D. Study Protocol v 5/31/17 (amended 8-20-18)

Hypothesis: Treatment with a low dose PPARγ agonist will slow cyst expansion in human ADPKD patients and delay the progression to renal complications and failure.

Specific Aim 1: To provide pilot data on the safety of low dose pioglitazone (15 mg daily) treatment in human ADPKD patients over a one year period. Tests will be conducted to monitor the known side effects of PPARγ agonist treatment, including fluid retention and edema. In addition, liver enzyme tests and risk of hypoglycemia will be routinely assessed.

Specific Aim 2: To provide pilot data on the efficacy of low dose pioglitazone therapy in human ADPKD patients over a one year period using MRI assessment of total kidney volume. This will help with power calculations for a future multi-center trial.

D.2.a.***Study design***: The proposed study is a double-blind, placebo controlled, cross-over trial of pioglitazone (15 mg/day) versus placebo therapy for the treatment of ADPKD. The study is a pilot study to test the safety and efficacy of pioglitazone to slow progression of PKD assessed by percent change in kidney volume by MRI compared to one year of placebo. **45 subjects will be enrolled**. A one year cross-over design provides the best opportunity to obtain meaningful efficacy and safety data in a short term protocol by allowing each patient to serve as his/her own control. This will allow an assessment of effect size and adverse events thereby facilitating the design of a future multi center randomized trial. Our protocol will be modeled on two previous studies using similar populations of ADPKD patients: One study examined safety and efficacy of long acting somatostatin in 12 patients [1] while the other examined the use of sirolimus in 10 patients [2] and both obtained statistically meaningful data.

D.2.b.***End points:***

Safety End Points:

1) Measures of volume overload/fluid retention:

a) Net change (decrease) in resistance (which converts to increase in total body water (TBW)) assessed by bio impedance analysis (BIA) over the course of each arm.

b) Episodes of congestive heart failure: New onset of pulmonary symptoms together with either increased interstitial edema on chest X-ray, or changes by echocardiogram (increase in end diastolic ventricular volume or new/increase pericardial effusion).

c) Edema: Number of episodes of edema, classified as either 1) sustained > 1 week of edema despite adjustment of diet or 2) unresponsive to diuretic therapy.

d) Change in echocardiography parameters consistent with coronary artery disease (reduction in systolic ejection fraction and/or wall motion abnormalities).

e) Any doctors' visit or hospitalization for new cardiac symptoms.

2) Hypoglycemia: Number of episodes of hypoglycemia (defined as blood glucose < 70 on routine labs).

3) Liver function: Number of episodes of elevated ALT or AST to > 2 times the upper limit of normal.

Efficacy End Points:

1) The primary efficacy outcome will be percent change in total kidney volume by MRI from baseline to 12 months for pioglitazone compared to placebo.

2)Measures of kidney function:

a) Change in the estimated GFR (eGFR) by CKDepi formula,

b) Change in the urine micro albumin/creatinine ratio,

c) Average MAP from both blood pressure reading taken at each visit over the 12 months.

3) Other PKD parameters:

a) Percent change in liver size by MRI,

b) Cumulative pain score (on 0 to 10 scale) as average area under the concentration time curve between baseline and last trial visit or last visit before requirement of surgical or medical therapy for pain.

D.2.c. ***Setting and Participants***: This pilot study that will enroll **45** patients with a diagnosis of ADPKD by standard clinical criteria. All patients will be screened and, if eligible, enrolled at the Indiana University Health Clinics under the supervision of Dr. Sharon Moe (PI) and PKD Clinic under the supervision of Dr. Robert Bacallao (Co-I). Dr. Blazer-Yost, (Co-PI) will assist in recruitment, especially with outreach, and help Dr. Moe and the Research Coordinator with other aspects of the study.

D.2.***d: Inclusion/Exclusion Criteria:***

Screening:

Patients will be initially assessed based on historical data available in the medical record or through discussion with patient/primary Nephrologist in the previous 3 months.

Inclusion criteria:

- Male or female ADPKD patients aged 18-55
- eGFR at or above ≥ 50 ml/min/1.73 m^2 by 4 parameter MDRD,CKD-Epi formula, or any other eGFR formula or urine creatinine clearance
- normal liver enzymes (ALT/AST)
- fasting blood glucose between 70 and120
- for female patients, a willingness to use double contraception to avoid pregnancy while in study
- able to give informed consent
- In the opinion of the investigator, high likelihood of progressive kidney disease

Exclusion criteria:

- diabetes, defined as any of the following: fasting blood sugar > 130 times two, HgbA1C > 7, on any blood sugar lowering medication, or past diagnosis of diabetes not occurring during pregnancy
- uncontrolled hypertension as determined by the examining physician
- history of impaired systolic function (ejection fraction < 50%) by previous ECHO or known ischemic cardiovascular disease
- findings suggestive of a kidney disease other than ADPKD
- systemic illness requiring immunosuppressive or anti-inflammatory agents
- congenital absence of a kidney or history of a total nephrectomy
- history of cyst reduction or partial nephrectomy
- history of renal cyst aspiration within the previous year
- History of bladder cancer, or gross hematuria
- inability to undergo MRI due to implantable devices or foreign objects that preclude MRI
- active renal transplant
- allergy or sensitivity to any of the components of the test materials
- institutionalized
- currently pregnant or plans to become pregnant during the study

Step 2 inclusion criteria: patients who fulfill these screening criteria will be asked to undergo further screening with a baseline MRI of the kidney ≤30 days prior to day 0. Patients with kidney volumes estimated to be in the following ranges on MRI imaging: 18-25 years old with TKV >750 ml, 26-35 years old with TKV > 1000 ml, 36-50years old with TKV >1500 ml define a high likelihood of rapid progression based on the CRISP study [3, 4]. For consistency with other studies, the MRI images from IUSM will be sent to the Mayo Clinic for analysis. The investigators at the Mayo Clinic are internationally known and some of the most experienced in interpretation of MRI results from ADPKD patients. The baseline scans will be re-read at the end of the study by the same observer. Thus the actual values for this step of inclusion will not be in the final analyses. In a study of 40 patients, the inter-observer variation had a confidence interval of roughly +/-10%. Thus, as discussed with our DSMB, in order to maximize inclusion, the minimum TKV criteria for randomization will be the above published criteria minus 10% as detailed below:

1: 18-25 years old with TKV ≥675 ml;
2. 26-35 years old with TKV ≥ 900 ml;
3. 36-50 years old with TKV ≥1350 ml

Depending on logistics and distance traveled for potential subjects, the MRI and baseline visit will occur the same day and drug overnight expressed to the patient if patient eligible.

D2.e. Interventions: Once all of the inclusion-exclusion criteria are met (including the kidney volume by MRI), patients will be randomized by an investigational pharmacist to placebo or pioglitazone (15 mg) as a tablet taken once a day. After one year, the patient will be transitioned to the opposite therapy (pioglitazone or placebo) for one year after a 2 week wash out. Study investigators will remain blinded to the study intervention and results until the end of the trial.

The Investigational Pharmacist will distribute the study medication to research coordinator and the research coordinator will give study medication to the patients. Patients will return study medication to research coordinator at which time compliance will be performed via pill count, prior to returning to IDS. IDS will also conduct compliance upon return to the pharmacy. Placebo and drug pills will appear identical. The Indiana Clinical and Translational Sciences Institute (CTSI) Accessing Technology Program (ATP) assists investigators in identifying pharmaceutical manufacturing sites for clinical trial materials. The site selected for manufacture of product for this study is The Foundation of The University of Iowa Pharmaceuticals (UIP). The UIP has been audited by a R.Ph. contracted by the ATP to ensure compliance with current Good Manufacturing Practices (cGMP) per 21CFR210,211. All manufacturing documents are approved by the investigator prior to manufacture and all release documents are approved by the investigator prior to acceptance of the product. The active material for this study includes over- encapsulation of Actos (pioglitazone) tablet purchased from a pharmaceutical company with microcrystalline cellulose as a filler. The placebo consists entirely of microcrystalline cellulose in a capsule identical to that used for the active ingredient. The PKD foundation has agreed to pay for costs of drug and over- encapsulation. See budget justification for University of Iowa quote and letter of support from the PKD foundation.

Study subjects will be contacted by phone and/or email once a month in between visits to encourage compliance by study coordinator and will be asked to return all unused pills to the research coordinator at the time of refill. Compliance will be defined as greater than 80% prescribed pill intake. Study visits will be done at baseline 1,3, 6, 9, and 12 months of each arm. At each visit standardized blood pressure and assessment of edema will be done by study research coordinator under the direct supervision of Drs. Moe or Bacallao.

Table for schedule of events for each arm:

	Screen #1	**Screen #2**	**Treatment period 1**						**Wash out**
Protocol Activity		≤30 days from day 0	day 0	Month 1 Day 30 (+/- 10 days)	month 3 Day 91 (+/- 10 days)	month 6 Day 182 (+/- 10 days)	month 9 *** Day 274 (+/- 10 days) **VISIT 9 IS OPTIONAL**	month 12 Day 365 (+/- 10 days)	2 weeks
Medical History	X		X	X					
Physical/ vital signs/standardized blood pressure (temperature will be captured only if subject reports symptoms/illness in which a change in temperature would be expected)	X**		X (no PE at day 0)	X	X	X**	X	X**	
Concomitant Medications	X		X	X	X	X	X	X	
Adverse Events		X	X	X	X	X	X	X	
Pill Count			X	X	X	X	X	X	
Laboratory and other testing									
CMP	X*		X	X	X	X	X	X	
Urine Alb/creatinine ratio/HCG	X*		X			X		X	
MRI		X						X	
Cardiac Echo			X (completed at V1 Arm 1 only)					X	
BIA			X	X	X	X	X	X	

* If not done in previous 3 months; CMP = comprehensive metabolic profile (includes liver enzymes and glucose); BIA = bioelectrical impedance analysis

** Physical exam will be completed by MD at screening, month 6, and month 12 visits. All other visits coordinator will assess subject and if any issues, subject will be seen by MD.

*** Visit 9 is optional if subject is unable to make visit due to logistic issues (i.e., cost, time to travel etc…)

Detailed Methods:

1) MR imaging without gadolinium enhancement will be conducted at the initiation, at the 1 year cross-over time and end of the study (total 3 per study participant) for determination of total kidney volume and total liver volume following the protocol developed by the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP)[4, 5]. MR images will be reviewed locally to ensure adequate imaging, and made available after anonymization to the Imaging Core of the Mayo Translational PKD Center using the National Biomedical Imaging Archive. At the Imaging Core, the images will be stored in a Radiology secured server and transferred to local PKD workstations for assessment of image quality and further processing. Kidneys or liver volumes will be measured from coronal T1-weighted images from MR or axial CT images, using a stereologic method with ANALYZE™ software (standard method used in multiple clinical, NIH and industry trials). Ten percent of the images from randomly selected patients will be routinely measured on two separate occasions (by at least 30 days) to assure reliable volumes. Initial measurements for screening will be done by one of three available radiologists, but actual study results will be read by a single radiologist blinded to study intervention.

2) Blood will be drawn for routine analysis (comprehensive metabolic panel) at the time of screening (if not available in medical history), at baseline (time of randomization), then month 1, 3, 6, 9, and 12 (all treatment visits will have a visit window of +/- 10 days) during the first treatment period (Year 1) and again at the same time points after the cross over during the second treatment period (Year 2). The comprehensive metabolic panel consists of 14 blood tests that include Albumin, Alkaline phosphatase, ALT (alanine aminotransferase), AST (aspartate aminotransferase), Urea Nitrogen (BUN), Calcium, Chloride, Carbon Dioxide, Creatinine, Glucose, Potassium, Sodium, Total Bilirubin, Total Protein and a calculation of the eGFR using the CKD-epi formula. At each visit up to 30ml of blood will be drawn for storage and future research studies.

3) Standardized blood pressure measurements will be taken at time of step 1 screening, and at each study visit and again at the same time points after the cross-over for the second treatment period. Blood pressure will be taken once when the patient has been sitting for 5 minutes, and then again, ≥5 minutes later.

4) Urine will be taken on first urine sample of the day (patient may bring to clinic) for urine albumin and creatinine ratio at baseline, and at months 6 and 12. For female patients of reproductive age, a urine pregnancy test (point of care) will be performed as well.

5) A cardiac echo will be performed on each patient at the beginning of Arm 1 and end of each arm, or in any patients with complaints of new dyspnea. The cardiac echo will be reviewed by clinical cardiologist with standard echocardiographic end points assessed (including left ventricular hypertrophy, ejection fraction, left atrial enlargement, and wall motion abnormalities)

6) Bioelectrical impedance analysis (BIA) will be done at baseline and every 3 months of each arm. This will be done using the RJL systems segmental BIA machine (RJL Sciences, Inc. Clinton Township, MI). The BIA will be conducted by the Research Coordinator who has been tried on the device. Segmental bio impedance (opposition to the flow of an electric current through body tissues) can be used to calculate total body water. The resistance in ohms (Ω) decreases with increased total body water. Patients with CKD have reduced resistance and increased TBW compared to normal controls[6]. In a randomized trial of amlodipine versus placebo in patients with hypertension, Schoeller et al found that such an assessment was comparable to the gold standard of water displacement and ankle circumference and more sensitive than clinical assessment of edema[7]. Total body water can then be derived by standardized formulas and can differentiate between intracellular and extracellular water[8, 9]. (In red as more information provided than in previous submission).

D.2.f. ***Recruitment:***

Indiana University Health is a statewide hospital network integrated with a common electronic medical record (EMR). The patients will be recruited from the following sites:

1) PKD clinic run by Dr. Robert Bacallao (Co-PI). Currently **35 patients are seen in this clinic per year**. Of the 35 patient, 2 are African American (5.7%), 0 are Asian, 1 is American/Indian/Alaska Native (2.8%). The

remaining patients are Caucasian. Of the 35, 20 are female and 15 are male.
2) All clinics where patients are seen by IU Health Physicians Nephrology group (the common practice plan of IU School of Medicine Nephrology division). Importantly, all of the 28 Nephrologists (including Dr. Moe) see PKD patients. A review of billing records from our Nephrology group using the 753.12, 753.19 and 753.13 ICD-9 codes identified over 390 unique patients with cystic disease in our data base seen in the last 5 years.

D.2.g. ***Compliance***
a) Good Clinical Practices: The investigators and research coordinators are all trained in Good Clinical Practices. The individuals who will have clinical interactions have conducted or been involved in several clinical research projects. Compliance with regulatory bodies including the Indiana University IRB is mandatory for the conduction of this study and will be continuously assessed by the investigators and on an annual basis or more frequently by the IRB if needed based on established criteria. A Data Safety Monitoring Board (DSMB) will monitor the ethical, medical and scientific conduct of the study (please see more details below). No members of the panel will be directly involved in the clinical grant.

b) Informed Consent: Potential candidates meeting eligibility criteria will be informed about the study, including potential risks and benefits. When patients are deemed clinically stable and cognitively able to give consent, an approved investigator and/or research coordinator will review the project and the informed consent with the patient providing ample time for the patients to ask questions and have them answered. Those who are interested will be asked to voluntarily participate and give written informed consent. Documentation of informed consent process will include not only the signed and dated informed consent forms, but also appropriate notes to file, per institutional requirements. Subjects must be given a copy of the informed consent. Subjects will be consented prior to any study interventions, including any additional blood tests (if not done in the requisite time period prior) or the MRI to assess kidney volume.

c) HIPAA authorization: Subjects must also sign a HIPAA authorization form and they will be provided with a copy of the form. Respect for patient confidentiality will be strictly maintained. Access to individually identifiable private information will be restricted to the IRB-approved investigators and/or research coordinators. Publications resulting from this research will not identify patients. No data containing private patient information will ever be transmitted to other institutions. Data sharing will occur in a HIPAA-compliant, de-identified manner supervised closely by the Data Safety Monitoring Board at Indiana University (see composition below). Study data maintained in paper format will be stored in locked cabinets and/or restricted-access areas. Research material includes the inpatient and outpatient source paper and electronic medical records at each site, including results of study tests and procedures, medical history, baseline laboratory results, physical examinations, coordinator assessments, vital signs, heart rate, concomitant medications, and baseline demographics. In addition, information will be collected regarding study drug accountability and adverse events. MRI data sets will be collected electronically and transmitted via a secured web site.

d) ClinicalTrials.gov Requirements: This application includes a clinical trial for which registration and results reporting in ClinicalTrials.gov will be required, pursuant to Public Law 110-85.

D.2.h. Statistical analyses:

Hypothesis: *Treatment with a low dose PPARγ agonist will slow cyst expansion in human ADPKD patients and delay the progression to renal complications and failure. Therefore, the overall objective of this study is to conduct a pilot study to obtain information on safety and feasibility that will be needed to design a larger, appropriately powered clinical trial.*

Specific Aim 1: ***To provide pilot data on the safety of low dose pioglitazone (15 mg daily) treatment in human ADPKD patients over a one year period. Tests will be conducted to monitor the known side effects of PPARγ agonist treatment, including fluid retention and edema. In addition, liver enzyme profiles, renal function and risk of hypoglycemia will be assessed routinely.***

Patients' characteristics including, demographics, kidney function at baseline will be summarized by treatment and placebo groups and compared using t-test or Chi-square test as appropriate. Nonparametric Wilcoxon test or transformation will be used if a continuous variable appears to be non-normal. All analysis will be performed using SAS 9.3 (Cary, NC).

Safety end points: The following safety end points will be summarized by group for all subjects at both periods and compared by t-test or Chi-square test as appropriate:

1) Measures of volume overload/fluid retention:

a) Net change (decrease) in resistance (which converts to increase in total body water (TBW)) assessed by bio impedance analysis (BIA) over the course of each arm.

b) Episodes of congestive heart failure: New onset of pulmonary symptoms together with either increased interstitial edema on chest X-ray, or changes by echocardiogram (increase in end diastolic ventricular volume or new/increase pericardial effusion).

c) Edema: Number of episodes of edema, classified as either 1) sustained > 1 week of edema despite adjustment of diet or 2) unresponsive to diuretic therapy.

d) Change in echocardiography parameters consistent with coronary artery disease (reduction in systolic ejection fraction and/or wall motion abnormalities).

e) Any doctors' visit or hospitalization for cardiac symptoms.

2) Hypoglycemia:

a) Number of episodes of hypoglycemia (defined as blood glucose < 70 on non-fasting labs, or <70 on fasting labs with symptoms or if reviewing physician suspects symptoms based on patient's description

b) Average blood glucose level. .

3) Liver function: Number of episodes of elevated ALT or AST to > 2 times the upper limit of normal.

4) Other adverse events noted in previous trials will be assessed: Episodes of gross hematuria, gastrointestinal symptoms (nausea/vomiting, diarrhea).

Specific Aim 2: To provide pilot data on the efficacy of low dose pioglitazone therapy in human ADPKD patients over a one year period using MRI assessment of total kidney volume.

1)The percent change in total kidney volume (TKV) by MRI is the primary efficacy end point. We will use the paired t-test to compare the difference of percent change of TKV between the two study periods. With the cross-over design, the paired t-test allows us to use the subjects as their own controls as has been done with other therapies in PKD at this stage of development[10]. A p-value of 0.05 will be considered as significant. We will evaluate the carry-over effect by comparing the total change in both periods in the two different treatment sequences[11].

The following end points will be summarized by group for all subjects at both periods and compared by paired t-test or Chi-square test as appropriate:

2)Measures of kidney function:

a) Change in the estimated GFR (eGFR) by CKD-epiformula,

b) Change in the urine micro albumin/creatinine ratio,

c) Average MAP over the 12 months for each blood pressure measurement. It is expected that there may be adjustments to medication dosage as part of standard of care. However, if a new medication is started for any reason this will be considered an adverse event. ..

d) Change in volume of 4 individual cysts (2 large and 2 small) over time in each kidney

3)Other PKD parameters:

a) Percent change in liver size by MRI,

b) Cumulative pain score (on 0 to 10 scale) as average area under the concentration time curve between baseline and last trial visit or last visit before requirement of surgical or medical therapy for pain. Since day-to-day fluctuations in pain normally occur with PKD due to the enlarged kidneys, pain events will not be called adverse events unless the pain is severe enough to require new analgesic treatment or doctor/ER/hospitalization.

Sample size: We calculated the power based on a paired t-test for comparison of the primary end point, change in total kidney volume (TKV) by MRI. With the paired t-test, power calculations take into account the difference between treatment groups (treatment effect), the Standard Deviation (SD) and the correlation

between the change in TKVs between two treatment periods. **With SAS our power calculations using paired mean t-test, mean difference of 2%, standard deviation of 4, correlation of 0.69, 5% Type I error, and power of 80% we need 22 subjects to complete the trial. If we assume a 20% drop out rate, we need to enroll 28 subjects. The rationale is detailed below:**

1) For the treatment effect, we assumed an annual 6% increase in TKV while on placebo and 4% while on drug (treatment effect of 2%). We feel that an annual growth of 6 %/year is a reasonable estimate based on controls of multiple clinical trials. Examples are: SUISSE study of sirolimus[12], 6.8-9.5%; everolimus study[13], 8.4%; SIRENA sirolimus study[14], 7.4%; Bergamo octreotide study[15],11.8%; the LOCKCYST of Lanreotide[16], 6.8%; Mayo octreotide study[10], 8.6%. This estimate is also consistent with the annualized rates of growth observed in the CRISP study in patients with baseline age and kidney volumes similar to those pre-specified by our inclusion criteria. The difference between the placebo and treatment arms is a conservative estimate based on our pre-clinical data; the purpose of this study is to identify the true difference for future trials.

2) We assumed a SD of 4% based on the inter-reviewer SD for MRI readings in the CRIC study.

3) As demonstrated in the CRIC study, those with higher TKV at baseline have faster progression with a correlation of 0.69[17]. We expect that the correlation between the percent change from the same subject under the two treatment conditions will be greater or equal to 0.69. In calculating the sample size, we took this correlation into account when calculating the power calculation for the paired t-test (versus an independent unpaired t test when the correlation is not taken into account).

D.3. DATA MANAGEMENT:

a. Clinical Trial Management: The study will be managed by the PIs and study coordinator using the OnCore CTMS. OnCore® is a Clinical Trial Management System (CTMS) developed by Forte Research Systems, Inc., and has been licensed by Indiana University to support the operations and study data capture of clinical research trials. The system has been installed and configured within a HIPAA aligned IT operations center supported by Indiana University's IT organization (UITS). OnCore® is web-based and provides users secure access from any location to record, manage, and report on data associated with the operation and conduct of clinical trials. The system is comprised of three specific applications—Clinical Research Management (CRM), Biospecimen Management (BSM), and Unified Registries Management (URM). Indiana University leverages OnCore® to support clinical research trials specifically as it relates to the following functions and processes: protocol and subject life cycle management, subject safety monitoring, coverage analysis, electronic data management, study financials management, subject visit management, correlative study sample management, annotation management, requisition and distribution management, inventory management, and reporting.

The software allows the investigative team to develop case report forms with real time validation rules (automated data type and range checks) that are integrated with a study schedule calendar. The central IU laboratory is integrated with the system allowing auto-population of laboratory tests for the chemistry and urine study results. The system can also be accessed by the Investigational pharmacy. Finally the output reports include summary reports for the DSMB (e.g. recruitment/retention) and SAS output.

b. Data Access: Only study investigators and coordinators will have access to the patient data. Advanced IT Core (AITC) staff, because they maintain the software, will have access to the data, but are trained to observe HIPAA rules.

c. Disposition of the Data

There are two secure means of access to the study data for study members who are granted access: 1) via the application by use of IU's Central Authentication Service (CAS) and project database specific permissions; and, 2) via direct access to the database by use of secure database authentication. In each case, the PI will identify who has relevant access to the study data and what permissions each individual shall have.
The deidentified MRI data will be shared with the Mayo Clinic using CDs.
Data will be stored for at least 7 years after the completion of the study.

d. Sharing Study Results

The volunteers in this study will have access to their own study results at the end of the study. It is anticipated that the results of this study will be published in scientific journals and at that point the de-identified data are publically available. If the outcome of the study is positive, organizations such as the PKD Foundation will likely interpret the peer-reviewed journal articles in lay language for their constituents.

e. Data integrity and quality

1. Quality Assurance procedures to a) ensure the validity and integrity of the data, b) ensure the accuracy and completeness of the data, and c) completeness, quality, and analysis of measurements. – to be completed periodically by other nephrology research staff
2. Site Monitoring Plan – The study records will be periodically reviewed by Indiana University Clinical and Translational Science Institute.

D.4**SAFETY:**

The primary concern with respect to subject safety is the development of edema/volume overload and hypoglycemia from the pioglitazone.

D.4.1**Potential Risks**

Edema: Some reports have indicated an increase in the incidence of edema in pioglitazone compared to control treatments. The specific risks from the pioglitazone based on interventional trials are summarized in the FDA Physician Desk Reference (PDR). Specifically, the following data were noted*: "In pooled data of 16 to 26 week placebo controlled trials of actos monotherapy, edema did not reach > 5% of subjects or differences between drug and placebo. However, in combination trials of Actos plus sulfonylurea edema was observed in 2.1% of placebo + sulfonylurea, 1.6% of Actos 15 mg plus sulfonylurea and 12.7% in Actos 30 mg + sulfonylurea (n = 187, 184, and 189 subjects, respectively). In studies with insulin, the addition of placebo, Actos 15 mg, or Actos 30 mg reported 7, 12.6 and 17.6% of subjects with edema in 187, 191, and 188 subjects, respectively. In an additional summary table (Table 12) of the PDR, a recorded AE of edema was 1.2% in placebo patients (n = 259), 2.5% (n = 81) in Actos 15 mg, 4.7% (n= 275) in 30 mg Actos, and 6.5% (n = 169) in Actos 45 mg."* Thus, edema appears to be dose related and increases with other diabetic therapies. In the present study, we will use only a 15 mg dose of pioglitazone and the patients will not be diabetic (and thus no other medications). Thus, the risk is relatively small.

2. Cardiovascular toxicity: There has been some controversy regarding the overall effects of PPARγ agonists on cardiovascular function. A beneficial drug-induced decrease in blood pressure is well established and a recent case report has suggested that pioglitazone can suppress primary aldosteronism and resistant hypertension[18]. However, the propensity towards fluid retention has had adverse clinical outcomes. A study showing a statistically significant increase in the incidence of ischemic cardiovascular events in patients treated with rosiglitazone[19] has caused a decrease in the use of this drug in the US and a suspension of marketing authorization in Europe[7]. In addition, PPARγ agonist-induced fluid retention, that is exacerbated by concomitant insulin treatment in diabetic patients, can lead to edema formation and heart failure[20] thus overshadowing any potential beneficial effects such as the trend toward reduced risk of cardiovascular events that was demonstrated in the PROActive (prospective pioglitazone clinical trial in macrovascular events) study[21].

Phase III studies and post marketing results revealed a measureable incidence of edema, congestive heart failure, and myocardial infarction/ischemic events in diabetics using pioglitazone. A meta analyses commissioned by the FDA to evaluate toxicities related to pioglitazone was published in 2009 (http://www.fda.gov/downloads/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm226071.pdf). The following is a summary of this special report: *"Dose-response analyses based on information from 24 of the 40 studies including over 9,000 patients show that there are visible dose-response trends of increased risk of myocardial ischemic symptoms, myocardial infarction, and congestive heart failure in pioglitazone. Among the 24 studies, the planned treatment duration of 23 studies was 6 months and under. The dose-response trends for myocardial ischemia (MIS) and Myocardial Infarction (MI) events were primarily driven by the differences between pioglitazone 30 and 45 mg. The risk increase in MIS in pioglitazone 45 mg from 30 mg was statistically significant. The incidence rate of MIS for pioglitazone 45 mg was 4.19 per 100*

patient-years, while the incidence rate for pioglitazone 30 mg was 1.98 per 100 patient-years (similar to the placebo rate). The incidence rate of MI for pioglitazone 45 mg was 1.60 per 100 patient-years, while the rate for 30 mg was 0.69 per 100 patient-years (also close to the placebo rate). The risk of CHF increased as the dose levels of pioglitazone increased."…. "No overwhelming evidence suggests that pioglitazone 30 mg or under had higher risk in MIS and MI."

In the present study we are using doses of 15 mg daily and thus the risk of these cardiovascular events is small.

3. Bladder cancer: Long term risks of pioglitazone include bladder cancer. An analysis of data retrieved from the FDA Adverse Events Reporting System between 2004-2009 found an association between pioglitazone and bladder cancer[12]. Both the FDA and the European Medicines Agency recommended new contra-indications and warnings for pioglitazone and advised prescribers to carefully select patients. However they also concluded that the increased risk of bladder cancer was very small and in patients responding to the anti-diabetic treatment, the benefits outweigh the risks. A recent news release revealed completion of a 10 year post marketing study which found no significant increase risk of bladder cancer in patients ever exposed to pioglitazone (http://www.prnewswire.com/news-releases/takeda-announces-completion-of-the-post-marketing-commitment-to-submit-data-to-the-fda-the-ema-and-the-pmda-for-pioglitazone-containing-medicines-including-actos-273044811.html) In accordance with agency recommendations, we will not enroll patients who have current, or a history of, bladder cancer or patients with uninvestigated macroscopic hematuria. Any subject developing gross hematuria will be promptly evaluated by a urologist.

4. Hypoglycemia: Given the intended use of this drug is for the treatment of diabetes related hyperglycemia, hypoglycemia is a potential risk. The drug has not been previously given in a non-diabetic population and thus the risk is unknown.

Elevated liver function tests: In phase 3 trials of Tolvaptan, there was a slight increase in the risk of elevated liver function tests. Adverse changes in hepatic function are not a common side effect of the PPARγ agonists that are currently approved for treatment of diabetes. In the PDR for pioglitazone, it was noted that there were post marketing reports of fatal and nonfatal hepatic failure in patients taking Actos, but probable cause could not be determined. In the controlled clinical trial database, there was no evidence of drug induced hepatoxicity. In addition, troglitazone, another drug in this class of compounds, was taken off the market due to liver toxicity in certain patients. Although liver function is generally normal in ADPKD despite the presence of liver cysts, we plan to closely monitor liver enzyme levels in the patients during therapy to avoid any potential problems. Monitoring of liver enzymes will take place as part of the serum comprehensive metabolic panel which will done quarterly on all volunteers.

6. **Risk to pregnant women**: Pioglitazone is a class C drug – risk unknown. No teratogenicity has been shown in animal studies but some embryo loss and delayed development of fetus has been reported in animals at 10X normal dose.

7. Risk of loss of Confidentiality:
The review of medical records carries potential risk of loss of privacy: There is a minimal risk of loss of privacy; however, appropriate methods will be implemented to maintain confidentiality (see above for additional details).

8. Risk of bleeding or infection at site of blood draw: There is minimal risk due to phlebotomy.

9. Risk of gastrointestinal symptoms (nausea/vomiting/diarrhea)

10. Fracture: Risk of fracture may be lower than in other studies because of the subject population's younger age, lower dose, and shorter time on the drug, but the precise risk is currently unknown.

D.4.2 Adequacy of Protection Against Risks:

1. Recruitment and Consent
Subjects will be recruited from the adult patients seen in CKD clinics. Potential candidates meeting eligibility criteria will be informed about the study, including its potential risks and benefits. When patients are deemed

clinically stable and cognitively able to give consent, an approved investigator and/or research coordinator will review the project and the informed consent with the patient, providing ample time for the patients to ask questions and have them answered. Those who are interested will be asked to voluntarily participate and give written informed consent. Documentation of informed consent will include not only the signed and dated informed consent forms, but also appropriate notes to file, per institutional requirements. Subjects will be given a copy of the informed consent and HIPAA authorization forms.

2: Protection Against Risks

The laboratory tests will be monitored by the site coordinator and PI. The protections (corresponding to risks noted above) are:

1. Edema: The subjects will be assessed for edema at each visit, and undergo BIA testing to detect subtle differences. If subjects develop edema they will be counseled by a dietician on a 2 gm sodium diet. If this fails to improve symptoms, they will be given low dose (20 mg) of furosemide until symptoms resolve. **If the edema fails to resolve on Lasix, results in congestive heart failure or pericardial effusion, or is considered bothersome by the patient despite diet and furosemide they will be discontinued from the study.**
2. Cardiovascular disease: The subjects will be excluded if they have known cardiovascular disease and will undergo an echocardiogram at baseline, 12 and 24 months. **If subjects develop new wall motion abnormalities or a significant (10%) change in ejection fracture or shows evidence of new significant diastolic dysfunction, they will be discontinued from the study.**
3. Bladder Cancer**: Subjects will be excluded if they have bladder cancer, and any subject developing gross hematuria will be promptly evaluated by a urologist.**
4. Hypoglycemia: Given the intended use of this drug is for the treatment of diabetes related hyperglycemia, hypoglycemia is a potential risk. However, diabetics are excluded and thus this risk is very small as there should be adequate insulin response. **Blood glucose levels will be monitored at each visit. At the physician's discretion, subjects with a glucose level <70, who show other hypoglycemic like symptoms (e/g dizziness, sweating, altered concentration) may be given a glucose monitor to assess blood glucose randomly.**
5. Abnormal Liver Function Tests: Patients will have monitoring of liver tests at each visit. **Any subject with elevated ALT or AST > 2 X ULN will have the blood test repeated within 48-72 hrs. If abnormal, the tests will be repeated one week later. Persistently elevated LFTs on two occasions at least one week apart will be discontinued from the study.**
6. Pregnancy**:** A urine pregnancy test will be performed, as point of care, each month and at each visit. Tests will be provided to subjects to take home for months in between visits. Subjects of child bearing potential will be questioned at each visit regarding any irregularities in menses or amenorrhea. Adequate birth control will be discussed at each visit. **If a woman becomes pregnant, she will be discontinued from the study.**
7. Loss of Confidentiality**:** Subject names will not be used in publications and access to private health information collected as a part of this project will be restricted to IRB-approved investigators and coordinators only and will never be made part of the central study data repository. Paper records will be stored in locked cabinets and/or in restricted-access areas at each site. Access to databases will be controlled through password protection and granted to approved personnel only.
8. Bleeding or infection due to blood draw: Blood will be drawn by an experienced technician.
9. Gastrointestinal symptoms: If these develop, patients will be instructed to take medication with meals and or symptoms treated conservatively.
10. 10. Fractures: Risk is limited given age of participants but this risk in included in the informed consent.

The Principal Investigator and Study Coordinator will review each subject's clinical course for immediate adverse events using medical records and subject observation. Serious adverse events meeting the criteria for prompt reporting will be reported to the local IRB within 5 business days. The HHS regulations (46.103) and Indiana University (IUPUI) Standard Operating Procedures for prompt reporting of unanticipated problems to the IRB, appropriate institutional officials, and OHRP will be followed. Adverse events will be graded according the system described below. In general, unanticipated serious adverse events attributable to the intervention will be promptly reported to the IRB within 5 days of date of discovery. Non-serious adverse events will be reported to the IRB at the time of continuing review.

This research will not involve pregnant women, human fetuses, prisoners, or those known to be cognitively impaired. Women of child bearing potential will be asked to use double contraceptive methods and complete urinary pregnancy tests as above.

D.4.d. Potential benefits of the proposed research to human subjects and others
A potential benefit to human subjects is that the treatment strategies being studied in this application may lead to treatments for slowing the progression of PKD. The dose is very low and thus it is expected that there will be minimal side effects. The risk is reasonable because the drug used in clinical practice for the treatment of hyperglycemia has minimal side effects and is usually used at doses higher than the proposed dose of 15 mg.

D.4.e. Importance of the knowledge to be gained
There is currently no FDA approved therapy for the treatment of PKD. Because this is an FDA-approved drug the risk to subjects participating in the study is small. On the other hand, the benefit in knowledge gain related to appropriate treatment of PKD is significant. We propose that the risk to subjects are reasonable compared to the anticipated knowledge to be gained.

D.4.f Prompt reporting of unanticipated problems:
All members of the research team are expected to comply with the highest standards of ethical and professional conduct in accordance with federal and state regulations and institutional policies. This project will be conducted in compliance with HHS regulations 46.103(b)(5) and 21 CFR 56.108 requiring "prompt reporting" of unanticipated problems involving risk to human subjects and/or any serious or continuing noncompliance with federal or local requirements (Guidance for Clinical Investigators, Sponsors and IRBs, January 2009; http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf).

Generally, the PIs and research coordinator will review study results for each subject as they are collected. The PIs and/or research coordinator will monitor subject recruitment, eligibility criteria, collected data, subjects' clinical course and adverse events. Given the nature of this project, adverse events are not anticipated beyond those which subjects might otherwise experience during routine clinical care. Nonetheless, the Principal Investigators and Study Coordinator will review each subject's clinical course for adverse events using medical records and subject observation. Unanticipated problems which are serious and require changes to the protocol or informed consent will be reported to the local IRB. All adverse events will be reported to the DSMB as detailed below. All non-serious adverse events that are not considered "unanticipated" will be reported in writing to the IRB at the time of continuing review.

All adverse events will be evaluated for grade and attribution to the study intervention using the following system:

Adverse event grading

a. Mild - Awareness of sign or symptom, but easily tolerated
b. Moderate - Interference with normal daily activities
c. Severe - Inability to perform normal daily activities
d. Serious/Life Threatening – any event that results in death or places subject at immediate risk of death from the reaction as it occurred; results in hospitalization or prolonged hospitalization, causes disability, results in a congenital anomaly, or may jeopardize the subject's health sufficiently to require medical or surgical intervention to prevent one of the other outcomes listed in this category.

Scale for determining the attribution/relationship of adverse events:

- Definite: Adverse event clearly related to study intervention
- Probable: Adverse event(s) likely related to study intervention
- Possible: Adverse event(s) may be related to study intervention
- Unrelated: Adverse event(s) clearly not related to study intervention

Plan for reporting serious adverse events
Serious adverse events that meet ALL of the following criteria will be reported to the DSMB in 24 hours and IRB within five business days.

a. caused harm to one or more subjects, or placed one or more subjects at increased risk of harm,
b. were unexpected (the frequency or severity of the event is not accurately reflected in the informed

consent document or is inconsistent with available literature),
c. were related to the research procedures,
d. require revision to the protocol or informed consent document.

D.5. Data Safety Monitoring Plan

D.5.a Membership:
A Data Safety Monitoring Board (DSMB) will be utilized to provide monitoring of the study. The board will include four members who have been chosen for their expertise in various important components of the study protocol. **Their biosketches are found in the appendix.** The Chair will be a PKD expert, Dr. Bennett. The local members who have agreed to serve are:

William Bennett, M.D., Legacy Good Samaritan Medical Center, Oregon will chair the DSMB. Dr. Bennett is a recognized expert in PKD and has substantial clinical trial experience. Dr. Bennett has agreed to serve as the chair of the DSMB.

Kieren Mather, M.D. Dr. Mather is an Associate Professor at the Indiana University School of Medicine (IUSM), in the Division of Endocrinology. He is a clinical investigator with expertise in clinical trials in diabetes and pre-diabetes. He is, therefore, very knowledgeable about the PPARγ agonists, their metabolic actions and potential side effects.

Rajiv Agarwal, M.D. Dr. Agarwal is a Professor of Medicine at IUSM in the Division of Nephrology. He is an expert in hypertension and chronic kidney disease. His knowledge in both renal and cardiovascular issues will be valuable to the committee.

Dr. Richard Kovacs, M.D. Dr. Kovacs is an Associate Dean for Clinical Research at IUSM. Dr. Kovacs has substantial experience in clinical trials and in drug induced cardiovascular changes. The DSMB will meet after the third patient is enrolled and every 6 months thereafter, by conference call. A report of serious adverse events (those which are felt possibly related or probably related to the study drug) and enrollment will be sent to the DSMB between meetings. Data from this study will be prepared by the statistical team and will be presented to the DSMB for review every 6 months. The DSMB will monitor the data quality, rate of subject recruitment, results of related studies, any adverse event data and procedures for protecting privacy. Information about all adverse events, whether volunteered by the subject, discovered by the investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded. Data may be reviewed in the aggregate and individual cases will be reviewed, as appropriate. Unanticipated problems requiring prompt reporting to the IRB will be reviewed by the DSMB. The DSMB may make recommendations regarding protocol changes to enhance safety. Written documentation of DSMB reviews, including recommendations regarding continuation or discontinuation of each of the treatment arms, will be based upon review of cases and adverse events and will be forwarded to the Study PI and the IRB.

D.5.b. Authority

The Data Safety Monitoring Board is an advisory committee and will review those aspects of the trial that are discussed in the Responsibilities section below. When the Board determines that changes should be made to the ongoing trial, it will make recommendations to the Study PI as outlined in the Recommendations section below.

D.5.c. Responsibilities

The DSMB will be responsible for:

1. Reviewing interim safety data for the trial and proposing corrective actions when the side effects for one or more treatments in the trial are unexpectedly severe. These corrective actions may include modification to one or more treatments, early closing or suspension of the trial, or limiting participation in the trial to a subset of the original subject population. This review of toxicity by the DSMB is in addition to that of the study chair and study team, who have primary responsibility for monitoring toxicity.

2. Reviewing end point data categorized by treatment A and B so that blinding is maintained and recommending changes in the study status on the basis of these analyses. These changes may include early termination of accrual, increases to the accrual goal or major changes to the eligibility criteria for the trial.

3. Assessing the impact of independent scientific investigations, especially other trials, on the trial being monitored and recommending changes based on those external results.

4. Reviewing and approving or disapproving requests for data from any other party. These responsibilities end after the unblinding of the trial. The DSMB would usually not be involved in further review of the trial after unblinding, but the Study Chair (Principal Investigator) may consult the DSMB on other issues, such as appropriate action for late toxicities, at any time. The scientific responsibilities for publishing or presenting the results of a trial to the scientific community and for using the results of a trial for planning future studies will continue to rest with the Study Chair and the protocol team.

D.5.d. Data and Safety Monitoring Plan

The Elements of the Data Safety Monitoring Plan which will be developed by the DSMB will include:
1. Summary of the protocol focusing on a) information on benefit/risk ratio of procedures and participant burden and b) the selection, recruitment, and retention of participants
2. Trial Management, organization and participating clinics/investigators.
3. Data Management and Analysis: Data acquisition and transmission, data entry methods, and data analysis plan.
4. Regulatory Issues: a) SAE reporting to the IRB, and FDA, b) reporting of IRB actions to the FDA, c) reporting of amendments to protocol, d) conflict of interest disclosures reporting and management
5. Protocol: Adherence to protocol requirements and amendments to the study protocol and consent forms.
6. Trial Safety: a) Risks and benefits for participants and informed consent procedures, b) AE reporting, c) management of risks, d) stopping rules, e) notification of and referral for abnormal findings.

D.5.e. Reports

A number of reports will be generated during the implementation of the study. These reports will be used for the assurance of subject safety and will be reviewed monthly by the co-Principal Investigators. A compilation of these monthly reports will be sent to the DSMB for review.

These reports will include: recruitment information; modified participation (withdrawn consent, drop in, etc.); visit completion, forms and protocol violations by site; adverse events with causality determinations and SAEs. The Study Statistician will also generate reports to the DSMB including recruitment information, protocol violations and dose modifications with reasons.

These reports will be circulated to the DSMB approximately three weeks before the meeting. Any member of the committee may request additional data after seeing the report.

1. At the DSMB meeting, there will be an open session, which will include a presentation on clinical issues, accrual, compliance, and toxicity by the Statisticians and Study Chair. Data presented in the open session will be aggregated across treatment arms.
2. The protocol statisticians will present outcome and safety data by blinded treatment code to the core DSMB in a closed session.
3. An executive session, which formulates recommendations, will include only voting members of the DSMB.

Any recommendations regarding the study must be approved by a majority vote of the DSMB members present at any executive session meeting. While all recommendations must be transmitted in writing to the PI, electronic mail or facsimile may be used in special circumstances requiring immediate decisions.

All deliberations of the DSMB are confidential, and all recommendations transmitted to the Study Chair must be considered confidential until implemented by the Study Chair. Any member who violates the confidentiality of the committee will be removed.

D.5.f. Recommendations

The DSMB will be responsible for sending recommendations to the Study Chair no later than one week following the meeting.

1. In the event that the DSMB recommends a study change for subject safety reasons (including early stopping of inferior therapy), the Study Chair will act to implement the change as expeditiously as possible. An amendment will be prepared and submitted to participating member institutions, which will reflect the recommendations of the DSMB and will provide the rationale for the changes.
2. In the event that the DSMB recommends the study be closed early due to slow accrual, then the recommendation of the DSMB would be processed as in (1) above.
3. In the event that the DSMB recommends a change in the study for reasons other than either subject safety (e.g., to extend accrual because of an event rate lower than expected) or study closure due to slow accrual, the DSMB will provide an adequate rationale to the Study Chair, then the recommendation of the DSMB would be processed as in (1) above.

E. Expected Results/Outcomes

Outcome 1: To provide information on the safety of pioglitazone therapy in human ADPKD patients over a one year period. The major side effects of drug treatment are expected to be manifested rather early during treatment. Thus, after one year of drug treatment we can use this moderate sample size to determine if there are any safety issues that frequently appear in PKD patients as opposed to the lack of such side effects in the normal population.

Outcome 2: To provide information on the efficacy of pioglitazone therapy in human ADPKD patients over a one year period using MRI monitoring of total kidney volume. The results obtained in this study, whether significant or not, will inform future deliberation on whether to pursue a larger and more prolonged clinical trial which can be scaled for additional outcomes such as a change in the decline of kidney function, changes in degree of hypertension and amelioration of pain.

F. Investigators: The team that has been assembled to carry out a proposed clinical trial has the expertise to accomplish the stated goals within the time-frame of the proposed studies.

Dr. Sharon Moe (Corresponding PI) is the Chief of the Nephrology Division at IU School of Medicine. She has substantial clinical research and clinical trial experience. Dr. Moe will oversee all patient procedures, will supervise the clinical study coordinator and will be responsible for responding to the FDA, IRB and DSMB.

Dr. Bonnie Blazer-Yost (Co-PI) was the senior investigator in all the published basic research and pre-clinical trials that showed the effectiveness of pioglitazone in decreasing the driving forces for cyst expansion by inhibiting the synthesis of the CFTR Cl^- channel. Dr. Blazer-Yost will also communicate with the PKD Foundation and others to champion external recruitment and engagement for the study. Drs. Moe and Blazer-Yost will jointly be responsible for communicating the findings of the study.

Dr. Robert Bacallao (Co-I) is the Director of the Polycystic Kidney Disease Clinic at the Indiana University School of Medicine. He will also recruit patients and will help with patient procedures.

Kristen Ponsler-Sipes, an experienced (over 6 year) clinical study coordinator at Indiana University School of Medicine in the Division of Nephrology, will be responsible to managing patient recruitment, testing and completion of case report forms. She will work with the PIs and Co-I to ensure IRB and FDA compliance.

Dr. Vicente Torres (Consultant) is a leader in the PKD field who will provide critical advice and oversight of the project. Dr. Bernard King (Consultant)), a radiologist and Director of the Human Imaging Core at the Mayo Clinic will oversee the MRI analyses at the Mayo Clinic. He will interface with the Radiology Department, specifically Dr. Lin Chen (Consultant), at the IU School of Medicine to optimize the local protocol and ensure high quality imaging necessary for the final volumetric analyses. Please see letters of confirmation from Drs. King and Chen who have already been in contact to discuss the IU/Mayo interaction.

Susan Perkins, PhD (consultant) is a Professor of Medicine in the Department of Biostatics and will be the statistician responsible for the study. Drs. Moe and Perkins will also oversee a Data Manager from the Department of Biostatistics who will be responsible for setting up the OnCore data capture system, preparation of initial case report forms in collaboration with the PIs, importing data from the laboratory system, performing data cleaning and checking and preparing data for DSMB report and final data analysis in this project. Dr. Perkins will also oversee a MS statistician who will help generate reports and conduct analyses.

G. SUMMARY STATEMENT

In summary, the proposed clinical trial will test the safety and efficacy of low dose pioglitazone (15 mg daily) for the treatment of ADPKD. The drug is already FDA approved for the treatment of diabetes and has been shown to have long-term safety profile that is better than any of the other pharmaceutical agents in clinical studies for PKD. If the proposed clinical trial shows positive results, the investigators will immediately seek funding for a long-term, multi-center phase III trial designed to move the drug to market. Based on basic research and pre-clinical studies, we have found that the effect of the drug is to inhibit the growth of cysts thereby delaying the progression of the disease. It is highly likely that decreased cyst growth will alleviate much of the pain that patients experience in mid-life. It is also anticipated that the drug treatment will delay or prevent the progression to end-stage renal failure that usually occurs in patients in their 5^{th} decade.

In addition, the PKD Foundation has been made aware of the studies and strongly supports this clinical trial. They have agreed to pay for the drug encapsulation to create a placebo pill. If the proposed proof-of-concept study has a positive outcome, the PKD Foundation has agreed to be a partner in the development of future funding and FDA approval process for the repurposing of this commercially available drug.

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PIOPKD

Use of Low Dose Pioglitazone to Treat Autosomal Dominant Polycystic Kidney Disease

Participant ID (MRN) ☐☐☐☐☐☐☐☐☐ Study ID (SEQ) ☐☐☐☐☐ Visit # ☐☐

Date of Visit ☐☐ / ☐☐ / 20☐☐ Participant Initials (first/ middle/ last) ☐☐☐

Pain Scoring Questionnaire

1.) In the past 12 months have you experienced pain that you believe was caused by your PKD? ☐ Yes ☐ No

If Yes:

A. Was your pain associated with an infection? ☐ Yes ☐ No

B. Which side was your pain on? ☐ Left ☐ Right ☐ Both Left and Right

☐ Front ☐ Back ☐ Both Front and Back

C. On a scale of 1 to 10, one being the least pain you have ever experienced , and 10 being the worst pain you have experienced how bad was that painful episode?

1 2 3 4 5 6 7 8 9 10
(least) (most)

(cicle one)

2.) Do you have a history of kidney stones? Yes ☐ No ☐

3.) Since you have enrolled in the study, or since you were last seen for the purpose of the study, have you had an episode of pain that you believe was caused by your PKD? Yes ☐ No ☐

If Yes:

A. Was your pain associated with an infection? Yes ☐ No ☐

B. Which side was your pain on? ☐ Left ☐ Right ☐ Both Left and Right

☐ Front ☐ Back ☐ Both Front and Back

C. On a scale of 1 to 10, one being the least pain you have ever experienced , and 10 being the worst pain you have experienced how bad was that painful episode?

1 2 3 4 5 6 7 8 9 10
(least) (most)

(cicle one)

D.) Was your pain caused by a urinary tract infection? Yes ☐ No ☐

Participant ID (MRN) | Study ID (SEQ) | Visit #

Date of Visit ___ / ___ / 20__ | Participant Initials (first/ middle/ last)

Pain Scoring Questionnaire

4.) Have you had a kidney stone since you have enrolled in the study or were seen in clinic for the purpose of the study?

☐ Yes ☐ No

☐ ☐

5. Have you had a urinary tract infection since you have enrolled in the study or were seen in clinic for the purpose of the study?

Yes No

Completed by signature

___ / ___ / 20__

Date of Signature

PIOPKD

Use of Low Dose Pioglitazone to Treat Autosomal Dominant Polycystic Kidney Disease

Participant ID (MRN) ☐☐☐☐☐☐☐☐☐ Study ID (SEQ) ☐☐☐☐☐ Visit # ☐☐

Date of Visit ☐☐ / ☐☐ / 20☐☐ Participant Initials (first/ middle/ last) ☐☐☐

Patient Self-Report of Clinical

Since your last study visit have you:

1.) Experienced shortness of breath that lasted more than two hours?	☐ Yes ☐ No
2.) Been to the emergency room or a doctor's office because of new chest pain or shortness of breath?	☐ Yes ☐ No
3.) Developed swelling of your lower extremities that last for more than 24 hours?	☐ Yes ☐ No
4.) Been told by a physician or nurse that you have edema or worsening swelling?	☐ Yes ☐ No
5.) Had your water pill (diuretic) dose increased?	☐ Yes ☐ No
6.) Gained more than 5 pounds?	☐ Yes ☐ No
7.) Had recurrent episodes (more than 2 times) of dizziness, shakiness, sweats, or nightmares?	☐ Yes ☐ No
8.) Noticed blood in your urine?	☐ Yes ☐ No
9.) Had diarrhea that lasted more than 2 days or recurred at least twice since you were last seen for a study visit?	☐ Yes ☐ No
10.) Had nausea or vomiting that lasted for more than 2 days or recurred at least twice since you were last seen for a study visit?	☐ Yes ☐ No
11.) Are you a female of child bearing potential?	Yes No
11a.) If Yes, are you actively using birth control?	☐ Yes ☐ No ☐ Not sexually active

Completed by signature /

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Date of Signature

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