
Supplement 1. Trial protocol

This supplementary material has been provided by the authors to give readers additional information about their work.
The DIPAK 1 Study

A randomised, controlled clinical trial assessing the efficacy of Lanreotide to halt disease progression in ADPKD
PROTOCOL TITLE:
A randomised, controlled, clinical trial investigating the efficacy of Lanreotide to halt
disease progression in ADPKD

Short title  The DIPAK 1 study
Version  4.9
Date  April, 2017

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<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>ABR</td>
<td>ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)</td>
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<tr>
<td>ACE</td>
<td>Angiotensin converting enzyme</td>
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<tr>
<td>ADPKD</td>
<td>Autosomal Dominant Polycystic Kidney Disease</td>
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<tr>
<td>AE</td>
<td>Adverse Event</td>
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<td>AR</td>
<td>Adverse Reaction</td>
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<td>ARB</td>
<td>Angiotensin receptor blocker</td>
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<tr>
<td>BSA</td>
<td>Body Surface Area</td>
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<td>CA</td>
<td>Competent Authority</td>
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<td>cAMP</td>
<td>Cyclic AMP</td>
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<td>CCMO</td>
<td>Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek</td>
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<td>CV</td>
<td>Curriculum Vitae</td>
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<td>DIPAK</td>
<td>Developing Interventions to halt Progression of Autosomal dominant polycystic Kidney disease</td>
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<tr>
<td>DSMB</td>
<td>Data Safety Monitoring Board</td>
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<tr>
<td>eGFR</td>
<td>Estimated Glomerular Filtration Rate</td>
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<td>EU</td>
<td>European Union</td>
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<td>EudraCT</td>
<td>European drug regulatory affairs Clinical Trials</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>IB</td>
<td>Investigator’s Brochure</td>
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<td>IC</td>
<td>Informed Consent</td>
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<td>IMP</td>
<td>Investigational Medicinal Product</td>
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<td>IMPD</td>
<td>Investigational Medicinal Product Dossier</td>
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<td>MDRD</td>
<td>Modification in Diet in Renal Disease</td>
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<td>METC</td>
<td>Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<td>mTOR</td>
<td>Mammalian target of rapamycin</td>
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<td>Pkd1/2</td>
<td>Polycystic kidney disease gene mutation 1/2</td>
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<td>(S)AE</td>
<td>(Serious) Adverse Event</td>
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<td>s.c.</td>
<td>subcutaneous</td>
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<td>SPC</td>
<td>Summary of Product Characteristics (in Dutch: officiele productinformatie IB1-tekst)</td>
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<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
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<td>TCC</td>
<td>Trial Coordination Center</td>
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<td>UMC</td>
<td>University Medical Center</td>
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<td>V2RA</td>
<td>V2 receptor antagonist</td>
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<td>Wbp</td>
<td>Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)</td>
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<tr>
<td>WMO</td>
<td>Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)</td>
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SUMMARY

Rationale:
Autosomal dominant polycystic kidney disease (ADPKD) is characterized by progressive
cyst formation in both kidneys, in most patients leading to end stage renal disease. It is
the most common hereditary disease, with a prevalence rate of 1 in 400 to 1 in 1,000
persons. The majority of patients also have progressive cyst formation in the liver,
leading to pain, gastrointestinal discomfort and sometimes the need for liver
transplantation. At present there is no proven therapeutic intervention to slow down
disease progression in human ADPKD. The development of renoprotective treatments
that are well tolerated, is therefore of major importance.

In this respect, somatostatin analogues are promising for especially polycystic liver
disease, but also for the renal phenotype. However, the studies that have been
performed thus far, were underpowered and of too short duration to reach a definitive
conclusion on the potential reno- and hepatoprotective efficacy of somatostatin
analogues. Therefore, the present study is designed as an investigator driven relatively
large scale randomised clinical trial with sufficient duration of follow-up to investigate
whether the somatostatin analogue Lanreotide slows progression of polycystic kidney
and liver disease in ADPKD-patients.

Objectives: First, to demonstrate whether Lanreotide attenuates progression of the renal
phenotype in ADPKD patients as measured by change in rate of renal function decline
and change in renal volume growth. Second, to demonstrate whether Lanreotide modifies
progression of the liver phenotype in the subset of ADPKD patients with moderate to
severe polycystic liver disease as measured by change in liver volume.

Study design: Randomized, multi-center, controlled clinical trial.

Study population: 300 subjects, diagnosed with ADPKD based on the revised Ravine
criteria with advanced disease and high likelihood of rapid disease progression (30 s;
eGFR s; 60 ml/min/1.73 m2 and 18 s; age s; 60 years).

Intervention: The patients will be randomized (1:1) into two groups. One group of
patients will receive a dose of Lanreotide120 mg sc every 28 days for 30 months. The
dose of Lanreotide is egFR (BSA unadjusted) dependent. Subjects that reach an egFR
<30ml/min during the study (assessed as two consecutive measures of an egFR < 30
ml/min) will receive Lanreotide 90 mg sc every 28 days. Downtitration will also occur in case of dose related side effects. The other group of patients will receive standard care.

**Main study endpoint:**
Change in renal function in Lanreotide versus not treated patients, as assessed as slope through serial eGFR measurements over time during the treatment phase of the trial, with the value obtained at month 3 as first eGFR value for slope analysis.

**Main secondary outcome variables**
- to demonstrate whether Lanreotide modifies ADPKD progression as measured by change in renal volume in the overall study population,
- to demonstrate whether Lanreotide modifies ADPKD progression as measured by change in liver volume in the subset of ADPKD patients with moderate to severe polycystic liver disease
- to demonstrate whether Lanreotide changes the quality of life
- to demonstrate whether Lanreotide is well tolerated

**Nature and extent of the burden and risks associated with participation, and potential benefits:**
When compared to routine clinical care the burden and risk associated with participation are:
- In general ADPKD patients with more advanced renal disease visit an out-patient department once every 3 months routinely. Therefore this study imposes at least 4 extra visits to an outpatient department planned (screening, baseline, month 1 and 2)
- For patients that are treated outside the participating UMCs hospital study visits to the UMCs may lead to extra travel time.
- In general ADPKD patients with more advanced renal disease when visiting an out-patient department collect a spot urine and blood is drawn for routine clinical chemistry. During the baseline visit extra blood will be drawn for biobanking and at each visit to the out-patient department 1 extra serum tube will collected and sent to the central laboratory for post-study central assessment of creatinine and cystatin C.
- 3 times a MRI of liver and kidneys
- 6 times a questionnaire
- half of the patients will be exposed to the somatostatin analogue Lanreotide.
The potential benefit for participating subjects are that Lanreotide may slow down the progression of ADPKD, thus reducing the rate of renal function deterioration, thereby potentially postponing the need for renal replacement therapy, and inducing less cyst growth, thereby potentially leading to less complaints that are related to cyst size and abdominal distension (e.g. abdominal pain, early satiety and dyspnoea).
1. INTRODUCTION AND RATIONALE

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common renal hereditary disease\(^1\). ADPKD is a systemic disorder characterised by progressive cyst formation in both kidneys, with progressive kidney enlargement often leading to end stage renal disease between the 4\(^{th}\) and 7\(^{th}\) decade of life. Consequently these ADPKD patients will need renal replacement therapy. Approximately 10\% of all patients undergoing renal replacement therapy are ADPKD patients\(^2\). Other kidney symptoms include pain, hypertension, gross hematuria, nephrolithiasis and mild albuminuria\(^2\). There are also extrarenal manifestations, such as hypertension and cerebral aneurysms.

Progressive cyst formation is found in the liver, with a prevalence of 95\% by the age of 35-45 years\(^1\). Symptoms in polycystic liver arise from enlarged volume and include abdominal distension, early satiety, dyspnea, and pain. In addition, polycystic liver may be complicated by cyst bleeding, infection, and/or rupture. Liver symptoms may be particularly severe in older patients who survived long enough to progress to end-stage renal disease and need renal replacement therapy\(^1\). In a limited number of cases liver transplantation is necessary.

In 90\% of cases the disease is caused by a mutation in the \(Pkd1\) gene (located at chromosome 16) and in 10\% of cases by a mutation in the \(Pkd2\) gene (located at chromosome 4)\(^3\). Although there are a large number of mutations known, these all lead to more or less the same phenotype. However, there is a difference in rate of disease progression between \(Pkd1\) and \(Pkd2\), with subjects with \(Pkd1\) mutations reaching end-stage renal disease in general at a younger age when compared to subjects with \(Pkd2\) mutations\(^4\). Furthermore, there are remarkable differences in rate of disease progression between families with a similar mutation, and even within affected families\(^5\). Known predictors so far of a more rapid disease progression are amongst others, total kidney volume, renal blood flow and albuminuria.

Current therapies are directed towards limiting morbidity and mortality from complications of ADPKD, but not specifically targeting the inhibition of cyst formation or renal function decline, since at present there is no proven therapeutic intervention to slow down disease progression in human ADPKD\(^6,7\). The development of renoprotective treatments is therefore of major importance for patients with ADPKD, as well for the community at large, since the costs involved with renal replacement therapy (including hemodialysis and transplantation) pose a high burden on health care costs.
Recent advances in the knowledge on the pathophysiological mechanism underlying the cellular abnormalities in ADPKD have led to the identification of several potential therapeutic targets. Animal experiments showed various classes of drugs directed at these targets to be indeed renoprotective. Three of these classes have been, or are tested in clinical trials: mTOR inhibitors, vasopressin V2 receptor (V2R) antagonists and somatostatin analogues.\(^6,7\)

The mammalian target of rapamycin (mTOR) is aberrantly activated in cystic epithelia in patients with ADPKD.\(^8\) Sirolimus inhibits mTOR, and in an orthologous mouse model of ADPKD\(^9\) and in other rodent models of polycystic kidney disease, sirolimus significantly improved renal cystic disease.\(^10\) Despite these encouraging in vivo data, two trials with mTOR inhibitors recently failed to show a beneficial effect on change in renal function and renal volume in early and later ADPKD.\(^11,12\)

The other two potential treatment options are based on regulating abnormal cyclic-AMP (cAMP) levels in cyst-lining epithelial cells. The abnormal cAMP levels are a consequence of reduced cytoplasmic Ca\(^{2+}\)-levels due to a defect in the regulation of calcium release from intracellular stores by the polycystin proteins.\(^13\) In renal tubular epithelial cells, intracellular calcium limits cAMP accumulation by inhibiting adenylyl cyclase and possibly by activating Ca\(^{2+}\)-dependent phosphodiesterase. cAMP stimulates chloride-driven fluid secretion and in conditions of calcium deprivation, as in PKD, it stimulates cell proliferation, thereby causing two important aspects of cyst formation: fluid accumulation and cell proliferation.\(^14\) One of the strategies to target these processes is to reduce production of cAMP. This can be done by stimulating inhibition of adenylyl cyclase by vasopressin V2 receptor (V2R) antagonists and somatostatin analogues.\(^15,16\)

As yet clinical trials are ongoing with the V2R-antagonist Tolvaptan and somatostatin analogues.\(^16,17,18\) The V2R antagonist is promising, but is likely to be only effective on cysts derived from the distal part of the nephron.\(^6\) It has been suggested that in ADPKD renal cysts may also originate from other parts of the nephron.\(^19\) V2R-antagonists are not expected to reduce the growth of these cysts, and furthermore not of liver cysts, because proximal nephron and liver cells lack V2R-receptors.\(^6\) In addition, we recently found in a Pkd1- mutant mouse model that a V2R-antagonist was effective in delaying disease progression when given in the early stage of ADPKD, but less effective in later stage ADPKD.\(^20\) A recent post-hoc analysis of two open-label studies with the V2R-antagonists, with matched untreated control subjects from historical ADPKD cohorts, also suggested renoprotection, but, in line with our experimental data, decreased renoprotection in later
stages of ADPKD\textsuperscript{16}. Lastly, there are undesirable side effects to V2R-antagonism (thirst, polydypsia, polyuria, nycturia and consequently disturbed night rest) that may limit their wide spread clinical use. Because of the three aforementioned reasons there will be a need for alternative therapeutic options, such as somatostatin analogues, even when V2R-antagonists will be proven renoprotective. As yet three small scale studies, with relatively short duration of follow-up have been performed with somatostatin analogues.

Ruggenenti et al\textsuperscript{16} performed a randomised, cross-over study comparing the effect of a 6 months treatment regime of octreotide administered in the normal clinical dose of 40 mg i.m. once every 28 days with no treatment in 14 ADPKD patients (mean baseline GFR 57.1 mL/min, range 24.4 - 95.3 mL/min). GFR, measured as iohexol clearance, did not change significantly during both treatment periods. Total kidney volume increased significantly by 71±107ml (p<0.05) and 162±114ml (p<0.01) in octreotide versus not treated patients, respectively. Consequently, there was a 60% reduction in kidney volume increase in the octreotide group (p<0.05).

Van Keimpema from the group of prof. Drenth (Radboud UMC Nijmegen, member of the Steering Committee of the present study) performed a randomised clinical study with a 6 months regimen of Lanreotide, administered in the normal clinical dose of 120 mg once every 28 days subcutaneously, in 54 patients with polycystic liver disease, of which 32 patients had ADPKD and the remainder non-ADPKD polycystic liver disease.\textsuperscript{21} Total liver volume decreased significantly in Lanreotide as compared to placebo treated patients in the overall study population, as well as in the ADPKD patients specifically (both p<0.01). In the ADPKD subjects, total kidney volume decreased 1.5% in the Lanreotide group and increased 3.4% in the not treated group. Again, this treatment induced difference in kidney volume change was statistically significant (p<0.02). Lanreotide treatment decreased serum creatinine levels, and this decrease was nearly significant versus controls (p=0.079). In addition, at 6 months Lanreotide improved general healthy perception.

Lastly, Hogan from the group of prof. Torres (Mayo Clinics, Rochester, USA, member of the Steering Committee of the present study) randomised 42 patients with polycystic liver disease (of which 34 had ADPKD) to 12 months treatment with the long-lasting somatostatin analogue octreotide or to placebo (2:1). Baseline GFR was 71 (range 20-124) mL/min/1.73m\textsuperscript{2}. Total liver volume decreased 4.95% in the octreotide group compared with an increase 0.92% in the placebo group. This difference in change in total liver volume was significant (p=0.048). Among ADPKD patients, total kidney volume
remained practically unchanged in octreotide treated patients (+0.25%) but increased significantly in non-treated patients (+8.61%). Consequently, kidney growth rate was significantly reduced in the octreotide group when compared to non-treated patients (p=0.045). GFR decreased 5.1% and 7.2% in the octreotide and the non-treated patients, respectively (NS)

Recent clinical studies indicate therefore that somatostatin analogues are promising for especially polycystic liver disease, but the studies that have been performed, among which two by members of the Steering Committee of this study, were underpowered (12 to 54 patients) and of too short duration (6 to 12 months) to reach a definitive conclusion on their possible renoprotective efficacy. As yet only two trials are ongoing with these compounds in ADPKD patients (n=42 directed at liver volume and n=78 directed at CT derived intermediate renal volume). Although these trials are important, they include a relatively small number of subjects, and consequently, they are not expected to provide a definite answer whether somatostatin analogues should be standard care for ADPKD patients.

We therefore aim to validate a possible therapeutic intervention in a relatively large scale randomized controlled trial with the somatostatin analogue Lanreotide versus standard care, including 300 ADPKD patients with advanced disease and high likelihood of disease progression (30 s; eGFR s; 60 ml/min/1.73 m² and 18 s; age s; 60 years).

2. OBJECTIVES
1) To demonstrate whether Lanreotide modifies progression of the renal phenotype in ADPKD patients as measured by change in rate of renal function decline and kidney volume growth.
2) To demonstrate whether Lanreotide modifies progression of the liver phenotype in the subset of ADPKD patients with moderate to severe polycystic liver disease as measured by change in rate of liver volume growth.
3. STUDY DESIGN

This study is designed as a multi-center, randomised, controlled, parallel-arm study in subjects with ADPKD and impaired renal function. Subjects meeting the entry criteria and completing baseline assessments will be enrolled by the 4 participating University Medical Centers. Patients will be drawn from the outpatient departments of these UMCs and of affiliated hospitals, that will refer patients meeting the eligibility criteria. Central coordination of this study will be performed by the UMC Groningen, and for the liver phenotype by the UMC Nijmegen. For a schedule of visits and timing of assessments, we refer to the study diagram.

After having obtained informed consent, eligibility will be assessed at a screening visit (SV). Because renal function estimation can be variable in some patients, in certain cases a secondary screening visit can take place. If renal function at screening visit is just below 30 (and not lower than 25) ml/min per 1.73 m² or just above 60 (and not higher than 65) ml/min per 1.73 m² and in the 3 months before screening visit there is an eGFR measurement 2: 30 and s;60 ml/min per 1.73 m² and the investigator is in the opinion that estimated GFR can be 2:30 and s;60 ml/min per 1.73 m² at the next visit, a secondary screening visit may be conducted for repeat measurement of estimated GFR and determine eligibility for the study. If this is the case, values of that second screening visit will be used. Subjects will visit the outpatient department for the baseline visit (BV) of the study within 1 month after their screening visit. Subjects will be randomized into 2 groups, with stratification for screening eGFR (<45 and 2: 45 ml/min per 1.73 m²), gender (male / female) and age (<45 and 2: 45 years). Subjects are evaluated at week 4 (T4), week 8 (T8), week 12 (T12) and every 3 months thereafter until the end of the trial (end of treatment visit scheduled to be at month 30, or earlier in case of premature withdrawal, ET). Of note, one month is defined as 28 days (being a 4-week period). Time window for visits T4, T8 and T12 is ±4 days, for T24, T36 and T48 and FU visits ±1 week, for visits T60, T72, T84, T96, T108 and EOS ±2 weeks. These time windows are calculated from baseline or date of approved MRI, which ever comes last. One week after approved MRI (performed close to the baseline visit), the patient will receive a phone call to assess adverse events. Time window for the first injection will be within working 5 days after approved MRI. After that, lanreotide injections will be administered every 28 days, always after the planned visit (window for following injections: +5 working days after the visit). The last dose of Lanreotide will be given at month 29. Subjects will be seen 12 weeks after the end of the trial for a follow-up visit (FU). During each visit concomitant medication, use of study medication, adverse events will be assessed, blood will be drawn (fasting at specific visits) to assess eGFR and safety endpoints. At specific visits,
subjects will be asked about pain attributed to their kidneys and their liver (on a 0-10 Visual Analogue Scale, and by specific questionnaires). Furthermore, an extensive physical examination will be performed yearly and before and after study medication use. In case a subject continues study participation, but treatment ends, an end of treatment visit (ET) will be performed within 1 week after the next injection should be administered (same assessments will be performed as EOS visit) and subject will continue regular study visits.

Please see addendum 1 for a specified flow chart of activities performed during study visits and addendum 2 for a specified flow chart of the laboratory determinations performed at each specific visit.

Blood and urine chemistry will be analyzed locally. In addition, a blood sample will be shipped to the core laboratory center for central storage (-80 Celsius) and central assessment of key efficacy variables (creatinine and cystatin C) to be done after completion of the study in 1 run per subject to minimise inter-laboratory and inter-assay variation. These centrally assessed laboratory variables will be used for the efficacy analyses. Of note, having blood samples at room temperature for up to 4 days does not influence creatinine\textsuperscript{27} and cystatin C concentration, nor has frozen storage at -80 Celsius during prolonged periods of time.\textsuperscript{28} In addition, of all subjects all eGFR measurements in the period of 3 years before the trial will be collected with a maximum of 1 representative measurement every 3 months (so 12 maximum) in case of availability. At the baseline visit, at the of the treatment phase of the study (month 30 or at early termination ± 8 days from visit) and at the follow-up visit (3 month after end of the treatment phase and ± 8 days from visit) magnetic resonance imaging (MRI) will be performed, using standardized procedures. MRI endpoint data will be analyzed and read centrally at the department of Radiology of the UMC Groningen.

Lastly, blood samples collected at the baseline visit will be used for eventual DNA diagnostics, e.g. PKD1/PKD2 gene mutation.

All subjects will be seen in one of the 4 participating UMCs for their screening, baseline, month 1, month 2, month 3, month 12, month 24, end of study (month 30 or at early termination) and follow-up visit. The remainder of study visits can take place in these UMCs, or in the affiliated hospitals that referred the subject (decision at the discretion of the treating physician). A web-based electronic CRF will be designed to enter study data to ensure correct and timely data collection in a central database. UMC hospital visits will
be centrally coordinated by the Central Study Coordinator and monitored and audited by monitors of the Trial Coordination Center (TCC) of the UMC Groningen.

The dose of Lanreotide during the study will be eGFR (BSA unadjusted) dependent. Subjects that reach an eGFR <30ml/min (assessed as two consecutive measures of an eGFR < 30ml/min) during the study will receive Lanreotide 90 mg sc every 28 days. Subjects suffering of intolerable side effects will also have their medication dose adjusted (120 mg --- 90 mg --- 60 --- 0 mg). Lanreotide will be administered and registered by trained nurses. In exceptional cases, if administration by a nurse will cause logistic problems, partners or patients themselves can be trained to perform the injections themselves. Safety assessments will consist of monitoring and recording all adverse events, including serious adverse events.

4. STUDY POPULATION

4.1 Population
For this study a total of 300 subjects with ADPKD and meeting the eligibility criteria will be enrolled. Inclusion criteria

1. Diagnosis of ADPKD, based upon the modified Ravine criteria (paragraph 10.4), or documented by their nephrologist or internist
2. 18 s; Age s; 60 years.
3. 30 s; eGFR (MDRD) s; 60 mL/min/1.73 m2
4. Providing informed consent.

4.2 Exclusion criteria
1. Patients who, in the opinion of the study investigator may present a safety risk.
2. Patients who are unlikely to adequately comply with the trial’s procedures (due for instance to medical conditions likely to require an extended interruption or discontinuation, history of substance abuse or noncompliance).
3. a. Patients taking medications likely to confound endpoint assessments (e.g. nephrotoxic medications such as chronic NSAID, cyclosporine, lithium immunosuppressant use)
3. b. Patients having concomitant illnesses likely to confound endpoint assessments (e.g. diabetes mellitus for which medication is needed and patients with proteinuria > 1 g /24hr).
4. 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 years of start of the study.

5. Patients taking other experimental (i.e., not approved by FDA/EMA for indication of ADPKD) therapies.

6. Patients having used Lanreotide (or another somatostatin analogue) in the 3 months before study start.

7. Patients known with intolerance for Lanreotide (or another somatostatin analogue).

8. Unwillingness to comply with reproductive precautions. Women who are capable of becoming pregnant must be willing to comply with approved birth control from two-weeks prior to, and for 60 days after taking investigational product.

9. Women, who are pregnant or breastfeeding.

10. Patients, who suffer from cardiac arrhythmia's, that are thought to be dangerous in combination with lanreotide administration.

11. Patients, who ever suffered from symptomatic gallstones and did not undergo cholecystectomy.

12. Patients, who have a medical history of pancreatitis.

13. Patients, who have a medical history of infected liver cysts

**In addition:**

A. Patients, who underwent liver cyst drainage or surgery in the year before, can enter the study, but will not be assessed for change in liver volume.

B. Patients having contraindications to, or interference with MRI assessments, as dictated by local regulation, will not be allowed to undergo MR imaging. However, these patients can enter the study, but will not be assessed for change in kidney and/or liver volume.

### 4.3 Sample size calculation

In a cohort of ADPKD patients participating in the MDRD Study (baseline GFR between 55-25 mL/min) mean slope of GFR decline on treatment was 5.1 mL/min/yr with a standard deviation of 4.2. In the recent Everolimus ADPKD Study (baseline eGFR 90-30 mL/min/1.73m²) the mean change in eGFR was 4.2 mL/min/1.73m² with a similar standard deviation of 4.3. Annual slope of eGFR in this study is expected to be similar to the MDRD Study and higher than in the Everolimus ADPKD Study since in the present study only subjects with already impaired renal function will be included (baseline eGFR between 60-30 mL/min). Assuming an average change in eGFR of 5.1 mL/min/1.73 m²/yr
in untreated patients, an average 30% reduction in rate of renal function loss deemed clinically significant, 80% power to detect this difference and a two-sided alpha of 0.05, then approximately 123 subjects per study group are needed. Taking into account the possibility of 20% protocol violators and/or dropouts, inclusion of 150 subjects per group is aimed. About 300 subjects will therefore need to be enrolled in the trial.
5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment
Lanreotide is a synthetic peptide analogue of natural somatostatin, with a stronger and longer lasting effect than natural somatostatin. At 6 hours after subcutaneous administration the maximum blood level is expected and the half-time is 33 days. Lanreotide inhibits the secretion of growth hormone and peptides from the endocrine system of the gastrointestinal tract and pancreas. In the European Union and the United States, Lanreotide is approved for acromegaly, for normalizing the secretion of growth hormone pre or post surgical interventions and/or radiotherapy. Secondly, for the treatment of carcinoid. Tertiary, for thyrotropic adenoma, when surgical intervention is not feasible or successful. For more information, please see also paragraph 6.

5.2 Use of co-intervention
Subjects are not allowed to participate in other (experimental) trials investigating pharmaceutical agents or strategies aimed at intervening with the natural disease course of ADPKD. Recommendation for dietary restrictions (such as restrictions for salt, protein and caffeine) is left to the discretion of the investigator, as these have not been proven unequivocally efficacious. Subjects with hypertension (defined as a diastolic blood pressure $\geq 90$ mmHg and/or a systolic blood pressure $\geq 140$ mmHg) will be treated with ACE inhibitors as first choice agents. In case of intolerance of ACE inhibitors, angiotensin receptor blockers will be prescribed. Although these two classes of blood pressure lowering agents have not been shown to alter the disease course of ADPKD, they are in clinical practice regarded as first choice agents in hypertensive subjects with chronic kidney disease, also in subjects with ADPKD. In case of hypertension despite the use of these agents, the choice of additional antihypertensive medication is left at the discretion of the treating physician. It is advised that subjects with an eGFR $< 45$ mL/min/1.73 m$^2$ and an elevated LDL ($> 2.6$ mmol/L) should be treated with a statin. The decision to do so is, however, left at the discretion of the treating physician. In case of complaints of loose, pale or fatty stools that do not recover spontaneously, and that persist after the first injection, pancreatic enzymes may be prescribed to improve these symptoms. 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 female ADPKD patients. The decision to do prescribe these drugs is, however, left to the discretion of the treating physician. Similarly, dietary advices (reduction in sodium, caffeine and protein intake, and increase in water intake) are left to the discretion of the treating physician, as
dietary interventions have yet not proven efficacious to ameliorate the rate of disease progression in ADPKD.

5.3 Escape medication
Since as yet no medication is known to alter the disease course of ADPKD the use of escape medication is not applicable.
6. INVESTIGATIONAL MEDICINAL PRODUCT

6.1 Name and description of investigational medicinal product(s)
Lanreotide (INN) acetate: [cyclo S-S]-3-(2-naphthyl)-D-alanyl-L-cysteinyl-L-tyrosyl-
D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-L-threoninamide, acetate is an intramuscular or
subcutaneously administered octapeptide analogue of somatostatin. Lanreotide has been
developed as a treatment for acromegaly to relieve clinical symptoms. It achieves its
effect by inhibiting growth hormone secretion and controlling serum concentrations of
growth hormone and insulin-like growth factor (IGF-1). It has also been investigated as
treatment for patients with carcinoid neuroendocrine tumours, thyrotropic adenoma and
polycystic liver disease. In the Netherlands Lanreotide has been approved for the
treatment of acromegaly, carcinoid tumors and thyreotropopid adenoma.

6.2 Summary of findings from non-clinical studies
Please find a summary of findings from non-clinical studies in the investigator's brochure.

6.3 Summary of findings from clinical studies
Recently, three relatively small scale studies of short duration investigated the effects of
the somatostatin analogues Lanreotide and octreotide in ADPKD.

Ruggenenti et al\textsuperscript{16} performed a randomised, cross-over study comparing the effect a 6
months treatment regime of octreotide administered in the normal clinical dose of 40 mg
once every 28 days subcutaneously with no treatment in 14 ADPKD patients (mean
baseline GFR 57.1 mL/min, range 22.4 – 95.3 mL/min). The total volume of both kidneys,
and that of the renal parenchyma and of cysts separately, were assessed by CT-
scanning and were evaluated and measured every 6 months. GFR, measured as iohexol
clearance) did not change significantly during both treatment periods. Total kidney
volume increased significantly by 71 ± 107ml (p<0.05) and 162 ±114ml (p<0.01) in
octreotide versus not treated patients, respectively. Consequently, there was a 60%
reduction in volume increase in the octreotide group (p<0.05). Furthermore, the use of
octreotide was safe and well tolerated in this study. One patient was withdrawn because
of non-symptomatic gallstones detected on a routine abdominal ultrasound. Watery
diarrhea was reported in three patients and spontaneously recovered in all within the first
month of treatment. There was a transient and marginal increase in alanine
aminotransferase levels in two patients on somatostatin and in one patient on placebo.
These abnormalities disappeared spontaneously within 1 or 2 months. In a post-hoc
analysis of the above study\textsuperscript{23}, it was shown that total liver volume also decreased significantly with octreotide treatment as compared with no treatment.

Van Keimpema from the group of prof. Drenth (Radboud UMC Nijmegen, member of the Steering Committee of the present study) performed a randomised clinical study with a 6 months regimen of Lanreotide, administered in the normal clinical dose of 120 mg once every 28 days subcutaneously, in 54 patients with polycystic liver disease, of which 32 patients had ADPKD and the remainder non-ADPKD polycystic liver disease\textsuperscript{21}. Total liver volume decreased significantly in Lanreotide as compared to placebo treated patients in the overall study population, as well as in the ADPKD patients specifically (both $p<0.01$). This beneficial effect was greater in subjects with large compared to small livers at baseline ($p<0.032$). In the ADPKD subjects total kidney volume decreased 1.5\% in the Lanreotide group and increased 3.4\% in the not treated group. Again, this treatment induced difference in kidney volume change was statistically significant ($p<0.02$).

Lanreotide treatment decreased serum creatinine levels, and this decrease was nearly significant versus control ($p=0.079$). Also, at 6 months, Lanreotide improved general healthy perception and no severe adverse events related to study medication. The most common adverse effect consisted of loose, pale, and fatty stools (19 patients), which typically started 24 hours after first injection of Lanreotide and lasted for 1-4 days, where after there was a spontaneous recovery in most patients. Because of ongoing symptoms six patients were treated with pancreatic enzymes, which readily improved these symptoms. Thirteen patients (48\%) on Lanreotide reported nodules on the injection site. No patient stopped study medication during the trial.

Lastly, Hogan from the group of prof. Torres (Mayo Clinics, Rochester, USA, member of the Steering Committee of the present study) randomised 42 patients with polycystic liver disease (of which 34 had ADPKD) to 12 months treatment with the long-lasting somatostatin analogue octreotide in the normal clinical dose of 40 mg sc every 28 days or to placebo (2:1)\textsuperscript{22}. Baseline GFR was 71 (range 20-124) mL/min/1.73m$^2$. Total liver volume decreased 4.95\% in the octreotide group compared with an increase 0.92\% in the placebo group. This difference in change in total liver volume was significant ($p=0.048$). Among ADPKD patients total kidney volume remained practically unchanged in octreotide treated patients (+0.25\%) but increased significantly in non-treated patients (+8.61\%). Consequently, growth rate was significantly reduced in the octreotide group when compared to non-treated patients ($p=0.045$). GFR decreased 5.1\% and 7.2\% in the octreotide and placebo group, respectively (NS). No significant change in health-related quality of life was measured in the octreotide group. The target dose was reached in 41
(97%) of 42 patients. The commonest reported side effect was injection site pain: 75% compared with 21% on placebo. Injection site granulomas were reported in 5 of 28 patients receiving octreotide, with no occurrence in the placebo group. Diarrhea grade 1 (an increase of less than four stools per day over baseline) was reported in 61%, and abdominal cramping, bloating, and gas in 50% of patients in the octreotide arm compared with 28% and 21%, respectively, in the placebo arm and resolved in most cases spontaneously. One patient on octreotide developed steatorrhea and weight loss. Despite withholding four doses and later recommencement of 20 mg while on pancreatic supplements, his symptoms persisted. Because he completed the 12 months in the study, his data were included in the analysis. Asymptomatic nonobstructing cholelithiasis was identified in one patient, and another had gallbladder sludge. Both findings were present before assignment to octreotide and remained clinically stable on therapy. One patient developed moderate alopecia after three full doses. Octreotide was held for 2 months for hair regrowth and then restarted 20 mg for 1 month and increased to 30 mg until completion with minimal hair loss. One patient receiving octreotide developed symptomatic bradycardia requiring an emergency room visit after her sixth 40-mg dose. One dose was held, and then the participant was recommenced on 20 mg for 5 months and then increased to 30 mg. No patient receiving placebo required a dose reduction. Over the 1-year study period, three patients receiving octreotide were hospitalized, all three for causes deemed unrelated to the study intervention (bacteremia associated with nephrolithiasis and a urinary infection, abdominal pain and fever responding to antibiotic treatment, and incarcerated abdominal hernia). No serious adverse events occurred in the first year in the patients receiving placebo. Plasma glucose levels increased 10% from baseline compared with a 2% increase in placebo (P=0.02) after commencing octreotide treatment, but no patient developed diabetes. No patient stopped study medication during the trial.

In summary, the aforementioned three studies suggest that in patients with ADPKD somatostatin analogues reduce growth of liver and kidney cysts and are in general well tolerated, with all but one patient maintaining study medication. Of note, all aforementioned studies included a relatively small number of subjects and were of too short duration of follow-up to demonstrate an effect on rate of renal function decline.

6.4 Summary of known and potential risks and benefits
The paragraph above summarizes the safety profile of somatostatin analogues in patients with ADPKD specifically. In addition, the Dutch “Farmacotherapeutisch Kompas”
provides the following information on side-effects of Lanreotide that has been obtained in non-ADPKD patients. Very common (> 10%) gallstones, diarrhea, flatulence, abdominal pain, nausea, vomiting, dyspepsia, headache. Common (1-10%): reaction at the injection site, sinus bradycardia. tiredness, dizziness. hypo-and hyperglycemia, elevated bilirubin levels, anorexia. Uncommon (0.1-1%): acute pancreatitis, steatorrhea, worsening diabetes mellitus, allergic skin reactions, hair loss. Rare (0.01-0.1) episodes of depression with signs of autonomic peripheral neuropathy, persistent induration at the injection site.

During the DIPAK 1 study six cases of liver cyst infections were observed. This type of AE can be part of the natural course of ADPKD, but it should be noted that at that moment all had occurred in lanreotide treated patients. In contrast, in the aforementioned RCTs no liver cyst infections were observed in placebo, but also not in somatostatin analogue treated subjects. All patients with liver cyst infections in the DIPAK 1 study were admitted for intravenous treatment with antibiotics and recovered without sequelae. Of note, three out of six liver cyst infections occurred in subjects with a history of liver cyst infections, whereas of the approximately 150 patients that had not experienced a liver cyst infection during the study at that moment only 3 had such a history. Although a causal association with the use of lanreotide cannot be formally proven, it was deemed prudent to exclude subjects with a history of liver cyst infection(s) from participation.

There may be a benefit for the subjects participating in this study. At this moment, no therapeutic options are available for ADPKD. If Lanreotide will indeed halt renal function decline, thus attenuating renal function deterioration, renal replacement therapy can be postponed, or perhaps may even be prevented.

6.5 Description and justification of route of administration and dosage
The dosage scheme in this study is chosen, because in the pivotal "pilot" study of Keimpema et al, a dosage of 120 mg given once every 28 days subcutaneously (which is the normal dosing schedule of Lanreotide for the EMA and FDA approved indications) was effective in decreasing the rate of liver and kidney volume growth in subjects with polycystic liver disease. The Investigators Brochure of Lanreotide does not recommend dose adjustment in specific populations such as patients with impaired renal function, as expected Lanreotide serum concentrations in the special populations for which Lanreotide is registered are well within the range of serum concentrations safely tolerated.
by healthy subjects given a dose that was titrated to achieve clinical effect. However, there is only limited information on the use of Lanreotide in specific populations. One study, performed in 12 patients with severe renal failure, all being treated with hemodialysis, showed a reduction in the total serum clearance and a decrease in the initial volume of distribution of Lanreotide and therefore advised Lanreotide dose adjustment in case of severe renal function impairment\textsuperscript{22}. A similar advice is given in the US Lanreotide Drug Information. Of note, the therapeutic index of Lanreotide is broad, and there is only limited correlation between serum Lanreotide concentration and side effects. However, given the aforementioned information and the fact that in the present study patients with mild to moderate (progressive) chronic kidney disease are included, it was decided to adjust the dose to renal function. Subjects with eGFR 2:30 ml/min (BSA unadjusted) should receive Lanreotide 120 mg and subjects with confirmed eGFR <30 mL/min (BSA unadjusted) should receive Lanreotide 90 mg. In case eGFR decreases during the study from values 2:30 to <30 mL/min (assessed as two consecutive measures of an eGFR < 30 ml/min) downtitration of Lanreotide dose will take place (from 120 to 90 mg). In case of dose related side effects down titration will also be necessary. Lanreotide is administered subcutaneously. This is the usual way of administration in clinical practice and used in other studies.
7. METHODS

7.1 Study parameters/endpoints

7.1.1 Main study parameter/endpoint
The primary outcome variables will be the change in renal function as assessed as slope through serial eGFR measurements over time during the treatment phase of the study, with the value obtained at month 3 as first eGFR for slope analysis.

7.1.2 Secondary study parameters/endpoints

Renal
- Change in renal function as assessed as average baseline eGFR (the average of the screening visit (SV) and at the baseline visit (BV)) versus eGFR 3 months after cessation of treatment (obtained at the follow-up visit, FU).
- Incidence of worsening renal function, as defined as 30% decrease in eGFR and/or incidence of need for renal replacement therapy computed from the average pre-treatment eGFR (the average of the screening visit (SV) and at the baseline visit (BV)).
- Change in height adjusted total renal volume (MRI) as assessed at the baseline visit before start of treatment (BV) versus the value obtained at 3 months after cessation of treatment (obtained at the follow-up visit, FU).

Quality of life
- Change in quality of life as assessed as at the baseline visit (BV) versus the value obtained at the end-of-treatment visit (EOT).

7.1.3 Study parameters/endpoints regarding the liver phenotype

Main efficacy endpoint
- Change in height adjusted total liver volume (htLV) in the subset of patients with moderate to severe PLD (defined as total liver volume >2000 mL) calculated as percentage difference between htLV at the baseline visit (BV) and htLV at the end of treatment (EOT).

Secondary efficacy endpoints
- Change in height adjusted total liver volume (htLV) in all patients will be calculated as percentage difference between htLV at the baseline visit (BV) and htLV at the end of treatment (EOT).

- Change in htLV in the subset of patients with moderate to severe PLD (defined as liver volume >2000mL) will be calculated as percentage difference between EOT and FU.
• BV and FU.

- Change in quality of life (PLD - specific) will be determined as the absolute difference in QoL in the subset of patients with moderate to severe PLD (defined as liver volume >2000mL) between reported quality of life at BV and EOT.

7.1.4 Other study parameters

Safety variables
(Severe) adverse events, vital signs (blood pressure), physical examinations (incl. body weight and height) and clinical laboratory test results (below).

Pharmacokinetic variables
Lanreotide serum levels will be measured after completion of the trial using blood samples obtained at baseline, month 3, 12 and 24 of treatment at the UMC Nijmegen. Blood samples will be taken prior to injection for measurement of minimum Lanreotide serum levels (Cmin) with baseline as a reference and determined after completion of the study. Serum concentrations of Lanreotide will be determined using a validated radioimmunoassay method. The limit of quantification for the method is 0.078 ng/mL, and the intra- and inter-assay coefficients of variation are less than 6.0% and 9.7%, respectively. Of note, there is a poor correlation between serum Lanreotide levels and side effect profile. For this reason serum Lanreotide levels are not measured in clinical practice. For the same reason assessment of serum Lanreotide levels during the trial will not be performed during the trial for dose adjustment, but only after completion of the study, for post-hoc assessment of the association between drug blood levels and efficacy.

Pharmacodynamic efficacy variables
• Serum or plasma concentrations of creatinine, and cystatin C
• MR imaging of kidney and liver volume

Demographic information, medical history, concomitant medications

Clinical laboratory tests
Hematology: White blood cell count, haemoglobin, platelet count,
Serum chemistry: Alanine Transaminase (ALT or SGPT), Albumin, Alkaline Phosphatase (ALP), Aspartate Transaminase (AST or SGOT), Bicarbonate (every 6 months), Bilirubin
(Direct and Indirect), Urea, Calcidiol (every 6 months), Calcium, Creatinine, Gamma Glutamyl Transferase (GGT), Glucose, HbA1c (every 6 months), Parathormone (every 6 months), Phosphate, Potassium, Sodium, Uric acid, Cholesterol, HDL cholesterol, Osmolality and eGFR. In addition, serum will be stored for post-study central analysis of creatinine and cystatin C.

Urinalysis (spot): Albumin, Creatinine, Sodium, Potassium, Protein, Sediment, Urea. Urine pregnancy test (only for women of child bearing potential) will only be performed at the baseline visit. If positive, a confirmatory serum pregnancy test will be performed, and if positive, this patient will be excluded from the study.

Urinalysis (24h urine): Albumin, Creatinine, Protein, Sodium, Potassium, Urea, Phosphate, Chloride, Osmolality.

DNA-diagnostics: Blood will be drawn for DNA diagnostics to investigate genes associated with disease progression (incl. Pkd1 and Pkd2 gene mutation) and the efficacy of Lanreotide to slow down disease progression. Given the high costs associated with DNA diagnostics may only be done in case the study shows positive results (i.e. Lanreotide slows disease progression in ADPKD).

Biobanking: Blood will be drawn and urine will be stored for post-hoc studies investigating potential biomarker that can predict disease progression and treatment efficacy. More specific information can be found in the biomarker protocol.

7.2 Randomisation and treatment allocation
Subjects will be randomized 1:1 to Lanreotide SC every 28 days for 30 months or to standard care. They will be randomized to one of these two treatment groups in a stratified manner. Stratification factors will be age ≥ 45 years, sex and baseline eGFR ≥ 45 mL/min/1.73m2. Randomisation will be performed using an IVRS (interactive voice response system), which acts on secured servers at the TCC, and which is fully backed up on a daily basis.

7.3 Study procedures
For each subject, the duration of the clinical trial will be 34 months, including screening visit, baseline visit, 30 months of treatment, and a 3 months post-treatment follow-up visit. A schedule of assessments is summarized in addendum 1.

Clinical laboratory tests
The clinical laboratory tests to be performed for safety are outlined in paragraph 7.1.3. Samples for clinical laboratory assessments will be collected (some fasting, some with food intake and hydration ad libitum, depending on the visit) according to the flow chart. Creatinine based eGFR will be assessed at each outpatient clinic visit by routine measurements by local clinical chemistry laboratories. Furthermore, blood will be taken and sent to the central laboratory site at the UMCG, for post-study assessment of creatinine and cystatin C. In this laboratory, all creatinine and cystatin C measurements per subject will be done in 1 run in order to avoid interlaboratory and interassay variation. These latter assessments will be used for the efficacy analyses of the RCT. Having blood samples at room temperature for up to 4 days does not influence creatinine and cystatin C concentration, nor has frozen storage at -80 Celsius during prolonged periods of time.

Physical examination and vital sign assessments
A complete medical history will be taken at the screening visit. An extensive physical examination (including head, eye, ear, nose and throat, thorax, abdomen, urogenital, extremities, neurological, skin and mucosae, body weight and blood pressure and height at screening visit) will be performed yearly and before- and after treatment (details will only be provided in case of clinically significant abnormal findings). Every other visit a short physical examination will be performed (only consisting of blood pressure and weight) and vital signs (including blood pressure) obtained at the times indicated in the flow-chart (addendum 1). Blood pressure will be measured at the visits to the UMC’s. The principal investigator or appointed MD designee is primarily responsible for performing the physical examination. Whenever possible, the same individual should perform all physical examinations for each subject. Any clinically significant condition present at the post-treatment physical examination that was not present at the baseline examination should be documented as an AE and followed to a satisfactory conclusion.

eGFR
In the present trial, renal function will be assessed as creatinine based estimated GFR applying the CKD-EPI equation. This methodology is widely used in clinical practice (implying good feasibility and external validity), and is also used in current and recent trials in ADPKD. Creatinine based eGFR will be assessed once every 3 months by routine measurements by local clinical chemistry laboratories. Furthermore, blood will be taken, frozen and shipped for assessment of creatinine and cystatin C at a central laboratory. In this laboratory all creatinine and cystatin C measurements per subject will be done in 1 run in order to avoid inter-assay variation. These latter assessments will be
used for the efficacy analyses of the RCT. Of note, the virtue of serial cystatin C measurements for assessment of changes in renal function over time is as yet scientifically not clear, and therefore not used as primary, but as secondary outcome measure in clinical trials.

**MRI**

MRIs will be performed to capture images of the kidney and liver per the study specific imaging protocol. MRIs will be performed according to the schedule of assessments (see flow chart). The MRI for baseline visit must be performed from 1 week before the baseline visit until 4 days there-after, but in each case before start of lanreotide injection. Time window for MRI at end of treatment visit is +/- 8 days from the clinic visit. However, it is recommended to have the MRI done on the same day as the clinic visit. Those subjects terminating early will have an MRI performed, but will continue their study visits, if possible.

The MRI contrast agent gadolinium will not be used for the purposes of this study due to an increased risk of nephrogenic systemic fibrosis in subjects with renal failure.

MRIs will be anonymized and sent electronically to the central MRI center at the UMCG. An immediate quality control procedure will take place that ensures that the MRI acquisitions follow the established protocol and that the images are of sufficient quality, so that if a visit MRI is not adequate for accurate measurements the center can be notified within a few days and the patient can be re-scanned. MRIs will be read centrally by an assessor blinded for study subject and treatment allocation to provide consistent data and evaluation methodology across all study subjects. Total kidney volume will be measured using Analyze-direct.

The parameter to be measured for primary analysis will be combined renal volume of both kidneys, and for secondary analysis also liver volume (in those subjects with a baseline total liver volume ≥2000 mL). Only in subjects with baseline liver volume ≥2000 mL liver volume will be scanned at the end of study MRI. Depending on feasibility, combined renal cyst volume (total cyst volume of both kidneys), combined renal parenchyma volume (total parenchyma volume of both kidneys) may be assessed at a later date (for a subset of subjects). Of note, results of MR images will not be routinely reported by a radiologist. In the ICF patients will be informed on this procedure. In case, however, a clinical question arises these MRIs will be available for post-hoc analyses.
Subjects with ferro-magnetic prostheses, aneurysm clips, severe claustrophobia or other contraindications for MRI assessment can be included in the study but will not be included for analyses of change in liver and/or renal volume.

7.4 Withdrawal of individual subjects
Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. All data generated up to the time of discontinuation from the study will be analyzed and the reason(s) for discontinuation will be recorded.

7.4.1 Specific criteria for withdrawal
All subjects have the right to withdraw at any point during treatment without prejudice. The investigator can discontinue a subject’s participation in the trial at any time if medically necessary. In addition, subjects meeting the following criteria must be withdrawn from the trial:

- occurrence of any AE, intercurrent illness or abnormality in a laboratory assessment which, in the opinion of the investigator, warrants the subject’s permanent withdrawal from the trial;
- treatment with a prohibited concomitant medication other than the use of appropriate medications for the treatment of adverse events under direction of the investigator;
- patient noncompliance, defined as refusal or inability to adhere to the trial schedule or procedures;
- at the request of the subject, investigator or regulatory authority;
- subject becomes pregnant;
- subject dies or is lost to follow-up.
- Subject reaches end stage renal disease and renal replacement therapy is started. (End of Study and follow up visit will be performed)

7.5 Replacement of individual subjects after withdrawal
In 4.4 the sample size calculation for this study is given. Taken into account is a 20% protocol violator and/or drop-out rate. Therefore an inclusion of 150 subjects per study group is aimed. However, protocol violators and/or drop-out from this study that occur during the first three months of treatment (i.e. before the first assessment of data that can be taken into account for the efficacy analyses) may be replaced in order to reach 123 subjects per study group to complete the study. If a subject discontinues from the study prematurely the reason must be fully evaluated and recorded appropriately in source
documentation and the CRF. If the subject is being withdrawn because of an AE, that AE must be indicated as the reason for withdrawal.

7.6 Follow-up of subjects withdrawn from the study

Subjects, who withdraw from the study will be seen for follow-up three months later (FU visit). Physical examination, concomitant medication, adverse events will be assessed. Then blood and urine chemistry will be analyzed for safety endpoints. In case a subject continues study participation, but treatment ends, an end of treatment visit (ET) will be performed within 1 week after the next injection should be administered (same assessments will be performed as EOS visit) and subject will continue regular study visits.

7.7 Premature termination of the study

Safety assessments will consist of monitoring and recording all adverse events, including serious adverse events. An independent data safety monitoring board (DSMB) will be formed to review safety data. This board will be managed by an independent statistical data analysis center (Trial Coordination Center, UMC Groningen). This board will meet regularly and advise the Steering Committee to continue the study, to implement protocol changes or to terminate this study. The DSMB will be guided by a charter defining their role and responsibilities, and methods specific to the committee.
8. SAFETY REPORTING

8.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

8.2 Adverse and serious adverse events

The Trial Coordination Center (UMCG), that will act as monitoring body, will be responsible to report (severe) adverse events on behalf of the coordinating investigator and the coordinating investigator will act as necessary to (serious) adverse events.

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

A serious adverse event (SAE) is any untoward medical occurrence or effect that at any dose:
- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc.

All SAEs will be reported through the web portal ToetsingOnline to the accredited METC that approved the protocol, within 15 days after the Trial Coordination Center has first knowledge of the serious adverse reactions. SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later
than 7 days after the coordinating investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

8.2.1 Suspected unexpected serious adverse reactions (SUSAR)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved IMP or Summary of Product Characteristics (SPC) for an authorised medicinal product).

The Trial Coordination Center on behalf of the coordinating investigator will report expedited the following SUSARs through the web portal ToetsingOnline to the METC:
- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the accredited METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.

The expedited reporting of SUSARs through the web portal ToetsingOnline is sufficient as notification to the competent authority.

The expedited reporting will occur not later than 15 days after the Trial Coordination Center has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

8.2.2 Annual safety report

In addition to the expedited reporting of SUSARs, the Trial Coordination Center will submit on behalf of the coordinating investigator, once a year throughout the clinical trial, a safety report to the accredited METC. This safety report consists of:
- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

8.3 Follow-up of adverse events
All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

8.4 Data Safety Monitoring Board (DSMB)
An independent data safety monitoring board (DSMB) will be formed. This committee will be guided by a charter defining their role and responsibilities, and methods specific to the committee. The DMSB is managed by representatives of the statistical data analysis center (Trial Coordination Center, UMC Groningen). The DMSB will advise the Steering Committee (SC) to continue, to adapt or to terminate the study. The SC will oversee the design, conduct and analysis of the study. The advices of the DSMB will be notified upon receipt by the Coordinating Investigator or Central Study Coordinator to the METC that approved the protocol. With this notification a statement will be included indicating whether the advice will be followed and if not, a rationale will be provided.
9. STATISTICAL ANALYSIS

9.1 Descriptive statistics

Demographic and baseline characteristics
Data on demographic and baseline characteristics will be summarized for continuous variables, in case of normal distribution by mean and standard deviation, and in case of non-normal distribution by median and interquartile range. For discrete variables (e.g., race and sex) data will be summarized by proportions (percentages).

Outcome variables
The primary outcome variable is rate of change in eGFR (in mL/min/1.73m²). The secondary pharmacodynamic outcome variables are change in eGFR (in mL/min/1.73m²), change in total renal and liver volume (in percentage per year), incidence of worsening renal function, need for renal replacement therapy and/or incidence of death (in percentage). Results will be summarized for continuous variables, in case of normal distribution by mean and standard deviation, and in case of non-normal distribution by median and interquartile range. For discrete variables (e.g., number of subjects experiencing worsening of renal function or need for renal replacement therapy) data will be summarized by proportions (percentages). Of note, patients who underwent liver cyst drainage or surgery in the year before, or during the study entry will only be assessed for change in renal function, and not for change in liver volume.

Safety data
All adverse events (including common and less frequent adverse events observed with Lanreotide administration) occurring during the study will be recorded in the patient's medical records. These will be coded using the most recent version of the MedDRA codelist. The incidence of events considered to be at least possibly related to the study treatment will be summarized by treatment group and severity.

Clinical laboratory data
Summary statistics for changes from baseline in the clinical laboratory measurements will be provided.

Physical examination and vital signs data
By-subject listings will be provided for physical examination results. Summary statistics for changes from baseline in vital signs will be provided.
9.2 Analysis
The outcome measures as defined in section 9.1 will be analyzed. For continuous data, Student's t test will be used to calculate differences between groups for normally distributed data or Mann-Whitney U test for non-normally distributed data. The $X^2$ test will be used to compare dichotomized outcomes between the groups. (Generalized) Mixed Models will be used to analyse our primary endpoint. In addition, we will perform linear regression analysis as sensitivity analysis. Incidence of worsening renal function, end stage renal disease and death will be investigated using a Cox proportional hazard models. Kaplan Meier graphs will be made. All $P$ values calculated 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. As a secondary analysis a per protocol analysis will be performed. The main analyses will also be performed in a priori defined subgroup analyses; these subgroups are defined in the statistical analyses plan. Of note, analyses for change in liver volume will be performed as secondary analysis with adjustment for use of estrogens or oral contraceptives. Furthermore, correlation analyses between kidney and liver volume changes over time will be performed.
10. ETHICAL CONSIDERATIONS

10.1 Regulation statement
The trial will be conducted according to the International Conference of Harmonization. Good Clinical Practice Guidelines and all other applicable regulatory requirements and adheres to the ethical principles that have their origin in the Declaration of Helsinki. Patient privacy is ensured by de-identifying all submitted data and using a subject identification code. All patients will have the right to withdraw from the study at any time during the trial.

10.2 Recruitment and consent
Subjects will be informed about the study by their treating physician. They will be invited for an informational meeting with one of the investigators, study doctors and/or study nurses, and receive an information letter. Thereafter, they will have the possibility to ask questions. They will be allowed to consider their participation for at least one week. After this period, subjects will be contacted and again, they will get the opportunity to ask questions. If the subject wants to participate, a meeting will be set for the screening visit. At this visit, an informed consent form will be signed before any study related procedure will take place.

10.3 Objection by minors or incapacitated subjects
Minors and incapacitated subjects will not be included in this study.

10.4 Justification of entry criteria and study parameters

Modified Ravine criteria
In 1992 Ravine et al published criteria to establish the clinical diagnosis ADPKD in families of unknown genotype based upon ultrasound. These criteria were modified in 2009 and read30:

In case of a positive family history:

- Age between 15 and 59 years, three or more (unilateral or bilateral) renal cysts and two cysts in each kidney are sufficient to establish the diagnosis.
- Age 60 years or older, four or more renal cysts and two cysts in each kidney are sufficient to establish the diagnosis.

In case of a negative family history:

- More than 10 cysts in each kidney and exclusion of other cystic disease
In case the diagnosis is made by MRI or CT (instead of ultrasound) the same criteria will be used, and only cysts will be counted measuring 10 or more millimetres in diameter to make a diagnosis of ADPKD using these imaging modalities. The Ravine criteria are widely accepted in the medical community to diagnose ADPKD and are the routine inclusion criteria for clinical trials in ADPKD.

**Baseline age / baseline eGFR**

In patients with ADPKD renal function remains fairly stable for a certain period of time after which a disease phase starts with accelerated renal function loss. The natural history of ADPKD, however, shows variation between individuals, even within families with the same genetic mutation. Some patients need renal replacement therapy at the age of 30, whereas others still have not reached end-stage renal failure at the each of 80. When the phase with accelerated renal function loss starts is difficult to predict in individual patients. Patient characteristics that herald a poor prognosis are a mutation in the \textit{Pkd1} gene (when compared to a mutation in the \textit{Pkd2} gene) and especially a large total kidney volume and a decreased renal function at relatively young age. To be able to show a relevant effect of study medication on the natural history of renal function decline it is important to include in this study ADPKD patients that are likely to progress insofar that they will show renal function loss during the study. For this reason the entry criteria are defined such (baseline eGFR between 30 and 60 mL/min/1.73m2 and age younger than 60 years) that A. included patients will have a high likelihood of disease progression, B. are easy to translate into clinical practice (high external validity), and C. will make it likely that in case the study is positive the use of Lanreotide may be expected to have a clinical relevant effect.

**Main study parameter**

The main study parameter will be rate of change in renal function, as assessed by regression analysis through serial eGFR values obtained per individual, with the eGFR value obtained at month 3 as the first eGFR value to be used for this regression analysis. The eGFR values obtained at month 1 and 2 during the treatment phase of the study will be used for safety analyses, but not for the efficacy analysis. This is done because in the first three months during treatment it may be necessary to down-titrate the dose of Lanreotide and/or up- or downtitration of antihypertensives, which may have an acute, reversible hemodynamic effect on eGFR, that may obscure the potential long-term, irreversible structural benefit that this study aims to investigate.
With respect to the primary endpoint variable and the change in this variable that is chosen to be clinically relevant (a 30% decrease in rate of renal function decline) it should be noted that the inclusion criteria for this study are ADPKD with an eGFR between 30 and 60 mL/min/1.73m² and an age <60 years conform the majority of ADPKD patients that were included in the MDRD study. In these patients the average rate of renal function decline was 5.2 mL/min/1.73m² per year. A 30% reduction implies an average rate of renal function loss of 3.6 mL/min/1.73m² per year. Renal replacement therapy (start of dialysis or a pre-emptive renal transplantation) is generally started at an eGFR of 10 mL/min/1.73m² per year. In case the average eGFR of the included ADPKD patients is 45 mL/min/1.73m² per year (arrhythmic mean of 30 and 60) the untreated patients are expected to enter renal replacement therapy after approximately 6.7 years (= 45-10 divided by 5.2) and the Lanreotide treated patients after approximately 9.7 years (=45-10 divided by 3.6). These data show that the start of renal replacement therapy can be postponed by 3.0 years. Of note, the yearly costs of renal replacement therapy in the Netherlands are estimated at 75.000 Euro per year. These data provide an insight in the potential relevance of this study in terms of individual patient and societal benefit.

Study design
The present RCT is designed as an open RCT. Administration of Lanreotide, which is a gel, will result in temporary injection infiltrates in the majority of actively treated subjects. Fabrication of a placebo that has a similar effect is not possible from a technical point of view. This precludes the execution of this trial as a double-blinded RCT. Therefore, efficacy endpoints 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).

10.5 Benefits and risks assessment, group relatedness
There may be a benefit for the subjects participating in this study. At this moment, no therapeutic options are available for ADPKD. In case Lanreotide will slow down the rate of renal function decline the timing of need for renal replacement therapy can be postponed, or perhaps even be prevented.

The risks related to study participation is predominantly that half of the included patients will be exposed to Lanreotide. Paragraphs 6.3 and 6.4 list the side effect profile of this drug.
10.6 Compensation for injury

The investigator has a liability insurance which is in accordance with article 7, subsection 6 of the WMO.

The investigator (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as verrichter' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

10.7 Incentives

Subjects will receive a reimbursement of travelling expenses for the extra visits necessary for the study.
11. ADMINISTRATIVE ASPECTS AND PUBLICATION

11.1 Handling and storage of data and documents
Design and maintenance of the database for the present study will be performed by the Trial and Coordination Center (TCC), the in-house CRO of the UMC Groningen. This will be the only party with access to unblinded data for the duration of the study. All data will be entered in an electronic CRF according to the standard operating procedures of the TCC. At the end of the study, the TCC will provide the database to the investigator.

11.2 Amendments
A substantial amendment is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:
- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

11.3 Annual progress report
The investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/serious adverse reactions, other problems, and amendments.

11.4 End of study report
The sponsor/investigator will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the investigator will notify the accredited METC
and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

11.5 Public disclosure and publication policy
The present study is investigator driven. The manufacturer of Lanreotide has no role in the design, carry-out, analysis nor publication process. The investigators will publish the study results in compliance with the prevailing CCMO publication policy.
12. REFERENCES


24. Torres VE. ClinicalTrials.gov NCT 00426153.

25. Ruggenenti P. ClinicalTrials.gov NCT 00309283.


