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Lanreotide Reduces Liver Growth In Patients With Autosomal Dominant Polycystic Liver and Kidney Disease

DIPAK-1 Investigators

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Lanreotide Reduces Liver Growth In Patients With Autosomal Dominant Polycystic Liver and Kidney Disease

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A 120-week randomized clinical trial

Autosomal Dominant Polycystic
Kidney and Liver Disease patients
with liver volume $\geq 2000\text{mL}$

Lanreotide 120 mg
sc every 28 days

Standard of care

Primary outcome

% change in height adjusted total
liver volume (hTLV) from baseline
to end of treatment (EOT)

Gastroenterology

Lanreotide Reduces Liver Growth In Patients With Autosomal Dominant Polycystic Liver and Kidney Disease

Short title: Volume reducing effect of lanreotide in ADPKD

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Abbreviations:

ADPKD	Autosomal dominant polycystic kidney disease
CT	Computed tomography
MRI	Magnetic resonance imaging
PLD	Polycystic liver disease
PLD-Q	Polycystic liver disease questionnaire
RCT	Randomized controlled trial
SAE	Serious adverse events
(h)TKV	(height adjusted) total kidney volume
(h)TLKV	(height adjusted) total liver- and kidney volume
(h)TLV	(height adjusted) total liver volume

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Disclosures:

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Author contributions:

EM, FWV, JPHD, JWdF, DJMP, JFW, RZ and RTG conceived and designed the trial. RMMvA, WK, TJG, MJP, RTG and JPHD were involved with data analysis. All authors were involved with data collection and interpretation except MP and WK, who delivered statistical support and data interpretation. EM, FWV and RTG provided management and oversight of the trial as sponsor representatives. RMMvA, WK, TJG, RTG and JPHD wrote the first draft of the manuscript. All authors provided critical content revisions and approved the final manuscript.

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ABSTRACT**Background and aims**

Polycystic liver disease is the most common extra-renal manifestation of autosomal dominant polycystic kidney disease (ADPKD). There is need for robust long-term evidence for the volume-reducing effect of somatostatin analogues. We made use of data from an open-label, randomized trial to determine the effects of lanreotide on height-adjusted liver volume (hTLV) and combined height-adjusted liver and kidney volume (hTLKV) in patients with ADPKD.

Methods

We performed a 120-week study comparing the reno-protective effects of lanreotide vs standard care in 305 patients with ADPKD (the DIPAK-1 study). For this analysis we studied the 175 patients with polycystic liver disease, with hepatic cysts identified by magnetic resonance imaging and liver volume ≥ 2000 ml. Of these, 93 patients were assigned to a group that received lanreotide (120 mg subcutaneously every 4 weeks) and 82 to a group that received standard care (blood pressure control, a sodium-restricted diet, and anti-hypertensive agents). The primary endpoint was percentage change in hTLV between baseline and end of treatment (week 120). A secondary endpoint was change in hTLKV.

Results

At 120 weeks, hTLV decreased by 1.99% in the lanreotide group (95% CI, -4.21 to 0.24) and increased by 3.92% in the control group (95% CI, 1.56–6.28). Compared to controls, lanreotide reduced the growth of hTLV by 5.91% (95% CI, -9.18 to -2.63; $P < .001$). Growth of hTLV was still reduced by 3.87% at 4 months after the last injection of lanreotide compared to baseline (95% CI, -7.55 to -0.18; $P = .04$). Lanreotide reduced growth of hTLKV by 7.18% compared with controls (95% CI, -10.25 to -4.12; $P < .001$).

Conclusion

In this subanalysis of a randomized trial of patients with polycystic liver disease due to ADPKD, lanreotide for 120 weeks reduced the growth of liver and combined liver- and kidney volume. This

effect was still present 4 months after the last injection of lanreotide. ClinicalTrials.gov no:

NCT01616927

Keywords: Polycystic liver disease; somatostatin analogues; liver size; drug

INTRODUCTION

Polycystic liver disease (PLD) is the most common extra-renal manifestation of autosomal dominant polycystic kidney disease (ADPKD).¹ The overall prevalence of hepatic cysts in ADPKD is 83%, and increases to more than 90% of patients older than 40-years-of-age.² While the majority of PLD patients will remain asymptomatic, some patients develop hepatomegaly leading to abdominal pain, early satiety, shortness of breath, poor nutritional status and decreased quality of life (QoL).^{3,4} Symptomatic PLD represents an unmet need for treatment aiming to reduce liver volume or reduce liver growth.⁵

Experimental data suggest that somatostatin analogues possess a liver volume reducing effect by inhibiting cAMP production and as a consequence, cell proliferation and fluid secretion. In a pooled analysis of three randomized controlled trials (RCTs), lanreotide or octreotide (both long-acting somatostatin analogues) reduced liver volume with an average of 3.6% and improved health related quality of life in 6-12 months⁶⁻⁹, but it is unclear whether the benefits extend beyond 12 months. A number of uncontrolled open label studies¹⁰⁻¹² and a post-hoc analysis of a RCT¹³ suggested that prolonged somatostatin analogue treatment may be effective to reduce liver volume, but that discontinuation of therapy leads to re-growth. The uncontrolled nature of these studies, the limited number of included patients and their relatively small liver volume did not allow firm conclusions with respect to the liver volume reducing effect of these drugs. There is therefore a need for robust evidence of long-term somatostatin analogue administration in PLD, especially in those with hepatomegaly. We hypothesized that a liver volume reducing effect can be achieved after 120 weeks of somatostatin analogue treatment, which persists at least four months after cessation of therapy.

In the DIPAK-1 study (an investigator driven, open-label randomized clinical, multicenter trial), 305 later stage ADPKD patients were randomized to lanreotide treatment for 120 weeks or standard care to evaluate renoprotective potential.¹⁴ Although lanreotide treatment did not preserve kidney function, data suggested a beneficial effect on the rate of total kidney volume (TKV) growth. For this report we assessed the long-term effect of lanreotide on height adjusted liver volume (hTLV) as well as on combined height adjusted liver and kidney volume (hTLKV) in PLD patients.

METHODS

Study design and participants

This study is a predefined sub-analysis of the DIPAK-1 study with focus on liver-related endpoints. A description of the design, outcome measures and rationale 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', has been published previously.¹⁵ The DIPAK-1 study included subjects aged 18-60 years, who had ADPKD based on the modified Ravine criteria¹⁶ and an estimated glomerular filtration rate (eGFR, MDRD) of 30-60 ml/min/1.73m².¹⁴ For the present study, we selected ADPKD patients with PLD and hepatomegaly, a priori defined in the study protocol as a liver volume ≥ 2000 ml at baseline.¹⁵

Randomization

In the DIPAK-1 study, after a screening and baseline evaluation, eligible patients were stratified by sex, age ($\leq$ or $>$ 45 years) and eGFR ($\leq$ or $>$ 45 ml/min/1.73m²). Patients were randomly assigned (1:1) with a block size of 6 to either lanreotide on top of standard care or to the control group that received standard care alone.¹⁴

Interventions

Standard care was defined as blood pressure control ($<140/90$ mmHg), if needed by treatment with a sodium-restricted diet and anti-hypertensives. Lanreotide treatment was dosed as 120 mg

subcutaneously (SC) every 4 weeks. Dosage was down-titrated to 90 mg SC every 4 weeks in case eGFR levels dropped below 30 ml/min. In patients who experienced significant side effects dosage was step-by-step down-titrated to 90 mg, 60 mg or stopped. Lanreotide was injected by trained nurses via a home care service.¹⁴

Study measurements

After the baseline visit, patients were seen at one of the four study centers (Groningen, Leiden, Nijmegen and Rotterdam) at weeks 4, 8, 12, 48, 96, 120 and at week 132. After week 120 (End of Treatment) treatment with lanreotide was discontinued and patients were seen again 12 weeks later at a post-treatment visit (week 132). In case patients dropped out before week 120, an early end of treatment and early post-treatment visit were performed. Blood samples for safety assessment were obtained every study visit. At baseline, end of treatment (or early end of treatment) and post-treatment visits, standardized MRI scans were obtained without use of contrast agent.¹⁷ Total liver volume (TLV) and total kidney volume (TKV) were assessed with manual tracing planimetry by trained reviewers blinded for patient identity, treatment allocation and order of study visit.¹⁵ TLV and TKV were adjusted for height (hTLV) by dividing TLV or TKV by length (in meters) of the patient.¹⁴ Combined height adjusted liver and kidney volume (hTLKV) was assessed as hTLV + hTKV.

Health related quality of life (HR-QoL) was measured using the gastrointestinal symptoms questionnaire.¹⁸ The 11 items were partially derived from the Gastrointestinal Symptom Score¹⁹ and modified with symptoms that are characteristic for symptomatic PLD based on expert opinion, and include: lower and upper abdominal pain, heartburn, regurgitation, nausea, vomiting, loss of appetite, early satiety, dyspnea, increase of abdominal waist and involuntary weight loss. All symptoms were assessed using a 7-point Likert scale, ranging from 1 ("none") to 7 ("very severe"). Symptom severity score was calculated by summing all scores and converting it to a score from 0 to 100.¹⁸

Outcome measures

Primary outcome was change in hTLV from baseline to end of treatment (week 120), calculated as percentage difference. Main secondary outcomes were: I) absolute change in TLV and hTLV between baseline and end of treatment (week 120), II) absolute change in TLV and hTLV, and proportional change in hTLV between baseline and post-treatment visit (week 132), III) absolute change in TLKV and hTLKV, and proportional change in hTLKV between baseline and end of treatment (week 120) as well as between baseline and post-treatment visit (week 132). Other secondary outcomes were change in symptom severity score and (serious) adverse events.

Ethical Considerations

This trial is registered with ClinicalTrials.gov (number NCT01616927). All patients provided written informed consent.¹⁴ Ethical considerations are outlined in the study protocol.¹⁵ All authors had access to the study data, and reviewed and approved the final manuscript.

Statistical analysis

Clinical outcome variables were analyzed with an intention-to-treat approach, for all patients for whom baseline and end of treatment MRI were available. Variables were expressed as mean (95% confidence interval [CI]) or median (interquartile range [IQR]). Differences in baseline characteristics were tested with independent *t*-tests for normally distributed data or Mann-Whitney *U* test for skewed data. Randomization did not include stratification for baseline volume, therefore our primary and main secondary endpoints were evaluated using an ANCOVA model with adjustment for baseline volume corresponding with the outcome to be analyzed. Data are presented as estimated marginal means (95% CI). Treatment effect was defined as difference in effect between the somatostatin analogue group and control group. A Spearman's rank order correlation was computed to assess the relationship between change in hTLV and hTKV.

A priori defined subgroup analyses were performed using ANCOVA with the primary or secondary endpoint as dependent variable, and as independent variables treatment group (yes/no), subgroup (by sex, age, hTLV at baseline, eGFR, alkaline phosphatase, gamma glutamyltransferase),

and an interaction term of treatment group times subgroup to investigate possible effect modification.

The number of included males in previous studies was low (9 patients or less) which limits the evidence for effect in this subgroup.^{7-9, 13} In this trial we expected a considerably larger number of male subjects to be included. We therefore analyzed the difference in treatment effect on hTLV and hTLKV in males and females separately, regardless whether gender was identified as a moderator for effect.

Genetic assessment showed that one patient was carrier of an extremely rare combined pathogenic truncating mutations in the *PKD1* as well as in the *PKD2* gene. This patient, who received lanreotide, had an extreme increase in TKV of 154% after 132 weeks (specific details of this patient have been published previously).¹⁴ Therefore we performed sensitivity analyses after removal of this outlier.

Analyses for symptom severity score were performed using ANCOVA models after adjusting for baseline score. All patients were included for safety analyses, all (serious) adverse events were reported. Statistical analyses were performed with SPSS Statistics version 22 and all calculated *P* values were 2-tailed with the level of significance set at $\alpha = 0.05$.

RESULTS

Study population

The original DIPAK-1 study included 305 patients.¹⁴ A total of 175 patients (80 males and 95 females) met our criteria (TLV ≥ 2000 ml) and were eligible for inclusion in the present analysis. A flowchart of the population of this study is shown in figure 1. A total of 93 patients received lanreotide while 82 were assigned to the control group. Baseline hTLV was higher in patients on lanreotide compared to controls (1528 ml/m [IQR 1250 – 2443] vs. 1376 [IQR 1219 – 1687]; $p = 0.04$), as was hTLKV (3006 ml/m [IQR 2460 – 4110] vs. 2694 [2183 – 3683]; $p = 0.04$). Other baseline characteristics were not different between groups (table 1). Of the 175 patients, 157 (83 lanreotide, 74 control) underwent at

least two MRI scans, at baseline visit and end of treatment (or early end of treatment), and were therefore eligible for our primary efficacy analysis (table S1). Figure 1 shows the reasons for loss to follow-up. We analyzed differences in baseline characteristics between patients who were lost to follow-up. In both groups, predominantly patients with relative high liver volume dropped out of the study (table S2 and S3), but there was no difference in characteristics of patients that were lost to follow-up in the two study groups.

Primary outcome

Between baseline and end of treatment, lanreotide decreased hTLV by 1.99%, while hTLV increased with 3.92% in controls (table 2 and figure 2A). Overall, the advantage of lanreotide over control was -5.91% (95% CI -9.18 to -2.63; $p < 0.001$). The difference in annualized percentage change in hTLV with lanreotide versus control was -3.37% (95% CI -5.56 to -1.19; $p = 0.003$) (table S4). Absolute treatment effect between the groups was 140 ml in TLV (95% CI -263 to -18; $p = 0.03$) and 79 ml/m in hTLV (95% CI -150 to -7; $p = 0.03$) (table 2). Individual patient analysis showed that the proportion of patients with a decrease in liver volume was 60.2% in the lanreotide group compared to 31.1% in the control group ($p < 0.001$) (figure 2B).

Secondary outcomes

We evaluated the effect on hTLV four months after cessation of lanreotide. Difference between the two groups remained significant with a beneficial effect of -3.87% (95% CI -7.55 to -0.18; $p = 0.04$) in favor of lanreotide (table 2). Overall difference in absolute change in TLV was -87 ml, (95% CI -237 to 63; $p = 0.25$). Pre-specified subgroup analyses revealed no subgroup that benefited differently from lanreotide between baseline and end of treatment, and between baseline and post-treatment (figure 2C; figure S1).

Next, we assessed volume change of combined polycystic liver and kidneys between baseline and end of treatment. hTLKV increased in the lanreotide group with 2.21% and in the control group with 9.39%, leading to an overall treatment effect of -7.18% (95% CI -10.25 to -4.12; $p < 0.001$) in favor of

lanreotide (table 3). The difference in annualized percentage change in hTLKV with lanreotide versus control was -3.70% (95% CI -5.74 to -1.67; $p < 0.001$) (table S4). Difference in absolute volume change in the lanreotide group compared to the control group was for TLKV 353 ml (95% CI -554 to -152; $p = 0.001$) and for hTLKV 192 ml/m (95% CI -306 to -77; $p = 0.001$) (table 3). Again, the proportion of patients who had a decrease in hTLKV was higher in the lanreotide group (37.3%) than in the control group (14.8%; $p < 0.001$). We performed similar pre-specified subgroup analyses for this secondary endpoint. No subgroup significantly moderated the effect on combined hTLKV from baseline to end of treatment (figure S2). In line with the results of the complete DIPAK-1 population, lanreotide significantly attenuated absolute and percentage growth in total kidney volume (table S5). We assessed the correlation between growth in hTLV and hTKV and found a positive correlation in the whole population ($r_s = 0.33$, $p < 0.001$). This correlation was significant in lanreotide treated patients ($r_s = 0.26$, $p = 0.02$) but not in controls ($r_s = 0.20$, $p = 0.09$).

A significant volume reducing effect of lanreotide on hTLKV was still present 4 months after cessation of lanreotide. At the post-treatment visit, patients in the lanreotide group had a 5.43% (95% CI -9.13 to -1.74; $p = 0.004$) less increase in hTLKV compared to the control group (table 3). Absolute treatment effect on TLKV was 256 ml (95% CI -515 to 4; $p = 0.05$).

To determine whether lanreotide treatment has an effect on symptoms, we assessed change in symptom severity score. Baseline symptom severity score was 9.1 (IQR 3.0 to 18.6) in the lanreotide group ($n = 93$) and 6.1 (IQR 1.5 to 15.5; $p = 0.1$) in the control group ($n = 81$). After correction for baseline score, symptom severity score increased with 2.7 (95% CI 0.7 to 4.7) in lanreotide treated patients and with 2.6 (95% CI 0.5 to 4.7) in controls. There was no difference in change in symptom severity score between the groups ($p = 0.9$). Median symptom severity score at baseline was added to our subgroup analyses and showed that it was no moderator for effect on our primary outcome change in hTLV ($p = 0.7$) nor for effect on symptom severity score ($p = 0.94$).

Additional analyses

A priori we defined to investigate the effect of lanreotide in both sexes separately. At baseline there were gender specific differences in liver and kidney volume. hTLV was significantly higher in females (1654 ml/m vs. 1283 ml/m; $p<0.001$) while hTKV was higher in males (1339 ml/m vs. 883 ml/m; $p<0.001$). Combined, baseline hTLKV was not different between males and females ($p=0.5$). After 120 weeks, liver growth in the control group was similar in males and females. However, only in females a significant treatment effect of lanreotide compared to controls was found (-7.68%, $p=0.001$). In males, the treatment effect of -4.05% did not reach clinical significance ($p=0.09$) (figure 3A).

The control group demonstrated that combined liver- and kidney volume growth was larger in males ($p<0.01$) compared to females, which can be fully attributed to the fast growth of kidney volume in males. If measured from baseline to end of treatment, the hTLKV treatment effect of lanreotide versus control group was significant in males (-6.59%, $p=0.002$) as well as females (-7.48%, $p<0.001$) (figure 3B). In general, subgroup analysis revealed that gender was not an effect modifier for change in hTLV ($p=0.3$) and hTLKV ($p=0.8$).

Several post-hoc analyses were performed. The observation period between baseline and end of treatment was shorter in the lanreotide group (2.06 ± 0.54 years) compared to controls (2.31 ± 0.06 years; $p<0.001$). We therefore examined whether the observed difference affected our primary outcome. Addition of the variable 'duration observation period' to our ANCOVA model excluded any effect on our results (between subjects effect: $p=0.9$).

As described in the original DIPAK-1 trial publication, one extreme outlier in the lanreotide group had a very rare combination of truncating mutations in both the *PKD1* and *PKD2* gene, most likely leading to very rapid increase of liver- and kidney volume.¹⁴ A sensitivity analysis after removal of this extreme outlier further strengthened our findings (table S6). For example, absolute treatment effect in TLKV was now significantly in favor of lanreotide with a total difference of 364 ml (95% CI -560 to -167 $p<0.001$) at the end of treatment and 282 ml (95% CI -508 to -56; $p=0.02$) at the post-treatment visit.

Safety

Lanreotide was down-titrated in 23 patients (to 90mg, subcutaneously, once every 4 weeks in 20 patients and to 60mg, subcutaneously, once every 4 weeks in three patients). In 8 patients, this titration was done per protocol because patients reached an eGFR less than 30mL/min/1.73 m². In 15 patients down-titration was done because of adverse events (7x gastrointestinal complaints, 3x fatigue/malaise, 2x bradycardia, 1x hypoglycemia, 1x hair loss and 1x liver cyst infection). Of these, 6 patients stopped lanreotide because of persistent complaints despite down-titration and 2 because of other reasons (nephrectomy and loss of confidence in the drug). In 6 out of 7 patients in which down-titration was done because of gastrointestinal symptoms, side effects were tolerable with lower dose. A total of 18 patients (19%) stopped lanreotide at once, of whom 14 did so because of adverse events (4x fatigue/malaise, 2x renal cyst bleeding, 6x liver cyst infection, 2x gastrointestinal symptoms). Of note, patients who discontinued lanreotide underwent an early MRI and were included in our analysis.

We assessed all (serious) adverse events (SAEs) in this population. SAEs occurred in 38 patients of which 28 (30.1%) in the lanreotide group and 10 (12.2%) in the control group (table S7). Aside from hepatic cyst infections, which have been described previously²⁰, there were no significant differences between SAE occurrence (at least possibly related to lanreotide) in both groups. A total of 14 SAEs (including 7 episodes of hepatic cyst infections) in the lanreotide group were at least possibly related to the drug. The proportional numbers of AEs in this subgroup are similar to the numbers of the complete DIPAK-1 population. Detailed information about specific adverse events have been published elsewhere.¹⁴

DISCUSSION

This study demonstrates that 120 weeks treatment with lanreotide in ADPKD patients with large livers results in a significant decrease in liver volume growth compared with standard of care. The

beneficial effect is still present four months after cessation of treatment. Lanreotide not only reduces liver volume by 5.9%, but also attenuates growth in kidney volume, resulting in a 7.2% reduction of combined liver- and kidney volume compared to standard of care.

The liver volume reducing effect of somatostatin analogues has been subject of several trials, mostly small and with a short follow-up, but a recent single center study had a longer duration of follow-up. That study evaluated 27 ADPKD patients and exposed them during 3 years to octreotide-LAR (40 mg monthly) or placebo. Liver volume decreased with octreotide and increased with placebo resulting in a net difference of -13.9% in favor of octreotide. The reductions in liver volume were maintained for 2 years after treatment ended.¹³ In this trial most patients did not have hepatomegaly (median TLV ~1500-1600) and would have been excluded from our study which hampers direct comparison with the present results.

In the present trial, 120 weeks of lanreotide treatment resulted in a 5.9% lower hTLV growth rate compared to 4.5% in a trial with a duration of 6 months⁷ or 5.9% in a trial of 12 months⁸ (table S8). This may suggest an absence of a linear relationship between treatment duration and treatment effect. It has been hypothesized that the expression of somatostatin receptors is down-regulated during prolonged treatment with somatostatin analogues.²¹⁻²³ SSTR down-regulation may explain why overall treatment effect is not linear to treatment duration. Several other factors, however, may also explain this finding. First, the DIPAK-1 trial has a large sample size including a large proportion of males, a broad spectrum of PLD severity and later stage ADPKD patients (table S8). It is known that young females respond better to somatostatin analogue treatment, and these were overrepresented in other trials.⁶ Second, some of the previous studies were performed with lanreotide⁷ and others with octreotide.^{8,9,13} Studies have suggested differences in receptor affinity between the various somatostatin analogues.²⁴ These two considerations make it clear that differences in patient characteristics, and differences in somatostatin analogues tested, do not allow a direct comparison of TLV growth rates across studies.

Literature has shown that somatostatin analogues have an acute repressive effect on TLV that is reversible after stopping (short-term) treatment.¹¹ This trial documents that the beneficial effects of 120 week treatment with lanreotide are seen immediate after stopping the drug but also persist throughout the washout period until at least 4 months after the last lanreotide injection. The half-life of prolonged-release lanreotide (90 mg) is 25.5 days, suggesting that exposure to lanreotide at 4 months would be well below target levels.²⁵ In addition, another trial suggested that the effect of somatostatin analogues on TLV persist even two years after cessation of treatment.¹³ These observations suggest that with 120 weeks of lanreotide not only an acute, reversible, possibly hemodynamic effect is obtained, but also a chronic, non-reversible, probably structural beneficial effect. Future studies will have to establish whether there is a linear relationship between treatment duration and this chronic effect of somatostatin analogues on TLV and TKLV.

An important finding in this study is that 120 weeks of lanreotide treatment decreased combined liver- and kidney volume growth by 353 ml in ADPKD patients which is a clinically relevant reduction.²⁶ Although liver and kidney volume are surrogate markers for disease severity in ADPKD, previous studies have shown that somatostatin analogues improve health related quality of life in symptomatic PLD.²⁶ Larger liver volumes are associated with symptomatic disease and lower QoL²⁷ and severity of hepatomegaly is associated with a 6-fold higher risk for pressure-related complications.²⁸ An analysis of baseline data of the DIPAK-1 study showed that both hTLV and even more strongly hTLKV were significantly associated with pain and gastrointestinal symptoms.¹⁸ These studies emphasize the need to prevent further liver- and kidney growth in ADPKD.

There is a phenotypic gender difference in ADPKD. Males have earlier need for renal replacement therapy and higher rates of kidney cyst expansion, but are less prone to develop polycystic livers than females do.²⁹ This is reflected by our finding that 80% of the male ADPKD patients in our trial had mild PLD (hTLV <1600 ml/m) compared to 46% of females. In this study, liver growth was suppressed in males on lanreotide compared to controls, albeit not to a significant level. It is possible that this study lacked the power to detect statistical significant differences in the male

subpopulation. The fact that we did not find effect modification by gender suggests that men too benefit from lanreotide.

Limitations

This study comes with several limitations. First, randomization in the original DIPAK-1 trial did not include stratification for baseline liver volume, which led to an imbalance in group distribution of hTLV and hTLKV. Lanreotide treated patients had higher liver volume at baseline, but similar age. Consequently, the subjects in the lanreotide group are likely to have faster liver disease progression, which can have led to an underestimation the true treatment effect of lanreotide. We adjusted all our analyses for baseline TLV to overcome this limitation. Second, the DIPAK-1 trial was not designed to show the effect of lanreotide on symptoms in PLD. On the basis of the assessment of patients at time of visits during this clinical trial we can state that the proportion of symptomatic PLD patients was low. Indeed, using the symptom severity score, most patients had a low score and did not show a benefit with lanreotide compared to control treatment. However, the symptom severity score that we used is not a validated patient reported outcome measure and may not be sensitive enough to detect change in symptoms. Only recently, a polycystic liver disease specific questionnaire (PLD-Q) was developed and validated to assess symptoms in PLD³⁰, but this questionnaire was not available at time of the study design. Although the patients may be less symptomatic compared to patients recruited for previous PLD trials, this trial demonstrates that lanreotide decreases liver volume which is accepted as a surrogate marker for PLD severity. Third, not using a placebo is a limitation. However, our primary and secondary endpoints are objective measures (MRI volume), and endpoint analysis was performed after the trial finished blinded for patient identity, treatment allocation and study visit which minimizes risk of bias.¹⁴

Clinical implications

Our findings help to improve the understanding of the possible place of lanreotide treatment for PLD in the context of ADPKD. It provides evidence that suppression of the growth of cystic organs is part of the biological effect of somatostatin analogues. Therefore, in ADPKD patients with symptomatic PLD, long-term treatment with lanreotide should be considered. In previous PLD studies, somatostatin analogue treatment effect was not affected by the underlying inherited polycystic disorder.^{6,8} This suggests that long-term somatostatin analogues treatment may not only be an option for ADPKD patients, but also for patients with the isolated form of polycystic liver disease (ADPLD). The benefit of somatostatin analogues with respect to intra-abdominal volume reduction should be weighed against a possible increased risk of hepatic cyst infections. This possible side effect has been described in detail elsewhere.²⁰

In conclusion, this predefined sub-analysis of the DIPAK-1 trial shows that treatment with lanreotide for 120 weeks significantly decreases the growth rates of liver volume and combined liver- and kidney volume. Although lanreotide failed to protect ADPKD patients from renal function deterioration, we suggest that somatostatin analogue treatment can still have an important role in the management of ADPKD patients with large livers and kidneys.

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Author names in bold designate shared co-first authorship

Figure legends

Figure 1. Patient enrollment

Abbreviations: TLV, total liver volume; BV, baseline visit; EOT, end of treatment; EET, early end of treatment; MRI, magnetic resonance imaging.

Figure 2. Change in hTLV between baseline and end of treatment A) Estimated percent change (mean $\pm$ 95% CI) in hTLV between baseline and end of treatment; B) percent change in hTLV, each bar represents 1 patient (dark bars – lanreotide, light bars – control group). All bars right from the scattered line represent decrease in hTLV, bars on the left represent increase in hTLV; C) subgroup analysis for the primary outcome.

Figure 3. Percent change (mean $\pm$ 95% CI) in A) height adjusted liver volume at end of treatment (week 120) compared with baseline value; and B) height adjusted liver- and kidney volume at end of treatment (week 120) compared with baseline. Analysis stratified for gender.

TABLES

Table 1: Baseline characteristics

Characteristic	Lanreotide (N=93)	Control (N=82)	P value
Male sex – no. (%)	40 (43.0)	40 (48.9)	0.45 [¥]
Age – yr	48.3 ± 6.2	48.0 ± 7.0	0.80
Race – no. (%)			0.79 [¥]
White	91 (97.9)	80 (97.6)	
Other	2 (2.2)	2 (2.4)	
Height – cm	1.78 ± 0.10	1.76 ± 0.10	0.45
Weight – kg	86.0 ± 17.4	87.1 ± 20.0	0.69
BMI – kg/m ²	27.2 ± 4.3	27.9 ± 5.4	0.35
Alkaline phosphatase – U/l	72.4 ± 23.2	70.9 ± 21.3	0.66
Gamma-glutamyltransferase – U/l	60.8 ± 51.2	53.8 ± 51.7	0.35
Serum creatinine [¶] – mg/dl	1.46 ± 0.35	1.47 ± 0.38	0.78
Estimated GFR [†] – ml/min/1.73m ²	50.5 ± 11.4	51.2 ± 11.8	0.71
CKD stages [†] – no. (%)			0.71 [¥]
2	24 (25.8)	23 (28.1)	
3a	33 (35.5)	31 (37.8)	
3b	36 (38.7)	27 (32.9)	
4	0	1 (1.2)	
Height adjusted total liver volume – ml/m	1528 (1250 – 2443)	1376 (1219 – 1687)	0.04 [¤]
Mild (<1600) – no. (%)	50 (53.8)	58 (70.7)	
Moderate (1600-3200) – no. (%)	30 (32.3)	19 (23.2)	
Severe (>3200) – no. (%)	13 (14.0)	5 (6.1)	
Height adjusted total kidney volume – ml/m	1150 (816 – 1778)	1029 (706 – 1920)	0.53 [¤]
Height adjusted total liver and kidney volume – ml/m	3006 (2460 – 4110)	2694 (2183 – 3683)	0.04 [¤]

Plus-minus values are means ± SD and tested with Independent Samples T test. [¤] Mann-Whitney U for non-parametric values (median (IQR)). [¥] Fisher's Exact test

Abbreviations: BMI, body mass index, GFR, glomerular filtration rate, CKD, chronic kidney disease

[¶] To convert the values for creatinine to micromoles per liter, multiply by 88.4.

[†] eGFR inclusion criterion for the trial was calculated with creatinine at the screening visit and the MDRD equation, whereas by protocol amendment eGFR results for the trial are calculated with the CKD-EPI equation (Levey 2009).

Table 2: Absolute and percentage change in (height adjusted) total liver volume (TLV)

	Baseline (week 0)	Change	
		End of treatment (week 120)	Post-treatment (week 132)
Total Liver Volume			
Absolute (change in) TLV			
Control – ml	2389 (2168 to 3029)	89 (0 to 177)	79 (-28 to 187)
N	82	74	70
Lanreotide – ml	2781 (2272 to 4230)	-52 (-135 to 32)	-8 (-110 to 94)
N	93	83	78
Difference - ml		-140 (-263 to -18)	-87 (-237 to 63)
P-value	0.01	0.03	0.25
Absolute (change in) hTLV			
Control – ml/m	1376 (1219 to 1687)	49 (-2.7 to 100.1)	40 (-22 to 102)
N	82	74	70
Lanreotide – ml/m	152 (1250 to 2443)	-30 (-78 to 19)	-4 (-63 to 54)
N	93	83	78
Difference – ml/m		-79 (-150 to -7)	-45 (-131 to 412)
P-value	0.04	0.03	0.31
Percentage change in hTLV vs baseline			
Control - %		3.92 (1.56 to 6.28)	2.71 (0.06 to 5.37)
N		74	70
Lanreotide - %		-1.99 (-4.21 to 0.24)	-1.15 (-3.66 to 1.36)
N		83	78
Difference - %		-5.91 (-9.18 to -2.63)	-3.87 (-7.55 to -0.18)
P-value		<0.001	0.04

Baseline data are presented as median (interquartile range). Change at end of treatment and follow-up is presented as estimated marginal means with 95% CI (corrected for baseline volume).

Table 3: Absolute and percentage change in (height adjusted) total liver- and kidney volume (TLKV)

	Baseline (week 0)	Change	
		End of treatment (week 120)	Post-treatment (week 132)
Combined Total Liver & Total Kidney Volume			
Absolute (change in) TLKV			
Control – ml	4632 (3906 to 6387)	518 (372 to 663)	532 (345 to 719)
N	82	74	70
Lanreotide – ml	5280 (4381 to 7214)	164 (27 to 301)	276 (99 to 453)
N	93	83	78
Difference – ml		-353 (-554 to -152)	-256 (-515 to 4)
P-value	0.03	0.001	0.05
Absolute (change in) hTLKV			
Control – ml/m	2694 (2183 to 3683)	283 (13 to 169)	288 (182 to 394)
N	82	74	70
Lanreotide – ml/m	3006 (2460 to 4110)	91 (13 to 169)	154 (54 to 254)
N	93	83	78
Difference – ml/m		-192 (-306 to -77)	-134 (-280 to 13)
P-value	0.04	0.001	0.07
Percentage change in hTLKV vs baseline			
Control - %		9.39 (7.17 to 11.61)	9.32 (6.66 to 11.99)
N		74	70
Lanreotide - %		2.21 (0.12 to 4.30)	3.89 (1.37 to 6.41)
N		83	78
Difference - %		-7.18 (-10.25 to -4.12)	-5.43 (-9.13 to -1.74)
P-value		<0.001	0.004

Baseline data are presented as median (interquartile range). Change at end of treatment and follow-up is presented as estimated marginal means with 95% CI (corrected for baseline volume).

Figure 1: Patient enrollment

SUPPLEMENTARY FILES

Supplementary Table 1: Baseline characteristics in patients included in our primary efficacy analysis

Characteristic	Lanreotide (N=83)	Control (N=74)	P value
Male sex – no. (%)	39 (47.0)	35 (47.3)	1.0 [‡]
Age – yr	48.2 ± 6.2	48.4 ± 6.9	0.89
Race – no. (%)			0.79 [‡]
White	81 (97.6)	72 (97.3)	
Other	2 (2.4)	2 (2.7)	
Height – cm	1.78 ± 0.10	1.76 ± 0.10	0.16
Weight – kg	87.4 ± 17.4	86.1 ± 18.5	0.65
BMI – kg/m ²	27.5 ± 4.4	27.8 ± 5.3	0.74
Alkaline phosphatase – U/l	71.1 ± 22.0	70.0 ± 20.3	0.76
Gamma-glutamyltransferase – U/l	57.8 ± 45.8	47.7 ± 36.8	0.13
Serum creatinine [¶] – mg/dl	1.46 ± 0.36	1.46 ± 0.39	0.89
Estimated GFR [†] – ml/min/1.73m ²	51.0 ± 11.3	51.7 ± 12.0	0.71
CKD stages [†] – no. (%)			0.68 [‡]
2	22 (26.5)	22 (29.7)	
3a	31 (37.4)	29 (39.2)	
3b	30 (36.1)	22 (29.7)	
4	0	1 (1.35)	
Height corrected total liver volume – ml/m	1514 (1248 – 2161)	1354 (1218 – 1627)	0.04 [‡]
Mild (<1600) – no. (%)	46 (55.4)	54 (73.0)	
Moderate (1600-3200) – no. (%)	27 (32.5)	17 (23.0)	
Severe (>3200) – no. (%)	10 (12.1)	3 (4.1)	
Height corrected total kidney volume – ml/m	1150 (813 – 1670)	993 (682 – 2057)	0.41 [‡]
Height corrected total liver and kidney volume – ml/m	2942.0 (2438 – 4105)	2582.6 (2178 – 3605)	0.04 [‡]
Duration of follow-up	2.06 ± 0.54	2.31 ± 0.06	<0.001

Plus-minus values are means ± SD and tested with Independent Samples T test . [‡] Mann-Whitney U for non-parametric values (median (IQR)). [‡] Fisher's Exact test

BMI body mass index, GFR glomerular filtration rate, CKD chronic kidney disease

[¶] To convert the values for creatinine to micromoles per liter, multiply by 88.4.

[†] eGFR inclusion criterion for the trial was calculated with creatinine at the screening visit and the MDRD equation, whereas by protocol amendment eGFR results for the trial are calculated with the CKD-EPI equation (Levey 2009).

Supplementary Table 2: Sensitivity analysis for patients lost to follow-up in the Lanreotide Group (n=93)

Characteristic	In analysis (N=83)	Lost to FU (N=10)	P value
Male sex – no. (%)	39 (47.0)	1 (10.0)	0.04 [¥]
Age – yr	48.2 ± 6.2	48.4 ± 6.7	0.94
Race – no. (%)			1.0 [¥]
White	81 (97.6)	10 (100)	
Other	2 (2.4)	0 (0)	
Height – cm	1.78 ± 0.10	1.72 ± 0.09	0.07
Weight – kg	87.4 ± 17.4	74.0 ± 12.1	0.02
BMI – kg/m ²	27.5 ± 4.4	24.6 ± 2.7	<0.05
Alkaline phosphatase – U/l	71.1 ± 22.0	83.1 ± 30.3	0.12
Gamma-glutamyltransferase – U/l	57.8 ± 45.8	85.2 ± 83.6	0.003
Serum creatinine [¶] – mg/dl	1.46 ± 0.36	1.42 ± 0.22	0.68
Estimated GFR [†] – ml/min/1.73m ²	51.0 ± 11.3	46.9 ± 12.1	0.29
CKD stages [†] – no. (%)			0.37 [¥]
2	22 (26.5)	2 (20.0)	
3a	31 (37.4)	2 (20.0)	
3b	30 (36.1)	6 (60.0)	
4	0	0 (0)	
Height corrected total liver volume – ml/m	1514 (1248 – 2161)	2429 (1388 – 3714)	0.08 [¶]
Mild (<1600) – no. (%)	46 (55.4)	4 (40.0)	
Moderate (1600-3200) – no. (%)	27 (32.5)	3 (40.0)	
Severe (>3200) – no. (%)	10 (12.1)	3 (30.0)	
Height corrected total kidney volume – ml/m	1150 (813 – 1670)	1314 (791 – 1945)	0.66 [¶]
Height corrected total liver and kidney volume – ml/m	2942.0 (2438 – 4105)	3264 (2815 – 5640)	0.17 [¶]

Plus-minus values are means ± SD and tested with Independent Samples T test . [¶] Mann-Whitney U for non-parametric values (median (IQR)). [¥] Fisher's Exact test

BMI body mass index, GFR glomerular filtration rate, CKD chronic kidney disease

[¶]To convert the values for creatinine to micromoles per liter, multiply by 88.4.

[†] eGFR inclusion criterion for the trial was calculated with creatinine at the screening visit and the MDRD equation, whereas by protocol amendment eGFR results for the trial are calculated with the CKD-EPI equation (Levey 2009).

Supplementary Table 3: Sensitivity analysis for patients lost to follow-up in the control group (n=82)

Characteristic	In analyses (N=74)	Lost to FU (N=8)	P value
Male sex – no. (%)	35 (47.3)	5 (62.5)	0.48 [¥]
Age – yr	48.4 ± 6.9	44.4 ± 7.4	0.12
Race – no. (%)			1.0 [¥]
White	72 (97.3)	8 (100)	
Other	2 (2.7)	0 (0)	
Height – cm	1.76 ± 0.10	1.81 ± 0.10	0.21
Weight – kg	86.1 ± 18.5	96.5 ± 30.9	0.16
BMI – kg/m ²	27.8 ± 5.3	29.1 ± 6.9	0.5
Alkaline phosphatase – U/l	70.0 ± 20.3	78.3 ± 29.2	0.30
Gamma-glutamyltransferase – U/l	47.7 ± 36.8	110.3 ± 112.8	<0.001
Serum creatinine [¶] – mg/dl	1.64 ± 0.39	1.46 ± 0.30	0.19
Estimated GFR [†] – ml/min/1.73m ²	51.7 ± 12.0	46.7 ± 10.0	0.26
CKD stages [†] – no. (%)			0.30 [¥]
2	22 (29.7)	1 (12.5)	
3a	29 (39.2)	2 (25.0)	
3b	22 (29.7)	5 (62.5)	
4	1 (1.35)	0 (0)	
Height corrected total liver volume – ml/m	1354 (1218 – 1627)	1842 (1374 – 4452)	0.06 [‡]
Mild (<1600) – no. (%)	54 (73.0)	4 (50.0)	
Moderate (1600-3200) – no. (%)	17 (23.0)	2 (25.0)	
Severe (>3200) – no. (%)	3 (4.1)	2 (25.0)	
Height corrected total kidney volume – ml/m	993 (682 – 2057)	1304 (1081 – 1721)	0.22 [‡]
Height corrected total liver and kidney volume – ml/m	2582.6 (2178 – 3605)	3589 (2674 – 5643)	0.07 [‡]

Plus-minus values are means ± SD and tested with Independent Samples T test . [‡] Mann-Whitney U for non-parametric values (median (IQR)). [¥] Fisher's Exact test

BMI body mass index, GFR glomerular filtration rate, CKD chronic kidney disease

[¶] To convert the values for creatinine to micromoles per liter, multiply by 88.4.

[†] eGFR inclusion criterion for the trial was calculated with creatinine at the screening visit and the MDRD equation, whereas by protocol amendment eGFR results for the trial are calculated with the CKD-EPI equation (Levey 2009).

Supplementary table 4: Annualized percentage change in height adjusted total liver volume and height adjusted total liver and kidney volume

	Change	
	End of treatment (week 120)	Post-treatment (week 132)
Percentage change per year in hTLV vs baseline		
Control - %/year	1.65 (0.08 to 3.23)	1.02 (-0.38 to 2.41)
N	74	70
Lanreotide - %/year	-1.72 (-3.21 to -0.23)	-0.73 (-2.05 to 0.59)
N	83	78
Difference - %/year	-3.37 (-5.56 to -1.19)	-1.75 (-3.68 to 0.19)
P-value	0.003	0.08
Percentage change per year in hTLKV vs baseline		
Control - %/year	4.06 (2.59 to 5.53)	3.63 (2.33 to 4.94)
N	74	70
Lanreotide - %/year	0.36 (-1.03 to 1.74)	1.32 (0.09 to 2.56)
N	83	78
Difference - %/year	-3.70 (-5.74 to -1.67)	-2.31 (-4.12 to -0.50)
P-value	<0.001	0.01

Change at end of treatment and follow-up is presented as estimated marginal means with 95% CI (corrected for baseline volume).

Supplementary Table 5: Absolute and percentage change in (height adjusted) total kidney volume (TKV)

	Baseline (week 0)	Change	
		End of treatment (week 120)	Post-treatment (week 132)
Total Kidney Volume			
Absolute (change in) TKV			
Control – ml	1874 (1253 to 3530)	392 (306 to 479)	420 (300 to 539)
N	82	74	70
Lanreotide – ml	2054 (1452 – 3012)	246 (165 to 328)	310 (197 to 422)
N	93	84	79
Difference - ml		-146 (-265 to -27)	-110 (-275 to 55)
P-value	0.48	0.02	0.19
Absolute (change in) hTKV			
Control – ml/m	1029 (706 to 1920)	217 (169 to 265)	232 (167 to 298)
N	82	74	70
Lanreotide – ml/m	1150 (81 to 1778)	135 (91 to 180)	170 (109 to 232)
N	93	84	79
Difference – ml/m		-82 (-147 to -16)	-62 (-152 to 28)
P-value	0.53	0.02	0.17
Percentage change in hTKV vs baseline			
Control - %		15.65 (12.74 to 18.55)	17.12 (12.90 to 21.34)
N		74	70
Lanreotide - %		7.62 (4.89 to 10.34)	10.45 (6.48 to 14.42)
N		84	79
Difference - %		-8.03 (-12.01 to -4.05)	-6.67 (-12.46 to -0.88)
P-value		<0.001	0.02

Baseline data are presented as median (interquartile range). Change at end of treatment and follow-up is presented as estimated marginal means with 95% CI (corrected for baseline volume).

Supplementary Table 6: Absolute and percentage change versus baseline in (height adjusted) total liver volume (TLV), total kidney volume (TKV) and total liver and kidney volume (TLKV), excluding the outlier with very rapid disease progression.

	Change	
	End of treatment (week 120)	Post-treatment (week 132)
Total Liver Volume		
Absolute change in TLV		
Difference - ml	-142 (-263 to -21)	-89 (-231 to 53)
P-value	0.02	0.22
Absolute change in hTLV		
Difference - ml/m	-80 (-151 to -10)	-48 (-130 to 34)
P-value	0.03	0.25
Percentage change in hTLV		
Difference - %	-5.94 (-9.22 to -2.67)	-3.93 (-7.60 to -0.26)
P-value	<0.001	0.04
Total Kidney Volume		
Absolute change in TKV		
Difference - ml	-165 (-278 to -52)	-154 (-290 to -18)
P-value	0.004	0.03
Absolute change in hTKV		
Difference - ml/m	-92 (-154 to -30)	-86 (-161 to -11)
P-value	0.004	0.03
Percentage change in hTKV		
Difference - %	-8.84 (-12.46 to -5.22)	-8.51 (-12.84 to -4.18)
P-value	<0.001	<0.001
Combined Total Liver & Total Kidney Volume		
Absolute change in TLKV		
Difference - ml	-364 (-560 to -167)	-282 (-508 to -56)
P-value	<0.001	0.02
Absolute change in hTLKV		
Difference - ml/m	-198 (-310 to -86)	-151 (-279 to -22)
P-value	0.001	0.02
Percentage change in hTLKV		
Difference - %	-7.29 (-10.34 - -4.24)	-5.70 (-9.25 - -2.15)
P-value	<0.001	0.002

Change at end of treatment and follow-up is presented as estimated marginal means with 95% CI (corrected for baseline volume).

Supplementary Table 7. Most common Serious Adverse Events. Listed are all serious adverse events with an incidence >2% or that were at least possibly related to lanreotide treatment.

	Lanreotide (N=93)	Control (N=82)
	<i>No. of patients with event (%)</i>	
Serious adverse events		
Any serious adverse event	28 (30.1%)	10 (12.2%)
Serious adverse event leading to withdrawal	4 (4.3%)	1 (1.2%)
Specific serious adverse events possibly related to lanreotide		
- Hepatic cyst infection	6 (6.5%)	0
- Renal cyst infection	2 (2.2%)	2 (2.4%)
- Pyelonephritis	1 (1.1%)	1 (1.2%)
- Epigastric pain	1 (1.1%)	0
- Fever	1 (1.1%)	0
- Urinary tract infection	1 (1.1%)	0
- Cholelithiasis	1 (1.1%)	0

Adverse events were collected by spontaneous report. A full list of adverse events of the complete DIPAK-1 study have been published elsewhere.¹⁴

* Adverse events were categorized according to the preferred terms of the *Medical Dictionary for Regulatory Activities* (MedDRA).

There were 6 patients with 7 episodes of hepatic cyst infections. Details of these patients have been published elsewhere²⁰

Supplementary Table 8: Summary of studies performed with somatostatin analogues in patients with polycystic kidney disease, and differences in characteristics with the present study.

Abbreviations: im, intramuscular; sc, subcutaneous; wks, weeks; N, number of patients; ADPKD, autosomal dominant polycystic kidney disease; ADPLD, autosomal dominant polycystic liver disease; PLD, polycystic liver disease; RCT, randomized controlled trial; GFR, glomerular filtration rate; SA, somatostatin analogues; Pla, placebo; Oct, octreotide; Lan, lanreotide;

Authors, Year	Somatostatin analogue	Trial design	Duration	Nr. of patients	Nr. of males in SA group	Baseline TLV	Baseline eGFR	Effect on TLV
Keimpema et al, 2009	Lanreotide 120 mg sc every 4 wks	RCT	6 months	N=53 ADPLD (N=22) ADPKD (N=31)	3	4606 (547-8401) [‡]	90	Pla: +1.6 vs Lan: -2.9% P<0.01
Hogan et al, 2010	Octreotide 40 mg im every 4 wks	RCT	12 months	N=42 ADPLD (N=8) ADPKD (N=34)	5	5908 ± 2915 [‡] (Oct group)	70	Pla: +0.92 vs Oct: -4.95% P<0.05
Caroli et al, 2010	Octreotide 40 mg im every 4 wks	Cross-over	6 months	N=12 ADPKD	9	1443 ± 170 [‡] (Oct group)	57	Pla: +1.0 vs Oct: -4.9% P<0.05
Pisani et al, 2016	Octreotide 40 mg im every 4 wks	Subanalysis RCT	3 years	N=27 ADPKD	5	1609 ± 501 [‡] (Oct group)	96	Pla: +6.1 vs Oct: -7.8% P<0.05
Van Aerts et al, 2018	Lanreotide 120 mg sc every 4wks	Subanalysis RCT	2,3 years	N=175 ADPKD	40	2781 [£] (2272-4230) (Lan group)	50	Control: +3.92% vs Lan: -1.99% P<0.001
			Long follow-up	Large sample size	Large number of males	Whole spectrum of PLD	Impaired kidney function	

[‡] Mean with 95%CI or standard deviation, [£] Median with interquartile range

Figure legends (supplementary figures)

Supplementary Figure 1. Subgroup analysis for the change in hTLV between baseline and post-treatment (week 132)

Supplementary Figure 2. Subgroup analysis for the change in hTLKV between baseline and end of treatment (week 120)