 3 months (± 4 days)	Early Termination/End of Trial Visit (+ 3 months)	Titration Contact (phone contact)	Follow-up 7 days post-treatment (+ 7 days)
Informed consent	X						
Inclusion/Exclusion	X	X					
Demographics, Medical/ADPKD history[b]	X						
Dietary review	X	X		X	X		
CCI [redacted]		[redacted]		[redacted]	[redacted]		
Vital signs[c]	X	X		X	X		X
Chemistry Blood Samples[d]							
Serum Chemistry Panel	X			X[e]	X		
Liver Function tests	X[f]		X[f]	X[f]	X[f]		X[f]
Sodium	X		X		X		
Creatinine	X		X		X		X
Hematology and coagulation	X				X		
Urinalysis	X			X	X		
Urine osmolality[g]	X			X	X		
Urine specific gravity	X			X	X		
Urine pregnancy test (WOCBP only)[h]	X			X	X		X
Urine at-home pregnancy test kits dispensed[i]		X		X			
Physical examination [j]	X	X	X		X		
Tolerability/Dosing Review		X	X		X	X	
Interactive Response Technology Entry	X	X	X		X	X[k]	
Drug dispensation		X	X			X[k]	
Drug reconciliation			X		X	X[k]	
Adverse events	X[l]	←----------	----------	----------	----------	----------	----------→
Concomitant medications[m]		←----------	----------	----------	----------	----------	----------→

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[a]The screening and baseline visits may be combined with the end of treatment (EoTx) visit from the previous protocol with all required assessments from each visit only performed once.
[b]Includes prior trial identifiers (screening identification [ID], subject ID, site ID).
[c]Vital signs at each visit include seated heart rate, calibrated blood pressure and post void body weight. Height should be performed only at screening and ET/EoTx visits.
[d]Local non fasting serum laboratory tests will be performed:

- Full chemistry panel including serum sodium, and serum creatinine at baseline and early termination/end of treatment (ET/EoTx)
- Hepatitis testing at screening will be optional.
- Upon request, if clinically indicated and approved by the medical monitor, subjects may have the following evaluations in addition to the protocol-specified chemistry panel: serum calcium, phosphorous, parathyroid hormone, vitamin D, and bicarbonate levels.

[e]Local Standard of Care laboratory assessments will be performed every 3 months per subject's individual clinical management needs.
[f]Liver function tests will be conducted as follows:

- At baseline, a full liver function panel will be assessed (ALT, AST, bilirubin total and direct, alkaline phosphatase)
- For subjects enrolling from the double-blind Trial 156-13-210. ALT levels will be assessed monthly for the first 18 months, quarterly (every 3 months) after 18 months of treatment, at the ET/EoTx and at the follow-up 7 Day visit.
- For subjects enrolling from the open-label Trial 156-08-271, ALT levels will be assessed quarterly (every 3 months), at the ET/EoTx and at the follow-up 7 Day visit.

Any subject with an ALT elevation > 1x ULN and < 3x ULN will be monitored monthly for an additional 6 months beyond the date of elevation, to establish that this level is stable and that further elevation does not occur. Any ALT level ≥ 3x ULN will require the addition of full liver function panel (ALT, AST, bilirubin total and direct, alkaline phosphatase) within 72 hours of the site being aware of this result. CCI [redacted]

[g]Urine osmolality is optional
[h]A urine pregnancy test for pregnancy for women of child bearing potential (WOCBP) will be performed at screening, at the quarterly visits, at the EoTx visit and at the follow-up visit. On suspicion of pregnancy, an unscheduled urine or serum pregnancy testing will be performed. Positive urine pregnancy tests should be confirmed with a serum pregnancy test
[i]At-home urine pregnancy test kits will be dispensed to WOCBP to be used if a menstrual period is missed between visits. Kits will be dispensed as needed throughout the trial at each quarterly visit.
[j]A full physical examination is required at screening, this may be combined with the EoTx visit from the previous trial. At other visits, an optional directed physical examination may be performed to focus on PKD-related signs and symptoms
[k]If during the titration contact the determination is made to adjust the dose-regimen, the subject status will be entered into the interactive response technology (IRT) and arrangements made for dispensation of a new IMP kit and reconciliation of returned IMP.
[l]At screening, AEs reported as ongoing or resolved at the end of the prior trial will be assessed to determine entry as either medical history or ongoing event for this trial.
[m]Only concomitant medications ongoing at the baseline visit and throughout the trial will be recorded.

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Revised Table 3.7-1 – Schedule of Assessments

Table 3.7-1 Schedule of Assessments

	Screening (-30 to -1 days prior to Baseline)[a]	Baseline/ Day 0	Monthly[b] (± 7 days)	Every 3 months[b] (± 14 days)	Early Termination/End of Treatment (+ 7 days)	Titration Contact (phone contact)	Follow-up 7 days post-treatment (+ 7 days)
Informed consent	X						
Inclusion/Exclusion	X	X					
Demographics, Medical/ADPKD history[c]	X						
Dietary review	X	X	X	X	X		
CCI [redacted]		[redacted]	[redacted]	[redacted]	[redacted]		
Vital signs[d]	X	X	X	X	X		X
Chemistry Blood Samples[e]							
Serum Chemistry Panel	X[f]				X		
Liver Function tests[g]	X		X	X	X		X
Sodium	X		X	X	X		
Creatinine	X		X	X	X		X
Hematology and coagulation	X				X		
Urinalysis	X		X	X	X		
Urine osmolality[h]	X		X	X	X		
Urine specific gravity	X		X	X	X		
Urine pregnancy test (WOCBP only)[i]	X		X	X	X		X
Urine at-home pregnancy test kits dispensed[j]		X	X	X			
Physical examination [k]	X	X	X	X	X		
Tolerability/Dosing Review		X	X	X	X	X	
Interactive Response Technology Entry	X	X	X	X	X	X[l]	X
Drug dispensation		X	X	X		X[l]	
Drug reconciliation			X	X	X	X[l]	
[redacted] CCI			[redacted]	[redacted]	[redacted]		

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	Screening (-30 to -1 days prior to Baseline)[a]	Baseline/ Day 0	Monthly[b] (± 7 days)	Every 3 months[b] (± 14 days)	Early Termination/End of Treatment (+ 7 days)	Titration Contact (phone contact)	Follow-up 7 days post-treatment (+ 7 days)
CCI [redacted]			[redacted]	[redacted]	[redacted]		
[redacted]			[redacted]	[redacted]	[redacted]		
Adverse events	X[n]	←----------	----------	----------	----------	----------	----------→
Concomitant medications[o]		←----------	----------	----------	----------	----------	----------→

[a]The last visit assessments from the previous protocol can be combined with the screening visit for this trial, with all required assessments from each visit performed only once.

[b]Monthly visits are for subjects < 18 months on tolvaptan, and every 3 month visits are for subjects > 18 months on tolvaptan.

[c] Includes prior trial identifiers (screening identification [ID], subject ID, site ID, prior tolvaptan ADPKD trial protocol number).

[d]Vital signs at each visit include seated heart rate, calibrated blood pressure and post void body weight. Height should be performed only at screening.

[e] Central laboratory non-fasting serum laboratory tests will be performed. All subjects must be monitored for hepatic safety monthly until they have known tolvaptan exposure data of at least 18 months. After that, and following the approval of the medical monitor, hepatic monitoring will take place every 3 months. Trial 156-13-210 subjects who are eligible for this trial will have trial visits/hepatic monitoring monthly for the first 18 months of this trial then every 3 months thereafter, because their tolvaptan exposure will be unknown. Once unblinding occurs, it can be determined which subjects received tolvaptan in Trial 156-13-210. These subjects may have their trial visits/hepatic transaminase monitoring changed to every 3 months sooner as their previous tolvaptan exposure in Trial 156-13-210 can count towards the 18 month threshold. Subjects who enroll from other ADPKD tolvaptan trials will be monitored for hepatic safely monthly for their first 18 months they are in this trial.

[f] Hepatitis testing at screening will be optional. If hepatitis testing is performed, then both pre- and post-counseling activities relating to hepatitis testing are to be carried out based on local requirements and best practices. Upon request, if clinically indicated and approved by the medical monitor, subjects may have the following evaluations in addition to the protocol-specified chemistry panel: serum calcium, phosphorous, parathyroid hormone, vitamin D, and bicarbonate levels.

[g]A full liver function panel (AST, ALT, alkaline phosphatase, BT) will be done at screening. All other liver function tests at subsequent visits are for ALT only, unless otherwise clinically indicated. Any transaminase or bilirubin values which exceed 2 × ULN should 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, and every 3 months as indicated by the results. Local liver function panel analyses will also be performed more frequently, if necessary.

[h]Urine osmolality is optional.

[i] A urine pregnancy test for pregnancy for women of childbearing potential (WOCBP) will be performed at screening, at every 3 months visits, at the End of Treatment (EoTx) visit, and at the follow-up visit. On suspicion of pregnancy, an unscheduled urine or serum pregnancy testing will be performed. Positive urine pregnancy tests should be confirmed with a serum pregnancy test.

[j] At-home urine pregnancy test kits will be dispensed to WOCBP to be used if a menstrual period is missed between visits. Kits will be dispensed as needed throughout the trial.

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[k]A full physical examination is required at screening. At other visits, an optional "directed" physical examination may be performed to focus on PKD-related signs and symptoms.
[l] If during the titration contact the determination is made to adjust the dose regimen, dose adjustments will be made using dispensed supply, and dose instructions will be provided by the investigator. The subject's current dose will be entered into the interactive response technology (IRT) at each visit. Drug dispensation/reconciliation will be conducted on a monthly basis for subjects who have monthly trial visits and once every 3 months for subjects who have trial visits every 3 months.
CCI [redacted]
At screening, AEs reported as ongoing or resolved at the end of the prior trial will be assessed to determine entry as either medical history or ongoing event for this trial.
[o]Only concomitant medications ongoing at the baseline visit and throughout the trial will be recorded. This would occur at the screening visit only if the screening visit occurs simultaneously with the last visit from a previous tolvaptan trial.

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Previous Table 3.7.2.2-1 - Clinical Laboratory Assessments:

Table 3.7.2.2-1 Clinical Laboratory Assessments

Hematology and Coagulation Panel: Hemoglobin Mean corpuscular hemoglobin concentration (MCHC) Mean corpuscular volume (MCV) Red blood cell (RBC) count White blood cell (WBC) count with differential Prothrombin time (PT) as international normalized ratio (INR) Activated partial thromboplastin time (aPTT) Urinalysis Panel: Appearance Color Blood Glucose Microscopic analysis, WBC/RBC counts per high power field pH Protein Urine Chemistry Osmolality Specific gravity Additional Tests: Urine (or serum) pregnancy for WOCBP Hepatitis (optional)	Serum Chemistry Panel: Albumin Blood urea nitrogen (BUN) Serum calcium Carbon dioxide Serum chloride Gamma-glutamyl transpeptidase Cholesterol, total Glucose Lactate dehydrogenase (LDH) Phosphorus Potassium Protein, total Uric acid Liver Function Panel: Alkaline phosphatase (ALP) Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Bilirubin, total (BT) Bilirubin, direct CCI [redacted]
Creatinine	**Sodium**

WOCBP=women of childbearing potential.

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Revised Table 3.7.2.2-1 - Clinical Laboratory Assessments:

Table 3.7.2.2-1 Clinical Laboratory Assessments	
Hematology and Coagulation Panel: Hemoglobin **Platelet count** Mean corpuscular hemoglobin concentration (MCHC) Mean corpuscular volume (MCV) Red blood cell (RBC) count White blood cell (WBC) count with differential Prothrombin time (PT) as international normalized ratio (INR) Activated partial thromboplastin time (aPTT) Urinalysis Panel: Appearance Color Blood Glucose Microscopic analysis, WBC/RBC counts per high power field pH Protein Urine Chemistry Osmolality **(optional)** Specific gravity Additional Tests: Urine (or serum) pregnancy for WOCBP Hepatitis (optional)	Serum Chemistry Panel: Albumin Blood urea nitrogen (BUN) Serum calcium Carbon dioxide Serum chloride Gamma-glutamyl transpeptidase Cholesterol, total Glucose Lactate dehydrogenase (LDH) Phosphorus Potassium Protein, total Uric acid Liver Function Panel: Alkaline phosphatase (ALP) Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Bilirubin, total (BT) Bilirubin, direct
Creatinine	**Sodium**

WOCBP=women of childbearing potential.

New Table 4.1-1 Moderate and Strong CYP3A4 Inhibitors (partial list):

Table 4.1-1 Moderate and Strong CYP3A Inhibitors (partial list)

amprenavir	atorvastin	aprepitant	chloramphenicol (if used orally)
cimetidine	clarithromycin	clotrimazole (if used orally)	danazol
delavirdine	diltiazem	erythromycin	fluconazole
fluvoxamine	indinavir	isoniazid	itraconzazole
josamycin	ketoconazole (if used orally)	nelfinavir	nefazadone
quinupristin/ dalfopristin	ritonavir	saquinavir	troleandomycin
verapamil	Seville orange products	grapefruit products	

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

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Administrative Change Number: 1

Issue Date: 05 September 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 safety endpoints between the synopsis and Section 3.5.1, and to clarify the timeline for when IRE forms must be completed and submitted to the sponsor. In addition, a statement at the beginning of Section 3.5.1 explaining that the trial would have no formal endpoints had been inadvertently deleted in an earlier draft.

BACKGROUND:

While reviewing the protocol before proceeding with the clinicaltrial.gov posting, a few inconsistencies were found. It was decided that fixing the inconsistencies would provide better clarity.

Sectional Revisions

Location	Old Text	Updated Text
Section 3.5.1 Safety Endpoints	Safety endpoints will be as follows: • Adverse events • Vital signs • Clinical laboratory assessments • Serum transaminase elevations for frequency (2x, 3x, 5x and 10x ULN), time to onset, time to peak levels, time of offset (< 3x, 2x, or 1x ULN), response to de-challenge and re-challenge and frequency of progression to Hy's laboratory criteria (ALT or AST > 3x ULN and bilirubin, total (BT), > 2x ULN without alkaline phosphatase ≥ 2x ULN) • Serum sodium excursions above 145, 150, or 155 mmol/L or below 135,	This trial will have no formal endpoints. Safety variables will be summarized by descriptive statistics, (eg, proportion, mean, median, standard deviation [SD], minimum, and maximum values). In general, summary statistics, including changes from baseline, will be provided for safety variables based on all available data. Safety endpoints will be as follows: • Adverse events • Vital signs • Clinical laboratory assessments • Serum transaminase elevations for frequency (2x, 3x, 5x and 10x ULN), time to onset, time to peak levels, time of offset (< 3x, 2x, or 1x ULN), response to de-challenge and re-challenge and frequency of

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Location	Old Text	Updated Text
	130, or 125 mmol/L • Interruptions of protocol-specifed therapies for hypernatremia or hyponatremia	progression to Hy's laboratory criteria (ALT or AST > 3x ULN and bilirubin, total (BT), > 2x ULN without alkaline phosphatase ≥ 2x ULN) • Serum sodium excursions above 145, 150, or 155 mmol/L or below 135, 130, or 125 mmol/L
Section 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, an AE that necessitates IMP discontinuation, any new liver result meeting the AE laboratory threshold criteria, any AE of special interest or a 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, email 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 laboratory 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, email, or overnight courier to the sponsor. (Please note that the IRE form is NOT the AE eCRF).
Appendix 5, Title change	Protocol Amendment	Protocol Amendments and Administrative Changes

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

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Amendment Number: 2

Issue Date: 25 February 2015

PURPOSE:

The primary purpose of this amendment was to add additional language at the request of the United Kingdom (UK)'s Medicines and Healthcare products Regulatory Agency (MHRA) and to correct the footnote in the Schedule of Assessments table to be consistent with protocol text.

BACKGROUND:

The UK MHRA wanted a more clearly defined end of trial date and more detailed language regarding abstinence as a birth control method.

Sectional Revisions

Location	Old Text	Updated Text
Synopsis, Trial Duration and Section 3.1, Type/Design of Trial	Trial duration is planned to continue • Until the last subject from Trial 156-13-210 completes 18 months of tolvaptan treatment in this trial • Subjects enrolling from other trials will conclude their participation once tolvaptan becomes available through routine prescription or through a CCI Trial 156-13-210 subjects may opt to conclude their participation in this trial if tolvaptan becomes available before they complete 18 months of treatment in this trial	Trial duration is planned to continue • Until the last subject from Trial 156-13-210 completes 18 months of tolvaptan treatment in this trial • All subjects will receive at least 18 months of tolvaptan treatment in the extension study. Trial 156-13-210 subjects or subjects enrolling from other trials may opt to conclude their participation in this trial if tolvaptan becomes available before they complete 18 months of treatment in this trial
Section 3.7, Trial Procedures, Table 3.7-1, Schedule of Assessments	Footnote g [g]A full liver function panel (AST, ALT, alkaline phosphatase, BT) will be done at screening. All other liver function tests at subsequent visits are for ALT only, unless otherwise clinically indicated. Any transaminase or bilirubin values which exceed 2 × ULN should prompt immediate retesting within	Footnote g [g]A full liver function panel (AST, ALT, alkaline phosphatase, BT) will be done at screening. All other liver function tests at subsequent visits are for ALT only, unless otherwise clinically indicated. Any transaminase values which exceed 2 × ULN should prompt immediate retesting within 72 hours. While

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Location	Old Text	Updated Text
	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, and every 3 months as indicated by the results. Local liver function panel analyses will also be performed more frequently, if necessary.	values remain in an abnormal range, testing frequency should be increased to at least weekly for the first month, gradually returning to monthly, and every 3 months as indicated by the results. Local liver function panel analyses will also be performed more frequently, if necessary.
Section 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 an 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.	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 an 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. Abstinence is only acceptable when part of the preferred and usual lifestyle of the subject; should that lifestyle change double barrier contraceptive methods should be employed.

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

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Amendment Number: 3

Issue Date: 06 Mar 2015

PURPOSE:

The purpose of this amendment was to increase the window from 30 days to up to 3 months to allow use of historical laboratory values for screening, to add flexibility and allow combining of screening and baseline visits in the trial, and to provide clarification on trial discontinuation. The list of vendors was updated. Minor linguistic changes were made for clarity and typographical errors were corrected.

BACKGROUND:

Eligible subjects enrolling from Trials 156-08-271 or 156-13-210 can enroll before they complete the last visit in their respective trials, and the last visit as well as the screening and baseline visit in this trial can be combined into one visit with all required assessments from each visit performed only once, so long as the time between the last visit assessments from the previous trial and the screening visit for this trial is within 30 days.

Other Revisions

Figure 3.1-1 - Trial Design Schematic

Table 3.4.2-1 - Inclusion Criteria

Table 3.4.3-1 - Exclusion Criteria

Table 3.7-1 - Schedule of Assessments footnotes

Sectional Revisions

Location	Old Text	Updated Text
Title page	A Phase 3b, Multi-center, Open-label Trial to Evaluate the Long Term Safety of Titrated Immediate-release Tolvaptan (OPC 41061, 30 mg to 120 mg/day, Split dose) in Subjects with Autosomal Dominant Polycystic Kidney Disease …	A Phase 3b, Multi-center, Open-label Trial to Evaluate the Long Term Safety of Immediate-release Tolvaptan (OPC-41061, 30 mg to 120 mg/day, Split dose) in Subjects with Autosomal Dominant Polycystic Kidney Disease … Date of Amendment 3, UK 06 March 2015

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Location	Old Text	Updated Text
Synopsis, Protocol Title	A Phase 3b, Multi-center, Open-label Trial to Evaluate the Long Term Safety of Titrated Immediate-release Tolvaptan (OPC 41061, 30 mg to 120 mg/day, Split dose) in Subjects with Autosomal Dominant Polycystic Kidney Disease	A Phase 3b, Multi-center, Open-label Trial to Evaluate the Long Term Safety of Immediate-release Tolvaptan (OPC-41061, 30 mg to 120 mg/day, Split dose) in Subjects with Autosomal Dominant Polycystic Kidney Disease
Synopsis, Trial Design	Subjects will be eligible for screening into this trial if they: • Completed and transferred from the double-blind Trial 156-13-210 (12-month period including post treatment follow-up, regardless of whether this was on-treatment or off-treatment), or • Completed Trial 156-08-271 or a prior tolvaptan ADPKD trial, or • Interrupted or discontinued treatment in a prior tolvaptan ADPKD trial (other than Trial 156-13-210). Subjects may be enrolled with medical monitor approval, and additional close monitoring may be required at the beginning of the trial	Subjects will be eligible for screening into this trial if they: • Completed and transferred from the double-blind Trial 156-13-210 (12-month period including post treatment follow-up, regardless of whether this was on-treatment or off-treatment), or have completed all but the last follow-up visit, which will be combined with the first visit in this trial or • Completed Trial 156-08-271 or a prior tolvaptan ADPKD trial, or have completed all but the end of trial visit, which will be combined with the first visit in this trial or • Interrupted or discontinued treatment in a prior tolvaptan ADPKD trial (other than Trial 156-13-210). Subjects may be enrolled with medical monitor approval, and additional close monitoring may be required at the beginning of the trial
Synopsis, Inclusion and Exclusion Criteria	• Estimated glomerular filtration rate (eGFR) $\geq$ 20 mL/min/1.73m^2 within 45 days of the baseline visit. Subjects who have an eGFR between 15 and 19 mL/min/1.73m^2 may be enrolled with medical monitor approval • Renal function will be assessed during screening by using historical values (in the last 30 days) for serum creatinine levels to calculate the eGFR. The eGFT values will be	• Estimated glomerular filtration rate (eGFR) $\geq$ 20 mL/min/1.73m^2 within **3 months** of the baseline visit. Subjects who have an eGFR $\leq$ 20 mL/min/1.73m^2 may be enrolled with medical monitor and sponsor approval and increased frequency of monitoring to ensure subjects' safety. • Renal function will be assessed during screening by using historical values (within **3 months** from the screening

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Location	Old Text	Updated Text
	estimated based on the Chronic Kidney Disease – Epidemiology (CKD-EPI) formula.	visit) for serum creatinine levels to calculate the eGFR. The eGFR values will be estimated based on the Chronic Kidney Disease – Epidemiology (CKD-EPI) formula.
Section 1.3, Known and Potential Risks and Benefits	... ...Subjects enrolling in this trial who were in a previous ADPKD tolvaptan trial other than Trials 156-13-210 and 156-08-271 will have monthly visits and transaminase level assessments for the first 18 months.	... ...Subjects enrolling in this trial who were in a previous ADPKD tolvaptan trial other than Trials 156-13-210 and 156-08-271 will have monthly visits and **alanine aminotransferase (ALT)** level assessments for the first 18 months.
Section 2.1, Trial Rationale	Evidence from previous studies suggests that during the first 18 months of long-term treatment in subjects with ADPKD, alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations and evidence of idiosyncratic DILI occurs at a greater frequency in tolvaptan treated subjects. ... CCI [redacted]	Evidence from previous studies suggests that during the first 18 months of long-term treatment in subjects with ADPKD, ALT and/or aspartate aminotransferase (AST) elevations and evidence of idiosyncratic DILI occurs at a greater frequency in tolvaptan treated subjects. ... CCI [redacted]
Section 3.1, Type/Design of Trial	... Eligible subjects will have an opportunity to enroll into Trial 156-13-211 immediately following completion of the follow-up visit(s) of the previous trial. The last visit assessments from the previous protocol can be combined with the screening visit for this trial, with all required assessments from each visit only performed once, as long as the time between the last follow-up visit assessments from the previous trial and the screening visit for this trial is within 30 days. ...	... Eligible subjects will have an opportunity to enroll into Trial 156-13-211 following completion of the follow-up visit(s) of the previous trial. Eligible subjects from Trials 156-08-271 and 156-13-210 can have the last visit assessments from their previous respective protocols (end of trial visit for 156-08-271 subjects and last follow-up visit for 156-13-210 subjects) overlap the first visit in this trial. These last visit assessments can be combined with the screening and baseline visits for

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Location	Old Text	Updated Text
	These subjects may have their trial visits/hepatic transaminase monitoring changed to every 3 months sooner as their previous tolvaptan exposure in Trial 156-13-210 can count towards the 18-month threshold.	this trial, with all required assessments from each visit performed only once, so long as the time between the last visit assessments from the previous trial and the screening visit for this trial is within 30 days. If the first visit in this trial combines the last visit from a previous trial with both the screening and the baseline visits in this trial, the results from laboratory assessments performed at this combined visit will not be immediately available. Should any laboratory abnormalities be identified, the investigator will need to notify the subject and provide instructions regarding dosing or returning to the site for additional assessments. ... These subjects may have their trial visits/hepatic transaminase monitoring changed to every 3 months sooner as their previous tolvaptan exposure in Trial 156-13-210 can count towards the 18-month threshold. Subjects from prior tolvaptan trials other than Trial 156-08-271 will have monthly trial visits/ALT level assessments for the first 18 months. After that, the trial visits/ALT monitoring will be conducted every 3 months after the change in frequency is confirmed with the medical monitor.
Figure 3.1-1	Day 1 No clinic visit First dose of the IMP	Day 1 No clinic visit First dose of the IMP in Trial 211
Table 3.4.2-1, Inclusion Criteria	1. Male and female subjects aged ≥ 18 years with confirmed diagnosis of ADPKD (during participation in prior tolvaptan trials) who have • Completed and transferred from the double-blind Trial 156-13-210 (12-month period including post-treatment follow-up, regardless of whether this was on-treatment or off-treatment), or	Male and female subjects aged ≥ 18 years with confirmed diagnosis of ADPKD (during participation in prior tolvaptan trials) who have • Completed and transferred from the double-blind Trial 156-13-210 (12-month period including post-treatment follow-up, regardless of whether this was on-treatment or off-treatment), or

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Location	Old Text	Updated Text
	• Completed Trial 156-08-271 or a prior tolvaptan trial, or • Interrupted or discontinued treatment in a tolvaptan trial other than Trial 156-13-210. Subjects may be enrolled with the medical monitor approval, and additional close monitoring may be required at the beginning of the trial • Renal function will be assessed during screening by using historical laboratory values (in the last 30 days) for serum creatinine levels to calculate the estimated glomerular filtration rate (eGFR). The eGFR values will be estimated based on the Chronic Kidney Disease - Epidemiology (CKD-EPI) formula. (Levey AS et al. Ann Intern Med. 2009; 150:604–612) 2. Estimated glomerular filtration rate ≥ 20 mL/min/1.73 m^2 (calculated using the CKD-EPI formula) within 45 days prior to the baseline visit. Subjects who have an eGFR between 15 and 19 mL/min/1.73 m^2 may be permitted with documented medical monitor approval prior to enrollment	• Completed Trial 156-08-271 or a prior tolvaptan trial, or • Interrupted or discontinued treatment in a tolvaptan trial other than Trial 156-13-210. Subjects may be enrolled with the medical monitor approval, and additional close monitoring may be required at the beginning of the trial • Renal function will be assessed during screening by using historical laboratory values (in the last **3 months**) for serum creatinine levels to calculate the eGFR. The eGFR values will be estimated based on the CKD-EPI formula. (Levey AS et al. Ann Intern Med. 2009; 150:604–612) 2. Estimated glomerular filtration rate **≥ 20** mL/min/1.73 m^2 (calculated using the CKD-EPI formula) within **3 months** prior to the baseline visit. Subjects who have an eGFR ≤ 20 mL/min/1.73 m^2 may be permitted to enter the trial with medical monitor and sponsor approval and increased frequency of monitoring to ensure safety of participants. At end of table, abbreviations added: eGFR=estimated glomerular filtration rate; CKD-EPI= Chronic Kidney Disease - Epidemiology
Table 3.4.3-1, Exclusion Criteria	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. … 4. Hepatic impairment based on liver function abnormalities other than that	1. 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. … 4. Hepatic impairment based on liver

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Location	Old Text	Updated Text
	expected for ADPKD with cystic liver disease during screening.	function abnormalities other than that expected for ADPKD with cystic liver disease during screening based on recent historical laboratory values (in the last 3 months).
Section 3.7, Trial Procedures, Table 3.7-1	Footnote a: [a]The last visit assessments from the previous protocol can be combined with the screening visit for this trial, with all required assessments from each visit performed only once. ... Footnote g: [g]A full liver function panel (AST, ALT, alkaline phosphatase, BT) will be done at screening. All other liver function tests at subsequent visits are for ALT only, unless otherwise clinically indicated. Any transaminase values which exceed 2 × ULN should 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, and every 3 months as indicated by the results. Local liver function panel analyses will also be performed more frequently, if necessary. ... Footnote l: [l]If during the titration contact the determination is made to adjust the dose regimen, dose adjustments will be made using dispensed supply, and dose instructions will be provided by the investigator. The subject's current dose will be entered into the interactive response technology (IRT) at each visit. Drug dispensation/reconciliation will be conducted on a monthly basis for subjects who have monthly trial visits and once every 3 months for subjects who have trial visits every 3 months. ...	Footnote a: [a]The last visit assessments from the previous **trial** can be combined with the screening **and baseline** visits for this trial, with all required assessments from each visit performed only once. ... Footnote g: [g]A full liver function panel (AST, ALT, alkaline phosphatase, BT) will be done at screening. All other liver function tests at subsequent visits are for ALT only, unless otherwise clinically indicated. An ALT elevation > 2 × ULN should trigger prompt testing of hepatic function within 72 hours. Any transaminase values which exceed 2 × ULN should 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, and every 3 months as indicated by the results. Local liver function panel analyses will also be performed more frequently, if necessary. ... Footnote l: [l]If during the titration contact the determination is made to adjust the dose regimen, dose adjustments will be made using dispensed supply, and dose instructions will be provided by the investigator. The subject's current dose will be entered into the interactive response technology (IRT) at each visit. Drug dispensation/reconciliation will be conducted on a monthly basis for subjects who have monthly trial visits and once every 3 months for subjects who have trial visits every 3 months. If additional drug supply is required for titration purposes, the site will arrange a subject visit for

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Location	Old Text	Updated Text
		dispensation. ...
Section 3.7.1.1, Screening (-30 days to 1 day prior to Baseline)	Screening for eligibility is required for all subjects. The screening visit may be combined with the last visit from the previous protocol with all required assessments from each visit only performed once. In some cases, if a subject enrolls in this trial from a prior tolvaptan trial, the end of trial visit for that trial and the screening visit for this one may occur simultaneously. Required assessments are as follows: 1. Obtain subject consent. 2. Determine subject eligibility through inclusion/exclusion criteria. 3. Record demographic information and prior trial identifiers (screening identification [ID], subject ID, site ID, prior tolvaptan ADPKD trial protocol number). 4. Record medical/ADPKD history using prior trial data. 5. Review dietary recommendations and compliance …	Screening for eligibility is required for all subjects. The screening **and baseline** visits may be combined with the last visit from either the 156-08-271 or 156-13-210 protocol with all required assessments from each visit performed only once. **Therefore,** in some cases, if a subject enrolls in this trial from a prior tolvaptan trial, the end of trial or last follow-up visit for that trial and the screening **and baseline** visit for this one may occur simultaneously. Required assessments for the screening visit are as follows: 1. Obtain subject consent. 2. **Obtain subject's new screening identifcation (ID) assigned by interactive response technology (IRT).** 3. Determine subject eligibility through inclusion/exclusion criteria. 4. Record demographic information and prior trial identifiers (screening ID, subject ID, prior tolvaptan ADPKD trial protocol number). 5. Record medical/ADPKD history using prior trial data. 6. Review dietary recommendations and compliance …
Section 3.7.2.4.1 Liver Test Abnormalities and Interruption/Discontinuation of Investigational Medical Product	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.	An ALT elevation > 2 × ULN or 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.
Section 3.7.5, Treatment Interruption and Discontinuation	... A subject who permanently discontinues IMP treatment may have the option to end trial participation (complete the early termination visit)	... A subject who permanently discontinues IMP treatment ends trial participation and the early termination visit should be

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Location	Old Text	Updated Text
	or to continue participation off IMP and complete ongoing trial assessments as per protocol or with a modified (ie, less frequent) schedule as outlined in Section 3.8.3.	completed.
Section 5.2, Eliciting and Reporting Adverse Events	… 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. …	… In addition, Quintiles (drug safety service) must be notified immediately by telephone or fax of any immediately reportable events according to the procedure outlined below in Section 5.3. …
Section 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 laboratory abnormality requiring special liver eCRF completion, or confirmed pregnancy, by telephone or by fax to the sponsor as outlined in Appendix 1. ...	The investigator must immediately report within 24 hours after either the investigator or site personnel become aware of any SAE, new liver laboratory abnormality requiring special liver eCRF completion, or confirmed pregnancy, by telephone or by fax to **Quintiles (drug safety service)** as outlined in Appendix 1. ...
Appendix 2	Safety Reporting Quintiles 5927 South Miami Blvd Morrisville, NC 27560, USA Phone: PPD Fax: PPD … Investigator Payments CFS Clinical 1000 Madison Ave, 1st Floor Audubon, PA 19403, USA Phone: PPD Fax: PPD … CCI [redacted] Phone: PPD	Safety Reporting Quintiles (Drug Safety Service) 5927 South Miami Blvd Morrisville, NC 27560, USA Phone: PPD Fax: PPD … Investigator Payments Quintiles, Inc. Investigator Payment Administration Department 10188 Telesis Court., Suite 400 San Diego, CA 92121, USA PPD … CCI [redacted] Phone: PPD

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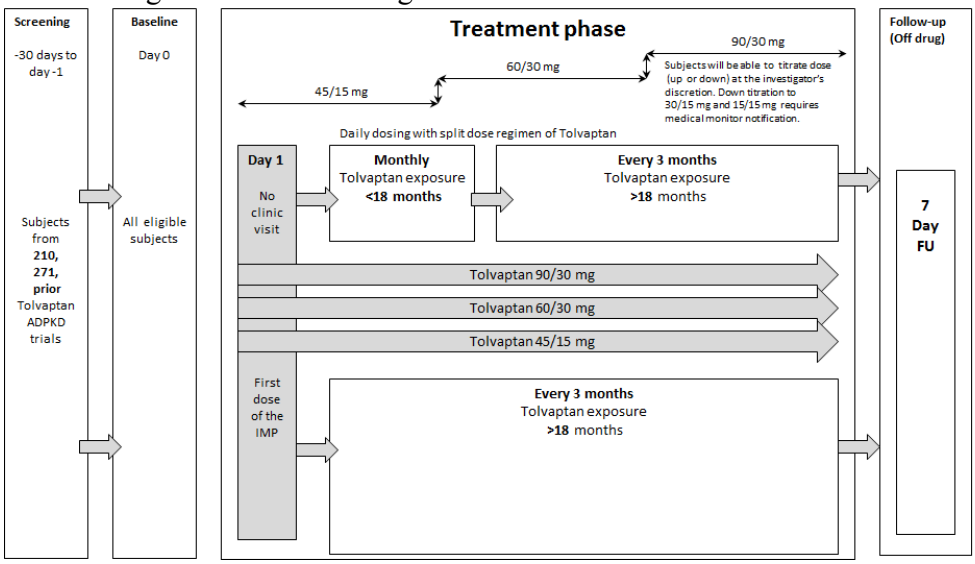
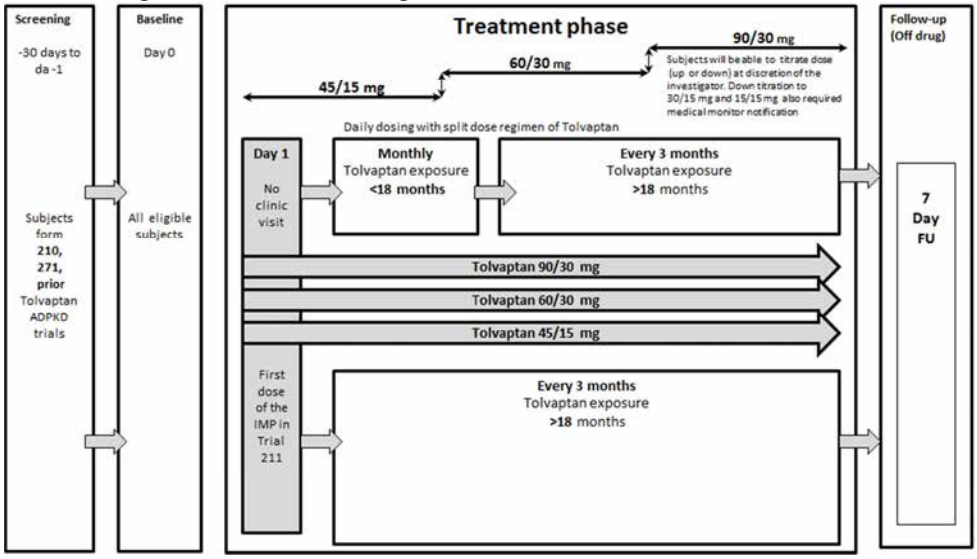
Previous Figure 3..-1 Trial Design Schematic



Revised Figure 3.1-1 Trial Design Schematic



ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

Protocol 156-13-211

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 trail 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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	Clinical Approval	09-Mar-2015 13:17 GMT+00
	Biostatistics Approval	10-Mar-2015 15:24 GMT+00