

## Feasibility Study of Metformin Therapy in ADPKD

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### Research Strategy

#### **Significance**

**Autosomal Dominant Polycystic Kidney Disease (ADPKD)** is the most common monogenic and potentially fatal disease, affecting about 600,000 Americans and over 12 million people worldwide.<sup>1-3</sup> It is characterized by progressive development and enlargement of renal cysts which eventually destroy the normal parenchyma, leading to end-stage renal disease (ESRD) in the majority of afflicted patients. Two genes can cause ADPKD, *PKD1* encoding polycystin 1, located on chromosome 16, and *PKD2* encoding polycystin 2, located on chromosome 4. Most (about 85%) ADPKD families have the more severe disease caused by a mutation in *PKD1*, with an average age at onset of ESRD of 56 years, and only 10-20% have the milder form caused by a mutation in *PKD2*, with an average age at ESRD of 73 years.<sup>1,3,4</sup> **However, to date there is only one approved therapy, tolvaptan, which has only modest effects on renal disease progression in adult patients with ADPKD.** Despite progress in basic research in ADPKD, the prognosis of patients has not substantially changed in the last 20 years,<sup>5-7</sup> emphasizing the need for additional and better treatments.

**Relationship between cyst growth and renal function decline in ADPKD.** Although renal cysts begin in fetal life, renal insufficiency is usually delayed beyond the fourth decade.<sup>1,3</sup> As cysts enlarge, renal parenchymal integrity is compromised and the efficiency of compensation for a reduced glomerular filtration rate (GFR) decreases.<sup>8</sup> Non-cystic nephrons undergo apoptosis and disappear, leaving behind a kidney extensively replaced by cysts and dense bands of fibrotic material.<sup>1,8</sup> A decline in GFR in ADPKD reflects extensive structural changes and therefore is a late event.<sup>8</sup>

At this time, the best **early biomarker for ADPKD progression is total kidney volume (TKV) determined by magnetic resonance imaging (MRI).**<sup>9</sup> The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) has clearly shown that increasing TKV, which reflects renal cyst growth, precedes the decline in GFR.<sup>10,11</sup> Specifically, a height-adjusted TKV of  $\geq 600$  mL predicted progression to chronic kidney disease (CKD) stage 3 within 8 years with 74% sensitivity and 75% specificity.<sup>12</sup> Moreover, MRI imaging can detect a decrease in TKV induced by the administration of tolvaptan within 8 days.<sup>13</sup> Several recent landmark clinical trials in ADPKD have used percent change in TKV as primary outcome parameter to assess effects of interventions in early ADPKD.<sup>14,15</sup> The relevance of TKV as a predictor of disease progression is further underscored by the recent Food Drug and Administration (FDA) draft guidance concerning TKV. The draft guidance provides qualification recommendations for use of TKV, measured at baseline, as a prognostic biomarker to select patients with ADPKD at high risk for a progressive decline in renal function (defined as a 30% decline in patient's eGFR) for inclusion in interventional clinical trials. **Overall, these findings suggest that kidney volume is an appropriate and important endpoint for evaluation of interventions in clinical trials of adult patients with ADPKD.**

**ADPKD and Metformin.** Although the exact mechanism of cyst formation in ADPKD is still unclear, cyst enlargement is driven by proliferation of cyst-lining epithelial cells and chloride secretion by these cells into the cyst lumen.<sup>1,3,8,16-18</sup> In addition, the cyst-lining epithelia produce growth factors and inflammatory cytokines, leading to oxidative stress, interstitial inflammation and fibrosis, and apoptosis of the normal tubules.<sup>8,19,20</sup> Key downstream molecules driving cyst expansion are cAMP (stimulates both proliferation and secretion)<sup>8,16,18,21</sup> and mammalian target of rapamycin (mTOR, stimulates proliferation), which is normally repressed by polycystin1.<sup>22</sup> Both cAMP and mTOR activity are increased in human cyst epithelia,<sup>1,16,22</sup> whereas AMP-activated protein kinase (AMPK), which antagonizes mTOR,<sup>23,24</sup> is decreased.<sup>25</sup> AMPK also inhibits the cystic fibrosis transmembrane regulator (CFTR) chloride channel, which is required for chloride secretion into the cysts.<sup>26,27</sup> **Therefore, drugs that activate AMPK, such as metformin, will decrease both cell proliferation and fluid secretion and thus reduce cyst growth.** Activated AMPK can also antagonize transforming growth factor- $\beta$  and inhibit epithelial-mesenchymal transition, both promoters of tubulointerstitial fibrosis.<sup>28-30</sup>

The efficacy of metformin in reducing cyst burden and preserving normal parenchyma was confirmed in 2 mouse models of rapidly progressive forms of ADPKD.<sup>24</sup> Daily intraperitoneal metformin injections led to a significant decrease in the histological cystic index compared to vehicle treated cystic control mice. Renal function or survival were not examined in this study.<sup>24</sup> The dose of metformin used in mice extrapolated to a dose of about 1500 mg daily for humans when calculated based on body surface area. Up-regulation of AMPK activity by metformin was also beneficial in a subtotal nephrectomy rat model of CKD.<sup>31</sup> Early continuous treatment with metformin prevented the progressive reduction of GFR and renal blood flow that was observed in control animals. While the control animals developed severe renal fibrosis, this was significantly attenuated in the metformin-treated rats.<sup>31</sup> These experiments suggest a direct renoprotective effect of metformin. In humans, a retrospective cohort study of 13,238 veterans who initiated either metformin or sulfonylurea therapy for type 2 diabetes showed that **over 5 years follow-up, metformin users had a significantly lower risk for renal function decline, ESRD or death**, even after adjustments for multiple time-varying covariates.<sup>32,33</sup>

**We conducted a retrospective cohort study of ADPKD patients with type 2 diabetes** using the Intermountain Healthcare Enterprise Data Warehouse (integrated healthcare delivery system) between 1/1/2000 and 12/31/2013.<sup>34</sup> We identified 31 subjects treated with metformin only who could be matched for age, sex, race, history of hypertension and coronary artery disease, and baseline renal function to 31 subjects not treated with metformin. The primary outcomes were incident ESRD and all-cause mortality. The baseline MDRD-eGFR in participants receiving and not receiving metformin was  $49 \pm 12$  and  $47 \pm 14$  mL/min/1.73m<sup>2</sup> ( $p=0.70$ ). After a median follow-up of 4.5 years, **incident ESRD occurred in 29% and 16% of those not exposed and exposed to metformin, respectively, with a OR of 2.13 (95% CI 1.10-3.46; p=0.02)**. Deaths occurred in 32% and 26% of those not exposed and exposed to metformin, with a OR of 1.37 (95% CI 0.5-2.47;  $p=0.60$ ). Therefore, metformin therapy may slow progression to ESRD in ADPKD adults with type 2 diabetes compared to other antidiabetic drugs.<sup>34</sup>

**Safety and tolerability of metformin in non-diabetic subjects.** Metformin has been used in women with the polycystic ovary syndrome, with or without diabetes, without significant side effects.<sup>35,36</sup> Nausea and diarrhea may occur in 10-25% of patients but is usually transient and responds to dose reduction.<sup>35</sup> **Long-term metformin administration to non-diabetic individuals** has been studied in the **Diabetes Prevention Program Outcomes Study (DPPOS)**, in which 924 subjects at risk for the development of type 2 diabetes were given metformin 850 mg twice daily for a median of 10 years.<sup>37</sup> Metformin therapy reduced the development of diabetes while no significant safety issues were identified.<sup>37</sup> However, these were subjects with impaired glucose tolerance; only a small study reported the safe administration of metformin (1000 mg/day) to normal-weight women with polycystic ovary syndrome who had normal glucose tolerance tests.<sup>38</sup> Nothing is known about the tolerability of metformin in non-diabetic ADPKD patients, who often are very health-conscious, slim and engaged in vigorous exercise. Therefore **our primary aim is to determine the feasibility, in terms of safety and tolerability, of prescribing metformin 1000 mg twice a day in ADPKD patients with an eGFR of 50-75 mL/min/1.73m<sup>2</sup>. Determining the safety of metformin in CKD stage 3 (eGFR 30-60 mL/min/1.73 m<sup>2</sup>) is of particular importance**, because these individuals have usually been excluded from treatment with metformin.

Lactic acidosis as a complication of metformin therapy is rare (a Cochrane analysis of 347 trials and cohort studies in type 2 diabetes found no cases of lactic acidosis in 70,490 patient-years of metformin use<sup>39</sup>), however, people with renal impairment may be at higher risk because metformin is 90% renally excreted.<sup>40,41</sup> Large observational studies of diabetic patients showed that metformin use was associated with lower cardiovascular mortality particularly if subjects also had stage 3 CKD.<sup>42,43</sup> Based on these reports several recent publications advocate continued use of metformin in diabetic patients with eGFR 45-60 ml/min/1.73 m<sup>2</sup>, while reducing the dose by 50% in those with eGFR 30-44 ml/min/1.73 m<sup>2</sup>.<sup>40,41,44-46</sup> The **Kidney Disease Improving Global Outcomes (KDIGO)** conference also reviewed this topic and **concluded that there was little evidence to support the relationship between metformin use and development of lactic acidosis in stable CKD patients.**<sup>47</sup> The **major precipitating factor for lactic acidosis** in persons receiving metformin is an **abrupt loss of tubular secretion** which is a characteristic feature of acute kidney injury due to rapid volume depletion or an intercurrent illness. The work group recommended that the dose of metformin should **only be reduced to a maximum of 1000 mg per day when eGFR falls below 45 ml/min/1.73m<sup>2</sup>**, and should be discontinued when eGFR reaches 30 ml/min/1.73m<sup>2</sup>. We will follow these dosing recommendations.<sup>47</sup>

**Summary of Significance.** The biomedical significance of the proposed work includes:

- ADPKD is the most common life-threatening genetic disease, resulting in ESRD and premature death in the majority of patients;
- Presently, there is only one approved treatment option to slow progression of ADPKD;
- Metformin has a known safety profile with minimal toxicity after decades of clinical experience in diabetic and non-diabetic subjects;
- Surprisingly little is known regarding the safety, tolerability and efficacy of metformin in adult patients with ADPKD and normal to mildly reduced renal function;
- This study will establish the safety of metformin in people with ADPKD;
- We will explore preliminary signals of efficacy of metformin to reduce cyst growth and renal function decline on the background of adequate blood pressure control.

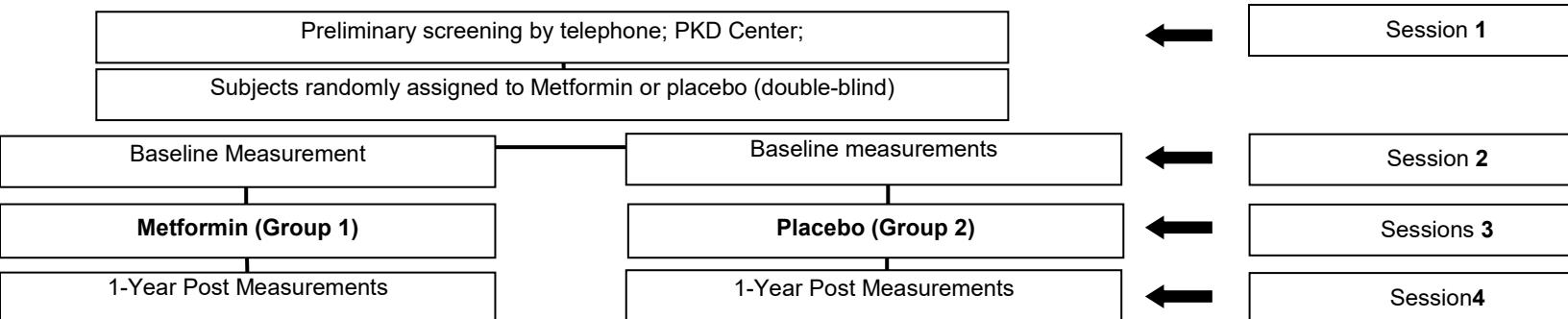
**Innovation.** Metformin has never been studied for the treatment of ADPKD. Therefore this is the first use of a randomized placebo-controlled, double-blind study design to determine the feasibility, in terms of safety and tolerability and potential efficacy of metformin in non-diabetic patients with ADPKD. We will also include subjects with stage 3 CKD who have traditionally been excluded from trials with metformin. In addition, our investigative team will use MRI for assessment of total kidney volume. **Overall, this work has the potential to provide important information that will allow us to launch a larger outcomes study that could shift clinical practice guidelines by establishing a novel, easy to deliver therapy for reducing renal structural and functional progression in patients with ADPKD.**

### **Approach**

**Subjects.** After obtaining their written informed consent, 50 non-diabetic men and women aged 30-60 years with a diagnosis of ADPKD based on Ravine criteria<sup>48</sup> and an eGFR 50-80 mL/min/1.73 m<sup>2</sup> will serve as subjects. (The application and the consent form reference 65 patients to account for screen failures and withdrawals.) Because we want to study the tolerability of metformin by non-diabetic subjects, those with diabetes will be excluded. Estimated GFR will be calculated using the chronic kidney disease-Epidemiology Collaboration (CKD-EPI) prediction equation.<sup>49</sup> Hypertensive subjects will have to be on a stable blood pressure (BP) medication regimen for at least 4 weeks, with BP controlled at  $\leq$  130/80 mmHg. Subjects who are not on BP medication but have BP  $\geq$  130/80 mmHg on at least 3 occasions will be required to have their BP controlled for at least 4 weeks before study entry. The first-line antihypertensive medication will be a renin-angiotensin-system blocking drug. Major inclusion/ exclusion criteria are presented in the table below (Table 1).<sup>50</sup>

<b>Table 1</b>	<b>Inclusion Criteria</b>	<b>Exclusion Criteria</b>
	<ul style="list-style-type: none"><li>• Aged 30-60 years</li><li>• Adults with diagnosis of ADPKD by modified Pei-Ravine criteria:<ul style="list-style-type: none"><li>➢ <i>With family history: several cysts per kidney (3 if by sonography, 5 if by computed tomography or magnetic resonance imaging)</i></li><li>➢ <i>Without family history: 10 cysts per kidney (by any radiologic method listed above) and exclusion of other cystic kidney diseases. Conditions to be excluded include: multiple simple renal cysts, renal tubular acidosis, cystic dysplasia of the kidney, multicystic kidney, multiocular cysts of the kidney, medullary cystic kidney and acquired cystic disease of the kidney.</i></li><li>➢ <i>Distribution and number of cysts consistent with the observed level of renal function. -OR-</i></li><li>➢ <i>Diagnosis based on genetic testing (PKD1)</i></li></ul></li><li>• Estimated GFR (CKD-EPI prediction equation) 50-80 mL/min/1.73m<sup>2</sup></li><li>• Controlled blood pressure at <math>\leq</math> 130/80 mmHg on a stable anti-hypertensive regimen for at least 4 weeks</li><li>• Free from alcohol dependence or abuse.</li><li>• Ability to provide informed consent</li><li>• Not currently participating in another interventional trial</li></ul>	<ul style="list-style-type: none"><li>• Uncontrolled hypertension</li><li>• Current smokers or history of smoking in the past 12 months</li><li>• Diabetes mellitus</li><li>• History of hospitalizations within the last 3 months</li><li>• History of severe congestive heart failure (i.e., ejection fraction &lt; 35%)</li><li>• History of liver disease (metformin is contraindicated in patients with liver disease due to increased risk of lactic acidosis)</li><li>• Active infection or antibiotic therapy</li><li>• Additional kidney disease (e.g, AKI) superimposed on ADPKD</li><li>• Need for treatment with drugs that may enhance the toxicity of metformin, e.g. lamotrigine, topiramate, zonisamide, carbonic anhydrase inhibitors</li><li>• Intolerance of metformin</li><li>• Immunosuppressive therapy within the last year</li><li>• Contraindication to undergoing MRI</li><li>• Females of childbearing age: Not willing to use contraception</li><li>• Pregnancy/lactation</li><li>• BMI <math>&lt; 21</math> kg/m<sup>2</sup></li></ul>

**Experimental Design (Figure 1).** A 1-year randomized, placebo-controlled, double-blind study with metformin will be conducted (see below for dosing). Subjects will undergo telephone and PKD center screening for inclusion/exclusion criteria during a 1-2 week period. After patients meet inclusion/exclusion criteria they will have an abdominal MRI using an established protocol for determination of TKV and liver volume (see below). Subjects will then be randomly assigned to either metformin (Group 1) or placebo (Group 2) which will ensure a balanced experimental design. Members of the investigative team involved in the acquisition and analysis of key outcomes will be blinded to the treatment status of the subjects.



**Figure 1**

Research participants will undergo the following research sessions:

**(i) Session 1: Screening** measurements: Medical history, physical examination, and blood chemistries for serum/plasma creatinine. Arterial BP will be measured in triplicate while seated at rest using an automated oscillometric machine (Dinamap).<sup>51</sup>

**(ii) Session 2: Baseline measurements:**

- Resting arterial blood pressure as above, complete blood count, and comprehensive metabolic panel including a serum/plasma creatinine to estimate GFR using the CKD-EPI prediction equation
- Total Kidney Volume (TKV) and Liver Volume by MRI
- Urine sample for measurement of urine protein and creatinine to estimate urine protein excretion
- Begin study treatment (metformin or placebo)
- Study participant will be given a glucometer and instructed on how to use it at home
- All participants will have the metformin or placebo provided every 3 months. Participants will be asked to return their medication dispenser for a pill count.
- Blood and urine sample will be stored for future measurement of biomarkers of ADPKD progression.

**(iii) Session 3 (Month 3, 6 and 9):** All subjects will be asked about any adverse effects, intercurrent illnesses or changes of their concomitant medications and will have safety laboratories at 3, 6 and 9 months which will include a basic metabolic panel (i.e., serum/plasma glucose and creatinine) to estimate eGFR using the CKD-EPI equation.<sup>48</sup> Study participants will be required to check their morning fasting blood sugars (BS) daily for the first week of treatment, then twice weekly for the following week, and at any time if they experience a hypoglycemic symptom (i.e., sweating, lightheadedness), and keep a log of their BS values. After each dose change of metformin during the titration period (see below) they will again check their fasting BS daily for one week and then twice weekly for the following week. These results will be reviewed during scheduled telephone interviews. Women will be counseled about contraception during the study. Should a pregnancy occur, women are requested to stop taking study drug immediately and contact the study coordinator.

(iv) **Session 4 (Month 12):** Identical to Session 2, with repeat TKV.

**Rationale for age range 30-60 years.** A narrow range for inclusion age criteria will ensure: (i) that the treatment and placebo group are well balanced; and (ii) exclusion of participants older than 60 years with relatively well preserved kidney function will ensure that only ADPKD patients with more advanced disease will be included in the study. Subjects younger than age 30 years very rarely have decreased renal function.

**Rationale for the metformin dosing:** After randomization subjects will start taking metformin/placebo 500 mg twice daily with meals. The dose will be up-titrated every 2 weeks by 500 mg, until 2000 mg/day (i.e., 1000 mg twice a day) is reached for subjects with eGFR > 45 ml/min/1.73m<sup>2</sup>. The metformin dose will be increased every 2 weeks if well tolerated, however dose increases may be delayed if the patient reports significant gastrointestinal or other adverse symptoms. In that case the uptitration schedule will be individualized and dose increases will happen when the patient's symptoms have resolved. Of note, these are the recommended dosing guidelines published by the KDIGO update on diabetic kidney disease. The dose of 2000 mg was chosen because it is generally considered the optimal dose for treatment of diabetes or for polycystic ovary syndrome.<sup>34</sup> This dose is also in an equivalent range to the dose used successfully in the mouse models when extrapolated to humans.<sup>21</sup> If intolerable gastrointestinal side effects occur on a higher dose, the dose will be reduced to the previously tolerated dose.

**Rationale for the placebo arm:** Although direct comparisons of the active treatment group with the placebo group will not be required to determine if the pre-specified benchmarks for the safety and tolerability endpoint are met, there are several reasons to include a placebo group in this pilot study. First, a placebo group is required for Specific Aim 2, which will explore differences in TKV and eGFR between subjects treated with metformin or placebo. Second, if a placebo group were not included the investigators and participants would know that they are receiving metformin, which could influence medical management during the study as well as participant's perception of side effects. Third, the inclusion of a placebo group will provide estimates of the proportions of participants who are classified as failures by the primary endpoint due to factors unrelated to metformin.

**Rationale for the duration of follow-up.** Safety and tolerability signals will show by 12 months and changes in eGFR have been described in ADPKD patients with mild CKD.<sup>15</sup> Changes in TKV due to natural progression of ADPKD can be measured after only 6 months<sup>52</sup> and during treatment with tolvaptan after only one week.<sup>13</sup>

**Safety monitoring.** The investigative team will establish an independent Data Safety Monitoring Board (DSMB) for this study. The DSMB will include experienced nephrologists, biostatisticians and endocrinologists. In general, the anticipated gastrointestinal side effects of metformin therapy can be medically managed through adjustment of medications. If medical management is ineffective, doses of the assigned intervention will be reduced by ½ followed by discontinuation of therapy if the side effect persists. The strategies for monitoring the anticipated adverse events are:

**(i) Symptomatic or Asymptomatic Hypoglycemia (glucose < 60 mg/dL):** Study participants will be instructed on management of hypoglycemia. Once symptoms are resolved the patient will be advised to reduce the dose by 50%. If glucose remains < 60 mg/dL in subsequent measurements despite these changes, the intervention will be discontinued. Continuous monitoring of blood glucose with a glucometer will be undertaken until hypoglycemia is resolved.

**(ii) Estimated GFR < 45 mL/min/1.73m<sup>2</sup>:** If eGFR falls below 45 ml/min/1.73m<sup>2</sup> and this is confirmed by a subsequent laboratory test 2 weeks later, metformin will be decreased to 1000 mg daily.

**(iii) Estimated GFR < 30 mL/min/1.73m<sup>2</sup>:** If eGFR falls below 30 ml/min/1.73m<sup>2</sup> and this is confirmed by a subsequent laboratory test 2 weeks later, metformin will be stopped, according to the KDIGO and American Diabetes Association recommendations.<sup>40,47</sup>

**(iv) Intercurrent illness:** If a research participant develops volume depletion or an acute intercurrent illness, the patient will be instructed to stop metformin until the illness has resolved. Lactic acid will be measured if suggested by symptoms or lab results (decreased CO<sub>2</sub>); if elevated, metformin will be stopped and the patient withdrawn from the study.

### **Outcome Measures:**

**Primary Outcome:** The primary analysis will examine, as co-primary endpoints, the percentage of participants that are *prescribed* at the end of the 12-month period: (a) the full randomized dose of metformin according to the protocol, *and* (b) at least 50% of the randomized metformin dose according to the protocol. Dose adjustments due to decreased GFR < 45 mL/min/1.73m<sup>2</sup> (see above) will count as the full dose because the exposure to metformin in these subjects will be equivalent to the full dose given to subjects with normal GFR.

The two proposed co-primary endpoints provide an assessment of the feasibility, in terms of safety and tolerability of metformin. These endpoints are influenced by a number of factors, including medication

intolerance (e.g., gastrointestinal symptoms), side effects (e.g., hypoglycemia), and participant drop-out or loss to follow-up. Compliance will not be considered in the co-primary endpoints because poor compliance will not trigger a reduction in the prescribed dose unless there is intolerability or an adverse safety event.

We anticipate that most participants in the metformin arm will complete the study with the prescribed full dose as randomized because they did not have a dose reduction due to side effects or intolerance. On the other hand, some participants may require a reduction in the prescribed dose due to side effects or intolerance. Participants who do not complete the study will be considered treatment failures.

The participant's prescribed dose at the end of the intervention period will be compared to the participant's randomized dose to determine if an intended dose reduction occurred. We would consider that the benchmark is achieved if: (i) at least 67% of participants in the metformin arm are prescribed the full randomized metformin dose at the end of the 12-month intervention period, *and* (ii) at least 80% of participants in the metformin arm are prescribed at least 50% of the randomized metformin dose at the end of the 12-month intervention period.

Our rationales for these benchmark cutoffs consider: (i) a potential loss to follow-up of 5% in the metformin arm, (ii) in order for a dose to be prescribed in a larger outcomes trial, the vast majority of participants who are not lost to follow-up should not require a dose reduction because of intolerance or adverse effects during this 12-month pilot study, and (iii) participants who take lower than the randomized doses may still benefit from the therapy, so long as the percentage of such participants is low in this Pilot Clinical Trial.

**Secondary (exploratory) outcomes:** (a) Change in TKV measured by MRI. **MRI Measurement of Total Kidney Volume:**

A 3.0 T Siemens system (Siemens, Malvern, PA) will be used for all studies. Renal images will be acquired in similar manner and volumetric measurements determined as described for the CRISP study.<sup>10-12,53</sup> Briefly, with subjects supine on the MR table, a phased-array surface coil will be positioned with its center over the expected location of the kidneys. Scout scans will be used to locate the scan range of the entire kidneys. A stack of axial images to cover the most anterocaudal and posterocranial aspects of the kidneys will be acquired. The field-of-view (FOV) will be kept as small as possible (30-35 cm) without producing wrap-around artifacts. The first scan will cover the posterior aspect of the kidney. Neighboring image groups will be overlapped by a single 3mm slice. The correct table position will be determined. Breath-hold coronal Regular T2 scan (SSFSE/HASTE with fat sat) of the kidneys with adjusted slice thickness, 3-9 mm, i.e. the slice thickness best attainable with a single breath-hold will be obtained. No contrast agents will be used. For analysis DICOM images will be de-identified and evaluated by a single analyst, Dr. Wei Wang using Analyze software (Analyze 9.0, Mayo Foundation, Rochester, MN). Reliability coefficients and coefficients of variation for TKV on repeatedly acquired images of individual patients will be acquired.

(b) Change in eGFR will be determined by the CKD-EPI equation using standardized serum/plasma creatinine measurements by the central laboratory of University Hospital at baseline and at 3, 6, 9 and 12 months.

**Sample Size Calculations and Statistical Analysis.** Participant characteristics will be summarized using standard descriptive statistics for all enrolled participants and, separately, by randomized group. The primary analysis of safety and tolerability will tabulate the proportions of the participants assigned to each of the 2 treatment groups who at the end of the study: (i) are prescribed the full randomized metformin dose (allowing for dose adjustments for decreased GFR), and (ii) are prescribed at least 50% of the randomized dose. The dose prescribed for each participant at the last treatment visit (Month 12) will be used to determine whether the participant completes the study on the full prescription or at least 50% of the randomized prescription. This will take into consideration any dose reductions due to adverse effects that would have occurred at the last on-treatment visit had the study continued. In further analyses, exact 90% binomial confidence intervals will be constructed for the proportions of subjects reaching each of the co-primary endpoints in each treatment group, and for differences between the proportions reaching each of the co-primary endpoints in the metformin group vs. the placebo group. In secondary analyses, exact 90% binomial confidence intervals will also be constructed for the proportions of individuals in the metformin and placebo group who: (i) reduce and/or discontinue treatment for safety reasons (e.g. hypoglycemia or increased lactic acid level); (ii) reduce and/or discontinue treatment because of medication intolerance or pill burden, and (iii) have  $\geq 80\%$  pill count compliance. These three endpoints will address the safety, medication intolerance/ pill burden, and compliance respectively for each treatment group during the intervention period. The statistical power for attaining the 67% benchmark will be 0.87 in the metformin group if the true percent prescribed the randomized dose is at least 72%. The

statistical power for attaining the 80% benchmark will be at least 0.84 in the metformin group if the true percent prescribed at least 50% of the randomized dose is at least 84%.

**Power calculation for the exploratory outcomes: a) change in TKV:** is based on findings from the Tolvaptan trial.<sup>14</sup> Annual increase in TKV was 5.5% in the placebo group and 2.8% in the tolvaptan group. We plan to recruit a total expected sample size of N = 50. Assuming a similar efficacy of metformin, we will have an 80% power to detect a similar difference with  $\alpha = 0.05$  for a two-sided test; **b) change in eGFR:** is based on the sample size (N=50) and on published observational and interventional studies in ADPKD.<sup>15,53,54</sup> We estimate the change in eGFR will be + 1 mL/min/1.73m<sup>2</sup> in the metformin group and - 4 mL/min/1.73m<sup>2</sup> in the placebo group during the 12-month study period. With 25 subjects in each group, an overall standard deviation of 8, and 2-tailed test with  $\alpha=0.05$ , we will have 80% power to detect this difference in eGFR change. We acknowledge that the power is limited for the proposed exploratory outcomes of TKV and eGFR, however, our primary goal is to establish the safety and tolerability of metformin in ADPKD patients. The data obtained on TKV and eGFR from this Pilot Clinical Trial will allow estimating sample size for a larger outcomes study.

**Recruitment Plans and Study Time Line.** Subject recruitment/screening will be performed in the initial 6-8 weeks and the first subjects will begin taking pills in month 3. We propose to complete measurements on the last of the 50 subjects during month 21. We will then have 3 months to complete data analysis. The University of Colorado PKD Center has contact information on approximately 500 ADPKD subjects who live in the Denver Metro Area. We have already received an IND waiver from the FDA and registered the study with our Institutional Review Board. Our PKD center has expertise and national recognition, attracting ADPKD patients for clinical studies (Please see description of the accessible population in the human subject section).

**Potential Problems and Alternative Strategies.** Although subject recruitment and retention always are challenging, we should be able to complete the study in the proposed time line given our location in the densely populated Boulder-Denver metro area. If recruitment falls short, we will then contact ADPKD patients living outside the State of Colorado. We recognize that alternative approaches exist for examining the effect of metformin in patients with ADPKD. For example, one alternative would be to undertake a larger outcomes trial to examine renal progression more definitively than in the proposed pilot investigation. However, although a large-scale clinical interventional trial will ultimately be required, a small Pilot Clinical Trial as proposed in this application is the most cost-effective approach to obtain confirmation of the study hypothesis.

**Future directions:** We anticipate that the results from this proposal will define the safety of metformin and the appropriate hard end points for a future larger trial that will culminate in therapeutic benefits of metformin for patients suffering from ADPKD. Our research team envisions a future trial testing the long-term efficacy of metformin on kidney function (i.e., 50% decrease in eGFR and progression to ESRD) against placebo.