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Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational Medicinal Product

OPC-41061 (Tolvaptan)

REVISED CLINICAL PROTOCOL

A Phase 3b, Two-part, Multicenter, One Year Randomized, Double-blind, Placebo-controlled Trial of the Safety, Pharmacokinetics, Tolerability, and Efficacy of Tolvaptan followed by a Two Year Open-label Extension in Children and Adolescent Subjects with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Protocol No. 156-12-298
IND No. 072975
EudraCT No. 2016-000187-42

CONFIDENTIAL – PROPRIETARY INFORMATION

Clinical Development Phase:	3b
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Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc. Name of Product: JINARC®, Tolvaptan (OPC-41061)		Protocol No.: 156-12-298 IND No.: 072975 EudraCT No.: 2016-000187-42
Protocol Title:	A Phase 3b, Two-part, Multicenter, One Year Randomized, Double-blind, Placebo-controlled Trial of the Safety, Pharmacokinetics, Tolerability, and Efficacy of Tolvaptan followed by a Two Year, Open-label Extension in Children and Adolescent Subjects with Autosomal Dominant Polycystic Kidney Disease (ADPKD)	
Clinical Phase/Trial Type:	Phase 3b, therapeutic confirmatory	
Treatment Indication:	ADPKD	
Objective(s):	Primary:	To assess the long term safety of treatment with tolvaptan in a pediatric and adolescent ADPKD population.
	Secondary:	To assess the pharmacodynamics (PD), pharmacokinetics (PK), and efficacy of tolvaptan in children and adolescent subjects with ADPKD.
Trial Design:	Phase A is a randomized, double-blind, placebo-controlled phase to compare tolvaptan with placebo. The duration of treatment is 12 months. It is open to subjects between the ages of 4 and 17 years, inclusive. Subjects between the ages of 12 and 17 years will be stratified by age and gender. When these stratified cohorts have been closed, enrollment for the trial will end. Qualified subjects who complete Phase A may continue in Phase B. A qualified subject is defined as one who has completed Phase A on investigational medicinal product (IMP), is willing to continue in the trial, and who does not have any adverse events (AEs), which would require IMP discontinuation. Phase B is an open-label phase during which qualified subjects will receive treatment with tolvaptan for 24 months.	

Subject Population:	In Phase A, the required population will consist of at least 60 male and female subjects aged 12 to 17 years (inclusive), with a diagnosis of ADPKD. Randomization will be 1:1; tolvaptan to placebo. Subjects ages 12 to 17 will be stratified by age and gender in the following age cohorts: • Female subjects ages 12 to 14 years, inclusive • Female subjects ages 15 to 17 years, inclusive • Male subjects ages 12 to 14 years, inclusive • Male subjects ages 15 to 17 years, inclusive The trial is also open to children between the ages of 4 to 11 years (inclusive) with ADPKD, who meet the study inclusion criteria and who, in the opinion of the investigator, would benefit from treatment. Including this latter group, the total trial population may, but is not required to, include approximately 100 subjects.
Inclusion/Exclusion Criteria:	<u>Key Inclusion Criteria</u>: • Male and female subjects aged 4 to 17 years (inclusive) with a diagnosis of ADPKD as defined by the presence of family history and/or genetic criteria AND who have at least 10 renal cysts, each of which measure at least 0.5 cm, confirmed upon magnetic resonance imaging (MRI) inspection; subjects under the age of 12 years must have at least 4 cysts that are at least 1 cm in size, confirmed by ultrasound. • Weight $\geq$ 20 kg. • Subjects with estimated glomerular filtration rate (eGFR) $\geq$ 60 mL/min/1.73m^2 within 31 days prior to randomization (using the Schwartz formula, eGFR = 0.413 × height [cm] /serum creatinine mg/dL). • Independent in toileting. • Ability to swallow a tablet. <u>Key Exclusion Criteria</u>: • Liver function tests including AST (aspartate aminotransferase), ALT (alanine aminotransferase) > 1.5 × the upper limit of normal (ULN). • Nocturnal enuresis. • Need for chronic diuretic use.

	• Subjects with advanced diabetes (eg, glycosylated hemoglobin > 7.5, and/or glycosuria by dipstick, significant proteinuria, retinopathy), evidence of additional significant renal disease(s) (ie, currently active glomerular nephritides), renal cancer, single kidney, or recent (within 6 months of screening) renal surgery or acute kidney injury. • Subjects having disorders in thirst recognition or inability to access fluids. • Subjects with critical electrolyte imbalances, as determined by the investigator. • Subjects with, or at risk of, significant hypovolemia as determined by investigator. • Subjects with clinically significant anemia, as determined by investigator. • Subjects 12 years of age and older having contraindications to, or interference with MRI assessments (eg, ferro-magnetic prostheses, aneurysm clips, severe claustrophobia). • Subjects with a history of taking a vasopressin agonist/antagonist. • Subjects taking medications or having concomitant illnesses likely to confound endpoint assessments, including taking approved (ie, marketed) therapies for the purpose of affecting polycystic kidney disease (PKD) cysts such as tolvaptan, vasopressin antagonists, anti-sense ribonucleic acid (RNA) therapies, rapamycin, sirolimus, everolimus, or somatostatin analogs (ie, octreotide, sandostatin). • Subjects who have had cyst reduction surgery within 6 weeks of the screening visit.
Trial Site(s):	The trial will be conducted at approximately 20 centers globally.

Investigational Medicinal Product(s), Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration:	Tolvaptan will be provided as 7.5, 15, and 30 mg spray-dried, immediate-release tablets with matching placebo. Tolvaptan will be administered as a split-dose, with the first dose taken upon awakening and the second dose taken approximately 8 hours later. Subjects will be randomized to receive IMP defined as either active tolvaptan or matching placebo for 12 months. Starting doses will be based on weight: • ≥ 20 kg to < 45 kg, 15/7.5 mg tolvaptan (TLV) split-dose or matching placebo • ≥ 45 kg to ≤ 75 kg, 30/15 mg TLV split-dose or matching placebo • > 75 kg, 45/15 mg TLV split-dose or matching placebo After 1 week, subjects will be asked to up-titrate once from their starting dose. • ≥ 20 kg to < 45 kg, 30/15 mg TLV split-dose or matching placebo • ≥ 45 kg to ≤ 75 kg, 45/15 mg TLV split-dose or matching placebo • > 75 kg, 60/30 mg TLV split-dose or matching placebo Subjects may down-titrate at any time during the trial, however subjects will be asked to stay on the highest tolerable dose (by weight group) if possible. It is recommended that each dose be administered with 240 mL of water, as part of the goal to maintain proper hydration status; the total 240 mL can be consumed over a 1-hour period following dosing.
Trial Assessments:	Efficacy: • Total kidney volume assessed by MRI or ultrasound • Assessment of renal function (eGFR by Schwartz formula) Pharmacokinetic: • PK blood samples - sparse sampling and dense sampling in a subset of subjects Pharmacodynamic: • Urine osmolality and specific gravity • 24-hour fluid balance • Serum sodium, creatinine, and osmolality • Urine volume and urine sodium, creatinine, and osmolality

	• Fluid intake • Palatability and acceptability of tolvaptan formulation Safety: • AE reporting • Clinical laboratory tests (hematology, chemistry, urinalysis) • Vital signs • Physical examination including body weight and growth percentile • Tanner Staging • Vital status Quality of Life (QoL): • Generic Pediatric QoL questionnaire • Daytime and nighttime voids
Criteria for Evaluation:	Primary and secondary endpoints include the agreed upon endpoints in the Paediatric Investigational Plan (PIP). In addition to the PD and PK objectives, the PIP requires the collection and descriptive analyses of safety and normal growth in this population. **Co-Primary Endpoints:** Change from baseline in spot urine osmolality (premorning dose) and specific gravity (premorning dose) after 1 week of daily dosing in Phase A. **Key Secondary Endpoint:** The percent change from Phase A baseline in height-adjusted total kidney volume (htTKV) as measured by MRI at 12 months. **Other Secondary Endpoints:** • 24-hour fluid balance prior to Week 1. • Change from baseline in renal function (eGFR by Schwartz formula) at each clinic visit (Week 1, Month 1, Month 6, Month 12) in Phase A. • Change from baseline in renal function (eGFR by Schwartz formula) at each clinic visit (Week 1, Month 1, Month 6, Month 12, Month 18, Month 24) in Phase B. • Percent change in htTKV as measured by MRI from Phase B baseline to Phase B Month 12. • Percent change in htTKV as measured by MRI from Phase B baseline to Phase B Month 24. • Pharmacodynamic (PD) endpoints of urine volume

	(including 24-hour fluid volume), fluid intake and fluid balance, sodium, creatinine, and free water clearance during dense PK sampling (after at least 1 month on IMP). • Proportions of each Tanner Stage by gender and age compared to normative populations at baseline, 6 months, and 12 months during the placebo-controlled phase (Phase A), and every 6 months during the open-label extension phase (Phase B). • Description of changes from baseline percentiles for height and weight by gender and age at baseline, 6 months, and 12 months during the placebo-controlled phase (Phase A), and every 6 months during the open-label extension phase (Phase B). • Safety variables (changes from baseline in creatinine, vital signs, laboratory values including liver function tests [LFTs], rate of aquaretic AEs) in placebo and tolvaptan.
Statistical Methods:	<u>Sample Size:</u> For the primary endpoint analysis, a sample size of at least 60 subjects from 12 to 17 years of age inclusive is proposed for the Phase A of this trial. Since the data collected will be summarized using descriptive statistics and not aimed at testing a specific hypothesis, no formal power calculations are undertaken. <u>Key Datasets for Analysis:</u> The following datasets are defined for the efficacy and safety analysis in this trial: Randomized: Consists of all subjects who were randomized in this trial. Full Analysis Set (FAS): Subjects who have been randomized to a treatment group, received at least 1 dose of the IMP, have both a Phase A baseline and at least 1 postbaseline efficacy evaluation.

	Safety: Subjects that were administered at least 1 dose of IMP. The FAS dataset, which is based on intent-to-treat principle, will be analyzed according to the treatment group to which each subject was randomized; the safety dataset will be analyzed according to the treatment received. <u>Efficacy Analysis:</u> Descriptive statistics will be presented on the co-primary endpoints, and key secondary endpoint by treatment groups. Other secondary endpoints will also be summarized using descriptive statistics by treatment groups. <u>Safety Analyses</u>: Safety variables will be analyzed including AEs, changes from baseline in creatinine, vital signs, laboratory values including LFTs, and rate of aquaretic AEs in placebo and tolvaptan. Summarized statistics will be provided for the safety variables based on all available data in Phase B as well.
Trial Duration:	Overall trial duration is expected to be approximately 4 years with a 1-year enrollment period. Phase A will last 1 year for each subject, and Phase B will last 2 years for each subject. Maximum trial duration for each subject is 3 years and 30 days. Follow-up visits will be conducted at 7 (+2) days after the last dose of tolvaptan, and a final safety follow-up telephone contact will be conducted at 14 (+2) days after the last dose of tolvaptan for all subjects.

Trial Conduct for COVID-19

All procedures and assessments in this protocol are to be followed to the fullest extent possible. The sponsor, in coordination with the site, investigator(s), and medical monitor, will continuously monitor and evaluate the benefits and risks to subject participation in the clinical trial as it related to COVID-19. If any protocol specified activities were not able to be performed, or cannot be performed due to COVID-19 considerations, refer to the COVID-19 Addendum for the appropriate measures to be followed. Appropriate measures may include replacing in-person visits with virtual visits (phone or video) as deemed necessary by the investigator to ensure subject safety and maintain protocol requirements.

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ADPKD	Autosomal dominant polycystic kidney disease
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{0-24h}	Area under the concentration-time curve from time zero to 24 hours
AVP	Arginine vasopressin
BT	Bilirubin, total
cAMP	Cyclic adenosine monophosphate
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease-Epidemiology
C_{max}	Maximum (peak) plasma concentration
C_{min}	Minimum plasma concentration
CRO	Clinical research organization
CSR	Clinical study report
CYP	Cytochrome P450
DILI	Drug-induced liver injury
DILIN	Drug Induced Liver Injury Network
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EoTx	End of Treatment
EudraCT	European Clinical Trial Data Base
FAS	Full Analysis Set
FDA	(United States) Food and Drug Administration
GCP	Good Clinical Practice
HAC	Hepatic adjudication committee
htTKV	Height-adjusted total kidney volume
IAF	Informed assent form
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	Identification
IDMC	Independent data monitoring committee
IEC	Independent ethics committee
IMP	Investigational medicinal product
IND	Investigational new drug
INR	International normalized ratio
IRB	Institutional review board
IRE	Immediately reportable event
IXRS	Interactive response system

LFT	Liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
OPDC	Otsuka Pharmaceutical Development & Commercialization
PD	Pharmacodynamic
PIP	Paediatric Investigational Plan
PK	Pharmacokinetic(s)
PKD	Polycystic kidney disease
PQC	Product Quality Complaint
QoL	Quality of Life
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
TEAE	Treatment-emergent adverse event
TKV	Total kidney volume
t_{max}	Time to maximum (peak) plasma concentration
TLV	Tolvaptan
US or USA	United States or United States of America
ULN	Upper limit of normal
V2	Vasopressin Type 2
WBC	White blood cell
WOCBP	Women of childbearing potential

1 Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is an inherited condition which leads to progressive destruction of normal kidney structure and ultimately to end-stage renal disease over decades. 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 and inflammation and fibrosis leading to progressive nephron loss. In earlier phases of the disease, the remaining nephrons are initially able to compensate through glomerular hyperfiltration. Eventually, nephron loss is so great that compensation is no longer adequate and renal function begins to decline. Clinical manifestations of ADPKD may be sporadic (hematuria, infections, pain), or chronic (hypertension, albuminuria, renal insufficiency), and indicate ongoing and cumulative damage to the kidneys.

In many cases, the clinical manifestations of ADPKD do not present until the middle decades of life, however, 2% to 5% of patients have an earlier onset of disease and can present with symptoms from birth through adolescence.[1]

Early onset of ADPKD symptoms predicts more severe disease which increases the likelihood of earlier loss of kidney function. Such individuals may benefit from earlier treatment to slow cyst formation as has been demonstrated in studies of preclinical models.[2,3]

Tolvaptan (OPC-41061) is a selective arginine vasopressin (AVP) type 2 (V2) receptor antagonist. Tolvaptan is approved for the treatment of ADPKD in Europe, Canada, and Japan having demonstrated reduced rates of total kidney volume (TKV) growth, and slowed deterioration of estimated glomerular filtration rate (eGFR) in rapidly progressing ADPKD.

This trial is part of the requirements of the Paediatric Investigational Plan (PIP) for tolvaptan and will be the first trial of tolvaptan in a pediatric ADPKD population. Refer to the tolvaptan Investigator's Brochure (IB) for more information about tolvaptan in the adult population.[4]

[redacted]

[redacted]

1.2 Clinical Data

In an international, multicenter, clinical trial in adult subjects with chronic kidney disease (CKD) stage 1 to 3 due to rapidly progressing ADPKD[7], tolvaptan was clinically effective in delaying decline of renal function, as determined by changes in serum creatinine concentrations over 3 years. These effects were consistent across each of these CKD stages, supporting the potential utility of tolvaptan 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 trial (Trial 156-09-283).[8] Thus, the clinical data have confirmed the nonclinical effects seen in animals (see Section 1.1) and support approval of tolvaptan as the first agent to slow the progression of ADPKD.[8]

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)		277/162	-2.15	-2.55	0.40	15%
Stage 2 (60-90)		411/216	-2.76	-3.90	1.13[a]	29%
Stage 3[b] (30-60)	3a (45-60)	128/69	-3.67	-5.30	1.63[a]	31%
	3b (30-45)	23/15	-3.85	-5.73	1.88[a]	33%

$eGFR_{CKD-EPI}$ = estimated glomerular filtration rate calculated by the Chronic Kidney Disease-Epidemiology (CKD-EPI) formula.

[a] $p < 0.005$.

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

Source: Otsuka's Response to Jinarc (Tolvaptan) Day 120 Question 39, Tables 3.2.3.7-4, 3.2.3.7-8, 3.2.3.7-12, and 3.2.3.7-16; data on file.

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 which a patient is willing to accept is a personal decision based on his/her individual and familial experience with the disease.

The most common observed risks of tolvaptan therapy in adults include those arising from aquaresis (eg, polyuria, pollakiuria, nocturia, thirst, dry mouth), dehydration, electrolyte abnormalities, and gout. While aquaretic events did not contribute to significant subject morbidity over 3 years of study in the pivotal placebo-controlled trial (Trial 156-04-251), they do represent adverse drug reactions which occur early (within days to weeks) and are most likely to limit a subject's ability to continue therapy over a duration of treatment that is likely to provide benefit. While the proposal of increased water ingestion as a mechanism of ameliorating CKD[9] has not reached medical equipoise, in this trial we believe a general recommendation to do so is reasonable and would recommend ingestion of water adequate to avoid thirst.

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

Significant events related to glaucoma and skin neoplasms were also observed; however the causal relationship to tolvaptan remains uncertain. These adverse events (AEs) and the above attributable adverse reactions should be considered in light of the benefits of a reduced risk of ADPKD kidney complications, including renal pain, urinary tract infection, hematuria, anemia, and nephrolithiasis.[10]

The treatment risks of tolvaptan in adults are well characterized, manageable, and must be weighed against the consequences of no other adequate treatment. With sufficient knowledge of the benefits and risks and risk mitigation strategies, patients and their physicians may make informed decisions about tolvaptan treatment. In the final

assessment, the overall benefit-risk profile of tolvaptan for the treatment of ADPKD appears favorable.

2 Trial Rationale and Objectives

2.1 Trial Rationale

Tolvaptan has been demonstrated to delay both the progression of the decline of eGFR as well as to slow the growth of TKV in adults with rapidly progressing ADPKD (CKD stages 1 to 3). This trial is part of the requirements of the PIP and will be the first trial of tolvaptan in a pediatric ADPKD population. The trial is designed to assess the effects of titrated oral tolvaptan on pharmacodynamics (PD), pharmacokinetics (PK), and biomarkers of efficacy (TKV) and safety (including growth and development) in children from 4 to 17 years of age diagnosed with ADPKD; followed by an open-label extension phase to collect additional safety and efficacy data.

2.2 Dosing Rationale

Successful treatment of ADPKD appears to require early and constant inhibition of the vasopressin V2 receptor. Maintenance of tolvaptan concentrations for 24 hours produced decreased rates of growth in kidney size in animal models and therefore, subjects are encouraged to take the maximally tolerated dose. The clinical formulation of tolvaptan was optimized to increase bioavailability which necessitates split-dosing to maintain suppression of AVP action across 24 hours. A higher dose is used early in the day, with a lower dose approximately 8 to 9 hours later in order to produce a maximal inhibition on waking, with a gradual fall-off of effect during the night when frequent urination could lead to interruption of sleep.

Adult treatment starts with a split-dose regimen of 45 mg in the morning and 15 mg in the afternoon. The child and adolescent subjects to be enrolled in this trial will have well preserved renal function and, therefore, at the adult dose will likely respond with potent diuresis and experience aquaretic-related AEs. The starting dose regimens in this trial are based on the adult starting dose, with adjustments for body weight. Subjects will be up-titrated to the equivalent of the starting dose used in adult trials at Week 1, and down-titration for tolerability will be allowed, see Section 3.2 for details.

In the pivotal trial for adult subjects with ADPKD (156-04-251), every subject started tolvaptan dosing with the 45/15mg dosing regimen regardless of their weight. When dose is expressed as mg/kg, as shown in Table 2.2-1, the maximum starting dose given to an adult subject was 1.11 mg/kg with the lowest dose being 0.34 mg/kg. This should

provide sustained suppression while ameliorating excess aquaretic effects in those with high functioning kidneys. The weight ranges for pediatric subjects were selected so that the maximal starting dose for each weight range was no higher than 67% of the maximal adult dose. The up-titrated morning doses, expressed as mg/kg, are also presented for comparison to the adult trial.

Table 2.2-1 Starting Dose and Up-titrated Doses for Pediatric Subjects Compared to Adults Enrolled in Pivotal Trial 156-04-251

Body Weight (kg)	Starting dose (mg)	Starting dose (mg/kg)	
		maximum	minimum
Adults			
40.6 to 133.6	45	1.11	0.34
Pediatric			
20 to <45	15	0.75	>0.33
45 to 75	30	0.67	0.40
>75	45	0.60	<0.60
Body Weight (kg)	Up-titrated morning dose (mg)	Up-titrated morning dose (mg/kg)	
		maximum	minimum
Adult			
40.6 to 133.6	60	1.48	0.45
Pediatric			
20 to <45	30	1.50	>0.67
45 to 75	45	1.00	0.60
>75	60	0.80	<0.80

Subjects who are unable to tolerate the initial starting dose regimen will be allowed to down-titrate to a dose as low as 7.5 mg once daily. This will allow for the collection of the most information on tolerability, safety, and potentially efficacy as the minimally effective dose of tolvaptan has not been determined. Animal studies indicated a dose response in tolvaptan efficacy with lower doses is still better than placebo. Adults in the pivotal 156-04-251 trial were titrated up in order to maximize inhibition of AVP but efficacy was observed in subjects who down-titrated to 45/15 mg and 60/30 mg regimens. In the phase 2 156-04-250 trial, subjects on the fixed regimen of 45/15 mg showed less efficacy when compared to subjects on 60/30 mg; however, both groups showed slower increase in TKV when compared to a matched control group.[8,11]

2.2.1 Dose Adjustments for CYP3A inhibitors

Dose adjustments will be constrained by the tablet sizes provided. Splitting or crushing tablets is not allowed.

Since tolvaptan is a sensitive Cytochrome P450 (CYP) 3A4 substrate, CYP3A4 inhibitors should be avoided during the trial, with the exception of amiodarone, which was found to have no effect on tolvaptan concentrations. If these drugs are to be used, the medical monitor should be contacted and investigational medicinal product (IMP) administration must be interrupted (see Section 3.8.3.1 and Section 4.1).

2.3 Trial Objectives

Primary: To assess the long term safety of treatment with tolvaptan in a pediatric and adolescent ADPKD population.

Secondary: To assess the PD, PK, and efficacy of tolvaptan in children and adolescent subjects with ADPKD.

3 Trial Design

3.1 Type/Design of Trial

The trial will comprise 2 phases as described below:

Phase A is a randomized, double-blind, placebo-controlled phase to compare tolvaptan with placebo. The duration of treatment is 12 months. It is open to subjects between the ages of 4 and 17 years, inclusive. Subjects between the ages of 12 and 17 years will be stratified by age and gender as described in Section 3.3. When these stratified cohorts have been closed, enrollment for the trial will end (Figure 3.1-1). Additionally, subjects aged 4 to 11 years may be eligible for participation following discussion with the medical monitor.

Qualified subjects who complete Phase A may continue into Phase B. A qualified subject is defined as one who is willing to continue in the trial and who does not have any AEs that would require IMP discontinuation.

Phase B is an open-label phase during which subjects who have completed Phase A of the trial will receive treatment with tolvaptan for 24 months (Figure 3.1-2). The purpose of Phase B is to obtain safety and efficacy data for long term use of tolvaptan.

When all subjects in Phase A have either completed the Month 12 visit or early terminated from the trial, a snapshot of the data will be taken. At that time, the snapshot will be unblinded, and results analyzed and reported in an interim clinical study report (CSR) to provide early information on safety. The protocol may be amended to further ensure continuing safety and tolerability measures are in place (Refer to Section 13 for the Amendment policy).

When all subjects in Phase B either complete the Month 24 visit, or the last ongoing subject terminates early, the database will be locked, and a final CSR will be provided to the regulatory authorities.

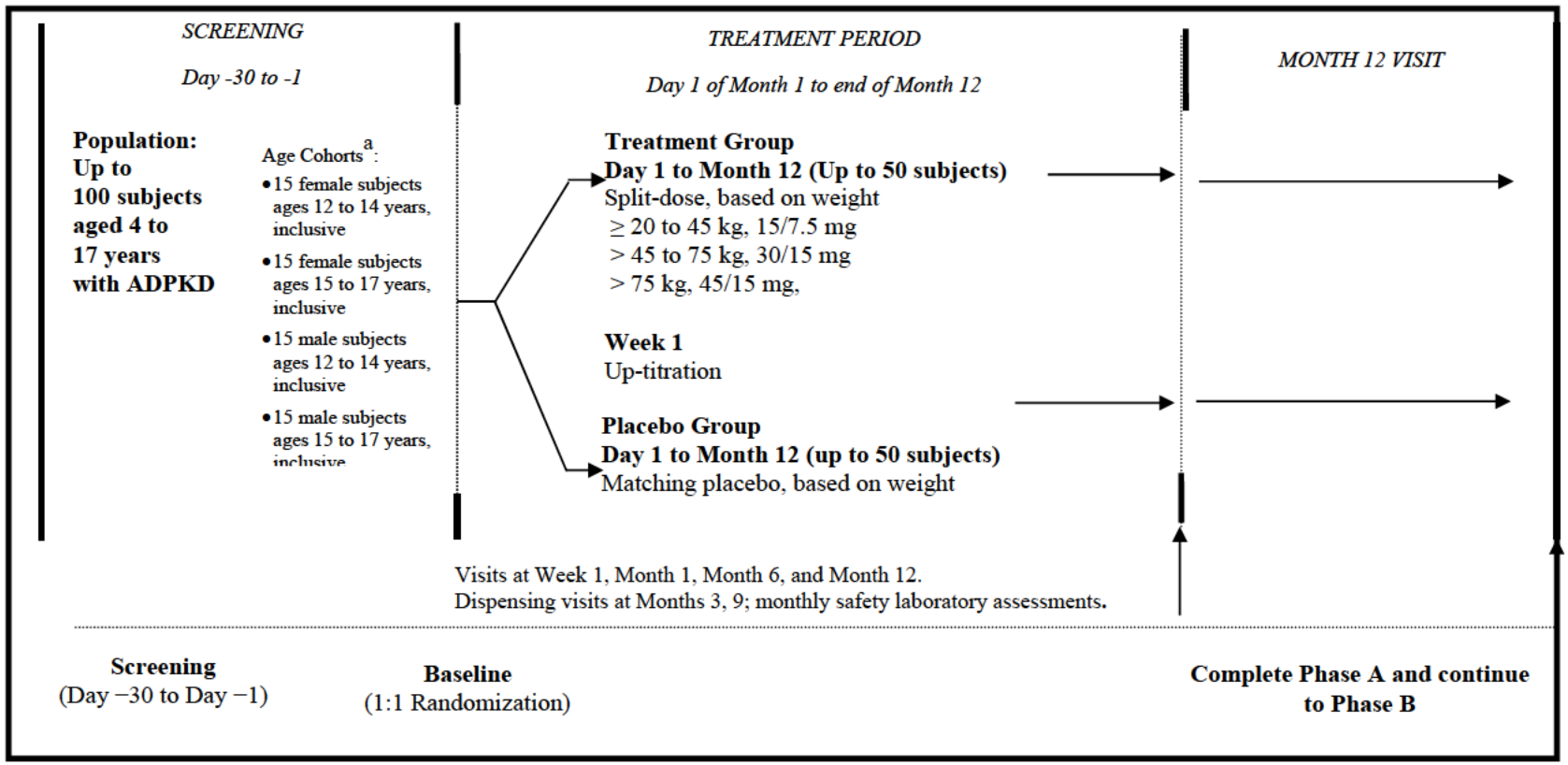

Figure 3.1-1 Trial Design Schematic Phase A, Randomized, Double-blind

[a]Subjects between the ages of 4 and 11 are eligible for the trial but are not included in the age cohorts.

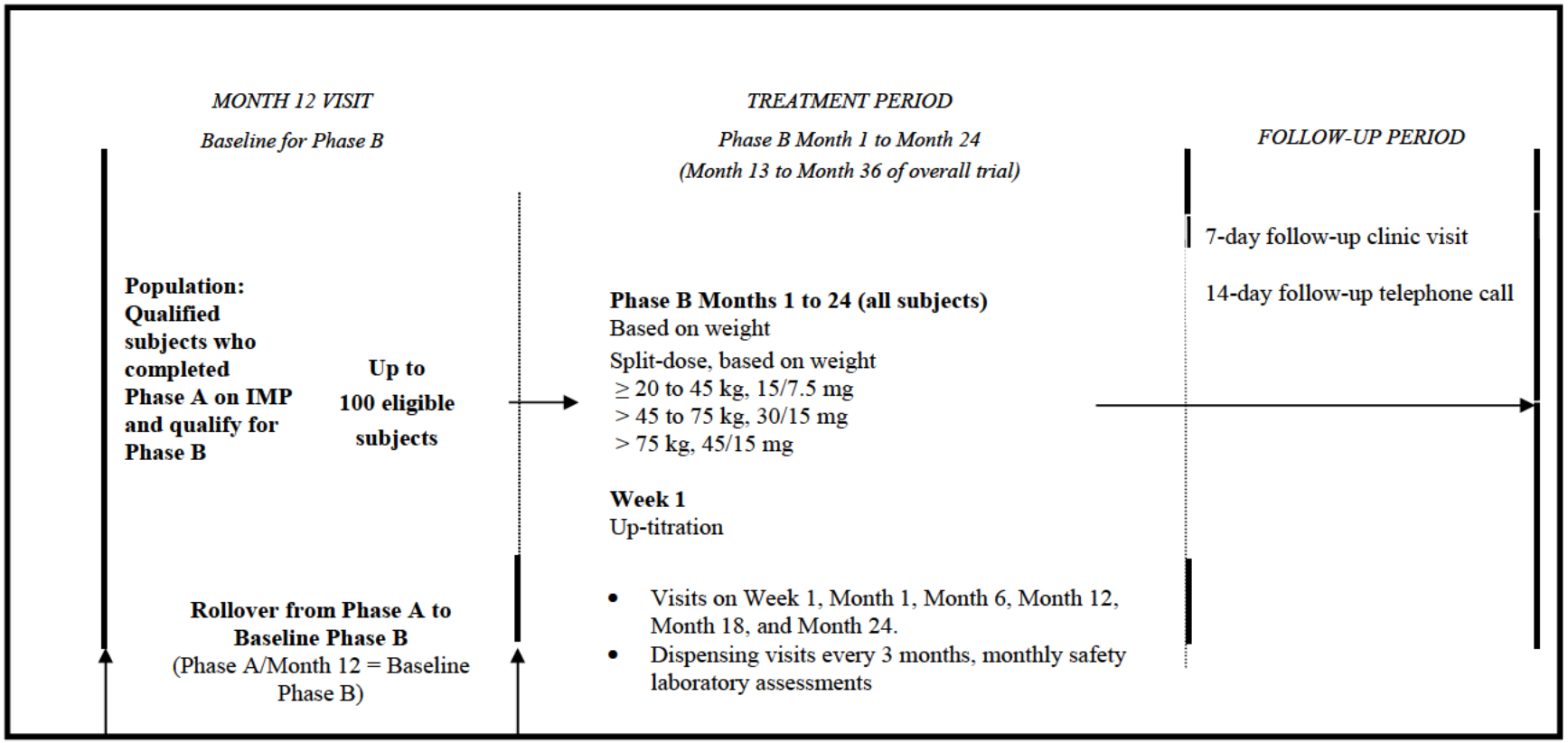

Figure 3.1-2 Trial Design Schematic Phase B, Open-Label

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3.2 Trial Treatments

Tolvaptan will be provided as 7.5, 15, and 30 mg spray-dried, immediate-release tablets with matching placebo. Tolvaptan will be administered as a split-dose, with the first dose taken upon awakening and the second dose taken approximately 8 hours later.

3.2.1 Phase A

Subjects will be randomized to receive IMP defined as either active tolvaptan or matching placebo for 12 months. Starting doses will be based on weight as denoted below in Table 3.2.1-1.

After 1 week, subjects who have tolerated their initial dose will up-titrate once from their starting dose (Table 3.2.1-2). Subjects may down-titrate at any time during the trial, however subjects will be asked to stay on the highest tolerable dose (by weight group) if possible (Table 3.2.1-3).

It is recommended that each dose be administered with 240 mL of water, as part of the goal to maintain proper hydration status; the total 240 mL can be consumed over a 1-hour period following dosing. Water intake will be recorded for all in-clinic dosing.

Table 3.2.1-1 Starting Tolvaptan Dose

Body Weight	Time	Split-dose[a]
≥ 20 kg to < 45 kg	Upon awakening / 8 hours later	15/7.5 mg TLV or matching placebo
≥ 45 kg to ≤ 75 kg	Upon awakening / 8 hours later	30/15 mg TLV or matching placebo
> 75 kg	Upon awakening / 8 hours later	45/15 mg TLV or matching placebo

TLV = tolvaptan.

[a]Split-dosing will be twice daily dosing with the larger dose taken upon awakening and the smaller dose taken approximately 8 hours later.

Doses may be titrated down dependent upon subject tolerability.

Table 3.2.1-2 Up-titration Steps

Current Dose	Up-titrated Dose	Body Weight
15/7.5 mg TLV or matching placebo	30/15 mg	≥ 20 kg to < 45 kg
30/15 mg TLV or matching placebo	45/15 mg	≥ 45 kg to ≤ 75 kg
45/15 mg TLV or matching placebo	60/30 mg	> 75 kg

Table 3.2.1-3 Down-titration Steps

Current Dose	Down-titrated Dose
7.5 mg once daily upon awakening	Subject to be withdrawn from IMP
7.5/7.5 mg	7.5 mg once daily upon awakening
15/7.5 mg	7.5/7.5 mg
22.5/15 mg	15/7.5 mg
30/15 mg	22.5/15 mg
45/15 mg	30/15 mg
60/30 mg	45/15 mg

Subjects should attempt to complete 7 days of dosing between down-titration steps to provide the best opportunity for a subject to be given their maximally tolerated dose.

3.2.1.1 Dosing for Dense PK and PD Sampling

A subset of 20 subjects, half on tolvaptan and half on placebo, in the 12 to 17 year old age group will have dense PK sampling after at least 1 month on IMP. The blind will be maintained by utilizing the Interactive response system (IXRS) to determine how many subjects on tolvaptan or placebo have been assessed and closing a group when 10 subjects have completed. The doses that the subjects will be given will be from their currently prescribed IMP. The morning dose will be administered at approximately 8:00 AM in the fasting state (no food within 8 hours prior to dosing or within 2 hours postdosing), the afternoon dose 8 hours later, and with dinner served at least 2 hours postdose. Each dose will be administered with 240 mL still, room temperature water; the total 240 mL can be consumed over a 1-hour period following dosing.

3.2.2 Phase B

Qualified subjects (as defined in Section 3.1) who have completed Phase A on treatment and continue in Phase B will receive open-label tolvaptan for up to 24 months. In order to preserve the blind in Phase A, subjects will be started at a dose based on their current body weight (see Table 3.2.1-1) and after 1 week, they will be asked to up-titrate once from their starting dose. Subjects who wish to lower their dose secondary to tolerance will have their doses adjusted as necessary.

3.3 Trial Population

3.3.1 Number of Subjects and Description of Population

The target trial population will be at least 60 male and female subjects aged 12 to 17 years (inclusive), with a diagnosis of ADPKD as defined by the presence of family history and/or genetic criteria AND who have at least 10 renal cysts, each of which

measures at least 0.5 cm confirmed upon magnetic resonance imaging (MRI) inspection. In accordance with the PIP requirements, the trial will also allow subjects aged 4 to 11 years who meet criteria for entry to be enrolled concurrently during the recruitment period for the target population. It is expected that the trial may enroll approximately 100 subjects.

Subjects who are MRI-naive or under the age of 12 should have at least 4 cysts that are at least 1 cm in size confirmed by ultrasound prior to MRI inspection.

Treatment groups for the required population will be stratified by age and gender in the following age cohorts:

- Female subjects ages 12 to 14 years, inclusive
- Female subjects ages 15 to 17 years, inclusive
- Male subjects ages 12 to 14 years, inclusive
- Male subjects ages 15 to 17 years, inclusive

When > 15 subjects are enrolled in an age cohort, new screening for that age cohort will be closed; subjects concurrently in screening for that age cohort may be enrolled if they meet inclusion/exclusion criteria. When the last subject in the final age cohort for the required population has been achieved, enrollment in the trial will cease.

The trial is also open to children between the ages of 4 to 11 years (inclusive) with ADPKD, who meet the above criteria and who, in the opinion of the investigator, would benefit from treatment. Subjects, aged 4 to 11 years (inclusive), must have an ultrasound to assess renal cysts.

Qualified subjects (as defined in Section 3.1) who complete Phase A on study medication are eligible to participate in Phase B.

3.3.2 Subject Numbering

All subjects will be given a unique 5 digit subject screening identification (ID) number that starts with the letter “S” (SXXXXX).

3.4 Eligibility Criteria

3.4.1 Informed Consent/Informed Assent

Written informed consent will be freely obtained from all subjects’ guardian(s) or legally acceptable representative(s), as applicable for local laws. Written informed assent will be freely obtained from all subjects. Consent/assent will be documented on a written informed consent form (ICF) and informed assent form (IAF). The ICF/IAF will be

approved by the same institutional review board/independent ethics committee (IRB/IEC) that approves this protocol.

Age-appropriate assent documents will be created and subjects who are able will be required to reconsent or assent as appropriate if they matriculate from one age group to another. Subjects who became legal adults during the trial will be required to provide written informed consent as soon as they reach legal age.

Each ICF/IAF will comply with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guideline[12] and local regulatory requirements. The investigator will ensure that the sponsor reviews and authorizes any written site-specific ICF/IAF used in the trial before 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/assent must be obtained and documented before initiation of any procedures that are performed solely for the purpose of determining eligibility for this trial, including withdrawal from current medication(s).

Potential subjects are free to refuse entry into the trial, or withdraw from the trial at any time, without justification, and there will be no consequences to their further care.

Once appropriate essential information has been provided and fully explained in layman's language to the subject by the investigator (or a qualified designee), and it has been documented that the subject has had the opportunity to ask questions, the IRB/IEC-approved written ICF/IAF will be signed and dated by both the subject and/or the subject's legally acceptable representative (eg, guardian) 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/IAF; the original shall be kept on file by the investigator.

Subjects may be asked to sign additional ICF/IAFs if the protocol is amended to significantly add or change procedures or if new safety information is determined.

Subjects who are not started on treatment after the ICF/IAF is signed are permitted to be rescreened under the conditions specified in Section 3.9 (Screen Failures). In the event that the subject is rescreened for trial participation, a new ICF/IAF must be signed.

If a subject is legally emancipated, informed consent must be sought directly from the subject. Subjects who turn age 18 (or the age of adulthood as specified by local laws or

regulations) during the trial may continue in the trial; however, must sign a new ICF at that time.

In addition to the English version of the ICF/IAF, the documents may also be translated into local languages for use in this trial. Translation with back-translation for confirmation will be utilized to ensure accuracy.

3.4.2 Inclusion Criteria

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

Table 3.4.2-1 Inclusion Criteria

1.	Male and female subjects aged 4 to 17 years (inclusive) with a diagnosis of ADPKD as defined by the presence of family history and/or genetic criteria AND who have at least 10 renal cysts, each of which measure at least 0.5 cm, confirmed upon MRI inspection; subjects under the age of 12 years must have at least 4 cysts that are at least 1 cm in size, confirmed by ultrasound.
2.	Weight ≥ 20 kg.
3.	Subjects with eGFR ≥ 60 mL/min/1.73m^2 within 31 days prior to randomization (using the Schwartz formula, eGFR = 0.413 × height [cm] /serum creatinine mg/dL).
4.	Independent in toileting.
5.	Trial-specific written informed consent obtained from a parent/guardian or legally acceptable representative, as applicable for local laws, at screening, prior to the initiation of any protocol required procedures. In addition, the subject must provide age-appropriate informed assent at screening and must be able to understand that he or she can withdraw from the trial at any time.
6.	Ability to swallow a tablet[a].
7.	Ability to commit to remain fully abstinent (periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] or withdrawal are not acceptable methods of contraception) or use two approved methods of birth control during the trial and for 30 days following the last dose of IMP for sexually active females of childbearing potential.

[a]Must also meet Health Authority/Ethics Committee age restrictions on tablet use (if applicable).

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.	Females who are breast-feeding and/or who have a positive pregnancy test result prior to receiving IMP.
2.	Liver function tests including AST, ALT ≥ 1.5 × ULN.
3.	Nocturnal enuresis.
4.	Need for chronic diuretic use.
5.	Subjects with advanced diabetes (eg, glycosylated hemoglobin [HgbA1c] > 7.5, and/or glycosuria by dipstick, significant proteinuria, retinopathy), evidence of additional significant renal disease(s) (ie, currently active glomerular nephritides), renal cancer, single kidney, or recent (within 6 months of screening) renal surgery or acute kidney injury.
6.	Subjects who have known clinically significant allergic reactions to chemicals with structure similar to tolvaptan (ie benzazepines): benzazepril, conivaptan, fenoldopam mesylate or mirtazapine.
7.	Subjects having disorders in thirst recognition or inability to access fluids.

Table 3.4.3-1 Exclusion Criteria	
8.	Subjects who have bladder dysfunction and/or difficulty voiding.
9.	Subjects with critical electrolyte imbalances, as determined by the investigator.
10.	Subjects with or at risk of significant hypovolemia, as determined by investigator.
11.	Subjects with a history of substance abuse (within the last 6 months).
12.	Subjects 12 years of age and older having contraindications to, or interference with MRI assessments (eg, ferro-magnetic prostheses, aneurysm clips, severe claustrophobia).
13.	Subjects taking a vasopressin agonist (eg, desmopressin).
14.	Subjects with a history of persistent noncompliance with antihypertensive or other important medical therapy.
15.	Subjects taking medications or having concomitant illnesses likely to confound endpoint assessments, including taking approved (ie, marketed) therapies for the purpose of affecting PKD cysts such as tolvaptan, vasopressin antagonists, anti-sense RNA therapies, rapamycin, sirolimus, everolimus, or somatostatin analogs (ie, octreotide, sandostatin).
16.	Has any medical condition that, in the opinion of the investigator, could interfere with evaluation of the trial objectives or safety of the subjects.
17.	Is deemed unsuitable for trial participation in the opinion of the investigator.
18.	Subjects who received any investigational agent in a clinical trial within 30 days prior to screening.
19.	Subjects who have a known lactose intolerance.
20.	Subjects who have had cyst reduction surgery within 6 weeks of the screening visit.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; PKD = polycystic kidney disease RNA = ribonucleic acid; ULN = upper limit of normal

Subjects must agree to the restrictions to medications and lifestyle as described in Section 4.

3.5 Endpoints

3.5.1 Primary Endpoint

The co-primary endpoints are the change from baseline in spot urine osmolality (premorning dose) and specific gravity (premorning dose) after 1 week of daily dosing in Phase A.

3.5.2 Secondary Endpoint(s)

The key secondary endpoint is the percent change from Phase A baseline in height-adjusted TKV (htTKV) as measured by MRI at 12 months.

Other secondary endpoints:

- 24-hour fluid balance prior to Week 1.
- Change from baseline in renal function (eGFR by Schwartz formula) at each clinic visit (Week 1, Month 1, Month 6, and Month 12) in Phase A.
- Change from baseline in renal function (eGFR by Schwartz formula) at each clinic visit (Week 1, Month 1, Month 6, Month 12, Month18, and Month 24) in Phase B.

- Percent change in htTKV as measured by MRI from Phase B baseline to Phase B Month 12.
- Percent change in htTKV as measured by MRI from Phase B baseline to Phase B Month 24.
- Pharmacodynamic endpoints of urine volume (including 24-hour fluid volume), fluid intake and fluid balance, sodium, creatinine, and free water clearance during dense PK sampling (after at least 1 Month on IMP).
- Proportions of each Tanner Stage by gender and age compared to normative populations at baseline, 6 months, and 12 months during the placebo-controlled phase (Phase A), and every 6 months during the open-label extension phase (Phase B).
- Description of changes from baseline percentiles for height and weight by gender and age at baseline, 6 months, and 12 months during the placebo-controlled phase (Phase A), and every 6 months during the open-label extension phase (Phase B).
- Safety variables (changes from baseline in creatinine, vital signs, laboratory values including liver function tests [LFTs], rate of aquaretic AEs) in placebo and tolvaptan.

- [redacted]

[redacted]

3.6 Measures to Minimize/Avoid Bias

Subjects satisfying the entrance criteria in Phase A will be randomized to the trial by the use of an IXRS. Subjects will receive tolvaptan or matching placebo in a randomized, double-blinded fashion. Randomization will be 1:1, tolvaptan to placebo, according to a computer-generated randomization schedule supplied by the sponsor. Subjects ages 12 to 17 will be stratified by age and gender.

The prescription of additional fluids to subjects in this trial will include ingestion of water or non-caloric fluids adequate to prevent excessive thirst throughout the daytime period and an additional 1 to 2 cups of water before bedtime with additional replenishment with each episode of nocturia to prevent dehydration (see Section 4.2). [redacted]

[redacted].

When all subjects in Phase A have either completed the Month 12 visit or early terminated from the trial, a snapshot of the data will be taken. This snapshot will be unblinded, and results analyzed and reported in an interim CSR. The sites will remain blinded until completion of the trial or a safety need arises.

3.7 Trial Procedures

Trial assessment time points are summarized in Table 3.7-1 for Phase A and in Table 3.7-2 for Phase B.

Table 3.7-1 Schedule of Assessments Phase A

	Screening (-30 to -1)	Baseline (D 1)	Wk 1 (-1/+3 D)	M1 (Wk 4) (±7 D)	M6 (±14 D)	Monthly Safety Visits: M2, 3, 4, 5, 7, 8, 9, 10, 11 (±4 D)[a]	Titration Contact (phone call or visit)	M12[b] (D365) (+14 D)/ End of Treatment (EoTx)[c,d]	Follow-Up[c,d]	
									7 D Post Last Dose (+2 D)	14 D Post Last Dose (+2 D)
Informed consent/assent	X									
Inclusion/exclusion	X	X								
Uroflowmetry Assessment	X									
Demographics, medical/ADPKD history[e]	X									
Tanner staging[f]		X			X			X		
MRI/ultrasound[g]	X							X		
Renal pelvic measurement[h]	X			X				X		
Vital signs[i]	X	X	X	X	X			X		
12-lead electrocardiogram	X									
Body height and weight/growth percentiles[j]	X	X[j]	X[j]	X[j]	X			X		
Serum chemistry/hematology/ urinalysis[k]	X				X			X		
Liver function tests/creatinine[k,l]	X	X	X	X	X	X		X	X	
Serum sodium[k]	X	X	X	X	X	X				

	Screening (-30 to -1)	Baseline (D 1)	Wk 1 (-1/+3 D)	M1 (Wk 4) (±7 D)	M6 (±14 D)	Monthly Safety Visits: M2, 3, 4, 5, 7, 8, 9, 10, 11 (±4 D)[a]	Titration Contact (phone call or visit)	M12[b] (D365) (+14 D)/ End of Treatment (EoTx)[c,d]	Follow-Up[c,d]	
									7 D Post Last Dose (+2 D)	14 D Post Last Dose (+2 D)
Urine osmolality[n]		X	X	X						
Urine specific gravity		X	X	X						
Urine or serum pregnancy test[o]	X	X		X	X	X		X		
Alcohol & drug screen[p]	X	X								
Physical examination[q]	X	X	X	X	X			X		
Randomization		X								
IMP administration[r]		X	X	X	X					
IMP dispensation[s]		X	X	X	X	X[m]	X			
IMP reconciliation[t]			X	X	X	X[m]		X		
Palatability and acceptability		X								
[redacted]										
ADPKD outcomes		X	X	X	X			X		
[redacted]										
PK & PD sample collection[w]			X	X	X			X[x]		
24-hour fluid balance			X							
Concomitant medications	X	←----------						----------→	X	X
Adverse events	X	←----------						----------→	X	X

EoTX = end of treatment

[a]Monthly safety visits: If it is more convenient for the subject, laboratory tests may be collected at a local laboratory; a clinic visit is not required. The PI is required to review monthly safety labs and record them in the electronic case report form (eCRF).

[b]The Month 12 visit will serve as the Baseline visit for Phase B. The subject's body weight at this visit will be used to determine the starting dose in Phase B.

[c]Any subject who discontinues IMP during Phase A will enter the Follow-up period and then be followed every 6 months through Phase A. The 14 day follow-up visit is a telephone contct only, a clinic visit is not required. Subjects who do not complete Phase A on treatment are not eligible to enter Phase B.

[d]An assessment of vital status will be conducted on subjects who terminate IMP prior to the Phase A Month 12 visit and do not agree to additional safety follow-up but do not withdraw consent for continued telephone contact. See Section 3.7.4.8.

[e]ADPKD genetic history to be collected if available, although it is not specifically required.

[f]A subject who reaches Stage 5 (both in pubic hair and genitalia) does not need to continue with Tanner Staging.

[g]MRI/ultrasound imaging: The baseline imaging used must be the same imaging used throughout the trial (Phase A and Phase B). It is recommended that subjects have their imaging done on the same day as the clinic visit; however imaging can be performed up to 30 days prior to the scheduled visit. The subject should be on IMP for 30 consecutive days prior to imaging (except screening). MRI/ultrasound is not required at the EoTx visit.

[h]Renal pelvic assessments will be done using ultrasound. The Month 1 assessment can be performed at any scheduled visit between Month 1 and Month 3 but cannot be conducted until 30 days after the subject has started IMP, see Section 3.7.4.5.

[i]Vital signs at each visit include seated heart rate and blood pressure (systolic and diastolic). Temperature will be collected only at the Phase A baseline visit.

[j]Body weight should be measured post-void. Growth percentile is not required at the baseline, Wk 1 and M1 visits. Body weight is not required at the Wk 1 and M1 visits. .

[k]Central laboratory serum laboratory tests will be performed for all visits (only monthly safety labs may be collected at a local laboratory). Fasting is required at the screening visit. Fasting is recommended for all other visits, but is not required. 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, phosphorus, parathyroid hormone, vitamin D, and bicarbonate levels.

[l]A full liver function panel (AST, ALT, alkaline phosphatase [ALP], bilirubin, total [BT]) will be done at screening. At subsequent visits, LFTs include AST and ALT only, unless otherwise clinically indicated. Laboratory samples for LFTs, serum sodium, and serum creatinine will be collected at baseline only if the baseline visit occurs > 7 days after the Screening visit. Monthly visits include LFTs, serum creatinine and pregnancy test. See Section 5.4 for handling abnormal LFTs.

[m]Months 3 and 9 are drug dispensing visits. Additional assessments to be completed at this visit are: drug dispensation and drug reconciliation.

[n]Spot urine sample collected predose on the morning of Day 1, prior to the morning dose on Week 1, and prior to the morning dose on Month 1. See Section 3.7.5.2 for sample collection details.

[o]A urine or serum pregnancy test for females of childbearing potential (all females ≥ 12 years of age and females < 12 years of age who have started menstruating) will be performed during the study. On suspicion of pregnancy, an unscheduled urine or serum pregnancy testing will be performed. Positive urine pregnancy tests must be confirmed with a serum pregnancy test. Investigator (or appropriate site staff) is advised to counsel participants on the risk of pregnancy while participating in a clinical trial as well as ensuring the child understands how pregnancies occur and can be avoided. This should be documented in source records.

[p]Alcohol/drug screen is performed per clinical judgment and institutional guidelines.

[q]A full physical examination is required at screening for the purposes of inclusion into the trial. At all other visits, as needed, a "directed" physical examination may be performed to focus on PKD-related signs and symptoms.

[r]The first dose of IMP will be administered to the subject in the clinic. If the visit occurs in the afternoon, the first dose will be the PM dose of IMP. The last dose of Phase A will be taken the evening prior to the Month 12 visit.

[s]If during the titration contact the determination is made to adjust the dose regimen, dose adjustments will be made using dispensed supply if possible, and dose instructions will be provided by the investigator. The subject's current dose will be recorded at each visit.

[t]Drug reconciliation will be conducted at every visit. If additional drug supply is required for titration purposes, the site will arrange a subject visit for dispensation.

[redacted]

[w]Dense PK and PD sampling will occur in a subset of subjects (see Section 3.7.5.1) after at least 1 month of dosing. These subjects will be hospitalized the evening prior to the scheduled PK sampling (typically a Friday evening) and discharged after the 24 hour PK sample collection (typically Sunday morning). [redacted]

[x]If the subject terminated IMP treatment early, a PK sample will be collected at the EoTx visit. PK samples at subsequent visits do not need to be collected.

Table 3.7-2 Schedule of Assessments Phase B

	Baseline[a] (D 1) See Phase A M12 Visit	Wk 1 (-1/+3 D)	M1 (Wk 4) (±7 D)	M6, M12, M18 (±14 D)	Monthly Safety Visits: M2, 3, 4, 5, 7, 8, 9, 10, 11, 13, 14, 15, 16, 17, 19, 20, 21, 22, 23 (±4 D)[b]	Titration Contact (phone contact)	M24 (±14 D) / End of Treatment (EoTx)[c]	Follow-Up	
								7 D post last dose (+2 D)	14 D post last dose (+2 D)[d]
MRI/ultrasound[e]				X[f]			X[f]		
Renal pelvic assessment[g]			X	X[g]					
Vital signs[h]		X	X	X			X		
Body height and weight/growth percentiles[i]		X[i]	X[i]	X			X		
Serum chemistry/Hematology[j]				X			X		
Liver function tests[j,k]		X	X	X	X[l]		X	X	
Serum sodium/Creatinine[j]		X	X	X	X[l]		X		
Urinalysis[j]				X			X		
Urine or serum pregnancy test[m]			X	X	X[l]		X		
Physical examination[n]		X	X	X			X		
Tanner staging[o]				X			X		
Drug administration[p]	X	X	X	X					
Drug dispensation[q]	X	X	X	X	X[l]	X			
Drug reconciliation[q]	X	X	X	X			X		
[redacted]									
24-hour fluid balance		X							
Concomitant medications		←					→	X	X

	Baseline[a] (D 1) See Phase A M12 Visit	Wk 1 (-1/+3 D)	M1 (Wk 4) (±7 D)	M6, M12, M18 (±14 D)	Monthly Safety Visits: M2, 3, 4, 5, 7, 8, 9, 10, 11, 13, 14, 15, 16, 17, 19, 20, 21, 22, 23 (±4 D)[b]	Titration Contact (phone contact)	M24 (±14 D) / End of Treatment (EoTx)[c]	Follow-Up	
								7 D post last dose (+2 D)	14 D post last dose (+2 D)[d]
Adverse events		←----------					----------→	X	X

[a]The Month 12 visit from Phase A will serve as the baseline visit for Phase B. The subject's body weight at this visit will be used to determine the starting dose in Phase B.

[b]Monthly safety visits: If it is more convenient for the subject, laboratory tests may be collected at a local laboratory; a clinic visit is not required. The PI is required to review monthly safety labs and record them in the electronic case report form (eCRF).

[c]Subjects who discontinue IMP during Phase B, will have safety laboratory tests (including LFTs) at the 7-day posttreatment follow-up visit, and then will be followed every 6 months through Phase B. An assessment of vital status will be conducted on subjects who terminate IMP prior to the Phase B Month 24 visit and do not agree to additional safety follow-up but do not withdraw consent for continued telephone contact. See Section 3.7.4.8.

[d]The 14 day follow-up visit is a telephone contact only, a clinic visit is not required.

[e]The baseline imaging used must be the same imaging used throughout the trial (Phase A and Phase B).

[f]MRI/ultrasound at Month 12 and 24 only. MRI/ultrasound is not required at EoTx visit.

[g]Renal pelvic assessments will be done using ultrasound. The Month 1 assessment can be performed at any scheduled visit between Month 1 and Month 3 but cannot be conducted until 30 days after the subject has started IMP, see Section 3.7.4.5. Renal pelvic assessment is also required at Month 12.

[h]Vital signs at each visit include seated heart rate and blood pressure (systolic and diastolic).

[i]Body weight should be measured post-void. Growth percentile and body weight is not required at the Wk1 and M1 visits.

[j]Central laboratory serum laboratory tests will be performed for all visits (only monthly safety labs may be collected at a local laboratory). Fasting is recommended for all, but is not required. 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, phosphorus, parathyroid hormone, vitamin D, and bicarbonate levels.

[k]Liver function tests are for AST and ALT only, unless otherwise clinically indicated. See Section 5.4 for handling abnormal LFTs. .

[l]Months 3, 9, 15, and 21 are drug dispensing visits. Additional assessments to be completed at this visit are: drug dispensation and drug reconciliation.

[m]A urine or serum pregnancy test for pregnancy for females of childbearing potential (all females ≥ 12 years of age and females < 12 years of age who have started menstruating) will be performed. On suspicion of pregnancy, an unscheduled urine or serum pregnancy testing will be performed. Positive urine pregnancy tests must be confirmed with a serum pregnancy test. Investigator (or appropriate site staff) is advised to counsel participants on the risk of pregnancy while participating in a clinical trial as well as ensuring the child understands how pregnancies occur and can be avoided. This should be documented in source records.

[n]As needed, a "directed" physical examination may be performed to focus on PKD-related signs and symptoms.

[o]A subject who reaches Stage 5 (both in pubic hair and genitalia) does not need to continue with Tanner Staging.

[p]The first dose of IMP will be administered to the subject in the clinic. The last dose of Phase B will be taken the evening prior to the Month 24 visit.

[q]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 recorded at each visit. Drug reconciliation will be conducted at every visit. If additional drug supply is required for titration purposes, the site will arrange a subject visit for dispensation.

[redacted]

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3.7.1 Schedule of Assessments

3.7.1.1 Randomized, Double-blind Phase A

3.7.1.1.1 Screening

The procedures listed below will be performed during the screening visit (Days −30 to −1) to ensure that the subject qualifies for the trial.

1) Trial procedures and information regarding the nature of the trial will be reviewed and written informed consent/assent will be obtained prior to any trial-related procedures.
   - Informed consent will be obtained from each subject's parent/legal guardian or legally acceptable representative prior to any trial procedures being conducted.
   - Each subject who is able will indicate willingness to participate in the trial by signing or marking an assent form (as applicable) supplied for this purpose.
   - Informed consent/assent needs to be obtained each time a subject matriculates into the next age group.
2) Inclusion and exclusion criteria will be reviewed and documented.
3) Uroflowmetry assessment will be performed.
4) Demographic information will be collected.
5) Medical and ADPKD history will be recorded.
   - Medical history should include the subject's current list of medical problems.
   - ADPKD medical history should include a diagnosis of ADPKD as defined by the presence of family history and/or genetic criteria AND who have at least 10 renal cysts, each of which measures at least 0.5 cm, confirmed upon MRI inspection. Younger subjects who are MRI-naive should have at least 4 cysts that are at least 1 cm in size, confirmed by ultrasound.
   - ADPKD genetic history to be collected if available, although it is not specifically required.
6) Renal pelvis assessment will be performed by ultrasound.
7) Magnetic resonance imaging or ultrasound will be performed to confirm eligibility for the trial and to measure TKV. The baseline imaging used must be the same imaging used throughout the trial (Phase A and Phase B).
8) Vital signs (seated blood pressure and heart rate) will be assessed. Vital signs should be assessed prior to blood draws.
9) A resting 12-lead electrocardiogram (ECG) will be performed after the subject has been supine and at rest ≥ 10 minutes.
10) Body height will be measured.
11) Body weight will be measured. Body weight should be measured post-void.
12) Growth percentile will be calculated.

13) Fasting laboratory samples for serum chemistry, hematology, and urinalysis will be collected for analysis at the central laboratory. Serum chemistry to include a full liver function panel (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], and bilirubin, total [BT]), serum sodium, and creatinine. 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, phosphorus, parathyroid hormone, vitamin D, and bicarbonate levels.
14) A urine or serum pregnancy test will be performed on all female subjects ≥ 12 years of age and all female subjects < 12 years of age if menarche has occurred. In the case of a positive urine pregnancy test result, a serum pregnancy test will be performed as confirmatory.
15) Alcohol/drug screen is performed per clinical judgment and institutional guidelines.
16) A full physical examination will be conducted.

[redacted]

18) Urine collection container will be dispensed to the subject or parent(s) or legal guardian(s) for collection of Day 1 sample for urine osmolality and specific gravity. Instructions for collection of urine sample will be reviewed with subject and parent(s) or legal guardian.

[redacted]

20) Concomitant medications ongoing at the screening visit and throughout the trial will be recorded.
21) Adverse events will be recorded.

3.7.1.1.2 Phase A Baseline (Randomization) (Day 1)

1) Inclusion and exclusion criteria will be reviewed and documented. Subjects who remain eligible for entry into the trial will be randomized using the trial's IXRS.
2) Tanner Staging will be performed.
3) Vital signs (seated blood pressure and heart rate) will be assessed prior to blood draws. Temperature will be collected at the baseline visit only.
4) Body height will be measured.
5) Body weight will be measured.
6) Laboratory samples for LFTs, serum sodium, and serum creatinine will be collected if the baseline visit occurs > 7 days after the screening visit. Liver function tests may be limited to include AST and ALT only, as clinically appropriate.

7) Urine sampling for urine osmolality and urine specific gravity. This sample should be obtained prior to the subject eating breakfast, from the urine void taken after the first morning's void, and will ideally be provided as a mid-stream, clean-catch sample. The sample will be brought to the clinic for testing.
8) A urine or serum pregnancy test will be performed on all female subjects ≥ 12 years of age and all female subjects < 12 years of age if menstruation has started. In the case of a positive urine pregnancy test result, a serum pregnancy test will be performed as confirmatory.
9) Alcohol/drug screen is performed per clinical judgment and institutional guidelines.
10) As needed, a directed physical examination focused on ADPKD-related signs and symptoms as well as any major changes from screening will be performed.
11) The IMP will be dispensed according to IXRS. The first dose of IMP will be administered to the subject in the clinic. If the visit occurs in the afternoon, the first dose will be the PM dose. The IMP will be administered with water; a total of at least 240 mL of still, room temperature water should be consumed within 1 hour of dosing.
12) Assess palatability and acceptability of the IMP for subjects immediately after dosing and again between 15 to 20 minutes after dosing.
[redacted]
14) Urine collection containers will be dispensed to the subject or parent(s) or legal guardian(s) for collection of Week 1 sample for urine osmolality and specific gravity and for the determination of the volume of each urine void in the 24-hour urine volume assessment.
[redacted]
17) A 24-hour fluid balance diary will be dispensed to the subject or parent(s) or legal guardian(s) for recording of 24-hour fluid intake and urine output. Subject or parent(s) or legal guardian(s) will be instructed to record all fluid intake and urine output in the 24 hours prior to the Week 1 visit. Refer to Section 3.7.5.2.2.
18) Concomitant medications will be recorded.
19) Adverse events will be recorded.

3.7.1.1.3 Week 1 (-1/+3 days)

1) Vital signs (seated blood pressure and heart rate) will be assessed prior to blood draws.
2) Body height will be measured.

3) Laboratory samples for LFTs, serum sodium, and creatinine will be collected for analysis at the central laboratory. Liver function tests may be limited to include AST and ALT only, as clinically appropriate.
4) Urine sampling for urine osmolality and urine specific gravity. This sample should be obtained prior to the subject eating breakfast, from the urine void taken after the first morning's void, and will ideally be provided as a mid-stream, clean catch sample.
5) As needed, a directed physical examination focused on ADPKD-related signs and symptoms as well as any major changes from screening will be performed.
6) IMP tolerability will be assessed. New IMP will be dispensed according to IXRS. Used IMP will be collected, and drug accountability will be performed.

[redacted]

10) Review 24-hour fluid balance diary, and record 24-hour fluid intake and urine output.
11) Urine collection container will be dispensed to the subject or parent(s) or legal guardian(s) for collection of Month 1 sample for urine osmolality and specific gravity.

[redacted]

14) Concomitant medications will be recorded.
15) Adverse events will be recorded.

3.7.1.1.4 Month 1 (Week 4) (± 7 days)

1) Renal pelvis assessment will be performed by ultrasound. The Month 1 assessment can be performed at any scheduled visit between Month 1 and Month 3 but cannot be conducted until 30 days after the subject has started IMP, see Section 3.7.4.5.
2) Vital signs (seated blood pressure and heart rate) will be assessed. Vital signs should be assessed prior to blood draws.
3) Body height will be measured.
4) Laboratory samples for LFTs, serum sodium, serum creatinine, and urine pregnancy testing (as applicable) will be collected. Liver function tests may be limited to include AST and ALT only, as clinically appropriate.
5) Urine sampling for urine osmolality and urine specific gravity. This sample should be obtained prior to the subject eating breakfast, from the urine void taken

after the first morning's void, and will ideally be provided as a mid-stream, clean catch sample.

6) A urine pregnancy test will be performed on all female subjects ≥ 12 years of age and all female subjects < 12 years of age if menstruation has started. In the case of a positive urine pregnancy test result, a serum pregnancy test will be performed as confirmatory.
7) As needed, a directed physical examination focused on ADPKD-related signs and symptoms as well as any major changes from screening will be performed.
8) New IMP will be dispensed according to IXRS. Used IMP will be collected and drug accountability will be performed.

[redacted]

13) Concomitant medications will be recorded.
14) Adverse events will be recorded.

3.7.1.1.5 Dense PK and PD Sampling

Dense PK and PD sampling will be conducted in a subset of subjects after they have received at least 1 month of IMP. These subjects will be hospitalized the evening prior to the scheduled PK sampling (typically a Friday evening) and discharged after the 24-hour PK sample collection (typically Sunday morning). Concomitant medications and adverse events will be recorded. See Section 3.7.5.3.1 and Section 3.7.5.3.

3.7.1.1.6 Monthly Safety Visits: Months 2, 3, 4, 5, 7, 8, 9, 10, 11 (± 4 days)

Subjects will be required to have monthly LFTs, serum sodium, serum creatinine, and urine pregnancy testing (as applicable). Liver function tests may be limited to include AST and ALT only, as clinically appropriate. These tests can be performed at a local laboratory and results provided to the investigator. Investigators and/or other appropriately medically trained personnel are encouraged to evaluate laboratory tests prior to initiating the next month of IMP to ensure transaminases are at appropriate levels. Concomitant medications and adverse events will be recorded.

At Months 3 and 9, subjects will be required to come to the clinic for IMP dispensation and accountability. [redacted]

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[redacted]

3.7.1.1.7 Month 6 (± 14 days)

1) Tanner staging will be performed.
2) Vital signs (seated blood pressure and heart rate) will be assessed. Vital signs should be assessed prior to blood draws.
3) Body height will be measured.
4) Body weight will be measured. Body weight should be measured post-void.
5) Growth percentile will be calculated.
6) Laboratory samples for serum chemistry, hematology, and urinalysis will be collected for analysis at the central laboratory. Fasting is recommended but not required. Serum chemistry to include LFTs, serum sodium, and creatinine. Liver function tests may be limited to include AST and ALT only, as clinically appropriate.
7) A urine pregnancy test will be performed on all female subjects ≥ 12 years of age and all female subjects < 12 years of age if menstruation has started. In the case of a positive urine pregnancy test result, a serum pregnancy test will be performed as confirmatory.
8) As needed, a directed physical examination focused on ADPKD-related signs and symptoms as well as any major changes from screening will be performed.
9) New IMP will be dispensed according to IXRS. Used IMP will be collected and drug accountability will be performed.

[redacted]

14) Concomitant medications will be recorded.
15) Adverse events will be recorded.

3.7.1.1.8 Month 12 (Day 365) or End of Treatment (+ 14 days)

The Phase A Month 12 visit serves as the baseline visit for Phase B.

1) Tanner staging will be performed.
2) An MRI or ultrasound will be performed to measure TKV only at the Month 12 visit. This assessment must be performed while the subject is taking IMP and can be performed within 30 days prior to the visit. The Month 12 Phase A MRI must

be conducted prior to the initiation of Phase B IMP. The imaging used at baseline must be the same imaging used throughout the trial (Phase A and Phase B).

3) Renal pelvis assessment will be performed by ultrasound the Month 12 visit only.
4) Vital signs (seated blood pressure and heart rate) will be assessed. Vital signs should be assessed prior to blood draws.
5) Body height will be measured.
6) Body weight will be measured. Body weight should be measured post-void.
7) Growth percentile will be calculated.
8) Laboratory samples for serum chemistry, hematology, and urinalysis will be collected for analysis at the central laboratory. Fasting is recommended but not required. Serum chemistry to include LFTs and creatinine. Liver function tests may be limited to include AST and ALT only, as clinically appropriate.
9) A urine pregnancy test will be performed on all female subjects ≥ 12 years of age and all female subjects < 12 years of age if menstruation has started. In the case of a positive urine pregnancy test result, a serum pregnancy test will be performed as confirmatory.
10) As needed, a directed physical examination focused on ADPKD-related signs and symptoms as well as any major changes from screening will be performed.
11) The last dose of IMP for Phase A will be taken the night prior to the Month 12 visit. All used Phase A IMP will be collected and drug accountability will be performed.
12) IMP for Phase B will be dispensed according to IXRS. The first dose of Phase B IMP will be administered to the subject in the clinic. If the visit occurs in the afternoon, the first dose will be the PM dose. IMP will be administered with water; a total of at least 240 mL of still, room temperature water should be consumed within 1 hour of dosing.

[redacted]

17) Urine collection container will be dispensed to the subject or parent(s) or legal guardian(s) for collection and determination of volume of each urine void for the Phase B Week 1 24-hour urine volume.
18) A 24-hour fluid balance diary will be dispensed to the subject or parent(s) or legal guardian(s) for recording of 24-hour fluid intake and urine output. Subject or parent(s) or legal guardian(s) will be instructed to record all fluid intake and urine output in the 24 hours prior to the Week 1 visit. Refer to Section 3.7.5.2.2.

19) Concomitant medications will be recorded.
20) Adverse events will be recorded.

3.7.1.1.9 Dosing and Titration Considerations

Subjects may be titrated down for tolerability at any time during the trial according to the titration schedule in Table 3.2.1-3. This titration may be done over the phone or in the clinic based on the investigator's judgment, although it is recommended that the subject be brought into the clinic if possible.

Planned drug interruptions are discouraged during the first month of dosing in Phase A and within the month prior to any MRI or ultrasound assessments. Refer also to Section 3.8.3.3 for additional information on drug interruption and drug discontinuation.

3.7.1.2 Open-label Phase B

3.7.1.2.1 Phase B Baseline (Day 1)

The Phase A Month 12 visit serves as the baseline visit for Phase B. See Section 3.7.1.1.8 for assessments to be collected. Subjects who have completed Phase A on treatment and continue in Phase B will receive open-label tolvaptan for up to 24 months. In order to preserve the blind in Phase A, subjects will be started at a dose based on their current body weight (see Table 3.2.1-1) and after 1 week, they will be asked to up-titrate once from their starting dose. Subjects who wish to lower their dose secondary to tolerance will have their doses adjusted as necessary.

3.7.1.2.2 Week 1 (-1/+3 days)

1) Vital signs (seated blood pressure and heart rate) will be assessed prior to blood draws.
2) Body height will be measured.
3) Laboratory samples for liver function tests, serum sodium and creatinine will be collected for analysis at the central laboratory. Liver function tests may be limited to include AST and ALT only, as clinically appropriate.
4) As needed, a directed physical examination focused on ADPKD-related signs and symptoms as well as any major changes from screening will be performed.
5) New IMP will be dispensed according to IXRS. Used IMP will be collected and drug accountability will be performed.

[redacted]

8) Review 24-hour fluid balance diary and record 24-hour fluid intake and urine output.
9) Concomitant medications will be recorded.

10) Adverse events will be recorded.

3.7.1.2.3 Month 1 (Week 4) (± 7 days)

1) Renal pelvis assessment will be performed by ultrasound. The Month 1 assessment can be performed at any scheduled visit between Month 1 and Month 3 but cannot be conducted until 30 days after the subject has started IMP, see Section 3.7.4.5.
2) Vital signs (seated blood pressure and heart rate) will be assessed prior to blood draws.
3) Body height will be measured.
4) Laboratory samples for LFTs, serum sodium, serum creatinine, and urine pregnancy testing (as applicable) will be collected. Liver function tests may be limited to include AST and ALT only, as clinically appropriate.
5) A urine pregnancy test will be performed on all female subjects ≥ 12 years of age and all female subjects < 12 years of age if menstruation has started. In the case of a positive urine pregnancy test result, a serum pregnancy test will be performed as confirmatory.
6) As needed, a directed physical examination focused on ADPKD-related signs and symptoms as well as any major changes from screening will be performed.
7) New IMP will be dispensed according to IXRS. Used IMP will be collected and drug accountability will be performed.

[redacted]

10) Concomitant medications will be recorded.
11) Adverse events will be recorded.

3.7.1.2.4 Month 6, Month 12 and Month 18 (± 14 days)

1) An MRI or ultrasound will be performed to measure TKV at the Month 12 visit only. This assessment must be performed while the subject is taking IMP and can be performed within 30 days prior to the visit. The same imaging must be used throughout the trial (Phase A and Phase B).
2) Renal pelvis assessment will be performed by ultrasound at the Month 12 visit only.
3) Vital signs (seated blood pressure and heart rate) will be assessed prior to blood draws.
4) Body height will be measured.
5) Body weight will be measured. Body weight should be measured post-void.
6) Growth percentile will be calculated.
7) Laboratory samples for serum chemistry, hematology, and urinalysis will be collected for analysis at the central laboratory. Fasting is recommended but not required. Serum chemistry to include serum sodium and creatinine. Liver

function tests may be limited to include AST and ALT only, as clinically appropriate.

8) A urine pregnancy test will be performed on all female subjects ≥ 12 years of age and all female subjects < 12 years of age if menstruation has started. In the case of a positive urine pregnancy test result, a serum pregnancy test will be performed as confirmatory.
9) As needed, a directed physical examination focused on ADPKD-related signs and symptoms as well as any major changes from screening will be performed.
10) Tanner Staging will be performed.
11) New IMP will be dispensed according to IXRS. Used IMP will be collected and drug accountability will be performed.

[redacted]

14) Concomitant medications will be recorded.
15) Adverse events will be recorded.

3.7.1.2.5 Monthly Safety Visits: Months 2, 3, 4, 5, 7, 8, 9, 10, 11, 13, 14, 15, 16, 17, 19, 20, 21, 22, 23 (± 4 days)

Subjects will be required to have monthly LFTs, serum sodium, serum creatinine, and urine pregnancy testing (as applicable) completed. Liver function tests to include AST and ALT only, unless otherwise clinically indicated. These tests can be performed at a local laboratory and results provided to the investigator. Investigators and/or other appropriately medically trained personnel are encouraged to evaluate labs prior to initiating the next month of IMP to ensure transaminases are at appropriate levels. Concomitant medications and adverse events will be recorded.

Drug dispensing visits will occur every 3 months at Months 3, 9, 15, and 21.

3.7.1.2.6 Month 24 or End of Treatment (± 14 days)

1) An MRI or ultrasound will be performed to measure TKV. This assessment must be performed while the subject is taking IMP and can be performed within 30 days prior to the visit. The same imaging must be used throughout the trial (Phase A and Phase B).
2) Vital signs (seated blood pressure and heart rate) will be assessed prior to blood draws.
3) Body height will be measured.
4) Body weight will be measured. Body weight should be measured post-void.
5) Growth percentile will be calculated.
6) Laboratory samples for serum chemistry, hematology, and urinalysis will be collected for analysis at the central laboratory. Fasting is recommended but not

required. Serum chemistry to include LFTs, serum sodium, and creatinine. Liver function tests may be limited to include AST and ALT only, as clinically appropriate.

7) A urine pregnancy test will be performed on all female subjects ≥ 12 years of age and all female subjects < 12 years of age if menstruation has started. In the case of a positive urine pregnancy test result, a serum pregnancy test will be performed as confirmatory.
8) As needed, a directed physical examination focused on ADPKD-related signs and symptoms as well as any major changes from screening will be performed.
9) Tanner Staging will be performed.

[redacted]

12) All used IMP will be collected and final drug accountability will be performed.
13) Concomitant medications will be recorded.
14) Adverse events will be recorded.

3.7.1.2.7 Dosing and Titration Considerations

Subjects may be down-titrated for tolerability at any time during the trial according to the titration schedule in Table 3.2.1-3. This titration may be done over the telephone or in the clinic based on the investigator's judgment. Drug interruptions are discouraged during the first month of dosing in Phase B and the month prior to any MRI assessments. Refer also to Section 3.8.3 for additional information on drug interruption and drug discontinuation.

3.7.1.3 Dehydration Monitoring Considerations

The aquaretic effects of tolvaptan are well known and can be managed adequately by the appropriate intake of fluid. In addition, any potential interactions of tolvaptan with diuretics, with particular focus on dehydration and decrease in renal function, should be monitored closely by the clinicians. Please see Section 4.2 for additional recommendations.

3.7.1.4 Follow-up Period

All subjects will be seen for a follow-up visit after they have discontinued from IMP. Subjects who discontinue IMP but continue to be followed for safety will complete the 7-day post last dose follow-up visit.

3.7.1.4.1 7 Days Post Last Dose Visit (+ 2 days)

All subjects will be seen in the clinic 7 days (+ 2) after their last dose of IMP. The following assessments will be completed:

1) Laboratory samples for liver function tests will be collected for analysis at the central laboratory. Liver function tests may be limited to include AST and ALT only, as clinically appropriate.
2) Concomitant medications will be recorded.
3) Adverse events will be recorded.

3.7.1.4.2 14 Days Post Last Dose Telephone Call (+ 2 days)

Subjects or their parent(s)/legal guardian(s) or legally acceptable representative(s) will be contacted via telephone or will be asked to come back to the clinic for a visit at 14 (+ 2) days post last dose to assess any new or ongoing AEs, and to collect information on any medications administered since the last visit. Ongoing follow-up may be required after a subject's trial completion for health status before the analysis of all trial results is completed.

3.7.2 Efficacy Assessments

3.7.2.1 MRI Assessments

MRI assessments will be performed according to the Schedule of Assessments Table 3.7-1 and Table 3.7-2 in all subjects aged 12 years and older. Specific parameters for MRI acquisition will be consistent with standards defined for assessing ADPKD TKV and cysts[7] and detailed in a separate Imaging Charter. Scans will be centrally read by individuals blinded to Phase A treatment assignment.

MRIs are scheduled to be performed 4 times during the trial: at the screening visit in Phase A, at Month 12 in Phase A, which is the same as the baseline visit in Phase B, at Month 12 and Month 24 in Phase B.

Subjects who have not discontinued treatment with IMP should be receiving IMP for 30 consecutive days prior to the MRI (with the exception of screening). The Phase A Month 12 MRI must be collected prior to the start of IMP in Phase B. For these subjects, if the subject has not been receiving IMP for 30 consecutive days, the medical monitor should be contacted prior to the collection of the MRI. For subjects who have discontinued IMP, MRI assessments will still be collected scheduled time points.

It is recommended that subjects have the MRI performed on the same day as the clinic visit; however MRIs can be performed up to 30 days prior to the scheduled visit. Ultrasounds may not be substituted for MRI assessments; the baseline method of imaging used must be consistent throughout the trial (Phase A and Phase B).

Subjects with ferro-magnetic prostheses, aneurysm clips, severe claustrophobia, or other contraindications or exclusions interfering with the MRI endpoint are not eligible to participate in this trial.

Primary efficacy analysis parameter (using a central reader) is combined renal volume of both kidneys (TKV). Upon request, sites may be provided the TKV values after database lock. No other interpretation or clinical assessment will be made. The subject may be granted access to MRI images in order to request any additional, non-trial, interpretations deemed necessary by their healthcare provider.

The MRI contrast agent gadolinium is not considered necessary for high quality interpretation and will not be used for the purposes of this trial due to an increased risk of nephrogenic systemic fibrosis or nephrogenic fibrosing dermopathy in subjects with renal failure, even though this population should be considered at lower risk.

3.7.2.2 Ultrasound Assessments

Subjects under 12 years of age will have ultrasound assessments in place of MRI assessments.

Subjects who have not discontinued treatment with IMP should be receiving IMP for 30 consecutive days prior to the ultrasound (with the exception of screening). The Phase A Month 12 ultrasound must be collected prior to the start of IMP in Phase B. For these subjects, if the subject has not been receiving IMP for 30 consecutive days, the medical monitor should be contacted prior to the collection of the ultrasound. For subjects who have discontinued IMP, ultrasound assessments will still be collected at the scheduled time points.

It is recommended that subjects have the ultrasound performed on the same day as the clinic visit; however ultrasound can be performed up to 30 days prior to the scheduled visit. MRI may not be substituted for ultrasound assessments; the baseline method of imaging used must be consistent throughout the trial (Phase A and Phase B).

Ultrasound axial measurements will be assessed locally. The htTKV will be estimated using an ellipsoid volume equation with 3 axes of measurement.

3.7.2.3 Renal Function

Changes from baseline in renal function (eGFR by Schwartz formula)[13] will be assessed at each scheduled visit. The formula for eGFR by Schwartz is:

$$eGFR = 0.413 \times \text{height [cm]} / \text{serum creatinine mg/dL}$$

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[redacted]

3.7.4 Safety Assessments

3.7.4.1 Adverse Events

Refer to Section 5, Reporting of Adverse Events.

3.7.4.2 Clinical Laboratory Assessments

Table 3.7.4.2-1 presents required clinical laboratory assessments (serum chemistry, hematology, and urinalysis). Clinical laboratory tests will be performed by a central laboratory for all scheduled trial visits. Subjects will have monthly liver function testing, creatinine, serum sodium, and urine or serum pregnancy testing (as applicable) at a local laboratory.

It is recognized that there may be limitations based on age and weight of children for the amount of blood that can be drawn at a single time point, per day, and the overall conduct of the trial. Wherever possible, it is encouraged to combine standard of care samples that would be taken regardless of trial participation with those samples required for the trial.

Table 3.7.4.2-1 Clinical Laboratory Assessments

Hematology:	Serum Chemistry:
Hemoglobin	ALP
Hematocrit	AST
Mean corpuscular hemoglobin concentration	ALT
Mean corpuscular volume	Bicarbonate (or carbon dioxide)
RBC count	BT
WBC count with differential	Urea or blood urea nitrogen
Platelet count	Calcium
RBC volume distribution width	Chloride
	Cholesterol, total
Urinalysis:	Creatinine
Color	Gamma glutamyl transferase
Appearance	Glucose
Albumin	Lactic dehydrogenase
Bilirubin	Potassium
Occult blood	Protein, total
Glucose	Sodium
Ketones	Triglycerides
Leukocytes	Uric Acid
Nitrites	
Protein	Additional Tests:
Urobilinogen	Urine or serum pregnancy for females of childbearing potential
Microscopic analysis, WBC/RBC counts per high powered field	
pH	Urine Drug Screen:
Protein	Alcohol[a]
Specific gravity	Amphetamines
	Barbiturates
	Benzodiazepines
	Cannabinoids
	Cocaine
	Methadone
	Opiates
	Phencyclidine

RBC = red blood cell; WBC = white blood cell

[a]Alcohol may be assessed using a breath alcohol test.

3.7.4.3 Physical Examination, Weight and Vital Signs

A full physical examination will be performed and documented at the Phase A screening visit. At other visits, as needed, a directed physical examination may be performed to focus on ADPKD-related signs and symptoms. Full and directed physical examinations will be performed and documented according to the Schedule of Assessments Table 3.7-1 for Phase A and Table 3.7-2 for Phase B.

The principal 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 by local regulations. Whenever possible, the

same individual should perform all physical examinations. Any undesirable condition present at a postscreening physical examination that was not present at the screening examination should be documented as an AE and followed to a satisfactory conclusion.

Full physical examination assessments should include assessments of all major body systems, including but not limited to, ears, nose, and throat, the thorax area, abdomen, urogenital, extremities, and skin and mucosae. Directed physical examinations should be focused on ADPKD-related signs and symptoms as well as any major changes from baseline. Any changes in medication or AEs will be recorded in the electronic case report form (eCRF).

Body height and weight will be measured (see Schedule of Assessments Table 3.7-1 for Phase A and Table 3.7-2 for Phase B). Every effort should be made to ensure that body weight measurements will be performed in a reproducible and consistent manner. Body weight measurements should be performed at the clinical trial site always using the same scale. Subjects should wear the same type of clothes at each measurement, preferably a gown and no shoes. All body weight measurements should be taken post-void. Subjects or their caregivers (if appropriate) will be instructed to obtain weight measurements on a weekly basis and report any changes (increase or decrease) greater than 3% to their physician.

Vital sign data including seated blood pressure (systolic and diastolic), heart rate, and temperature, will be taken at the visits identified in the Schedule of Assessments (Table 3.7-1 for Phase A and Table 3.7-2 for Phase B). Vital signs should be assessed prior to the collection of any blood draws.

3.7.4.4 Hepatic Monitoring

Refer to Section 5.4 for details on hepatic monitoring.

3.7.4.5 Renal Pelvis Assessment

Assessment of the renal pelvis (measurement of anterior-posterior diameter) for both kidneys will be performed using ultrasound at screening for all subjects. This assessment will be repeated between Months 1 to 3 in Phase A, but no earlier than 28 days after starting IMP and at the Phase A Month 12 visit. In Phase B, this assessment will be repeated between Months 1 to 3, but no earlier than 28 days after starting IMP and at the Phase B Month 12 visit.

3.7.4.6 Tanner Staging

Tanner Staging must be completed together with the physical examination, preferably by the same trial-affiliated clinician in the most inconspicuous manner for the subject as

possible. Tanner Staging could be completed by the trial-affiliated pediatrician or family practitioner (additionally physician's assistant or nurse practitioner where licensing permits). A subject who reaches Stage 5 (both in pubic hair and genitalia) at screening does not need to continue with Tanner Staging and the same stage will be carried forward to the remaining study visits. Sites should make attempts to have examiners of both sexes. Attempts should be made to have the examination performed by the same sex personnel as the subject. Otherwise, trial-affiliated personnel of the same sex as the subject (eg, nurse) should be in the same examination room as the subject.

Tanner Staging assessment consists of 2 domains (pubic hair and breast development) for girls and 3 domains (pubic hair, penis development, and testes development) for boys. The Tanner Staging assessment as a reference for the completing clinician is included in Appendix 2. The investigator will arrive at a single score summarizing the domains (not individual domain scores) when evaluating the subject.

3.7.4.7 Electrocardiogram Assessments

One ECG will be recorded at screening, prior to any blood draws. Twelve-lead ECGs will be recorded with the subject supine and at rest (for at least 10 minutes). Heart rate, PR interval, QRS duration, and QT interval will be evaluated. The principal investigator or designee will review, sign, and date each ECG reading. Any abnormalities should be reported as part of the medical history.

3.7.4.8 Vital Status

An assessment of vital status will be conducted on subjects who terminate IMP prior to the Phase A Month 12 visit or the Phase B Month 24 visit, and do not agree to additional safety follow-up and do not withdraw consent for continued telephone contact. The telephone contact will be made on the date at which the subject would have reached the Phase A or Phase B completion visit (eg, Month 12 Phase A or Month 24 Phase B) [+ 2 weeks]), and will be conducted with a reliable informant; either the subject and/or the parent/legal guardian, per investigator discretion. Vital status collected and recorded will be:

- Subject alive or deceased (date of death, cause of death)
- Whether the subject had a kidney transplant (date) or renal replacement therapy (date of initiation)

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3.7.5 Pharmacokinetic/Pharmacodynamic Assessments

[redacted]

3.7.5.2 Pharmacodynamic Assessments

3.7.5.2.1 Urine Osmolality and Specific Gravity

A spot urine sample for determination of both urine osmolality and specific gravity will be obtained at the following times during Phase A: predose on the morning of Day 1, prior to morning dose at Week 1, and prior to morning dose at Month 1.

The morning predose sample should be obtained prior to the subject eating or drinking anything for breakfast, from the urine void taken after the first morning's void, and will ideally be provided as a mid-stream, clean catch sample. Date and time of the urine sample, as well as the date and time of the last preceding dose of IMP should be noted in the eCRF.

The urine samples will be shipped to the central clinical laboratory for analysis. Detailed handling, including volume of sample needed, and shipping instructions with be provided in the laboratory manual.

3.7.5.2.2 24-hour Fluid Balance

Twenty-four hour fluid intake and urine volume output will be recorded for all subjects prior to up-titration in Phase A (Week 1) and Phase B (Week 1). Subjects will be instructed to record all fluid taken and all urine output for this 24-hour period. Volume measurement and urine collection containers will be provided to the subjects.

3.7.5.2.3 Palatability and Acceptability Assessment

A questionnaire will be administered to all subjects immediately after dosing to assess palatability to rate flavor/taste, smell, sweetness, and overall liking of the IMP. Subjects will also be asked about the ease of swallowing the IMP. Between 15 to 20 minutes after dosing, subjects will again be asked to assess overall liking of the IMP. Palatability and acceptability will be assessed once during Phase A, at the baseline (Day 1) visit.

3.7.5.3 Dense PK and PD Sampling

A subset of 20 subjects in the 12 to 17 year-old age group will have dense PK and PD sampling conducted at selected sites after at least 1 month of IMP treatment. The 20 subjects will be assigned by IXRS and will include 10 placebo subjects and 10 IMP subjects. This cohort will close when 20 subjects have completed.

Assessments collected are described below.

3.7.5.3.1 PK Cohort Sampling

Blood samples (4 mL) will be taken at predose (within 15 minutes prior to the morning dose), 1, 2, 4, 8 (within 15 minutes prior to the afternoon dose), 12, and 24 hours post the morning dose. Where possible, samples should be collected from the same needle stick as used to collect the PD samples.

Each dose will be administered with 240 mL still, room temperature water; the total 240 mL can be consumed over a 1-hour period following dosing. These subjects will be hospitalized the evening prior to the scheduled PK sampling (typically a Friday evening) and discharged after the 24 hour PK sample collection (typically Sunday morning).

Plasma will be collected and shipped to central clinical laboratory for storage. Detailed handling and shipping instructions are provided in Appendix 1.

3.7.5.3.2 PD Serum Sampling

Serum samples for determination of sodium, creatinine, and osmolality will be taken predose and at 2, 4, 8, 12, and 24 hours post the morning dose. Samples will be sent to the clinical chemistry laboratory for analysis. Where possible, samples should be collected from the same needle stick as used to collect the PK samples. Detailed handling, including volume of sample needed, and shipping instructions with be provided in the laboratory manual. Refer also to Appendix 1.

3.7.5.3.3 PD Urine Volume and Sampling

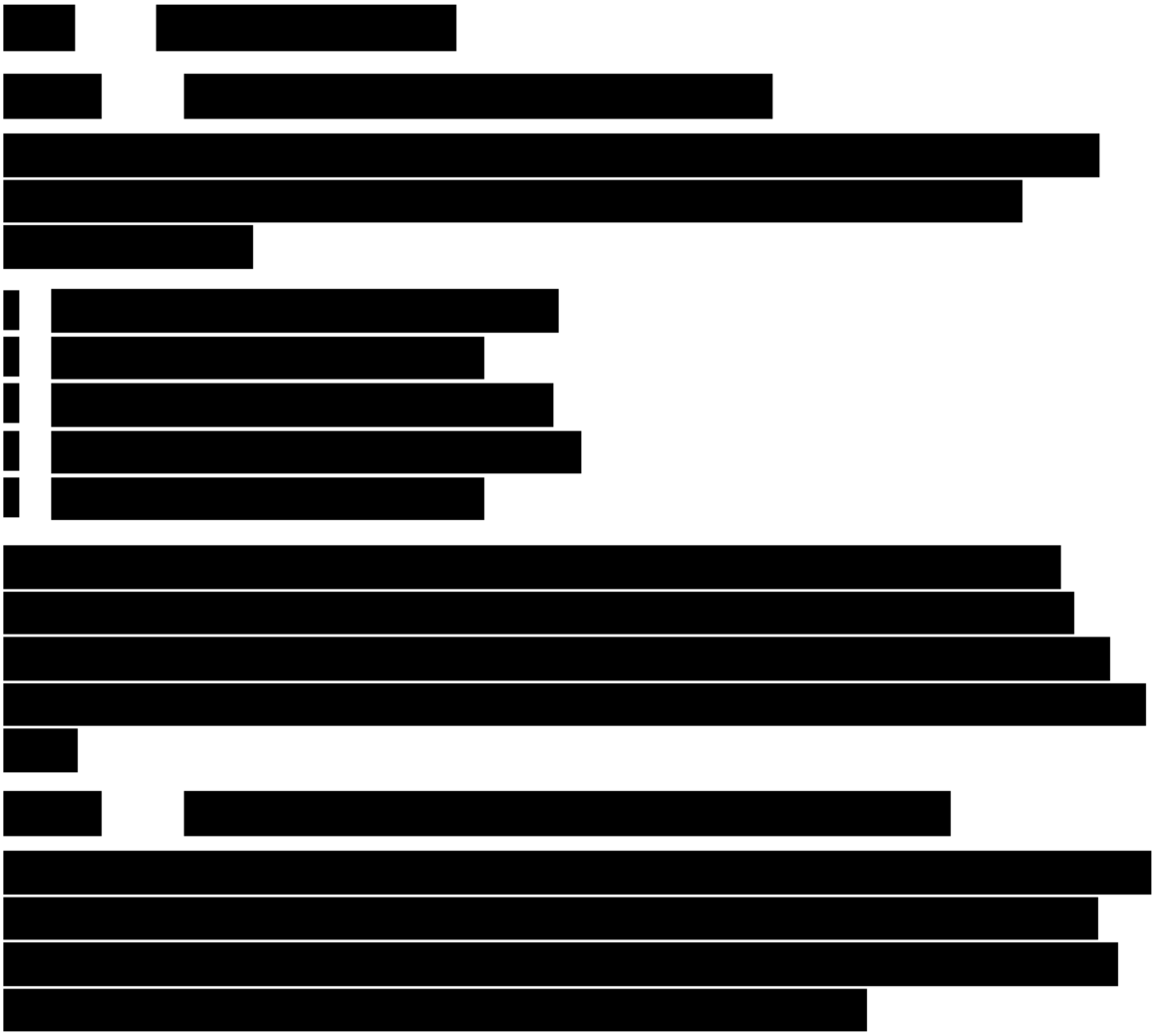
Urine (mL) will be collected for 0 to 2, 2 to 4, 4 to 8, 8 to 12, and 12 to 24 hours post the morning dose. Urine collection should begin with subjects voiding within 30 minutes prior to the morning dose. Subjects should be asked to void prior to the end-time of the collection interval. All voids collected within a collection interval will be pooled at the end of each of the collection interval, at which time the volume (mL) per interval will be determined and recorded in the source notes and eCRF.

Once pooled, the urine should be thoroughly mixed to ensure uniformity. An aliquot will be taken for determination of sodium, creatinine, and osmolality. Samples will be sent to

the clinical chemistry laboratory for analysis. Detailed handling, including volume of sample needed, and shipping instructions will be provided in the laboratory manual. Refer also to Appendix 3.

3.7.5.3.4 Fluid Intake

Fluid intake (mL) should be recorded for the intervals of 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hours. Intake will include fluid used for dosing (IMP and any concomitant medication) and food items that include significant amounts of water (eg, Jello® [including gelatin or jelly dessert], or soup). The fluid for the morning dose will be included in the 0 to 4 hour interval and for the afternoon dose in the 8 to 12 hour interval.



3.7.7 End of Treatment/End of Trial

If a subject discontinues IMP before Month 12 in Phase A or Month 24 in Phase B, the last date that the subject received IMP will be recorded as EoTx. See Section 3.8 for more information on EoTx rules for this trial.

The end of trial date is defined as the last date of contact or the date of final contact attempt from the posttreatment follow-up eCRF page for the last subject completing or withdrawing from the trial.

3.7.8 Independent Data Monitoring Committee

An independent data monitoring committee (IDMC) will be established for this trial. This committee 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. It may make recommendations to the sponsor and trial steering committee to amend or terminate the trial based on grounds of safety, futility, or greater than expected efficacy as defined by the accepted statistical practices and procedures to be detailed in their charter. The specific duties of the IDMC will be detailed in a separate IDMC charter document.

3.7.9 Hepatic Adjudication Committee

A hepatic adjudication committee (HAC) has been convened for the purpose of oversight of hepatic events. The HAC will independently determine probable cause(s) of any hepatic event occurring during the trial and will communicate with the IDMC that oversees the trial.

3.8 Stopping Rules, Withdrawal Criteria, and Procedures

3.8.1 Entire Trial or Treatment Arm(s)

The sponsor may terminate the trial for any reason(s) including if new information is made available due to which the benefit/risk ratio of the study must be assessed as unfavorable.

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

3.8.2 Individual Site

Individual trial site participation may be discontinued by the sponsor, the investigator, or the IRB/IEC if judged to be necessary for medical, safety, regulatory, ethical, or other

reasons consistent with applicable laws, regulations, and GCP. The investigator will notify the sponsor promptly if the trial is terminated by the investigator or the IRB/IEC at the site.

3.8.3 Individual Subject Discontinuation

3.8.3.1 Treatment Interruption

In this 3-year trial, it is expected that subjects may have 1 or more treatment interruptions during the double-blind, randomized treatment period (Phase A) or the open-label treatment period (Phase B). If a subject's IMP treatment must be interrupted for medical or surgical reasons; liver test abnormalities; use of a prohibited concomitant medication; or other reasons (eg, hospital admission for an invasive procedure, a major medical condition, surgery, dental work, or a temporary situation that prevents subject compliance with the IMP administration schedule), the medical monitor should be consulted. Scheduled treatment interruption is discouraged during the first month of treatment in Phase A and within 30 days of any scheduled MRI and/or ultrasound assessment. The medical monitor should be contacted if IMP interruption is needed during these time points.

If a subject develops a medical need for cyst reduction therapy, during trial participation, this will be addressed with the appropriate physician. The subject would then be discontinued from treatment at the time of surgical intervention. The subject will remain in the trial and may restart treatment 6 weeks after surgical intervention at the discretion of the investigator.

3.8.3.2 Treatment Discontinuation

After randomization, a subject may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a subject who is not satisfied with treatment or may become medically necessary due to AEs, required treatment with a disallowed medication or therapy, or other issues, as determined by the investigator. However, each investigator must comprehensively review the circumstances and offer the subject options for continued treatment to the degree possible as described in Section 3.8.3.4.

Subjects who have sustained electrolyte excursions (eg. increased serum sodium) that are considered clinically significant by the investigator and that are not able to be resolved by increasing the subject's daily water intake should be discontinued from treatment.

A subject who discontinues treatment will be recorded as an IMP discontinuation on the eCRF. They will have an EoTx visit, which should be scheduled as soon as possible after

the subject's last dose of IMP to conduct the assessments defined in the Schedule of Assessments, Table 3.7-1 for Phase A and Table 3.7-2 for Phase B.

Subjects who discontinue IMP during Phase A, will have safety laboratory tests (including LFTs) at the 7-day posttreatment follow-up visit (see Section 3.7.1.4.1), and then will be followed every 6 months through Phase A (see Schedule of Assessments Table 3.7-1). Collection of an MRI/Ultrasound TKV measurement at the Phase A Month 12 visit will be encouraged regardless of whether the subject continues on IMP.

Subjects who discontinue IMP during Phase B, will have safety laboratory tests (including LFTs) at the 7-day posttreatment follow-up visit (see Section 3.7.1.4.1), and then will be followed every 6 months through Phase B (see Schedule of Assessments Table 3.7-2). Collection of an MRI/Ultrasound TKV measurement at the Phase B Month 12 and Phase B Month 24 visit will be encouraged regardless of whether the subject continues on IMP.

Subjects whose consents are completely withdrawn will be discontinued from the trial. These subjects' vital statuses will be collected if possible at the time points defined in Section 3.7.4.8.

3.8.3.3 Documenting Reasons for Treatment Interruption/Discontinuation

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

- Reasons related to AE:
  - Subject could not tolerate IMP due to an AE that is annoying or uncomfortable but not serious or hazardous
  - Physician determined that there are potential IMP related safety concern or serious AE (SAE) placing subject at undue hazard
  - SAE
  - Progression of disease leading to dialysis, transplantation, or eGFR decline as determined by the investigator
  - Liver test abnormalities meeting criteria for permanent discontinuation (see Section 5.4.2.3)
  - Clinical signs of DILI (eg, jaundice, right upper quadrant pain)
- Death
- Reasons unrelated to medical condition
- Withdrawal of informed consent (partial related to IMP or complete written withdrawal of consent form)

- Lost to follow-up (detailed procedures to prevent subjects from becoming "lost to follow-up" will be provided in the operations manual. These procedures must be followed by the investigator, their staff, or other designated trial personnel)
- Pregnancy (see Section 5.5)
- Termination of all or part of the trial by the sponsor

If the subject temporarily interrupts or discontinues IMP due to an AE, the investigator or other trial personnel, will make every effort to follow the event until it has resolved or stabilized.

3.8.3.4 Withdrawal of Consent/Assent

All subjects have the right to withdraw their consent/assent from further participation in the trial at any time without prejudice. Subjects cannot withdraw consent/assent for use of data already collected as part of the trial, but only for future participation. The investigator can also discontinue a subject's participation in the trial at any time if medically necessary. Unless the subject provides their written withdrawal of consent/assent or there is other written documentation by the investigator confirming the subject's verbal intent to completely withdraw from the trial, subjects should be followed for all protocol-specified evaluations and assessments, if possible.

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

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

Withdrawal of consent/assent is a critical trial event and therefore should be approached with the same degree of importance and care as is used in initially obtaining informed

consent. The reasons for a subject's intended withdrawal need to be completely understood, documented, and managed to protect the rights of the subject and the integrity of the trial. A subject may initially express their desire to interrupt or discontinue IMP administration, which is not equivalent to a complete withdrawal of consent/assent for further participation (see Section 3.8.3.1 and Section 3.8.3.2). A subject may, however, indicate that further trial participation is creating a burden on their work/school or social schedule. Therefore, the investigator should follow the procedures outlined in Section 3.8.3.3 to determine if the subject can continue participation in the trial if modifications to his/her treatment and/or schedule of assessments can be accommodated. Only subjects who withdraw their permission for all of the above degrees of follow-up are considered to have completely withdrawn their consent/assent to participate in the trial.

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 randomized or otherwise-assigned treatment (ie, washout or placebo).

For the purposes of this trial, treatment begins with the first dose of IMP. If a subject fails to qualify for the trial during screening, he/she is permitted to be rescreened at a later date. However, a new ICF/IAF must be signed prior to reinitiating screening procedures. Subjects are permitted to be rescreened only once. Rescreened subjects will be assigned a new screening number.

3.10 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for primary and/or secondary objectives of the trial irrespective of whether or not the subject actually consumed all doses of the IMP. Subjects who are evaluated at the last scheduled visit during the treatment period will be defined as trial completers. For purposes of this trial,

- Subjects who are randomized and take IMP through the Month 12 visit in Phase A and complete some or all of the trial visit assessments will be defined as *Phase A on-treatment completers*.
- Subjects who are randomized and discontinue IMP prior to the Month 12 visit in Phase A and complete some or all of the trial visit assessments will be defined as *Phase A off-treatment completers*.

- Subjects who take IMP through the Month 24 visit in Phase B and complete some or all of the trial visit assessments will be defined as *On-treatment trial completers*.
- Subjects who discontinue IMP prior to the Month 24 visit in Phase B and complete some or all of the trial visit assessments will be defined as *Off-treatment trial completers*.
- Subjects who are randomized, take IMP but do not complete the Phase A Month 12 visit or the Phase B Month 24 visit will be defined as *Trial non-completers*.

3.11 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on or before their last trial visit during the treatment period, who do not have a known reason for discontinuation (eg, withdrew consent or AE), and for whom a survival status at the end of the trial cannot be determined will be classified as "lost to follow-up" as the reason for discontinuation. Vital status can be determined from a variety of sources, either by obtaining acceptable documentation for death (ie, death certificate, medical records, public records, 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).

The site will make 3 documented attempts to contact the subject by telephone and in the event the site is unable to reach the subject by telephone, the site will attempt to contact the subject via certified mail or an alternative similar method, where appropriate, before assigning a "lost to follow-up" status.

3.12 Subject Compliance

The date and time of the first dose of IMP administration will be recorded in source documentation and the eCRF. The date and time of each dose administered in the clinic will also be recorded. Information regarding any missed or inappropriately administered doses will also be documented in source documentation and the eCRF.

Accountability and compliance verification should be documented in the subject's trial records. Subjects must be counseled on the importance of taking the IMP as directed at all trial visits and work with their physicians around planned interruptions. If poor compliance continues (eg, multiple missed doses resulting in < 80% overall compliance at any point in the trial), discontinuation from the trial should be considered. This decision will be documented by the investigator in consultation with the medical monitor.

3.13 Protocol Deviations

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

4 Restrictions

4.1 Prohibited Medications

Medications or surgical therapies used for the purpose or potential for modifying the progression of PKD cyst growth or development will be prohibited. These include, but are not restricted to, somatostatin agonists, rapamune (sirolimus), anti-sense ribonucleic acid (RNA) therapies, tolvaptan, and other vasopressin antagonists eg, OPC-31260 (mozavaptan), Vaprisol (conivaptan), or agonists (eg, desmopressin). If a subject develops a medical need for cyst reduction therapy, during trial participation, this will be addressed with the appropriate physician. The subject would then be discontinued from treatment at the time of surgical intervention. The subject will remain in the trial and may restart treatment 6 weeks after surgical intervention at the discretion of the investigator.

Continuous or short-term use of other medications, while not prohibited, may be restricted by the investigator because of their potential for interference with metabolism or efficacy endpoints. This includes the use of diuretics which may be used intermittently, but not within 7 days of a urine assessment. Diuretics are not generally recommended in ADPKD due to their tendency to increase AVP levels through relative dehydration or volume depletion; thus, chronic use of diuretics (eg, for hypertension) will be prohibited due to potential endpoint interference and is an exclusionary criterion for this trial. Subjects taking such agents must first sign an ICF and then agree to be switched to an alternate form of therapy in order to be eligible for the trial. Subjects must be on a stable dose of their antihypertensive medications at randomization.

Some drugs are known to alter creatinine concentrations so, while not prohibited, subjects should alert their trial doctor, and any other healthcare providers, to take this into consideration when considering changes in their prescribed or over-the-counter

medications. A brief list would include: cimetidine, nonsteroidal antiinflammatory drug medications like aspirin or ibuprofen, chemotherapy drugs, and cephalosporin.

Since tolvaptan is a sensitive CYP3A4 substrate, CYP3A4 inhibitors should be avoided during the trial, with the exception of amiodarone, which was found to have no effect on tolvaptan concentrations. CYP3A4 inducers should also be avoided. If these drugs are to be used, the medical monitor should be contacted and IMP administration must be interrupted (see Section 3.8.3.1). A partial list of CYP3A4 inhibitors can be found in Table 4.1-1.

Table 4.1-1 CYP3A4 Inhibitors (Partial List)

boceprevir	clarithromycin	clotrimazole (if used orally)	indinavir
itraconazole	ketoconazole (if used orally)	lopinavir	mibefradil
nefazadone	nelfinavir	posaconazole	ritonavir
saquinavir	telaprevir	telithromycin	voriconazole

4.2 Dietary Restrictions and Recommendations

Fluid intake is generally encouraged in subjects with PKD. Given the potential for dehydration with tolvaptan treatment, all subjects should be instructed to ingest water or noncaloric fluids in anticipation of, or at the first sign of thirst in order to avoid excessive thirst or dehydration. Upon consent, all subjects should receive the recommendation to ingestion of at least 1.5 to 2 liters of fluid (including in solid, semi-solid, and liquid foods) per day. 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 juice or other products would be expected to increase tolvaptan concentrations and these should be not be consumed during trial participation.

5 Reporting of Adverse Events

5.1 Definitions

An AE is defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. AEs would not include information recorded as medical history at screening for pre-planned procedures for which the underlying condition was known and no worsening occurred. An adverse reaction is any untoward and unintended response to an IMP related to any dose administered.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the IMP caused the AE. For the purpose of Investigational New Drug (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.

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

- Death.
- 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.
- Persistent or significant incapacity/disability or substantial disruption of the ability to conduct normal life functions.
- Requires in-patient hospitalization or prolongs hospitalization.
    - Hospitalization itself should not be reported as an SAE; whenever possible the reason for the hospitalization should be reported.
    - Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other non-medical need) are not considered SAEs.
- Congenital anomaly/birth defect.
- 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 Adverse Events are all AEs that do not meet the criteria for a "serious" AE.

Immediately Reportable Event (IRE):

- Any SAE.

- Any AE related to occupational exposure.
- Potential DILI case (see Section 5.4.1) and any new liver abnormality requiring the liver eCRF completion.
- 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 the sponsor. Pregnancy will only be documented on the AE eCRF page if there is an abnormality or complication.
- Additionally, in the European Union, events involving overdose, misuse, and abuse as well as reported lack of efficacy must also be reported as IREs.

Clinical Laboratory Test Value 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 in source documents. 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 considered medically relevant by the investigator (subject is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory value leads to discontinuation, and/or fulfills a seriousness criterion, this is considered an AE.

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

1 = Mild:	Discomfort noticed, but no disruption to daily activity.
2 = Moderate:	Discomfort sufficient to reduce or affect normal daily activity.
3 = Severe:	Inability to work or perform normal daily activity.

IMP Causality: Assessment of causal relationship of an AE to the use of the IMP is defined as follows:

Related:	There is a reasonable possibility of a temporal and causal relationship between the IMP and the AE.
Not Related:	There is no temporal or causal relationship between the IMP and the AE.

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5.2 Eliciting and Reporting Adverse Events

The investigator will periodically assess subjects for the occurrence of AEs. To avoid bias in eliciting AEs, subjects should be asked the nonleading 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. AE collection (serious and nonserious) is to begin after a subject has signed the ICF.

Use medical terminology in AE reporting. Adverse events should be reported as a single unifying diagnosis whenever possible or, in the absence of a unifying diagnosis, as individual signs or symptoms. Exacerbation or disease progression should be reported as an AE only if there are unusual or severe clinical features that were not present, or experienced earlier, or not expected based on the course of the condition.

In addition, the sponsor must be notified immediately by telephone, fax, or e-mail of any IREs 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 (ie, within 24 hours) report after either the investigator or site personnel become aware of any IREs as defined in Section 5.1 by telephone, fax, or e-mail to the sponsor using the contact information on the cover page of this protocol. An IRE form must be completed and sent by e-mail, fax, or overnight courier to the sponsor. (Please note that the IRE form is NOT the AE eCRF page.)

Subjects experiencing IREs 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 and will provide prompt updates on the subject's status to the sponsor.

5.4 Assessment of Liver Symptoms, Signs or Test Abnormalities

5.4.1 Potential Drug-Induced Liver Injury

For a subject who experiences an elevation in AST or ALT that is ≥ 3 times the upper limit of normal (ULN), BT and ALP should also be evaluated. If significant abnormalities in transaminases and/or bilirubin are confirmed, other testing to fully evaluate the likely proximate cause should be undertaken with the option of consulting with local hepatic experts for interpretation and guidance. All results should be made available to the sponsor and the HAC.

If BT is ≥ 2 times the ULN, complete an IRE form with all values listed and also report as an AE on the CRF.

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

5.4.2 Requirements for Repeated Liver Testing

5.4.2.1 Liver Transaminase Elevations

Management of abnormal liver function test results should be based on the investigator's clinical judgment. The appearance of any suspicious symptom or sign should trigger prompt testing of hepatic function (ie, within 48 to 72 hours). A liver function test result that is 2 × ULN is generally accepted as a clinically significant occurrence across various medical disciplines.

For a subject who experiences an elevation in AST or ALT that is ≥ 2 × ULN or whose levels increase ≥ 2 times their initial baseline value in subjects with an elevated baseline value, a BT level should also be evaluated. Elevated values should be confirmed via retest within 48 to 72 hours.

5.4.2.2 Guidelines for Repeat Liver Testing in Subjects with Normal Values at Screening

The appearance of any suspicious symptom or sign should trigger prompt testing of hepatic function (ie, within 48 to 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 48 to 72 hours. While values remain in an abnormal range, testing frequency should be increased to at least weekly for the first month, gradually returning to monthly as indicated by the results.

If hepatic injury is suspected, tolvaptan should be promptly discontinued, appropriate treatment should be instituted, and investigations should be performed to determine probable cause. Such an event should be reported and followed until resolution.

5.4.2.3 Subjects with Elevated Liver Transaminase at Screening

Subjects found to have liver laboratory abnormalities at screening or who have a history of non-ADPKD-related liver disease will require further evaluation. These subjects will need to have the special liver eCRF (see Section 5.4.5) completed and additional testing

will be required during screening to confirm the stability of the abnormality prior to randomization to confirm eligibility. Management of such subjects should be closely coordinated with the trial's medical monitor. In these subjects, further changes in liver test levels of > 2 × upper limit of their highest screening value at any point postscreening should prompt re-testing within 48 to 72 hours. Should such an increase occur during treatment with IMP, the subject will be immediately discontinued from treatment. IMP should not be resumed until monitoring indicates abnormalities have resolved, are stable or are not rapidly increasing, and then only with an increased frequency of monitoring.

5.4.3 Guidelines for Repeat Testing of Liver Transaminases

The following guideline for repeat testing may be used by investigators as a reference for any subject with an ALT or AST ≥ 2 × ULN:

- ALT, AST, ALP, and BT should be repeated within 48 to 72 hours (needed to confirm abnormalities and determine if they are increasing or decreasing).
- Inquiries should be made about symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, and/or rash) and signs like jaundice or yellowish discoloration of sclera.
- Close observation is required if symptoms persist or repeat testing shows ALT or AST ≥ 3 × ULN for subjects with normal baseline measures OR 2-fold increases above baseline values for subjects with elevated values before drug exposure. If close monitoring is not possible, the drug should be interrupted until such monitoring is possible or the drug should be permanently discontinued.
- All trial subjects with evidence of possible DILI should be followed until all abnormalities return to normal or to the baseline state.

Close observation may involve:

- Repeating liver enzymes and serum bilirubin tests 2 or 3 times weekly.
- Frequency of retesting can decrease to once a week or less if abnormalities stabilize or if the trial drug has been interrupted/discontinued and the subject is asymptomatic.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, special diets, and change in diet.
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis, nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy, and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (eg, international normalized ratio [INR], direct bilirubin).
- Considering gastroenterology or hepatology consultations.

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

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

A subject must be discontinued from the trial on confirmation of any of the following criteria:

- ALT or AST ≥ 8 × ULN
- ALT or AST ≥ 5 × ULN for more than 2 weeks
- ALT or AST ≥ 3 × ULN and (BT ≥ 2 × ULN or INR > 1.5)
- ALT or AST ≥ 3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%) and signs of jaundice

If an investigator has any question about how to proceed with a particular subject's case, he/she should contact the regional medical monitor to discuss. The United States Food and Drug Administration (US FDA) has issued a guidance for industry regarding this topic. The sponsor is integrating many of the recommendations in this guidance into all of its clinical research programs. Links to this guidance and information from the FDA regarding DILI are provided in the references.[14,15]

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

The purpose of the liver disease eCRF and optional additional testing is to facilitate review of each subject who presents with, or develops, a liver abnormality during the trial or and to determine the probable cause(s) of these abnormalities. The review will be performed by a blinded, independent, hepatic, adjudication committee using Drug Induced Liver Injury Network (DILIN) probability criteria:[16]

- < 25% = unlikely
- 25% to 50% = possibly
- 51% to 75% = probably
- 76% to 95% = very likely
- >95% = definite

The result of these analyses may be presented separately from the CSR.

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

1) Discontinues treatment due to a liver-related AE,
2) Reports a serious liver-related AE,
3) With normal screening levels develops ALT or AST levels ≥ 3 × ULN,
4) With normal screening levels develops BT levels ≥ 2 × ULN, or

5) With an abnormal screening liver test level develops abnormalities in that test that are > 2 × the upper limit of their highest screening value.

All subjects meeting any 1 of the above criteria will also be asked to provide an additional set of blood and urine biomarker samples at the time of the event. Additional clinical testing (such as testing for hepatitis serology) may also be indicated and their results reported according to local guidelines.

The liver eCRF and IRE form (see Section 5.3) should be updated as new information becomes available.

5.5 Pregnancy

For the purposes of this pediatric trial, women of childbearing potential (WOCBP) are defined as female subjects ≥ 12 years of age and all female subjects < 12 years of age, if menstruation has started.

For WOCBP and for men who are sexually active, there must be a documented agreement that the subject and/or their partner will take effective measures (eg, double-barrier method) to prevent pregnancy during the course of the trial and for 30 days after the last dose of IMP. Unless the subject is sterile (ie, women who have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 consecutive months; or men who have had a bilateral orchidectomy) or remains fully abstinent; 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pills, birth control depot injection, birth control implant, condom with spermicide, or sponge with spermicide. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) or withdrawal are not acceptable methods of contraception. The contraceptive method will be documented at each trial visit.

Before enrolling females of childbearing potential in this clinical trial, investigators must review the below guidelines about trial participation with all WOCBP. Investigator (or appropriate site staff) is advised to counsel participants on the risk of pregnancy while participating in a clinical trial as well as ensuring the child understand how pregnancies occur and can be avoided. This should be documented in source records. The topics should generally include:

- General information
- Informed consent form
- Pregnancy prevention information

- Drug interactions with hormonal contraceptives
- Contraceptives in current use
- Guidelines for the follow-up of a reported pregnancy

Before trial enrollment, females of childbearing potential must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The subject or the subject's parent/legal guardian or legally acceptable representative must sign an ICF stating that the above-mentioned risk factors and the consequences were discussed with the subject and/or the parent/legal guardian or legally acceptable representative.

A urine and/or serum pregnancy test for human chorionic gonadotropin will be performed at screening on all females of childbearing potential. If a urine test is performed and is positive, the investigator will follow-up with a confirmatory serum test.

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

If a subject is suspected to be pregnant before she receives IMP, 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 test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety) and the subject will be withdrawn from the trial.

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 from the date of birth.

5.6 Procedure for Breaking the Blind

Unblinding a subject's treatment assignment in a double-blind, controlled trial should never be undertaken lightly as it can introduce bias in assessment of safety or efficacy. However, in circumstances where immediate knowledge of treatment assignment will meaningfully influence the current or future management of potentially serious AEs, breaking the blind may be appropriate.

Unless the need for unblinding is urgent and obvious, the investigator is encouraged to contact the sponsor/Clinical Research Organization (CRO) medical advisor to discuss their rationale for unblinding. However, to prevent delays to the investigator or medical personnel responding to a potentially emergent situation, unblinding of IMP will not be dependent upon the investigator receiving approval from the sponsor/CRO medical advisor (ie, the investigator will be able to obtain the code break information independent of the sponsor/CRO medical advisor). The investigator must contact the sponsor/CRO medical advisor by telephone or e-mail with an explanation of the need for opening the treatment assignment code within 24 hours of opening the code. If the blind is broken, the Clinical Safety and Pharmacovigilance department must be notified immediately (see the cover page of this protocol for contact information). Documentation of breaking the blind should be recorded in the subject's medical record with the date and time the blind was broken and the names of the personnel involved. Once the blind is broken for a subject, that subject may not reinitiate treatment with the IMP.

5.7 Follow-up of Adverse Events

For this trial, information on AEs will be collected from the signature of the informed consent until 14 days after the last dose of IMP has been administered or until 7 days in subjects who discontinued prior to randomization. Follow-up of AEs is described below.

5.7.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded on the AE eCRF page with the current status noted. All nonserious events that are ongoing at the last scheduled contact will be recorded as ongoing on the CRF. For any AE having been identified throughout the trial, during analysis, additional relevant medical history information may be requested to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history and occupation).

The investigator will follow all AEs until the events are resolved, stabilized, or the subject is lost to follow-up. Resolution means that the subject has returned to the

baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the subject's condition.

5.7.2 Follow-up of Serious Adverse Events

Serious AEs that are **identified or ongoing at the last scheduled contact** must be recorded on the AE CRF page and reported to the sponsor according to the reporting procedures outlined in Section 5.3. This may include **unresolved previously reported SAEs, or new SAEs.** The investigator will follow SAEs and report any significant follow-up information to the sponsor until the events are resolved, stabilized, or the subject is lost to follow-up.

5.7.3 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 (last contact includes telephone contact)**, and are determined by the investigator to be reasonably associated with the use of the IMP, should be reported to the sponsor. The investigator should follow SAEs identified after the last scheduled contact and report any significant follow-up information to the sponsor until the events are resolved, stabilized, or the subject is lost to follow-up.

6 Pharmacokinetic and Pharmacodynamic Methods

6.1 Pharmacokinetic Methods

6.1.1 Dense Sampling

Tolvaptan concentrations will be analyzed by noncompartmental methods. Concentrations will be summarized with descriptive statistics by total daily dose of tolvaptan and time point. Pharmacokinetic parameters will be summarized with descriptive statistics by total daily dose of tolvaptan.

[redacted]

6.2 Pharmacodynamic Methods-Dense Sampling

Urinary excretions will be determined as urine concentration × urine volume; missing values will not be imputed. If urine concentration or volume is missing for any interval, the 0 to 24 hour values will not be determined. Urine volumes of zero, and consequently nor reportable urine concentration, are not considered as missing data; values of 0 will be reported for volume and excretion.

Free water clearance will be determined as urine excretion rate − osmolar clearance.

Osmolar, sodium, and creatinine clearances will be determined by standard methods with average serum concentration determined by averaging the concentrations at the beginning and end of the urine collection interval. If urine volume for a collection interval is 0, then the clearance value for that interval and the following interval will be determined by using the average value of the 3 serum concentrations, the urine volume of the second interval and the total time of the 2 collection intervals (eg, 2 to 4 hour collection has urine volume of 0 mL). Clearance for the 2 to 4 and 4 to 8 hour intervals will be determined using serum concentrations at 2, 4, and 8 hours, the urine volume from 4 to 8 hour interval and total collection time of 6 hours (8 minus 2).

Values of urine osmolality will be summarized with descriptive statistics by total daily dose (all placebos grouped together) and collection interval. Sodium and creatinine urine concentrations will only be listed.

Values of excretions (osmoles, sodium, and creatinine) and clearances (free water, sodium, and creatinine) will be summarized with descriptive statistics by total daily dose (all placebos grouped together), collection interval, and 0 to 24 hours.

Serum concentrations (osmolality, sodium, and creatinine) and change from predose will be summarized with descriptive statistics by total daily dose (all placebos grouped together), analyte, and time point.

7 Statistical Analysis

7.1 Sample Size

A sample size of at least 60 subjects from 12 to 17 years of age inclusive is proposed for the Phase A of this trial. It is expected that the trial may enroll approximately 100 subjects in total. Since the data collected will be summarized using descriptive statistics and not aimed at testing a specific hypothesis, no formal power calculations are undertaken.

7.2 Datasets for Analysis

The following samples are defined for the efficacy and safety analysis in this trial:

- Randomized: consists of all subjects who were randomized in the trial.
- Full Analysis Set (FAS): subjects who have been randomized to a treatment group, received at least 1 dose of the IMP, have both a Phase A baseline and at least 1 post-baseline efficacy evaluation. They will be analyzed according to the treatment group to which they were randomized. The FAS, which is based on intent-to-treat principle, will be the primary analysis set for efficacy analyses on the primary/key secondary endpoints and other secondary endpoints.

  Safety: all subjects who were administered at least 1 dose of IMP will be included in the safety dataset and analyzed according to the treatment received. The safety dataset will be used for safety analyses.

7.3 Handling of Missing Data

All safety/efficacy data will be summarized for observed (non-missing) values only. Missing data will be mitigated by encouraging subjects who withdrew from treatment to return for their remaining visits for collection of assessments as noted in the Schedule of Assessments, Table 3.7-1 for Phase A and Table 3.7-2 for Phase B.

7.4 Analysis of Demographic and Baseline Characteristics

Demographic characteristics, disease severity, and medical history at (predose) baseline will be summarized by descriptive statistics, eg, proportion, mean, median, standard deviation, minimum, and maximum values. These summary statistics will be reviewed to identify any potential lack of balance between the treatment groups.

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7.5 Primary and Secondary Endpoint Analyses

7.5.1 Primary Endpoint Analysis

The co-primary endpoints for the trial are the change from Phase A baseline in spot urine osmolality (premorning dose) and specific gravity (premorning dose) to Week 1.

Descriptive statistics will be presented on the co-primary endpoints, respectively:

- Change from Phase A baseline in spot urine osmolality (premorning dose) to Week 1
- Change from Phase A baseline in specific gravity (premorning dose) to Week 1

7.5.2 Key Secondary Endpoint Analysis

The key secondary endpoint is the percent change from Phase A baseline in htTKV as measured by MRI at 12 months. Descriptive statistics will be presented on the key secondary endpoint.

7.5.3 Secondary Endpoint Analysis

Other secondary efficacy endpoints include:

- 24-hour fluid balance prior to Week 1.
- Change from baseline in renal function (eGFR by Schwartz formula) at each clinic visit (Week 1, Month 1, Month 6, and Month 12) in Phase A.
- Change from baseline in renal function (eGFR by Schwartz formula) at each clinic visit (Week 1, Month 1, Month 6, Month 12, Month 18, and Month 24) in Phase B.
- Percent change in htTKV as measured by MRI from Phase B baseline to Phase B Month 12.
- Percent change in htTKV as measured by MRI from Phase B baseline to Phase B Month 24.
- Pharmacodynamic endpoints of urine volume (including 24-hour fluid volume), fluid intake and fluid balance, sodium, creatinine, and free water clearance during dense PK sampling (after at least 1 Month on IMP).
- Proportions of each Tanner Stage by gender and age compared to normative populations at baseline, 6 months, and 12 months during the placebo-controlled phase (Phase A), and every 6 months during the open-label extension phase (Phase B).
- Description of changes from baseline percentiles for height and weight by gender and age at baseline, 6 months, and 12 months during the placebo-controlled phase (Phase A), and every 6 months during the open-label extension phase (Phase B).
- Safety variables (changes from baseline in creatinine, vital signs, laboratory values including LFTs, rate of aquaretic AEs) in placebo and tolvaptan.

For all of the secondary efficacy endpoints, descriptive statistics by visit will be presented.

7.6 Subgroup Analysis

Subgroup analyses on the primary and key secondary efficacy endpoints will be performed to examine the differences in treatment response based on Phase A baseline status (eg, gender, age stratum). Details will be provided in the statistical analysis plan (SAP).

[redacted]

7.8 Interim Analysis

No interim analysis is planned before all randomized subjects either complete the Month 12 visit or early terminate in Phase A, the double-blind, placebo controlled portion of this protocol. A snapshot of the database will be taken after all subjects in Phase A have completed or early terminated, these data will be unblinded, and an interim CSR will be written to provide early information on safety.

7.9 Safety Analysis

In general, Phase A baseline measurements of safety variables are defined as their last measurements prior to the randomization for the safety population. Safety analysis will be conducted based on the safety population, defined in Section 7.1. Standard safety variables to be analyzed include AEs, change from baseline in creatinine, vital signs, laboratory values including LFTs, and rate of aquaretic AEs in placebo versus tolvaptan. In general, summarized statistics of changes from Phase A baseline will be provided for safety variables based on all available data.

Summarized statistics of changes from Phase B baseline will be provided for safety variables based on all available data in Phase B as well.

7.9.1 Adverse Events

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

- Treatment-emergent AEs (TEAEs)
- TEAEs by severity
- TEAEs potentially causally related to the IMP
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP

7.9.2 Clinical Laboratory Data

Summary statistics for changes from baseline in the clinical laboratory measurements will be provided for the safety population. Potentially clinically significant results in laboratory tests identified using prospectively defined criteria will also be summarized for the safety population.

In addition, laboratory measurements that signal the potential for Hy's Law will be reported. An incidence table and a listing will be provided for subjects who meet one or combinations of following criteria, without initial findings of cholestasis (ALP activity $> 2 \times$ ULN):

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

7.9.3 Physical Examination and Vital Signs Data

By-patient listings will be provided for physical examination. Summary statistics for changes from baseline in vital signs and potentially clinically significant results in vital signs will be summarized for the safety population.

7.10 Other Analysis

The analyses for medical history, concomitant medications, and protocol deviations will be proposed with details in the SAP.

8 Management of Investigational Medicinal Product

8.1 Packaging and Labeling

Trial medication will be provided to the investigator(s) by the sponsor (or designated agent). Tolvaptan will be supplied as 7.5 mg (6 mm), 15 mg (8 mm), and 30 mg (8 mm) spray-dried tablets and matching placebos. Each package used in the dosing period will be labeled to clearly disclose the subject ID, compound ID, trial number, the sponsor's name and address, instructions for use, route of administration, appropriate precautionary statements, and other information required by local regulatory authorities.

The current tolvaptan tablet formulation is limited to administration to those who can easily swallow a 6 or 8 mm tablet and who weigh ≥ 20 kg.

8.2 Storage

Tolvaptan and matching placebo tablets (IMP) should be stored according to the storage conditions indicated on the clinical label. The clinical trial site staff or designated personnel will maintain a temperature log in the drug storage area recording the temperature at least once each working day. The IMP will be stored in a securely locked cabinet or enclosure. Access will be limited to investigators and their designees. Neither investigators nor any designees may provide IMP to any subject not participating in this protocol.

8.3 Accountability

The investigator or designee must maintain an inventory record of tolvaptan (including investigational, active control, or placebo) received, dispensed, administered, destroyed, and returned.

8.4 Returns and Destruction

Upon completion or termination of the trial, all unused and/or partially used IMP will be returned to the sponsor or a designated agent or destroyed at the clinical sites. IMP may be destroyed by the clinical sites only if approved by the sponsor and IMP destruction meets all local regulations.

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.

8.5 Reporting of Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or verbal communication by a healthcare professional, consumer, subject, medical representative, Competent Authority, regulatory agency, partner, affiliate or other third party that alleges deficiencies or dissatisfaction related to identity, quality, labeling, packaging, reliability, safety, durability, tampering, counterfeiting, theft, effectiveness, or performance of a drug product or medical device after it is released for distribution. Examples include, but are not limited to, communications involving:

- Failure/malfunction of a product to meet any of its specifications
- Incorrect or missing labeling
- Packaging issues (eg, damaged, dirty, crushed, missing product)
- Blister defects (eg, missing, empty blisters)
- Bottle defects (eg, under/over-fill, no safety seal)
- Vial defects
- Product defect (eg, odor, chipped, broken, embossing illegible)
- Loss or theft of product

8.5.1 Eliciting and Reporting Product Quality Complaints

The investigator or designee must record all PQCs identified through any means from the receipt of the IMP from the sponsor, or sponsor's designee, through and including reconciliation and up to destruction, including subject dosing. The investigator or designee must notify the sponsor (or sponsor's designee) by e-mail or telephone within 24 hours of becoming aware of the PQC according to the procedure outlined below.

Identification of a PQC by the subject should be reported to the site investigator, who should then follow one of the reporting mechanisms above.

8.5.2 Information Required for Reporting Purposes

- Description of compliant
- Reporter identification (eg, subject, investigator, site)
- Reporter contact information (eg, address, phone number, e-mail address)
- ID of material (product/compound name, coding)
- Clinical protocol reference (number and/or trial name)
- Dosage form/strength (if known)
- Pictures (if available)
- Availability for return

8.5.3 Return Process

Indicate during the report of the PQC if the complaint sample is available for return. If complaint sample is available for return, return it in the product retrieval package, which will be provided by the sponsor.

It must be documented in the site accountability record that a complaint sample for a dispensed kit has been forwarded to the sponsor for complaint investigation.

8.5.4 Assessment/Evaluation

Assessment and evaluation of PQCs will be handled by the sponsor.

9 Records Management

9.1 Source Documents

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

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. In all cases, subject confidentiality must be maintained in accordance with local regulatory requirements.

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;
- Documentation of the investigator's decision to enroll the subject into the trial, the review of all inclusion/exclusion criteria prior to IMP administration, and confirmation of the subject's actual participation in the trial;
- 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. If electronic data systems are being utilized, a full audit trail of changes must be maintained.

Information from the trial progress notes and other source documents will be entered by investigative site personnel directly onto electronic CRFs 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 E6[12] and as required by applicable local regulations. The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

9.4 Records Retention at the Trial Site

Regulatory requirements for the archival of records for this trial necessitate that participating investigators maintain detailed clinical data for the longest of the following 3 periods:

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

The investigator must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) provision of an opportunity for sponsor to collect such records. The investigator will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated

during this trial including any data clarification forms received from the sponsor. 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 in accordance with established research principles, the ICH E6 GCP: Consolidated Guidance, 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, e-mail, and written communications. In addition, all investigators and clinical site personnel will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

10.2 Auditing

The sponsor's Quality Assurance 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 CRFs 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, FDA regulations, ICH GCP Guideline (E6), international ethical principles derived from the Declaration of Helsinki, and Council for International Organizations of Medical Science guidelines, and applicable local laws and regulations. Each trial site will seek approval/favorable opinion by an IRB or IEC according to regional requirements, and the investigator will provide that documentation to the sponsor. The IRB/IEC will evaluate the ethical, scientific and medical appropriateness of the trial. Further, in preparing eCRFs, the investigator, sub-investigator and their staff will take measures to ensure adequate care in protecting

subject privacy. To this end, a subject number and subject identification code will be used to identify each subject.

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

12 Confidentiality

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior written permission. Subject confidentiality requirements of the region(s) where the trial is conducted will be met. However, authorized regulatory officials and sponsor personnel (or their representatives) may be allowed full access to inspect and copy the records, consistent with local requirements. 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 unique subject numbers in eCRFs. If further subject identification is required, subjects' full names may be made known to a regulatory agency or other authorized officials if necessary, subject to local regulations.

13 Amendment Policy

The investigator will not make any changes to this protocol without the sponsor's prior written consent and subsequent approval/favorable opinion by the IRB/IEC. Any permanent change to the protocol, whether 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, as required by local regulations. Except for "administrative" or "non-substantial" amendments, investigators will wait for IRB/IEC approval/favorable opinion 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 after agreement by the sponsor and investigator, followed by IRB/IEC notification within local applicable timelines. The sponsor will submit protocol amendments to the applicable regulatory agencies within local applicable timelines.

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, after approval/favorable opinion of the new ICF by the IRB/IEC, repeat written informed consent will be obtained from subjects enrolled in the trial before expecting continued participation and before the amendment-specified changes in the trial are implemented.

14 Publication Authorship Requirements

Authorship for any Otsuka-sponsored publications resulting from the conduct of this trial will be based on International Committee of Medical Journal Editors (ICMJE) authorship criteria (http://www.icmje.org/recommendations). According to ICMJE guidelines, one may be considered an author only if the following criteria are met:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors must meet the above criteria, and all who qualify for authorship based on the above criteria should be listed as authors.

Investigators or other trial participants who do not qualify for authorship may be acknowledged in publications resulting from the trial. By agreeing to participate in the trial, investigators or other trial participants consent to such acknowledgement in any publications resulting from its conduct.

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Appendix 2 Tanner Staging

Classification of Sex Maturity Stages in Girls

Stage	Pubic Hair	Breasts
1	Preadolescent	Preadolescent
2	Sparse, lightly pigmented, straight, medial border of labia	Breast and papilla elevated as small mound; areolar diameter increased
3	Darker, beginning to curl, increased amount	Breast and areola enlarged, no contour separation
4	Coarse, curly, abundant but amount less than adult	Areola and papilla form secondary mound
5	Adult feminine triangle, spread to medial surface of thighs	Mature; nipple projects, areola part of the general breast contour

Classification of Sex Maturity Stages in Boys

Stage	Pubic Hair	Penis	Testes
1	Preadolescent	Preadolescent	Preadolescent
2	Scanty, long, slightly pigmented	Slight enlargement	Enlarged scrotum, pink texture altered
3	Darker, starts to curl, small amount	Longer	Larger
4	Resembles adult type but less in quantity; coarse, curly	Larger; glans and breadth increase in size	Larger, scrotum dark
5	Adult distribution, spread to medial surface of thighs	Adult size	Adult size

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Appendix 3 Dense PK and PD Sampling: Assessment Schedule

Phase A Time Point	PK Plasma Sampling	PD Serum Sampling[c]
Predose (within 15 min prior to the morning dose)	X	X
1 hr postdose	X	
2 hr postdose	X	X
4 hr postdose	X	X
8 hr postdose[a,b]	X	X
12 hr postdose[b]	X	X
24 hr postdose[b]	X	X

[a]Within 15 minutes prior to the afternoon dose

[b]Post the morning dose

[c]Serum samples for determination of sodium, creatinine, and osmolality

Phase A Time Point	PD Urine Volume & Sampling	Fluid Intake
0-2 hr post morning dose	X	
2-4 hr post morning dose	X	
0-4 hr post morning dose		X
4-8 hr post morning dose	X	X
8-12 hr post morning dose	X	X
12-24 hr post morning dose	X	X

[redacted] [redacted]

[redacted]

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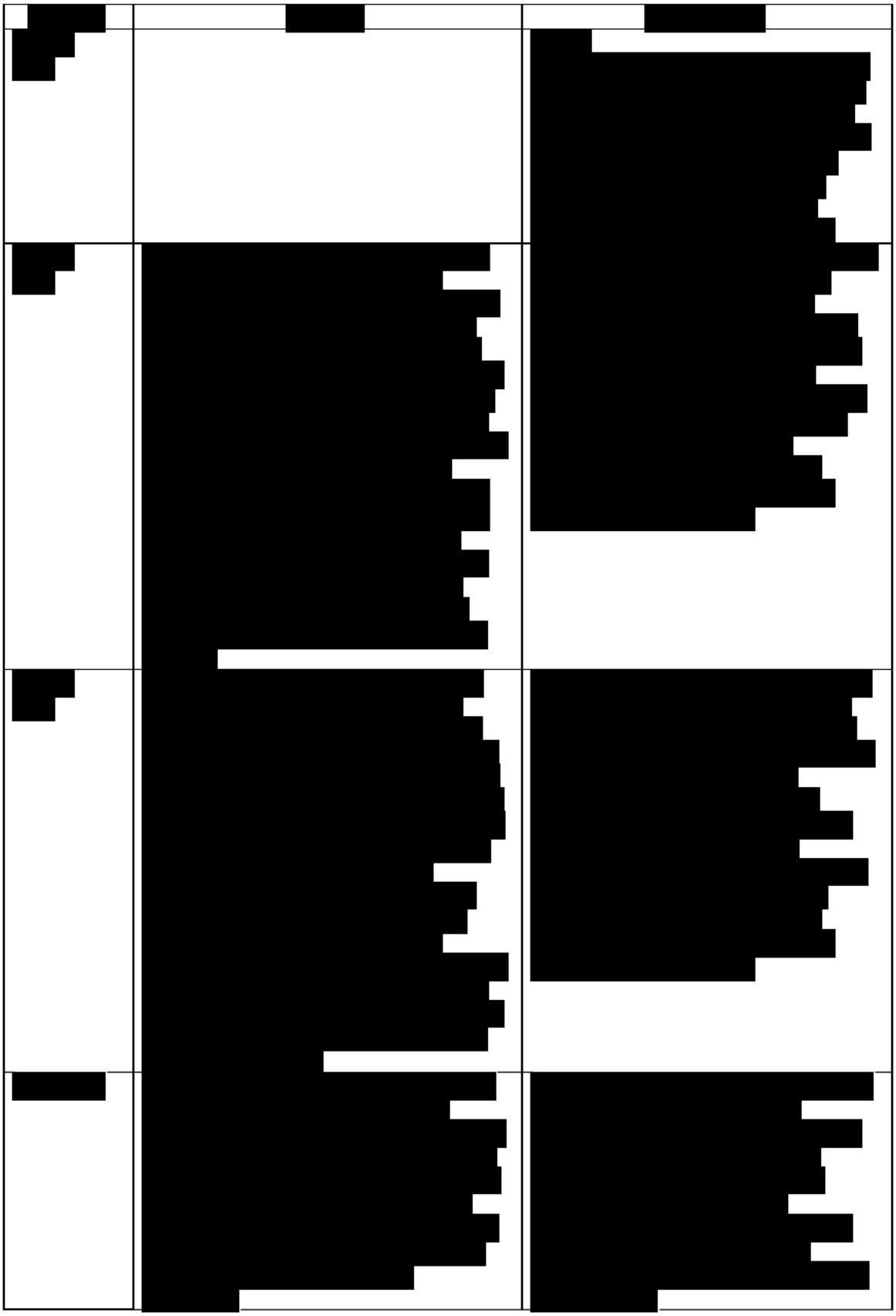

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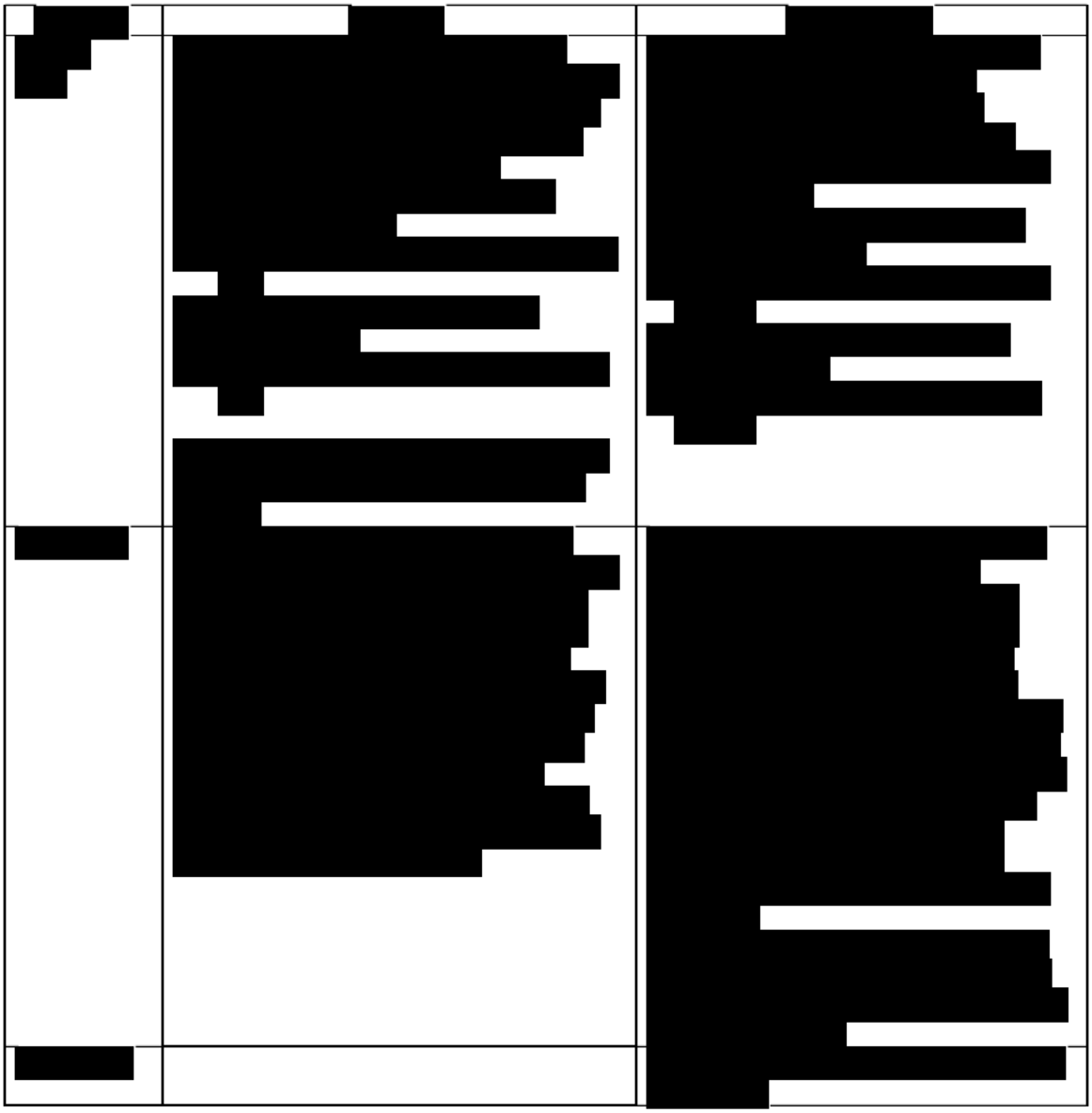

Protocol 156-12-298

Amendment Number: 2

Approval Date: 29 Jul 2020

PURPOSE:

The purpose of this protocol amendment is to introduce a COVID-19 Addendum for any protocol-specified activities that are not able to be performed or cannot be performed due to COVID-19 considerations. Refer to the COVID-19 Addendum for the appropriate measures to be followed. Minor editorial revisions were also made, for consistency with Otsuka style and for internal consistency.

BACKGROUND:

Protocol Amendment 2 revisions were made to introduce a COVID-19 addendum and to add a revised schedule of assessments for only Phase B as all assessments for Phase A have been completed at the time of this amendment.

MODIFICATIONS TO PROTOCOL:

General Revisions:

- Updated the names and contact information of Sponsor representative on title page.
- Added trial conduct information after the title page to introduce the COVID-19 Addendum.
- Added text in “other secondary endpoints” in Protocol Synopsis.
- Updated text in Section 7.5.2 “Key Secondary Endpoint Analysis.”
- Updated text in Section 7.5.3 “Secondary Endpoint Analysis.”
- Deleted text in Section 7.7 “Exploratory Endpoint Analysis.”

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects. A complete redline version of this amendment showing all changes from the previous version will be produced and available upon final approval of this amendment.

Protocol 156-12-298

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 Trial 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, tolvaptan, 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 receive a favorable opinion by the Independent Ethics Committee (IEC) responsible for such matters in the clinical trial facility where tolvaptan 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 the sponsor's Clinical Trial 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 and designee 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 substantial 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 the required local applicable timelines. Administrative changes to the protocol will be transmitted to the IRB/IEC for informational purposes only, if required by local regulations.

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 Trial Agreement and the relevant regional regulation(s) and guideline(s). I further agree to provide all required information regarding financial certification or disclosure to the sponsor for all investigators and sub-investigators in accordance with the terms of the relevant regional regulation(s). I understand that participation in the protocol involves a commitment to publish the data from this trial in a cooperative publication before publication of efficacy and safety results on an individual basis may occur, and I consent to be acknowledged in any such cooperative publications that result.

_____	_____	_____
Principal Investigator Print Name	Signature	Date

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SIGNATURE PAGE

Document Name: 156-12-298 Protocol Amendment 2

Document Number: [redacted]

Document Version: 8.0

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:min) - UTC timezone
[redacted]	Clinical Pharmacology Approval	29-Jul-2020 01:15:59
[redacted]	Clinical Approval	29-Jul-2020 12:02:03
[redacted]	Biostatistics Approval	28-Jul-2020 21:22:07

Otsuka Pharmaceutical Development & Commercialization, Inc

Investigational Medicinal Product

OPC-41061 (Tolvaptan)

ADDENDUM FOR CLINICAL PROTOCOL FOR TRIAL 156-12-298

A Phase 3b, Two-part, Multicenter, One Year Randomized, Double-blind, Placebo-controlled Trial of the Safety, Pharmacokinetics, Tolerability, and Efficacy of Tolvaptan followed by a Two Year Open-label Extension in Children and Adolescent Subjects with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Protocol No. 156-12-298
IND No. 072975
EudraCT No. 2016-000187-42

CONFIDENTIAL – PROPRIETARY INFORMATION

Clinical Development Phase:	3b
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Boulevard Rockville, Maryland 20850
Immediately Reportable Event	Syneos Health Pharmacovigilance & Drug Safety [redacted]
Issue Date:	29 Jul 2020

Protocol 156-12-298

Trial Conduct for COVID-19

All procedures and assessments in the protocol are to be followed to the fullest extent possible. The sponsor, in coordination with the site, investigator(s), and medical monitor, will continuously monitor and evaluate the benefits and risks to subject participation in the clinical trial as it relates to COVID-19. If any protocol-specified activities were not able to be performed, or cannot be performed due to COVID-19 considerations, the appropriate measures to be followed will be provided in this document.

Table of Contents

List of In-text Tables

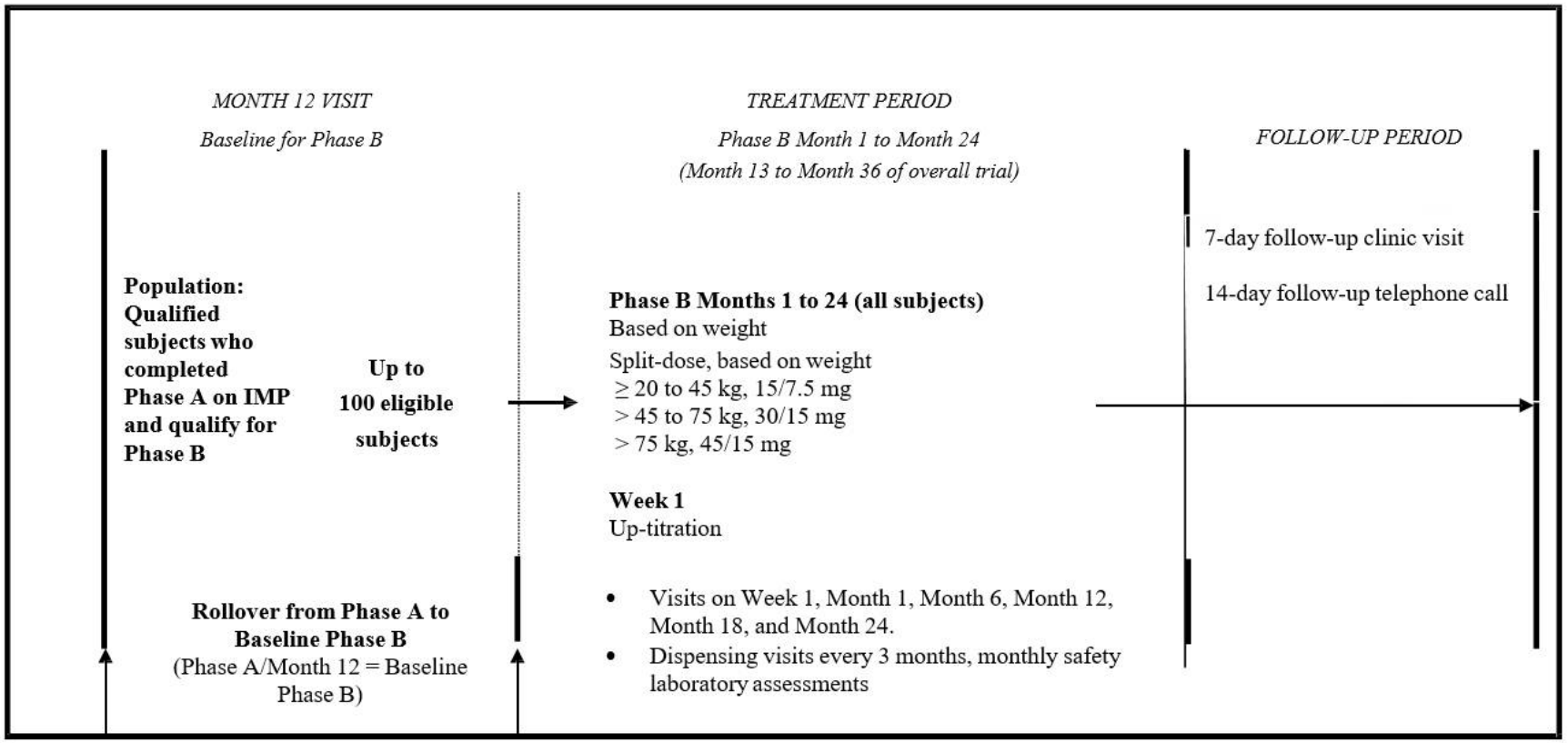
List of In-text Figures

List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ADPKD	Autosomal dominant polycystic kidney disease
AE	Adverse event
CRO	Clinical research organization
D	Day
eCRF	Electronic case report form
EoTx	End of Treatment
EudraCT	European Clinical Trial Data Base
FOCBP	Females of child bearing potential
IMP	Investigational medicinal product
IND	Investigational new drug
LFT	Liver function test
MRI	Magnetic resonance imaging
OPDC	Otsuka Pharmaceutical Development & Commercialization
PE	Physical Examination
QoL	Quality of Life
SAE	Serious adverse event
Wk	Week

1 Trial 156-12-298 COVID-19 Protocol Summary

1.1 Trial Design Schematic



IMP = Investigational medicinal product

Figure 1.1-1 COVID-19 Impact Trial Design Schematic (Phase B)

1.2 Schedule of Assessments

Sites were informed to complete the in-clinic visits via telephone/telemedicine. Details were provided on how to perform the following assessments: Directed PE, collection of vital signs/weight/temperature, [redacted], MRI/ultrasound, and collection of AEs and Concomitant Medications with the details listed in the footnotes in Table 1.2-1. The renal pelvis assessment via ultrasound and Tanner Staging would not be performed as these assessments require a subject to be in-clinic. It was offered to the sites to use a courier service to send IMP to the subjects if needed at the appropriate visits. In the event of any future resurgence of COVID-19, the sites will be notified to follow the assessments listed in this addendum. The sponsor will continue to monitor and evaluate the benefits and risks to subject participation in the clinical trial as it relates to COVID-19.

Table 1.2-1 COVID-19 Impact Schedule of Assessments Phase B

	Baseline[a] (D 1) See Phase A M12	Wk 1 (-1/+3 D)	M1 (Wk 4) (±7 D)	M6, M12, M18 (±14 D)	Monthly Safety Visits: M2, 3, 4, 5, 7, 8, 9, 10, 11, 13, 14, 15, 16, 17, 19, 20, 21, 22, 23 (±4 D)[b]	Titration Contact (phone contact)	M24 (±14 D) / End of Treatment[c]	Follow-Up	
								7 D post last dose (+2 D)	14 D post last dose (+2 D)[d]
	In person	In person	In person	Remote	Remote	Remote	Remote	Remote	In person
MRI/ultrasound[e,f]				X[g]			X[g]		
Renal pelvic assessment[h,i]			X	X[h]					
Vital signs[j,k]		X	X	Remote			Remote		
Body height and weight[k]/growth percentiles[l]		X[l]	X[l]	Remote			Remote		
Serum chemistry/Hematology[m,n]				Remote			Remote		
Liver function tests[m,o,n]		X	X	Remote	Remote[p]		Remote	Remote	
Serum sodium/Creatinine[m,n]		X	X	Remote	Remote[p]		Remote		
Urinalysis[m,n]				Remote			Remote		
Urine or serum pregnancy test[q,r]			X	Remote	Remote[p]		Remote		
Physical examination[s,t]		X	X	Remote			Remote		
Tanner staging[u,i]				X			X		
Drug administration[v]	X	X	X	Remote					
Drug dispensation[w]	X	X	X	Remote	Remote[p]	Remote			
Drug reconciliation[w]	X	X	X	Remote			Remote		
[redacted]									
[redacted]									

	Baseline[a] (D 1) See Phase A M12	Wk 1 (-1/+3 D)	M1 (Wk 4) (±7 D)	M6, M12, M18 (±14 D)	Monthly Safety Visits: M2, 3, 4, 5, 7, 8, 9, 10, 11, 13, 14, 15, 16, 17, 19, 20, 21, 22, 23 (±4 D)[b]	Titration Contact (phone contact)	M24 (±14 D) / End of Treatment[c]	Follow-Up	
								7 D post last dose (+2 D)	14 D post last dose (+2 D)[d]
	In person	In person	In person	Remote	Remote	Remote	Remote	Remote	In person
24-hour fluid balance		X							
Concomitant medications[z]		←----------Remote----------→						Remote	X
Adverse events[z]		←----------Remote----------→						Remote	X

D = Day; IMP = Investigational medicinal product; MRI = Magnetic resonance imaging; EoTx = End of Treatment; Wk = Week.

[a]The Month 12 visit from Phase A will serve as the baseline visit for Phase B. The subject's body weight at this visit will be used to determine the starting dose in Phase B.

[b]Monthly safety visits: If it is more convenient for the subject, laboratory tests may be collected at a local laboratory; a clinic visit is not required. The PI is required to review monthly safety labs and record them in the electronic case report form (eCRF).

[c]Subjects who discontinue investigational medicinal product (IMP) during Phase B, will have safety laboratory tests (including LFTs) at the 7-day posttreatment follow-up visit, and then will be followed every 6 months through Phase B. An assessment of vital status will be conducted on subjects who terminate IMP prior to the Phase B Month 24 visit and do not agree to additional safety follow-up but do not withdraw consent for continued telephone contact. See Section 3.7.4.8.

[d]The 14 day follow-up visit is a telephone contact only, a clinic visit is not required.

[e]The baseline imaging used must be the same imaging used throughout the trial (Phase A and Phase B).

[f]If there were safe and appropriate protective approaches in place to obtain the MRIs at the site, then it was acceptable to complete. Obtaining the MRI scans were not considered a protocol requirement during COVID-19.

[g]MRI/ultrasound at Month 12 and 24 only. MRI/ultrasound is not required at EoTx visit.

[h]Renal pelvic assessments will be done using ultrasound. The Month 1 assessment can be performed at any scheduled visit between Month 1 and Month 3 but cannot be conducted until 30 days after the subject has started IMP, see Section 3.7.4.5. Renal pelvic assessment is also required at Month 12.

[i]Renal pelvic assessment and tanner staging are not required during COVID-19.

[j]Vital signs at each visit include seated heart rate and blood pressure (systolic and diastolic).

[k]Subjects can take their own measurements remotely. If the subject cannot collect the measurements for two consecutive visits, treatment interruption should be considered per principal investigator discretion.

[l]Body weight should be measured post-void. Growth percentile and body weight is not required at the Wk1 and M1 visits.

[m]Central laboratory serum laboratory tests will be performed for all visits (only monthly safety labs may be collected at a local laboratory). Fasting is recommended for all, but is not required. 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, phosphorus, parathyroid hormone, vitamin D, and bicarbonate levels.

[n]Subjects can have the labs drawn at a local lab or have a home health nurse draw the labs at the subject's home. If the monthly safety lab visits cannot be completed, a treatment interruption is required.

[o]Liver function tests are for AST and ALT only, unless otherwise clinically indicated. See Section 5.4 for handling abnormal LFTs.

[p]Months 3, 9, 15, and 21 are drug dispensing visits. Additional assessments to be completed at this visit are: drug dispensation and drug reconciliation.

[q]A urine or serum pregnancy test for pregnancy for females of childbearing potential (all females ≥ 12 years of age and females < 12 years of age who have started menstruating) will be performed. On suspicion of pregnancy, an unscheduled urine or serum pregnancy testing will be performed. Positive urine pregnancy tests must be confirmed with a serum pregnancy test. Investigator (or appropriate site staff) is advised to counsel participants on the risk of pregnancy while participating in a clinical trial as well as ensuring the child understands how pregnancies occur and can be avoided. This should be documented in source records.

[r]For the initial remote visit, two dipsticks will be sent to the subject to allow for a repeat in case the test is positive; however, if the pregnancy test cannot be completed, please review the general considerations in Section 4.1.2.

[s]As needed, a "directed" physical examination may be performed to focus on PKD-related signs and symptoms.

[t]A Directed physical examination cannot be performed per protocol. In lieu of the Directed physical examination, the assessment is to be completed via phone and through an interview to obtain the information.

[u]A subject who reaches Stage 5 (both in pubic hair and genitalia) does not need to continue with Tanner Staging.

[v]The first dose of IMP will be administered to the subject in the clinic. The last dose of Phase B will be taken the evening prior to the Month 24 visit.

[w]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 recorded at each visit. Drug reconciliation will be conducted at every visit. If additional drug supply is required for titration purposes, the site will arrange a subject visit for dispensation.

[redacted]

[z]Contact the subject via phone to ask if there have been any new medications or changes to existing medications, any potential adverse events, and any changes related to ADPKD-related morbidities. It is expected that this information will be obtained from the subject/caregiver.

2 General Considerations

2.1 Reconsent

If there is an immediate need to reconsent subjects during the period of COVID-19 restrictions, a paper reconsent process will be followed and sites are encouraged to contact the contract research organization (CRO) and sponsor with questions.

2.2 Protocol Deviations

Protocol deviations that occur as a direct result of the COVID-19 pandemic must be recorded in electronic case report form (eCRF) separately from other protocol deviations as soon as they are identified and will be recorded as "Major" in eCRF for data capture purposes. Examples of the types of COVID-19 related deviations to be reported may include: missed visits, missed assessments, assessments performed remotely (completed outside of protocol procedure), missed investigational medicinal product (IMP) dose, IMP dispensed/returned via courier, IMP not returned to site/site unable to verify IMP compliance, out of window visits, and prohibited concomitant medications. A "direct result" is defined as being due to actual illness, or as a result of quarantine, social distancing, or site closures. All other deviations will follow the normal deviation process described in the protocol and should not be entered proactively by sites.

2.3 Guidance to Record Adverse Events and Discontinuations Due to COVID-19

If a subject tests positive with COVID-19, the subject must have a treatment interruption until the subject is no longer considered to have active virus and is free of any medical conditions associated with the infection. An adverse event (AE) of "Coronavirus Infection" OR "Coronavirus Positive Test Result" should be recorded on the AE page of the eCRF. A positive test result is not automatically a serious adverse event (SAE), unless an SAE criterion is met (eg, hospitalization). If the event meets the criteria for an SAE, the subject may restart treatment per Investigator clinical judgement and with Sponsor Medical Monitor approval. The subject must no longer be considered to have active virus infection and is free of any medical conditions associated with the infection. Baseline laboratory tests, including liver function, must be performed prior to reinitiating tolvaptan therapy.

If, per the discretion of the investigator, a subject discontinues the trial due to COVID-19 either because they test positive OR are presumed positive with COVID-19, then the primary reason for discontinuation should be reported as "Adverse Event" and indicate the AE number in the "Specify the reason for discontinuation" space that corresponds with the AE of "Coronavirus Infection" OR "Coronavirus Positive Test Result." Remember to enter an AE on the AE page for the "Coronavirus Infection" OR "Coronavirus Positive Test Result."

If a subject discontinues due to COVID-19 other than the subject testing positive OR being presumed positive with COVID-19, then the primary reason for discontinuation should be reported as "Other." Be sure to specify the reason as "COVID-19" followed by the reason ensuring that the prefix of the description includes "COVID-19."

2.4 Statistical Analyses

Any impact of COVID-19 on the planned statistical analyses for the trial will be described in the final statistical analysis plan.

[redacted]

3 Trial Population

3.1 Inclusion Criteria

There are no changes to the inclusion criteria due to COVID-19 for purposes of this addendum.

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3.2 Exclusion Criteria

There are no changes to the exclusion criteria due to COVID-19 for purposes of this addendum.

4 Trial Procedures

4.1 Safety Assessments

4.1.1 Vital Signs

Blood pressure, heart rate, weight, and temperature will all be measured as described in the protocol at the time points defined in this COVID-19 Addendum Schedule of Assessments (Table 1.2-1) with the following changes, if remote visits are necessary:

- Subjects will be asked to use any collection device, if available, until devices can be provided to subjects.
  - Where possible, site staff will remotely supervise the collection of measurements via video on the appropriate visits.
  - If remote supervision is not possible, subjects will be instructed to be as consistent as possible regarding the time of day the measurement is taken and how the measurement is taken. Subjects or their parent/guardian will notify site staff of the measurement results via telephone or other means, on the appropriate visits.
- Site staff will instruct the subjects or their parent/guardian to follow the procedures in the trial guidance for blood pressure and heart rate collection.
- Site staff will be instructed to record the measurement in the subject's eCRF, and if there are believed to be any errors, inconsistencies, or safety concerns with the home measurement, the medical monitor should be notified.

4.1.2 Pregnancy

Pregnancy tests will be performed as described in the protocol at the time points defined in this COVID-19 Addendum Schedule of Assessments (Table 1.2-1) with the following changes:

- For planned visits that require a pregnancy test for females of child bearing potential, the site will take dipstick(s) from the central lab kit/bulk supply and include it with the IMP delivery package.

  - For the initial remote visit, two dipsticks will be sent to the subject to allow for a repeat in case the test is positive.
  - For subsequent visits, the site will decide whether to send 2 dipsticks at each subject shipment, or whether to help the subject manage the dipsticks at sequential visits (eg, test is negative, one dipstick left at subject home, the subject will be instructed to retain the spare dipstick for next testing, thus sending only one; or just sending 2 dipsticks to subject every time just to be on the safe side).

- Site will inform the subject (or caregiver, as applicable) of instructions (verbally or in writing within the shipment, if EC approval is received).
- Applicable subjects will perform a pregnancy test prior to dosing with IMP, ensuring a date and time-stamped picture or video of the result is taken, followed by notification to the site staff of the results via telephone, or other means, on the appropriate visits. Subjects will also provide the site staff with the date- and time-stamped picture/video.
  - If negative, site to inform the subject to proceed with dosing.
  - If positive, the site must instruct the subject to immediately stop taking IP, and the site will refer to the Pregnancy section of the protocol for appropriate immediately reportable event reporting.
- Further instruction must be agreed upon in consultation with the sponsor but an option may include the site informing the subject to continue to withhold IMP and to perform a repeat urine pregnancy test in 2 days (> 48 hours from first test). Subjects would again be asked to take a date and time-stamped picture or video of the result, followed by notification to the site staff of the results via telephone, or other means. Subjects would also provide the site staff with the date- and time-stamped picture/video.
  - If the second result is positive, the subject will be discontinued from the trial, and be instructed to contact their healthcare professional and the trial site (if possible) for further instructions.
  - If the second result is negative, the site will contact the CRO and sponsor for guidance and next steps.

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4.1.3 Laboratory Tests

The liver function test (LFT), serum chemistry, hematology, serum sodium, creatinine and urinalysis should be completed at a local laboratory or via a home health nurse. The local lab should have the proper protections in place for the subject to limit the exposure to COVID-19 and following the current local restrictions, guidance, and regulatory authority directions. The monthly safety labs must be completed in order for the subject to remain on IMP. If the subject is unable to have the labs drawn, the subject must have a treatment interruption until the labs can be completed. All labs should be assessed at the same time as the LFTs; however, if the results for serum chemistry, hematology, serum sodium, creatinine and urinalysis are not available, the subject can continue in the study. All attempts to obtain the required lab results should be made. How the labs were obtained (ie, via local lab, home health nurse) should be documented in the subject's source.

4.1.4 Adverse Event/Concomitant Medication

The site should contact the subject by telephone at each visit to periodically assess for the occurrence of AEs. To avoid bias in eliciting AEs, subjects should be asked the nonleading 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.

5 Investigational Medicinal Product

Clinical sites are permitted to ship IMP directly to subjects per agreed study processes due to COVID-19 restrictions.

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Document Name: 156-12-298 Protocol Addendum

Document Number: [redacted]

Document Version: 3.0

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:min) - UTC timezone
[redacted]	Clinical Approval	29-Jul-2020 12:00:36
[redacted]	Biostatistics Approval	28-Jul-2020 21:22:37
[redacted]	Clinical Pharmacology Approval	29-Jul-2020 01:16:28