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Rationale and Design of the DIPAK 1 Study: A Randomized Controlled Clinical Trial Assessing the Efficacy of Lanreotide to Halt Disease Progression in Autosomal Dominant Polycystic Kidney Disease

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Abstract

Background—There are limited therapeutic options to slow the progression of autosomal dominant polycystic kidney disease (ADPKD). Recent clinical studies indicate that somatostatin analogues are promising for treating polycystic liver disease and potentially also for the kidney phenotype. We report on the design of the DIPAK 1 (Developing Interventions to Halt Progression of ADPKD 1) Study, which will examine the efficacy of the somatostatin analogue lanreotide on preservation of kidney function in ADPKD.

Study Design—The DIPAK 1 Study is an investigator-driven, randomized, multicenter, controlled, clinical trial.

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SUPPLEMENTARY MATERIAL Table S1: Specified laboratory flow chart.
Table S2: Withdrawal criteria for individual participants in DIPAK 1 study.
Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2013.10.011) is available atwww.ajkd.org

Setting & Participants—We plan to enroll 300 individuals with ADPKD and estimated glomerular filtration rate (eGFR) of 30-60 mL/min/1.73 m^2 who are aged 18-60 years.

Intervention—Patients will be randomly assigned (1:1) to standard care or lanreotide, 120 mg, subcutaneously every 28 days for 120 weeks, in addition to standard care.

Outcomes—Main study outcome is the slope through serial eGFR measurements starting at week 12 until end of treatment for lanreotide versus standard care. Secondary outcome parameters include change in eGFR from pretreatment versus 12 weeks after treatment cessation, change in kidney volume, change in liver volume, and change in quality of life.

Measurements—Blood and urine will be collected and questionnaires will be filled in following a fixed scheme. Magnetic resonance imaging will be performed for assessment of kidney and liver volume.

Results—Assuming an average change in eGFR of 5.2 ± 4.3 (SD) mL/min/1.73 m^2 per year in untreated patients, 150 patients are needed in each group to detect a 30% reduction in the rate of kidney function loss between treatment groups with 80% power, 2-sided $\alpha = 0.05$, and 20% protocol violators and/or dropouts.

Limitations—The design is an open randomized controlled trial and measurement of our primary end point does not begin at randomization.

Conclusions—The DIPAK 1 Study will show whether subcutaneous administration of lanreotide every 4 weeks attenuates disease progression in patients with ADPKD.

Keywords

Polycystic kidney disease (PKD); cyst progression; glomerular filtration rate (GFR); kidney volume; quality of life (QoL); disease trajectory; renal disease; somatostatin analog

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Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease.[1,2] It is characterized by progressive cyst formation in both kidneys, often leading to end-stage kidney disease between the fourth and seventh decades of life.[1-3] Approximately 10% of patients receiving renal replacement therapy have ADPKD as the underlying disease.[1] Cyst formation also is found in the liver, with an overall prevalence of 83% in a cohort of patients with early ADPKD.[4] Symptoms of polycystic liver disease include abdominal distension, early satiety, dyspnea, and pain.[5]

The development of renoprotective treatments for ADPKD is of major importance for patients with ADPKD. Increasing knowledge of the pathophysiology of ADPKD has allowed the identification of several potential therapeutic targets, and animal experiments have confirmed that drugs directed at these targets are renoprotective. Three drug classes have been tested in clinical trials: mammalian target of rapamycin (mTOR) inhibitors, vasopressin V_2 receptor (V_2R) antagonists, and somatostatin analogues.[6-9]

Despite encouraging animal data with mTOR inhibitors,[10-12] 2 controlled trials recently failed to show a beneficial effect on decline in kidney function in patients with ADPKD.[13,14] A post hoc analysis of 2 open-label studies involving V_2R antagonists, with matched untreated controls from historical ADPKD cohorts, suggested that these agents had

renoprotective effects.[15] Recently, a large randomized clinical trial with V_2R antagonist treatment showed a reduction in kidney growth and preservation of kidney function in 1,445 patients with ADPKD with a mean estimated creatinine clearance of 81 mL/min.[16] These results are promising because for the first time, a drug was shown to slow the decline in kidney function in patients with ADPKD.

However, there are a number of limitations to the use of V_2R antagonists. First, the effect of these drugs probably is limited to renal tubular cells in the distal nephron and collecting duct.[7] Although these are the predominant cysts in adult patients with ADPKD, kidney cysts also may originate from other parts of the nephron.[17] Whether V_2R antagonists will be effective in patients with chronic kidney disease (CKD) stages 3-4 is not known. Furthermore, V_2R antagonists have adverse effects that may limit widespread clinical use, such as thirst, polydipsia, polyuria, and nycturia, which can cause sleep disturbance. A final consideration is that polycystic liver disease is a common manifestation of ADPKD and curtailing the growth of the liver is a desirable therapeutic target. Because the V_2R is not expressed in liver tissue, no liver-specific therapeutic action of V_2R antagonists may be expected.

Recent randomized clinical trials suggest that somatostatin analogues ameliorate polycystic liver disease.[18-22] These trials included only a limited number of patients with ADPKD, making it difficult to reach a definitive conclusion on the possible renoprotective efficacy of these drugs. Therefore, these trials do not allow one to conclude that somatostatin analogues should be standard care for patients with ADPKD at high risk of disease progression.

The DIPAK (Developing Interventions to Halt Progression of Autosomal Dominant Polycystic Kidney Disease) 1 Study is designed to validate the efficacy of the somatostatin analogue lanreotide to reduce disease progression in patients with ADPKD with CKD stage 3.

METHODS

Study Setting and Population

The DIPAK 1 Study is designed as a multicenter, open-label, randomized, controlled, parallel-arm trial in 300 participants with ADPKD and a high likelihood of disease progression. It will include individuals with an ADPKD diagnosis based on Ravine criteria,[23] aged 18-60 years, with an estimated glomerular filtration rate (eGFR)[24] of 30-60 mL/min/1.73 m^2. Detailed patient inclusion and exclusion criteria are listed in Box 1. The eGFR cutoff values in combination with the age criteria ensure that only individuals with a high likelihood of disease progression will be included. Also, the inclusion criteria are easy to translate into clinical practice (in contrast to inclusion criteria based on total kidney volume), which increases the external validity of the data. Furthermore, interventions initiated in individuals with eGFR < 30 mL/min/1.73 m^2 are less likely effective.

Study Design

Individuals meeting the entry criteria and completing baseline assessments will be enrolled in 1 of the 4 participating University Medical Centers in the Netherlands (Groningen,

Leiden, Nijmegen, and Rotterdam). The planned recruitment period is 21 months. After informed consent is obtained and eligibility is assessed (Box 1), patients will be randomly assigned to standard care (control) or standard care plus 4-weekly lanreotide injections. Randomization will be performed using an interactive voice response system, with stratification for eGFR at time of screening (≤45 and >45 mL/min/1.73 m^2), sex (male/female), and age (≤45 and >45 years). There are no specific demands set to the number of patients to be included per stratum.

Figure 1 presents a schematic of the trial design. One week after the first injection, the patient will receive a telephone call to assess adverse events. Participants will be evaluated in person at weeks 4 (T4), 8 (T8), and 12 (T12) and every 12 weeks thereafter until the end of the trial (end-of-treatment visit scheduled to be at week 120). The last dose of lanreotide will be given at week 116. Participants will be seen 12 weeks after the end of the trial for a follow-up visit. Total duration of the study therefore will be 132 weeks. In case a participant does not tolerate medication and treatment ends, an early end-of-treatment visit will be performed within 1 week after the next injection should have been administered and the participant will continue regular study visits.

Trial Treatments

Treatment will consist of 120 mg of lanreotide administered subcutaneously every 4 weeks. The dosage will be eGFR (body surface area unadjusted) dependent. Participants who reach for the second time an eGFR < 30 mL/min during the study will receive lanreotide, 90 mg, subcutaneously every 28 days. Participants experiencing intolerable adverse effects will also have their medication dose adjusted (stepwise, from 120 to 90 to 60 to 0 mg). Lanreotide will be administered by trained nurses.

The dosage and frequency of treatment with lanreotide is based on a pilot study[18] in which a dosage of 120 mg subcutaneously once every 28 days was effective in decreasing the rate of liver and kidney volume growth in individuals with polycystic liver disease. The dosing scheme of 120 mg once every 28 days furthermore is approved by the European Medicines Agency and US Food and Drug Administration for other indications. There is only limited information on the use of lanreotide in individuals with decreased kidney function.[25] Although the therapeutic index of lanreotide is broad, we decided to adjust the dose of lanreotide to kidney function given the limited pharmacokinetic data.

Standard Care

Participants will not be allowed to participate in other (experimental) trials investigating pharmaceutical agents or strategies aimed at intervening with the natural disease course of ADPKD. Participants with hypertension (defined as systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg) will be treated with angiotensin-converting enzyme inhibitors, or in case of intolerance for angiotensin-converting enzyme inhibitors, with angiotensin receptor blockers. Although definitive evidence is lacking, these 2 classes of antihypertensive drugs are regarded as first-line agents for the treatment of hypertension in individuals with CKD, including ADPKD.[1,26,27] If hypertension remains despite the use of these agents, the choice of additional antihypertensive medication will be at the discretion

of the treating physician. Use of estrogens and oral contraceptives is discouraged per protocol in women with significant liver cysts because these drugs may increase liver cyst growth in women with ADPKD.[28,29] However, the decision to prescribe these drugs will be at the discretion of the treating physician. Similarly, dietary advice (reduction in sodium, caffeine, and protein intake and increase in water intake) will be at the discretion of the treating physician because dietary interventions have not yet been proven to decrease the rate of disease progression in ADPKD.

Primary End Point

The primary outcome variable is rate of change in kidney function for lanreotide-treated versus control patients. This is defined as the slope through serial eGFR values over time during the treatment phase of the study. The value obtained at week 12 will be used as the first eGFR for slope analysis. If participants reach end-stage kidney disease or die, only eGFR values before these events will be taken into account.

Kidney function has been chosen as the primary end point instead of total kidney volume because the clinical relevance of this latter parameter is still uncertain. eGFR values obtained at weeks 4 and 8 during the treatment phase of the study will be used for safety analyses, but not for efficacy analysis. Kidney function will be estimated using the creatinine-based 4-variable MDRD (Modification of Diet in Renal Disease) Study equation.[24] This equation is validated in individuals with eGFR < 60 mL/min/1.73 m^2 and generally is used in Dutch clinical practice. Furthermore, to rule out an effect of change in muscle mass or tubular creatinine secretion due to treatment, as a sensitivity analysis, cystatin C will be measured to estimate GFR (using the CKD-EPI [CKD Epidemiology Collaboration] equation).

Secondary End Points

Secondary end points are separated into end points for the kidney, liver, and quality of life and are listed in Box 2.

We thought that it was useful to assess change in liver volume only in participants who have a polycystic liver and therefore decided not to analyze this secondary end point in those who have no or only a limited number of liver cysts because this will only dilute the effect size of the drug under investigation.

Data Collection

Figure 1, Table 1, and Table S1 (provided as online supplementary material) show the data to be obtained during study visits. Health-related quality of life will be assessed using an ADPKD-specific questionnaire, including questions regarding polycystic liver disease.[30] Blood pressure will be assessed with an automatic device for 10 minutes during study visits. Blood and urine chemistry will be analyzed locally. In addition, a blood sample will be shipped to the core laboratory for storage (−80°C), and assessment of key efficacy variables (creatinine and cystatin C) will be performed after completion of the study in one run per participant to minimize interlaboratory and interassay variation. These centrally assessed laboratory variables will be used for efficacy analyses. Of note, storing blood samples at

room temperature for up to 4 days does not influence creatinine[31] and cystatin C concentrations, nor does frozen storage at −80°C for prolonged periods.[32]

At the baseline visit, at the end of the treatment phase of the study (week 120 or at early termination visit), and at follow-up, magnetic resonance (MR) imaging (MRI) will be performed, using a standardized protocol without use of intravenous contrast. The MRI acquisition protocol includes T2-weighted single-shot fast gradient spin-echo images with fat-saturation. MR images will be sent to the central reading facility, using a secure server. MRI end point data will be analyzed and read centrally using Analyze 11 software (AnalyzeDirect Inc) to assess total kidney volume with a stereology method. To ensure that valid MR images are obtained, quality control will be performed within 48 hours by trained personnel. In case a scan is rejected, it will be repeated before the injection of lanreotide.

Lanreotide serum levels will be measured after completion of the trial using blood samples for post-hoc assessment of the association between drug blood levels and efficacy.

A web-based electronic case report form has been designed to enter study data to ensure correct and timely data collection in a central database.

Estimation of Power and Sample Size

In a cohort of patients with ADPKD participating in the MDRD Study (baseline measured GFR, 25-55 mL/min), the mean slope of GFR decline on treatment was 5.2 mL/min per year with a calculated standard deviation of 4.3.[33] In the recent Everolimus ADPKD Study (baseline eGFR, 30-90 mL/min/1.73 m^2), mean change in eGFR was 4.2 mL/min/1.73 m^2 with a similar standard deviation of 4.3.[13] The annual slope of GFR in this study is expected to be similar to the MDRD Study and steeper than in the Everolimus ADPKD Study because in the present study, only individuals with decreased kidney function will be included (CKD stage 3). Assuming an average change in eGFR of 5.2 mL/min/1.73 m^2 per year in untreated patients and a standard deviation of 4.3 in both treatment groups, 120 individuals per study group are needed to detect a 30% reduction in the rate of kidney function loss between treatment groups, with 80% power to detect this difference and 2-sided $\alpha = 0.05$. Taking into account the possibility of 20% protocol violators and/or dropouts, our aim is to include 150 participants per group.

Statistical Analyses

Analyses will be done after completion of the study. To assess differences between treatment groups in baseline characteristics for continuous data, *t* test will be used for normally distributed data, and Mann-Whitney *U* test, for non-normally distributed data. The χ^2 test will be used to compare dichotomized variables between groups. (Generalized) mixed models will be used to analyze the primary end point (difference in change in kidney function in lanreotide-treated patients vs controls). All available eGFR values will be taken into account until a participant reaches end-stage kidney disease. We will explore whether missing eGFR values are random, and if necessary, we will use other statistical models that handle informative dropout.

In addition, we will perform linear regression analysis (calculating a slope through the available eGFR values per individual) as sensitivity analysis for the primary end point and secondary end points involving change in a variable. Incidences of worsening kidney function, end-stage kidney disease, and death will be investigated using Cox proportional hazard models. Kaplan-Meier graphs will be prepared. All *P* values will be 2 tailed, and the level of significance will be set at $P < 0.05$. All analyses will be performed as intention-to-treat analyses. Perprotocol analyses will be done as secondary analyses. The main analyses also will be performed in a priori–defined subgroups: baseline age younger than or equal to/older than median, baseline eGFR less than or equal to/greater than median, baseline total kidney volume less than or equal to/greater than median, and men versus women. Of note, we will perform analyses for change in liver volume as a secondary analysis, with a sensitivity analysis with adjustment for use of estrogens or oral contraceptives. To control for type I errors, $P < 0.01$ will indicate statistical significance for the subgroup analyses. Furthermore, we will investigate correlations investigating changes in kidney volume versus changes in liver volume over time.

Ethical Considerations

The Medical Ethics Committee of the University Medical Center Groningen approved the protocol and informed consent form. The trial is to be conducted in accordance with the International Conference of Harmonization Good Clinical Practice Guidelines and will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

All participants have the right to withdraw at any time during the study. Further stopping rules for patients and the trial are given in Table S2.

Study Organization

A steering committee oversaw the design and will overview the conduct of the study; a central study coordinator will coordinate the study. An independent data safety monitoring board has been established to monitor the safety and efficacy of the trial and can advise to stop the study based on serious adverse events and/or interim analysis of adverse effects. An academic contract research organization will monitor study progress and quality and completeness of study data.

DISCUSSION

The DIPAK 1 Study seeks to determine whether lanreotide attenuates kidney function deterioration in patients with ADPKD.

In ADPKD, well-described genetic defects initiate the formation of cysts.[34-37] Cysts further expand due to disturbances in cell proliferation, apoptosis, cell-matrix interactions, and fluid secretion. One of the factors that potentially can affect these processes is 3′,5′-cyclic adenosine monophosphate (cAMP). Elevated cAMP levels might hasten cyst growth and overall kidney enlargement in patients with PKD.[38] cAMP production can be inhibited by blocking the V_2R, but also by activation of the somatostatin receptor.[6,39,40] There are 5 receptors for somatostatin. Octreotide and lanreotide bind with high affinity to somatostatin receptor 2.[39,41,42] Detection of the so matostatin receptor 2 in kidney tubules and its

inhibitory effect on cAMP production suggest a potential effect of somatostatin on cyst fluid secretion and enlargement in patients with ADPKD.[43,44] In experimental models of PKD, somatostatin analogues have been shown to inhibit hepatorenal cystogenesis.[45,46]

In humans, to date, only 3 small-scale studies have been performed with somatostatin analogues in ADPKD. In these studies, kidney function was not a primary outcome measure. Ruggenenti et al[8] performed a randomized crossover study comparing the effect of a 6-month treatment regimen of octreotide, a long-lasting somatostatin analogue, with no treatment in 14 patients with ADPKD (mean baseline measured GFR, 57.1 [range, 24.4-95.3] mL/min). GFR, measured using iohexol clearance, did not change significantly during both treatment periods. Although total kidney volume increased significantly in both groups, the increase in kidney volume was reduced, with 60% reduction by administration of octreotide ($P < 0.05$).

van Keimpema et al[18] performed a randomized clinical study with a 6-month regimen of lanreotide, administered in the normal clinical dose of 120 mg once every 28 days subcutaneously in 54 patients, 32 of whom had ADPKD. In participants with ADPKD, total liver volume decreased significantly with lanreotide compared to placebo ($P < 0.01$), and total kidney volume decreased by 17 mL (1.5%) in the lanreotide group and increased by 50 mL (3.4%) in the placebo group (absolute difference, $P < 0.02$). This beneficial effect was maintained in the following 6 months.[47] Lanreotide treatment decreased serum creatinine levels ($P = 0.079$). In addition, at 6 months, lanreotide improved general healthy perception.

Hogan et al[19] randomly assigned 42 patients with polycystic liver disease (of whom 34 had ADPKD) to 12 months' treatment with octreotide or placebo. Mean baseline GFR was 71 (range, 20-124) mL/min/1.73 m^2. Total liver volume decreased 4.95% in the octreotide group compared with an increase of 0.92% in the placebo group (P = 0.048). Among patients with ADPKD, the kidney growth rate was significantly reduced in the octreotide group compared with nontreated patients (0.25% vs 8.61%, respectively; $P = 0.045$). GFR decreased by 5.1% with octreotide and 7.2% with placebo (difference not statistically significant).[19] After 2 years of octreotide treatment, the reduction in total liver volume was maintained (−5.96% compared to baseline), but the inhibition of kidney growth during the first year was not sustained during the second year.[48]

Caroli et al[22] recently reported results of a single-blind randomized controlled trial involving 79 patients with ADPKD with eGFR ≥ 40 mL/min/1.73 m^2. Total kidney volume increased significantly less with octreotide compared to placebo after 1 year of treatment. After 3 years of treatment, the mean increase in total kidney volume again was smaller in the treated group, but results were not statistically significant. During the entire follow-up period, the rate of eGFR decline (measured by iohexol clearance) tended to be slower in the octreotide group than in the placebo group, but the difference was not statistically significant. After 1 year of treatment, there was no difference in GFRs. The long-term GFR decline from year 1 to year 3 was almost 50% slower in the octreotide group than in the placebo group (2.28 vs 4.32 mL/min/1.73 m^2 per year, respectively; $P = 0.03$). It should be noted that at baseline in the placebo group, GFR was lower and total kidney volume was higher, which may have led to a worse prognosis in the placebo group independent of treatment. These data led the

authors to conclude that their findings present the background for large randomized controlled trials to assess the protective effect of somatostatin analogues against loss of kidney function and progression to end-stage kidney disease.[22]

To our knowledge, 3 trials are ongoing with somatostatin analogues in patients with ADPKD (n = 48 with pasireotide and n = 43 with lanreotide, both directed at liver volume,[49,50] and n = 80 with octreotide directed at kidney volume and rate of GFR decline[51]). Although these trials are important, the lower number of included patients may preclude definitive conclusions on the efficacy of somatostatin analogues for renoprotection in this patient group.

The most common adverse effects of lanreotide are injection-site discomfort and erythema, diarrhea, abdominal cramping, (asymptomatic) biliary sludge or gallstones, and abnormal glucose metabolism.[52] Less common adverse effects are allergic skin reactions and acute pancreatitis. Diarrhea and abdominal cramping are expected to occur in the first days after the first injections when lanreotide reaches peak blood concentrations. These symptoms resolve spontaneously in most cases during continued use when more stable blood concentrations are reached (steady-state phase).[53] In case these symptoms do not resolve, pancreatic enzymes may be prescribed, which generally improve these symptoms.[18] Of the 118 patients with ADPKD who were included in the 3 aforementioned studies with somatostatin analogues, only 2 patients stopped study medication permanently, and in only 4 patients did dosages have to be lowered.[8,18,19]

The present costs associated with lanreotide are a disadvantage. In the Netherlands, a 120-mg lanreotide injection costs $2,310. This is approximately $30,000 per year for an injection schedule of once every 4 weeks. If proved effective, new price agreements may be necessary to improve the cost-effectiveness ratio of lanreotide administration for ADPKD.

Recently, the Tolvaptan Efficacy and Safety in Management of ADPKD and Its Outcomes (TEMPO) 3-4 Study, a randomized controlled trial in 1,445 patients with ADPKD, showed renoprotection of the V_2R antagonist tolvaptan.[16] Inclusion criteria were different from those in this study. Only patients with ADPKD with estimated creatinine clearance > 60 mL/min were included. The efficacy and safety of tolvaptan in patients with ADPKD with CKD stages 3-4 are unproved to date. Patients with ADPKD with lower eGFRs have higher vasopressin levels.[54,55] Consequently, such individuals might require higher dosages of a V_2R antagonist to effectively block the receptor. We found in an experimental model for ADPKD that a fixed dose of a vasopressin receptor antagonist showed less efficacy when administered at a later stage of disease.[56] Because V_2R antagonists might be less effective in a later stage of disease, we chose to compare lanreotide with standard care and not in addition to vasopressin receptor antagonists. The positive findings in the TEMPO 3-4 Study nevertheless are encouraging for the present study because both V_2R antagonists and somatostatin analogues lower intracelluar cAMP levels.[6]

Study limitations include the design as an open randomized controlled trial. Administration of lanreotide, which is a gel, will result in temporary injection infiltrates in the majority of actively treated individuals. Manufacturing a placebo that has a similar effect is not possible

from a technical point of view. This precludes execution of this trial as a double-blinded randomized controlled trial. To minimize bias, efficacy end points will be assessed in a blinded fashion (eGFR and MRI kidney and liver volume measurements will be done centrally by personnel blinded for treatment allocation).

Furthermore, the primary outcome is change in kidney function from 12 weeks after the start of treatment, instead of from randomization. This is done because in the first 3 months during treatment, dose adjustments of lanreotide and/or antihypertensive drugs may be needed, which may induce acute renal hemodynamic effects that may compromise an accurate assessment of eGFR slope.[57] However, a necessary assumption for this end point to be valid is that changes in eGFR during the first 12 weeks after randomization are fully reversible during the 12 weeks after discontinuation of the drug, after completion of the intervention. We cannot prove this assumption until the trial has finished. Therefore, after completion of the trial, this will be studied extensively, and in case the change in eGFR is not fully reversible, our primary end point requires support by one or more secondary kidney end points.

Another limitation is that kidney function will be estimated and not measured, potentially inducing more variability. However, serial measurement of kidney function in 300 patients with ADPKD in 4 different centers is not feasible, and it recently has been shown that measured GFR and eGFR in ADPKD are highly correlated.[58] Finally, in this study, total kidney volume will be measured using MRI, a method that is well validated.[4,14]

In conclusion, to our knowledge, the DIPAK 1 Study is the first larger scale clinical study that will investigate the efficacy of somatostatin analogue on attenuation of kidney function decline in ADPKD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Box 1

Eligibility Criteria of the DIPAK 1 Study

Inclusion criteria

- Diagnosis of ADPKD, based on modified Ravine criteria[23]
- Age 18-60 years
- $eGFR_{MDRD}$ of 30-60 mL/min/1.73 m^2
- Providing informed consent

Exclusion criteria

- Patients who, in opinion of study investigator, may present a safety risk
- Patients who are unlikely to adequately adhere to trial's procedures (due, eg, to medical conditions likely to require an extended interruption or discontinuation, history of substance abuse or nonadherence)
- Patients taking medications likely to confound end point assessments (eg, long-term nonsteroidal anti-inflammatory drug, cyclosporine, lithium, immunosuppressant use)
- Patients having other systemic diseases that have potential to influence kidney function (eg, systemic lupus erythematosus, diabetes mellitus requiring treatment, and proteinuria > 1 g/24 h)
- Patients who underwent surgical or drainage interventions for cystic kidney disease the year before study entry or are likely candidates for these procedures within 2 y of start of study (eg, a patient who had previous successful cyst reduction surgery and now pain attributed to 1 dominant cyst)
- Patients taking other experimental (ie, not approved by US Food and Drug Administration or European Medicines Agency for indication of ADPKD) therapies aimed at attenuating disease progression in ADPKD
- Patients having used lanreotide (or other somatostatin analogue) in 3 mo before study start
- Patients with known intolerance of lanreotide (or other somatostatin analogue)
- Patient's unwillingness to adhere to reproductive precautions; women who are capable of becoming pregnant must be willing to adhere to approved birth control from 2 wk prior to and 60 d after taking investigational product
- Women who are pregnant or breastfeeding
- Patients who have cardiac arrhythmias that are thought to be dangerous in combination with lanreotide administration
- Patients who ever had symptomatic gallstones and did not undergo cholecystectomy

- Patients who have a medical history of pancreatitis

Note: Patients having contraindications to or interference with magnetic resonance imaging assessments can enter the study, but will not be assessed for change in kidney and/or liver volume.

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; DIPAK, Developing Interventions to Halt Progression of ADPKD; $eGFR_{MDRD}$, estimated glomerular filtration rate calculated by Modification of Diet in Renal Disease Study equation.

Box 2

Primary and Secondary End Points in the DIPAK 1 Study

Primary End Point

Rate of change in kidney function for lanreotide-treated vs control patients (ie, the slope through serial eGFR values over time during treatment phase of study, where value obtained at week 12 is used as first eGFR for slope analysis and only eGFR values prior to end-stage kidney disease or death are taken into account).

Secondary End Points

Kidney function

1. Change in kidney function, assessed as pretreatment eGFR (average of at screening visit and at BV) vs eGFR 12 wk after cessation of treatment (obtained at F/U visit)
2. Incidence of confirmed 30% decrease in eGFR and/or need for kidney replacement therapy computed from pretreatment

Kidney volume

- Change in total kidney volume (by MRI) as assessed at BV before start of treatment vs value obtained 12 wk after cessation of treatment (obtained at F/U visit)

Liver

- Change in total liver volume (by MRI) in subset of participants with moderate to severe polycystic liver disease (defined as liver volume ≥ 2,000 mL), as assessed at BV vs value obtained 12 wk after cessation of treatment (at F/U visit)

Quality of life

- Change in quality of life as assessed at BV vs value obtained 12 wk after cessation of treatment (obtained at F/U visit)

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; BV, baseline visit before start of treatment; DIPAK, Developing Interventions to Halt Progression of ADPKD; eGFR, estimated glomerular filtration rate; F/U, follow-up; MRI, magnetic resonance imaging.

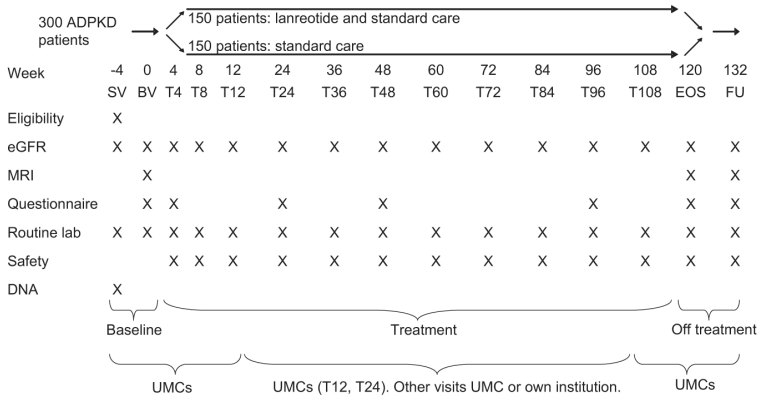

Figure 1.

Trial design of the DIPAK (Developing Interventions to Halt Progression of ADPKD) 1 Study. Abbreviations: ADPKD, auto-somal dominant polycystic kidney disease; BV, baseline visit before start of treatment; eGFR, estimated glomerular filtration rate; EOS, end-of-study; FU, follow-up; lab, laboratory; MRI, magnetic resonance imaging; SV, screenings visit; UMC, University Medical Center.

Table 1

Specified Flow Chart of the DIPAK 1 Study

	SV	BV	T1	T4	T8	T12	T24	T36	T48	T60	T72	T84	T96	T108	EOS	F/U	EET
Week	−4	0	1	4	8	12	24	36	48	60	72	84	96	108	120	132	NA
Time window[a]	NA	≤4 wk after SV	±1 d	±4 d	±4 d	±4 d	±1 wk	±1 wk	±1 wk	±2 wk	±2 wk	±2 wk	±2 wk	±2 wk	±2 wk	±1 wk	NA
Activity																	
Demographics	X																
Informed consent	X																
Inclusion & exclusion criteria	X	X[b]															
Medical history[c]	X																
Questionnaire		X				X			X				X		X	X	X
Physical examination	X					X			X				X		X	X	X
Vital signs	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
MRI[d]		X													X	X	X
Randomization		X															
Study completion																X	
Concomitant medication	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study medication summary			X	X	X	X	X	X	X	X	X	X	X	X	X		X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; BV, baseline visit before start of treatment; DIPAK, Developing Interventions to Halt Progression of ADPKD; EET, early end of treatment; eGFR, estimated glomerular filtration rate; EOS, end-of-study; F/U, follow-up; MRI, magnetic resonance imaging; NA, not applicable; SV, screenings visit; Tx, week x of the trial.

[a] From BV or date of approved MRI (whichever comes last), for F/U from EOS.

[b] Only pregnancy test in women with childbearing potential.

[c] ADPKD related, risk factors, other current and past.

[d] BV: −8 days until +4 days after BV; EOS/EET/F/U: −8 days from visit.