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

Investigational Medicinal Product

OPC-41061

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

Protocol No. 156-13-211
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Statistical Analysis Plan

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Date of Amendment 2 06 March 2015

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List of Abbreviations and Definition of Terms

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CRF	Case report form
CRO	Clinical Research Organization
ECG	Electrocardiogram
EDC	Electronic data capture
EU	European Union
EudraCT	European Clinical Trial Data Base
FDA	(United States) Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
IND	Investigative new drug
IRB	Institutional review board
IRE	Immediately reportable event
MedDRA	Medical Dictionary for Regulatory Activities
PE	Physical examination
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event
US or USA	United States or United States of America
ULN	Upper limit of normal

1 Introduction

This Statistical Analysis Plan (SAP) documents the statistical methodology and data analysis algorithms and conventions to be applied for statistical analysis and reporting of efficacy and safety data of study 156-13-211. The original protocol (dated 20 May 2014), the Amendment 1 (dated 14 July 2014), and the Amendment 2 (dated 06 March 2015) are taken into consideration in developing this SAP.

2 Trial Objective

The primary objective of this trial is to evaluate and describe the long-term safety of Tolvaptan.

3 Trial Design

3.1 Design of Trial

This trial is a phase 3b, multi-center, open-label trial. Eligible subjects have an opportunity to be enrolled into Trial 156-13-211 following completion of the follow-up visit(s) of the previous trial.

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

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

After consenting, subjects will be assigned a new screening number. Subjects who are found to be eligible will retain the same subject number they had been assigned in their

previous trial. For purposes of ensuring subject safety, tolvaptan exposure of at least 18 months is required for all subjects.

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

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

The duration of this trial is planned to continue

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

The study schema, presented in Figure 3.1-1, depicts the overall study design.

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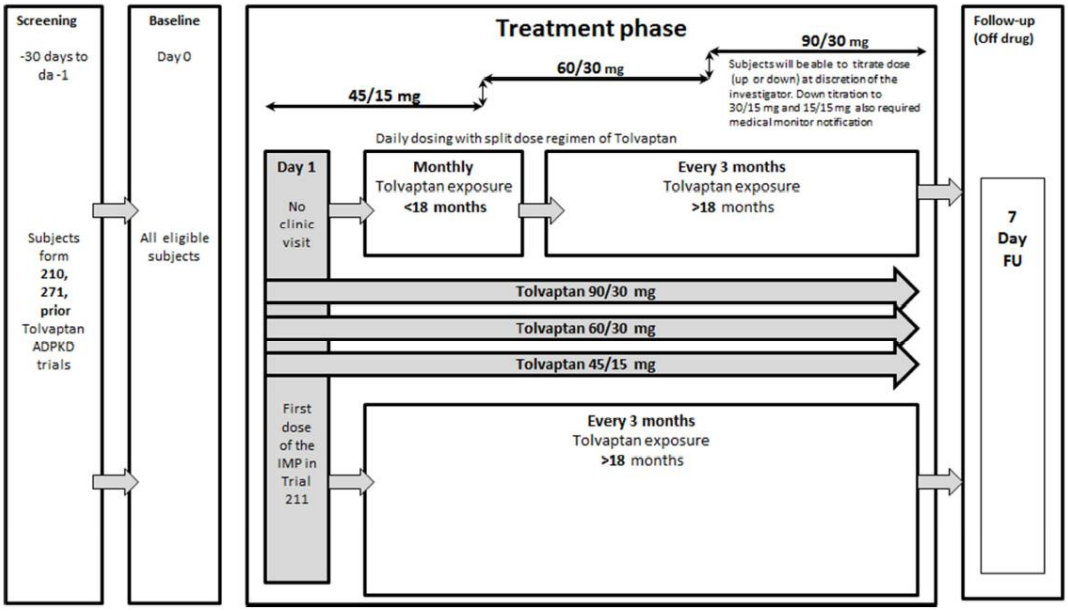
Figure 3.1-1 Study Design and Treatment Schema -Extension Study



Note: FU=follow-up

3.2 Treatments

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

Subjects will receive open-label tolvaptan for the duration of the trial. All subjects will be administered tolvaptan tablets in a daily split-dose, once upon awakening and another approximately 8 to 9 hours later (twice daily dosing). The exact time of dosing may be adjusted based on wake/sleep habits (eg, standard 8 AM and 5 PM may be switched to 10 PM and 7 AM if working a night shift). However, dosing times should be consistent for each individual's daily dose to maximize receptor suppression. Doses will be recorded as early dose/late dose (eg, 60/30 mg).

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

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

- **Prior tolvaptan trials**- initiated on tolvaptan at a split-dose of 45/15 mg with upward titration every 3 to 4 days to 60/30 mg or 90/30 mg per day according to tolerability.

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

3.3 Trial Population

This trial will include approximately 2,500 subjects over the age of 18 years with ADPKD diagnosed by Pei-Ravine criteria[1,2] (modified by magnetic resonance imaging [MRI]) who completed or participated in a prior tolvaptan trial.

3.4 Trial Visit Window

Due to the extended duration of the study, the individual patient data will be summarized by period.

For assessments recorded at clinic visits, except for the hepatic monitoring for the subjects from Trial 156-08-271, data will be derived by mapping the study day of the assessment into corresponding time windows as specified in Table 3.4.1. Study day is calculated as: date of assessment - date of enrollment (ie, screening or baseline date) + 1. If there are multiple observations within the same study time window, only the last observation within that study week will be used for the summary tables. The time window mapping rules are applicable to all post first dose safety and efficacy assessments (unless otherwise stated) that are assessed at the scheduled or unscheduled visits (excluding early termination visits/end of treatment visits).

Table 3.4.1 Mapping of clinic visit assessments to study month (except for hepatic monitoring for Subjects from Trial 156-08-271)

Study Month	Study Day Interval
Monthly Visit	
Month 1	2 – 46
Month 2	47 – 76
Month 3	77 – 107
Month 4	108 – 137
Month 5	138 – 168
Month 6	169 – 198
Month 7	199 – 229
Month 8	230 – 259
Month 9	260 – 290
Month 10	291 – 320
Month 11	321 – 351
Month 11	352 – 381
Month 13	382 – 412
Month 14	413 – 442

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Month 15	443 – 473
Month 16	474 – 503
Month 17	504 – 534
Month 18	535 – 595
Every 3 Months	
Month 21	596 – 686
Month 24	687 – 778
Month 27	779 – 869
Month 30	870 – 961
Month 33	962 – 1052
Month 36	1053 – 1144
Month 39	1145 – 1235
Month 42	1236 – 1327
Month 45	1328 – 1418
Month 48	1419 – 1510
Month 51	1511 – 1601
...	...

Note: Early Termination/End of Treatment (± 7 days)

Once Trial 156-13-210 unblinding occurs, it can be determined which subjects received tolvaptan in Trial 156-13-210. These subjects may have their trial visits/hepatic transaminase monitoring changed to every 3 months sooner as their previous tolvaptan exposure in Trial 156-13-210 can count towards the 18-month threshold.

For assessments for hepatic monitoring recorded at clinic visits, for the subjects from Trial 156-08-271, data will be derived by mapping the study day of the assessment into corresponding time windows as specified in Table 3.4.2.

Table 3.4.2 Mapping of clinic visit assessments for hepatic monitoring for Subjects from Trial 156-08-271 to study month

Study Month	Study Day Interval
Every 3 Months (± 45 days)	
Month 3	2 – 137
Month 6	138 – 229
Month 9	230 – 320
Month 12	321 – 412
Month 15	413 – 503
Month 18	504 – 595
Month 21	596 – 686
Month 24	687 – 778
Month 27	779 – 869
Month 30	870 – 961
...	...

Note: Early Termination/End of Treatment (± 7 days)

4 Sample Size

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

5 Statistical Analysis Datasets

5.1 Data for Analysis

The following datasets are defined for this trial:

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

5.2 Handling of Missing Data

The majority of missing data are expected to be caused by patients who dropped out of the study before completion. The pattern of drop out will be summarized by disposition of patients and reasons for discontinuation.

All safety/efficacy data will be summarized for observed (non-missing) values only.

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

6 Summary of Study Data

6.1 Subject Disposition

Disposition of all enrolled patients, as well as reasons for discontinuation, will be summarized by parent study and the treatment groups in the parent study (rollover from Trial 156-08-271, Trial 156-13-210 and Other Trials).

In addition, the number (percentage) of patients completing a certain number of months (in the categories of ≥ 1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 21, 24, 27 months) will be tabulated by parent study.

6.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics (including medical history) will be from either the last visit assessments from parent trials or the screening visit from this trial (the time between the last visit assessments from the previous trial and the screening visit for this trial is within 30 days). Summary statistics including mean, median, minimum, maximum, and standard deviation will be used to describe continuous variables such as age. Frequency distributions will be tabulated for categorical variables such as race. Demographic and baseline characteristics will be tabulated and presented for all patients in the Safety Analysis Set by parent study, also by the treatment group in the parent study.

6.3 Baseline Disease Evaluation

A short PKD history survey will be completed during screening to capture information from the subject's recollection, and documented past medical history where available. Baseline disease evaluation will be tabulated and presented for all patients in the Safety Analysis Set by parent study, also by the treatment group in the parent study.

6.4 Treatment Compliance

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

Treatment compliance will be calculated by dividing the total dosage taken by the total dosage the subjects are scheduled to take during the treatment phase based on the Study Medication panel of the case report form (CRF).

6.5 Prior and Concomitant Medications

Concomitance medications are coded using WHO Drug B2 Enhanced version March 1, 2010. Incomplete/missing start dates of concomitant medications will be imputed by the following rules:

- If the year is missing, default to the same year the patient was enrolled, or the stop year (when the stop year is not missing) whichever occurred earlier;
- If the month is missing, default to '01';
- If the day is missing, default to '01';

Incomplete/missing stop dates of concomitant medications will be imputed by similar rules as for AE stop dates in Section 8.1.2.

All concomitant medications will be summarized using the Safety Analysis set for 3 periods, ie, prior to, during and after the IMP treatment period. A concomitant medication will be counted toward a period if it is taken during that period. Summaries will be presented for maintenance opioids, breakthrough opioids, and other general concomitant medications separately.

6.6 Protocol Deviations

Protocol deviations occurring to patients will be listed and summarized (only for major protocol deviations) by patient type by parent trial.

7 Efficacy Analysis

No efficacy analyses are planned.

8 Safety Analyses

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

In general, baseline measurements of safety variables are defined as the last measurements prior to the first dose of IMP in Trial 156-13-211. Safety variables will be summarized by descriptive statistics, (eg, proportion, mean, median, SD, minimum, and maximum values). Summary statistics, including changes from baseline, will be provided for safety variables based on all available data. No inferential statistical analyses of the safety variables will be performed.

Safety variables to be analyzed include:

- Adverse events
- Vital signs
- Clinical laboratory assessments
- Serum transaminase elevations for frequency (2x, 3x, 5x and 10x ULN), time to onset, time to peak levels, time of offset (< 3x, 2x, or 1x ULN), response to de-challenge and re-challenge and frequency of progression to Hy's laboratory criteria (ALT or AST > 3x ULN and bilirubin, total (BT), > 2x ULN without alkaline phosphatase > 2x ULN)
- Serum sodium excursions above 145, 150, or 155 mmol/L or below 136, 130, or 125 mmol/L

8.1 Adverse Events

ADPKD is a progressive disorder involving the kidney, liver and occasionally other organ systems. A number of AEs may be associated with this disorder including urine

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

8.1.1 Definitions

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

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

A serious adverse event (SAE) includes any event that results in any of the following outcomes:

1. Death
2. Life-threatening, ie, the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
3. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
4. Requires inpatient hospitalization or prolongs hospitalization (NOTE: A pre-scheduled hospitalization is not considered an SAE.)
5. Congenital anomaly/birth defect
6. Other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above, eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Nonserious AEs are all AEs that do not meet the criteria for a "serious" AE.

Immediately Reportable Event (IRE):

- Any SAE
- Any AE (whether serious or nonserious) that necessitates discontinuation of IMP.
- Any subject with a new liver test abnormality meeting the AE (whether serious or nonserious) or laboratory threshold criteria (whether considered an AE or not) for hepatic eCRF reporting.
- Any subject reporting an AE of special interest (eg, skin neoplasms or glaucoma).
- Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, it will mandate IMP discontinuation and must be reported on an IRE form to Otsuka

Pharmaceutical Development & Commercialization, Inc. (OPDC). Pregnancy will only be documented on the AE eCRF if there is an abnormality or complication.

- Additionally, in the EU region, events involving overdose, misuse and abuse as well as reported lack of efficacy must also be reported as IREs.

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

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

Additionally, if the laboratory value is determined by the investigator to be an abnormal change from baseline for that subject, this is considered an AE.

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

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

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

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

8.1.2 Handling of Missing/Incomplete AE start/stop dates

Incomplete/missing start dates of AEs will be estimated by the following rules:

- If the year is missing, default to the same year the patient received the first dose of study medication, or the stop year (when the stop year is not missing) whichever occurred earlier. For an enrolled patient without using study medication, default to the same year the patients was enrolled, or the stop year (when the stop year is not missing) whichever occurred earlier;
- If the month is missing:
  - If the start year equals to the stop year, then default to the first dose month or stop month whichever occurred earlier;
  - Otherwise, default to the first dose month or enrollment month for an enrolled patient without using study medication;
- If the day is missing:

  - If the start year equals to the first dose year, start month equals to the first dose month, and first dose day is the last day of a month, default to the first dose day; otherwise, default to the day after the first dose; If also the start year equals the stop year, and the start month equals to the stop month, default to the day gotten from the above rule or the day before the stop day, whichever occurred earlier when stop day is not the first day of a month; otherwise, default to the day gotten from above or the stop day, whichever occurred earlier;
  - Otherwise, default to '01'

Incomplete/missing stop dates of AEs will be estimated by the following rules:

- If the year is missing:
  - If a patient died, default to the year the patient died;
  - Otherwise, default to the year the patient was enrolled, or the start year, whichever occurred later;
- If the month is missing:
  - If a patient died, and the stop year equals to the year the patient died, default to the same month the patient died;
  - Otherwise, default to the same month the AE started.
- If the day is missing:
  - If a patient died, and if the stop year equals to the year the patient died, and the stop month equals to the month the patient died, default to day the patient died;
  - Otherwise, default to the last day of the stop month;

8.2 Clinical Laboratory Test Results

The observed laboratory test results at last Visit/ET as well as their changes from baseline will be summarized (mean, standard deviation, minimum, maximum, and median) by parent study and prior treatment for the Safety Population. The shift from baseline for normality status will also be summarized, using an out of range flag (low, normal, and high). Potentially clinically significant results in laboratory tests identified using prospectively defined criteria, including criteria for liver enzyme elevations, will also be summarized by parent study and prior treatment for the Safety Population. In addition, by-subject listings will be provided for data of local laboratory tests. Criteria for identifying potentially clinically significant laboratory test abnormalities (Modified NCI Criteria) are listed in Appendix 1.Appendix 1Appendix 1Appendix 1Appendix 1Appendix 1Appendix 1Appendix 1Appendix 1Appendix 1Appendix 1Appendix 1Appendix 1Appendix 1

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

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

8.3 Vital Signs Data

Summary statistics for changes from baseline in vital signs and potentially clinically significant results in vital signs will be summarized by parent study (and prior treatment).

Incidence of potentially clinically significant vital sign results will be summarized by parent study (and prior treatment). Criteria of potentially clinically significant vital sign abnormalities are provided in Appendix 2.

8.4 Serum Sodium

The following will be summarized by parent study (and prior treatment):

- Serum sodium excursions above 145, 150, or 155 mmol/L or below 136, 130, or 125 mmol/L

Interruptions of protocol-specified therapies for hypernatremia or hyponatremia.

9 CCI [redacted]

[redacted]

9.2 CCI [redacted]

[redacted]

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10 CCI [redacted]

[redacted]

11 Interim Analysis

There is no interim analysis performed for this trial.

12 Monitoring of Safety Data

For this trial, an Independent Data Monitoring Committee (IDMC), also known as a Data Safety and Monitoring Committee, will be established. The role of the IDMC shall be delineated in a separate IDMC Charter document, but in general this group will meet on a regular basis to ensure the safe and ethical treatment of trial subjects, ensure the scientific integrity of the trial, and to ensure the trial is conducted within the bounds of ethical medical practice. Adjudication results as determined by the HAC will be reported to the IDMC on a quarterly basis or more frequently as necessary. This IDMC may make recommendations to the sponsor and trial steering committee to amend or terminate the trial based on grounds of safety, futility, or greater than expected efficacy as defined by the accepted statistical practices and procedures detailed in their Charter.

13 Changes in the Planned Analyses

None.

References

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

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

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Appendices

Appendix 1 Criteria of Potentially Clinically Significant Laboratory Test Abnormalities (Modified NCI Criteria)

(Laboratory Test Abnormalities due to Test Value Increase)

Test	Abnormality	Test Result Grade				
		0	1	2	3	4
APTT (sec)	Increase	ULN	>ULN - 1.5xULN	>1.5xULN - 2xULN	>2xULN	
ALT (SGPT) (IU/L)	Increase	ULN	>ULN - 3xULN	>3xULN - 5xULN	>5xULN - 20xULN	>20xULN
AST (SGOT) (IU/L)	Increase	ULN	>ULN - 3xULN	>3xULN - 5xULN	>5xULN - 20xULN	>20xULN
Bilirubin, Total (mg/dL)	Increase	ULN	>ULN - 2xULN	>2xULN - 3xULN	>3xULN - 10xULN	>10xULN
Creatinine (mg/dL)	Increase Pre-randomization	AB*	>AB – 1.5xAB	>1,5 x AB – 3 x AB	> 3 x AB – 6 x AB	> 6 x AB
Creatinine (mg/dL)	Increase Post-randomization	< 1.33 x PR*	1.33 x PR - < 2x PR	2 x PR – < 3 x PR	3 x PR – 6 x PR	>6xPR
Eosinophils, Absolute (Thous/µL)	Increase	≤0.65	>0.65-1.5	>1.5-5	>5	
Glucose (mg/dL)	Increase	≤115	>115-160	>160-250	>250-500	>500
Hemoglobin (g/dL)	Increase	ULN	>ULN-20	>20-21	>21-22.5	>22.5
Potassium (mEq/L)	Increase	ULN	>ULN-5.5	>5.5-6	>6-7	>7
INR	Increase	ULN	>ULN - 1.5xULN	>1.5xULN - 2xULN	>2xULN	
Sodium (mg/dL)	Increase	<=145	146 - 150	151 - 155	156 - 160	>160
Triglycerides (mg/dL)	Increase	ULN	>ULN - 2.5xULN	>2.5xULN - 5xULN	>5xULN - 6xULN	>6xULN
Urea Nitrogen (mg/dL)	Increase	≤22	>22-26	>26-31	>31	
White Blood Count (Thous/µL)	Increase	≤10.799	>10.799-15	>15-20	>20-25	>25

* Baseline creatinine is expected to be elevated in this population. Average baseline (AB) is equal to the mean baseline value collected during screening period.
During treatment with tolvaptan, serum creatinine is expected to increase by approximately 5-10%. When these tables are generated during the double-blind conduct, the post-randomization comparisons will be made to the post-randomization (PR) value which equals the value collected post-randomization at Month 1 visit. After data-base lock, final reporting of unblinded tables and listings, APR should be changed to the highest value obtained during the run-in period matching the subject's assigned treatment, ie, either placebo or tolvaptan run-in periods.

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(Laboratory Test Abnormalities due to Test Value Decrease)

Test	Abnor-mality	Test Result Grade				
		-4	-3	-2	-1	0
Glucose (mg/dL)	Decrease	<30	30-<40	40-<55	55-<65	≥65
Hemoglobin (g/dL)	Decrease	<6.5	6.5-<8	8-<10	10-<LLN	LLN
Lymphocytes, Absolute (Thous/µL)	Decrease	<0.2	0.2-<0.5	0.5-<0.8	0.8-<LLN	LLN
Neutrophils, Absolute (Thous/µL)	Decrease	<0.5	0.5-<1	1-<1.5	1.5-<LLN	LLN
Platelet Count (Thous/µL)	Decrease	<25	25-<50	50-<75	75-<LLN	LLN
Potassium (mEq/L)	Decrease	<2.5	2.5-<3		3-<LLN	LLN
Sodium (mg/dL)	Decrease	<120	120-124	125-129	130-135	≥136
White Blood Count (Thous/µL)	Decrease	<1	1-<1.5	1.5-<2.5	2.5-<3.501	≥3.501

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Appendix 2 Criteria of Potentially Clinically Significant Vital Sign Abnormalities

Test Type	Test Parameters	Unit	Sex	Criteria (meet either one will count)	
				Limit	Change from baseline
VITAL SIGNS	SBP, SITTING	mmHg	Male/Female	>=180	>=20
VITAL SIGNS	SBP, SITTING	mmHg	Male/Female	<=90	<=-20
VITAL SIGNS	DBP, SITTING	mmHg	Male/Female	>=105	>=15
VITAL SIGNS	DBP, SITTING	mmHg	Male/Female	<=50	<=-15
VITAL SIGNS	HEART RATE	bpm	Male/Female	>=120	>=15
VITAL SIGNS	HEART RATE	bpm	Male/Female	<=50	<=-15
VITAL SIGNS	TEMPERATURE	degree C	Male/Female	>=38.3	>=1.1
VITAL SIGNS	WEIGHT	kg	Male/Female		>= 7 percent

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