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Lanreotide Reduces the Volume of Polycystic Liver: A Randomized, Double-Blind, Placebo-Controlled Trial

Short title: *Lanreotide reduces volume of polycystic liver*

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Abbreviations:

ADPKD:	autosomal dominant polycystic kidney disease
ATP:	adenosine triphosphate
cAMP:	cyclic adenosine monophosphate
Cmin:	minimum serum level
CRISP:	Consortium for Radiologic Imaging Studies in Polycystic kidney disease
CT:	computerised tomography
GFR:	glomerular filtration rate
GGT :	γ glutamyl transferase
Gi:	inhibitory G protein
HRQoL:	health-related quality of life
PCLD:	polycystic liver disease
PCK:	polycystic kidney
PKD:	polycystic kidney disease
sc:	subcutaneous
SF-36:	Medical Outcomes Study Form 36

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ABSTRACT

Background & Aims: Therapy for polycystic liver is invasive, expensive and has disappointing long-term results. Treatment with somatostatin analogues slowed kidney growth in patients with polycystic kidney disease (PKD) and reduced liver and kidney volume in a PKD rodent model. We evaluated the effects of lanreotide, a somatostatin analogue, in patients with polycystic liver due to autosomal-dominant (AD)PKD or autosomal-dominant polycystic liver disease (PCLD).

Methods: We performed a randomized, double-blind, placebo-controlled trial in 2 tertiary referral centers. Patients with polycystic liver (n=54) were randomly assigned to groups given lanreotide (120 mg) or placebo, administered every 28 days for 24 weeks. The primary endpoint was the difference in total liver volume, measured by computerized tomography at Weeks 0 and 24. Analyses were performed on an intention-to-treat basis.

Results: Baseline characteristics were comparable for both groups, except that more patients with ADPKD were assigned to the placebo group (p=0.03). The mean liver volume decreased 2.9%, from 4606 mL (95% CI 547–8665) to 4471 mL (95% CI 542–8401), in patients given lanreotide. In the placebo group, the mean liver volume increased 1.6%, from 4689 mL (95% CI 613–8765) to 4895 mL (95% CI 739–9053) (p<0.01). Post-hoc stratification for patients with ADPKD or PCLD revealed similar changes in liver volume, with statistically significant differences in patients given lanreotide (P<0.01 for both diseases).

Conclusions: In patients with polycystic liver, 6-months of treatment with lanreotide reduces liver volume.

INTRODUCTION

Polycystic liver represents a late stage of disease that is common to two inherited disorders: autosomal dominant polycystic kidney disease (ADPKD) and autosomal dominant polycystic liver disease (PCLD). ADPKD is the most common inherited nephropathy and the second most common inherited syndrome, affecting an estimated 0.2% of the population.[1] Of ADPKD patients, 58% in 15–24 year, 85% in 25–34 year, and 94% in 35–46 year olds suffer from polycystic liver in addition to polycystic kidneys.[2] ADPKD is caused by gene mutations in *PKD1* and *PKD2*.[3, 4] By contrast, polycystic kidneys are lacking in patients with PCLD an infrequent inherited disorder caused by mutations in *PRKCSH* and *SEC63*.[5, 6]

The natural history of the disease suggests a continuous increase with age in the volume of the affected polycystic liver.[2] This is in part due to an increase with age in the number of hepatic cysts,[7] but also because the individual cyst volume grows from 0.25 mL to 22.8 mL over 10 years.[8] There is a gender disparity as cross-sectional studies in ADPKD have indicated that total liver cyst volume is significantly greater in women than in men.[2, 9] Symptoms in polycystic liver arise from enlarged liver volume, and include abdominal distension, early satiety, dyspnoea, and pain.[4, 10, 11] In addition, polycystic liver may be complicated by cyst bleeding, infection and/or rupture.[12]

Current therapeutic options aim to reduce liver volume and include a variety of surgical procedures such as aspiration-sclerotherapy, laparoscopic or laporotomic fenestration, and partial liver resection.[4, 13, 14] The drawbacks common to all of these procedures are their only partial effectiveness, their invasive nature, and their related morbidity and mortality. Most importantly, they do not change the natural course of the disease as symptoms recur, due to growth of new cyst or regrowth of treated cysts.[12] Consequently, there is a clear unmet need for other therapeutic options.

Liver cysts arise from cholangiocytes,[15] and its fluid homeostasis appears to be dynamic in nature, as secretin increases the fluid secretion in hepatic cysts.[16] Secretin is a potent stimulator of adenylate cyclase, which converts adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). cAMP acts as second messenger in the intracellular signal transduction and stimulates cyst growth by two major mechanisms: increase of release of electrolyte and water secretion from biliary epithelial cells,[17] and stimulation of cholangiocyte proliferations.[18, 19] Somatostatin inhibits fluid secretion and proliferation by reducing cAMP in cholangiocytes.[17, 20] In a rodent model for polycystic liver, the polycystic kidney (PCK) rats, administration of octreotide, a somatostatin analogue, prevented outgrowth of liver and kidney cysts.[21]

A 3–6 month treatment with somatostatin analogues in two patients with polycystic livers, led to impressive reductions in liver volume of 14.9% and 38.3 %, respectively.[22] This success stimulated us to assess the effect of the long-acting somatostatin analogue lanreotide in patients with polycystic liver due to either ADPKD or PCLD. To this end, we initiated a multicentre, randomized, double-blind, placebo controlled trial: the LOCKCYST trial.

MATERIALS AND METHODS

Patients

This study was performed in Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands and University Hospital Gasthuisberg, Leuven, Belgium. Men and women aged 18 years and older, with more than 20 liver cysts revealed by computerised tomography (CT) scan, were enrolled. Use of oral contraceptives or oestrogen supplementation was not allowed. Additionally, patients were excluded if they were pregnant or breast-feeding; had symptomatic gallstones; required haemodialysis; had a history of or other severe illnesses which would make that patient unsuitable for the study.

ADPKD was diagnosed in case of presence >5 kidney cysts in either of both kidneys were visible on CT, otherwise the patient was diagnosed with PCLD.

Ethical issues

The protocol was approved by the institutional review boards of the participating institutions according to their national guidelines and the study was performed according the Declaration of Helsinki and international standards of good clinical practice. All patients provided written informed consent. The trial had been registered at clinicaltrials.gov (NCT00565097). CONSORT guidelines were followed for the reporting of the study.[23]

Study design and outcome measures

Randomisation numbers were generated using the SAS RANDO (SAS Institute Inc., Cary, NC) randomisation tool. Randomisation was performed by an unblinded investigational pharmacist in blocks of four and the two treatment arms were allocated in a 1:1 ratio within each block. Participants and investigators were blinded to group assignment until database lock. Study medication was assigned to each participant according to the randomization code

either to the long-acting somatostatin analogue, lanreotide autosolution 120 mg, or to placebo (containing normal saline) administered subcutaneously (sc) every 28 days for 24 weeks. Physicians performing the assessments and patients were unaware of treatment assignment. Active drug and placebo were administered by independent physicians/nurses. Unblinding of investigators and participants was performed after all data collection was finished.

The primary endpoint was change in liver volume measured on CT scan at baseline and after 24 weeks of treatment. Secondary endpoints were change in kidney volume in ADPKD, change in abdominal symptoms and health-related quality of life (HRQoL), assessed on the same time points. Type and severity of gastrointestinal symptoms, that is, abdominal and epigastric pain, regurgitation, heartburn, and loss of appetite, were assessed on a valid seven-point adjectival scale.[24] HRQoL was assessed using the Medical Outcomes Study Form 36 (SF-36),[25] which comprises nine minor domains (physical functioning, social functioning, physical role functioning, emotional role functioning, mental health, vitality, bodily pain, change in health perception and general health perception) which can be summarised into a physical and a mental component. Lower scores indicate worse HRQoL.

Safety analyses were performed for all patients. Standard clinical and laboratory tests were performed at baseline, Week 4, Week 12 and Week 24.

CT scanning and 3D volumetry

CT scans at baseline and week 24 were performed on a multidetector CT scanner (Somatom Sensation 16 or 64, Siemens Medical Solution AG, Erlangen, Germany). (supplementary file) All CT scans were blinded to patient identity and date of birth as well as date of scan. In random order, measurements of liver and kidney volume in ADPKD patients were performed as previously described.[14] Unblinding of CT scans was performed after all liver and kidney volumes were measured

Lanreotide serum levels

Lanreotide serum levels were measured at week 0 and week 12 in patients who received lanreotide in the Radboud University Nijmegen Medical Center. Blood samples were taken prior to injection at weeks 0 and 12 for measurement of minimum lanreotide serum levels at 12 weeks (Cmin) with baseline as a reference. Serum concentrations of lanreotide were determined using a validated radioimmunoassay method as described before.[26]

Statistical analysis

Sample sizes were determined prospectively with reference to two previous (pre)clinical studies that used similar end points.[21, 27] We hypothesized detection of a difference (effect size) of 50 percentage points between response rates in the two groups (30% in the placebo group; 80% in the lanreotide) for the primary outcome. For a statistical power of 80% and a probability of a type I error of 0.05 using a two-sided test, we calculated that the sample size for this trial should be at least 38 patients (19 per group). Taking into account the possibility of protocol violation and/or drop-outs, we aimed at inclusion of 27 patients per group. Statistical analysis was performed on an intention-to-treat analysis, defined as all randomly assigned patients who received at least one dose of study drug. For continuous data, Student's *t*-test was used to calculate differences between groups for normally distributed data or Mann-Whitney *U*-test for non-normally distributed data. The Pearson Chi-Squared test was used to compare dichotomised outcomes between the groups.

All statistical analyses were undertaken with SPSS statistical software package version 16.0 (SPSS Inc., Chicago, IL, USA). All p-values calculated were two-tailed and the level of significance was set at α=0.05.

RESULTS

Baseline characteristics

A total of 113 consecutive patients with polycystic liver were assessed during the study period. Of these, 56 patients declined to participate and three patients were excluded as they did not fulfill the inclusion criteria. Between October 2007 and February 2008, the remaining 54 patients were randomly assigned to receive lanreotide 120 mg or placebo sc every 28 days. Baseline characteristics are shown in table 1. One female patient, who was randomly assigned to placebo, withdrew after 14 weeks of the study, as she was diagnosed with breast carcinoma. One patient on lanreotide omitted the injection at week 4, as he experienced very severe diarrhea and abdominal cramps. One patient on placebo did not receive injection 6 (at Week 20) (Figure 1). The treatment group and placebo group were similar for most characteristics, except for the genetic background (ADPKD versus PCLD) ,and relatively more PCLD patients (68%) than ADPKD patients (38%) received lanreotide.

Liver volume

The mean liver volume decreased from 4606 (95% CI 547–8665) to 4471 (95% CI 542–8401) mL in patients assigned to 6-month treatment with lanreotide, an average reduction of 2.9% (95% CI -11.1–5.4). In contrast, patients in the placebo group had an increase in mean liver volume from 4689 (95% CI 613–8765) to 4896 (95% CI 739–9053) mL, an average increase of 1.6% (95% CI -5.2–8.4) over the same time span (table 2). The difference in change in liver volume between treatment arms was statistically significant ($p<0.01$). Of patients on lanreotide, 85% showed a decrease of liver volume, compared with 27% of patients receiving placebo (figure 2). There was a correlation between liver volume at baseline and response to treatment: we saw that larger livers had proportionally more volume reduction than smaller livers ($r = -0.42$, $p=0.032$).

Next, we explored whether genetic cause of the disease affected the primary outcome. We performed post-hoc stratification using ADPKD and PCLD as variables. The change in liver volume was similar in both groups and independent of cause of disease, and for both disorders differences between placebo and lanreotide were statistically significant (both $p<0.01$) (table 2).

Kidney volume

We assessed volume of polycystic kidneys in ADPKD patients. Combined mean kidney volume decreased from 1000 mL (95% CI -39–2039) to 983 mL (95% CI -62–2028), a decrease of 1.5% (95% CI -13.2–10.3) in patients treated with lanreotide. In contrast, mean kidney volume increased from 1115 mL (95% CI -519–2748) to 1165 mL (95% CI -541–2870) (3.4%; 95% CI -7.1–14.0) in the placebo group. Again, the treatment differences in volume change were statistically significant ($p=0.02$) (table 2).

Laboratory results

Baseline laboratory results did not differ between treatment arms. Liver synthesis capacity was normal in all patients during the study. Biochemical and haematological changes during the trial were comparable between groups with the exception of γ glutamyl transferase (GGT) levels (table 3). Treatment with lanreotide led to a significant increase in GGT levels at t=24 weeks compared with placebo. The difference was significant within the individual treatment arms ($p=0.03$) as well as between placebo and lanreotide ($p=0.03$). We were interested in the effect of lanreotide on renal function and assessed serum creatinine levels. In comparison to placebo, we found that lanreotide treatment decreased serum creatinine levels, although this did not reach statistical significance ($p=0.079$).

Gastrointestinal symptoms and health-related quality of life

We observed no significant changes in gastrointestinal symptoms (Supplementary table 1). A single subdomain score of the HRQoL questionnaire (SF-36), that is, current health perception, improved significantly from 42 (95% CI -11–94) to 62 (95% CI 18–106) in patients treated with lanreotide ($p<0.01$) and this change was also significant ($p<0.01$) compared with placebo where values remained stable (43 [95% CI -4–90] to 41 [95% CI 4–78]). No other HRQoL subdomains changed over the course of the study (Supplementary table 2).

Adverse events

There were no severe adverse events related to the study medication. No important changes occurred in the monitored laboratory parameters (table 3), and no changes in body weight were observed. The most common side 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 (table 4). Six patients were treated with pancreatic enzymes, which readily improved the symptoms. Thirteen patients (48%) on lanreotide reported nodules on the injection site.

Lanreotide serum levels

Lanreotide measurements were performed in 30 samples at two time points for 15 patients. At baseline, lanreotide concentration was below the lower limit of quantification (0.078 ng/mL). At week 12, mean lanreotide concentration had risen to 3.36 ng/mL (95% CI 0.53–6.18). There was no correlation between lanreotide serum level and response to treatment, suggesting that the achieved serum levels surpassed the treatment threshold.

DISCUSSION

Our results demonstrate that injections of lanreotide 120 mg given once a month for 6 months result in a significant mean reduction of liver volume of 134 mL (2.9%) in patients with polycystic liver. The improvement was independent of genetic cause of the polycystic liver, as PCLD and ADPKD patients benefited similarly, but we observed that larger livers benefited most. In contrast, patients who received placebo ran an unfavourable course with a mean increase of liver volume of 1.6% over 6 months. Moreover, lanreotide improved the general health perception of patients with polycystic liver at 6 months.

Although it was not the primary purpose of our study to demonstrate that lanreotide had extra-hepatic beneficial effects, we saw an improvement in the renal phenotype in ADPKD. At 6 months, the volume of polycystic kidneys had grown by 3.4% in the placebo group but decreased by 1.5% with lanreotide, a difference of 4.9% at 6 months. Data from a large observational trial, the Consortium for Radiologic Imaging Studies in Polycystic kidney disease (CRISP) study,[8] indicate that kidney volume in ADPKD patients at high risk for renal insufficiency increases annually by 5.3%. We studied a population with milder ADPKD: despite this difference, average size of polycystic kidneys at baseline (~1000 mL) and average growth in ADPKD patients on placebo (3.4% per 6 months) is comparable with the average size and annual growth seen in the CRISP study.

We had several reasons to select somatostatin analogues as a therapeutic option in polycystic liver. It is known that somatostatin receptors are expressed on cholangiocytes and rodent liver cyst epithelia.[20, 21] After binding to these somatostatin receptors, somatostatin activates signalling cascades through the inhibitory G (Gi) protein, which suppresses cAMP. cAMP appears to be an important stimulator of fluid secretion and cell proliferation of renal cysts in ADPKD, [28] and also of liver cysts in appropriate rodent models.[21] A randomized study in ADPKD patients, studied the effect of slow-release octreotide 40 mg or placebo on

polycystic kidney volume.[27] Octreotide possessed a treatment advantage by reducing kidney volume increase by 60% at 6 months compared with placebo, but there was still an ongoing increase of kidney volume in both groups (2.2% octreotide; 5.9% placebo). This contrasts with our study where long-acting lanreotide resulted in a decrease of kidney volume by 1.5%. It is unclear whether a distinct pharmacokinetic and pharmacodynamic profile explains the differences. We treated our patients with lanreotide 120 mg, which is equivalent to octreotide 60 mg, suggesting that higher serum levels were probably present in our study.[29] In contrast, somatostatin receptor affinity of octreotide is higher compared with that of lanreotide, which may offset the higher serum levels.[30]

Lanreotide was well tolerated in all patients. We did not observe any unexpected severe adverse events.[31-33] The most commonly reported adverse event was diarrhoea associated with abdominal cramps. Symptoms improved over the course of a few days and stopped after repeated injections or after administration of pancreatic enzymes. Gluteal nodules following injection were reported in 48% of patients.

At baseline, GGT was elevated in both groups. During treatment with lanreotide, GGT increased further. GGT is a component on the brush border of hepatic cyst epithelium and it is thought to be released in case of cyst epithelium degeneration.[16] This could be a possible explanation for the elevation of GGT in the treated group.

How do results from this study compare with other treatment modalities? A recent case series noted that aspiration and sclerosis of individual liver cysts reduced liver volume by 19%.[13] However, these were patients with one or more large dominant liver cysts, whereas most patients with a polycystic liver have widespread disease that is not amenable to this therapy. Alternatively, (laparoscopic) fenestration might be used as an option.[14, 34-37] The risk : benefit ratio of this procedure is suboptimal with a moderate reduction of liver volume (12.5%) and high complication risk (0–33%).

This study comes with several limitations. We excluded patients requiring haemodialysis because of renal failure. There was a slight decrease of serum creatinine in patients treated with lanreotide compared with placebo, suggesting a beneficial effect on renal function. As patients had a relatively well preserved renal function, we do not expect large changes in glomerular filtration rate (GFR). On the other hand, another randomized study with octreotide witnessed an increase of serum creatinine and GFR in ADPKD patients.[27] Again, this might be due to differences in the pharmacological profile of the two drugs, but also because patients in the octreotide trial had worse renal function from the outset. The nature of this study did not allow us to assess long-term safety. Nevertheless, we did not observe any new types of adverse events compared with other randomized trials with lanreotide.[32] We chose a 6-month treatment regimen, and it is unclear whether a longer treatment would have demonstrated better results; experiments in a rodent model for polycystic disease suggest that the beneficial effects of somatostatin analogues are time- and dose-dependent. [21] This suggests that longer treatment might result in more substantial effects. Indeed, prolonged lanreotide administration is feasible, as long term studies in patients with acromegaly have shown that treatment up to 4 years is well tolerated.[32] Further, little is known about the optimal dosage of somatostatin analogues. We chose for the highest licensed dose of lanreotide at 120 mg. In addition, it is not known whether the observed effect in this study is reversed after discontinuation of the drug, or in case of continuation lanreotide becomes less effective.

This study demonstrates that lanreotide is able to change the natural disease course of polycystic livers in ADPKD and PCLD. The modest effect calls for further clinical trials, prior to adoption into clinical practice.

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TABLES:

***Table 1*: Demographics and baseline clinical characteristics.** Data are mean (95% CI).

	Lanreotide group (N=27)	**Placebo group (N=27)**	**p**
Age (years)	49.6 (34.4–64.8)	50.3 (32.6–68.1)	0.752
Sex (male/female)	3/24	4/23	0.685
Diagnosis (ADPKD/PCLD)	12/15	20/7	0.027
Centre (Leuven/Nijmegen)	12/15	12/15	1.000
Body mass index (kg/m^2)	26.1 (18.7–33.5)	25.7 (18.6–32.8)	0.733
Liver volume (mL)	4606 (547–8665)	4689 (613–8765)	0.698
Right and left kidney volume (mL)*	1000 (-39–2039)	1115 (-519–2748)	0.673

*Only ADPKD patients

ADPKD, autosomal dominant polycystic kidney disease; PCLD, polycystic liver disease.

Table 2: **Outcomes** Data are mean (95% CI).

	Diagnosis	Lanreotide			Placebo			p
		Baseline	**End**	**Absolute change**	**Baseline**	**End***	**Absolute change***	
Liver volume (mL)	**Both**	4606 (547–8665)	4471 (542–8401)	-134 (-476–207)	4689 (613–8765)	4896 (739–9053)	92 (-320–504)	<0.01
		-2.9% (-11.1–5.4)			1.6% (-5.2–8.4)			
Liver volume (mL)	**PCLD**	4195 (437–7952)	4138 (462–7814)	-57 (-337–223)	3855 (-338–8047)	4428 (-140–8996)	213 (-268–695)	<0.01
		-1.1% (-7.3–5.0)			3.8% (-3.9–11.4)			
Liver volume (mL)	**ADPKD**	5119 (762–9476)	4888 (645–9130)	-231 (-555–93)	4981 (1000–8963)	5036 (925–9148)	55 (-318–428)	<0.01
		-5.0% (-13.8–3.7)			9.9% (-5.2–7.2)			
Kidney volume (mL)	**ADPKD**	1000 (-39–2039)	983 (-62–2028)	-17 (-126–93)	1115 (-519–2748)	1165 (-541–2870)	50 (-99–199)	0.018
		-1.5% (-13.2–10.3)			3.4% (-7.1–14.0)			

*Not of all patients end data available: baseline n=27, end n=26

ADPKD, autosomal dominant polycystic kidney disease; PCLD, polycystic liver disease.

Table 3: **Laboratory results**. Data are mean (95% CI).

	Lanreotide			**Placebo**		
	Baseline	**End**	**Absolute change**	**Baseline**	**End***	**Absolute change***
Creatinine (μmol/L)	83 (8–158)	80 (8–153)	-2 (-20–15)	91 (9–173)	96 (-12–205)	4 (-29–38)
AST (U/L)	29 (-16–74)	31 (-10–73)	2 (-15–19)	23 (8–39)	28 (8–48)	4 (-13–21)
ALT (times ULN)	1.1 (0.2–2.1)	1.1 (0.3–2.0)	-0.0 (-0.5–0.5)	1.1 (0.6–1.6)	1.1 (0.3–1.9)	0.0 (-0.8–0.8)
Alkaline phosphatase (times ULN)	1.3 (-0.0–2.5)	1.4 (-0.6–3.3)	0.1 (-0.7–1.0)	1.0 (0.9–1.2)	1.0 (0.8–1.3)	0.0 (-0.1–0.1)
γ Glutamyl transferase (times ULN)	3.4 (-3.6–10.4)	4.1†‡ (-5.2–13.3)	0.7†‡ (-2.2–3.5)	2.5 (-2.5–7.6)	2.5 (-2.0–7.0)	-0.1 (-1.7–1.6)
Bilirubin (μmol/L)	10 (-3–23)	11 (-1–23)	1 (-8–9)	10 (1–18)	11 (2–20)	2 (-6–9)
Albumin (g/L)	43 (34–51)	44 (37–52)	2 (-3–6)	43 (36–50)	44 (36–52)	1 (-4–5)

*Not of all patients end data available: baseline n=27, end n=26

†p<0.01 vs baseline;

‡p=0.03 vs placebo

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit of normal.

Table 4: **Adverse events**

Adverse event	**Lanreotide n/N* (%)**	**Placebo n/N* (%)**
Digestive tract		
Diarrhoea	19/27 (70)	3/27 (11)
Pale stools	11/27 (41)	0/27 (0)
Abdominal cramps	14/27 (52)	0/27 (0)
Flatulence	2/27 (7)	0/27 (0)
Constipation	1/27 (4)	0/27 (0)
Other		
Nodules at injection side	13/27 (48)	0/27 (0)
Rash	2/27 (7)	0/27 (0)
Breast carcinoma	0/27 (0)	1/27 (4)

* Denominators is total of patients in study arm

FIGURE LEGENDS

Figure 1: **Trial profile**

Figure 2: **Absolute change in liver volume in all patients** Each bar represents one patient (n=53)

Figure 1
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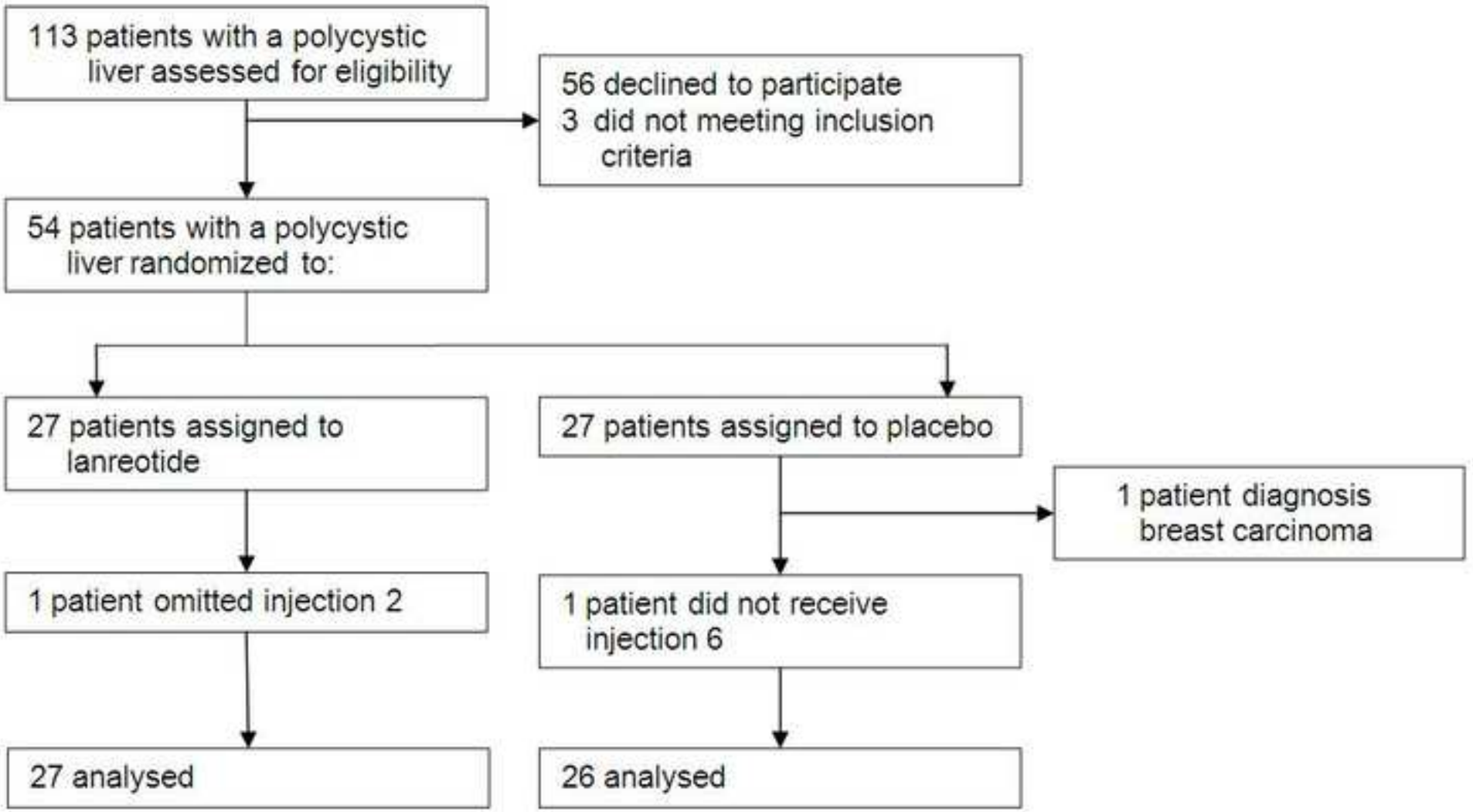

Figure 2

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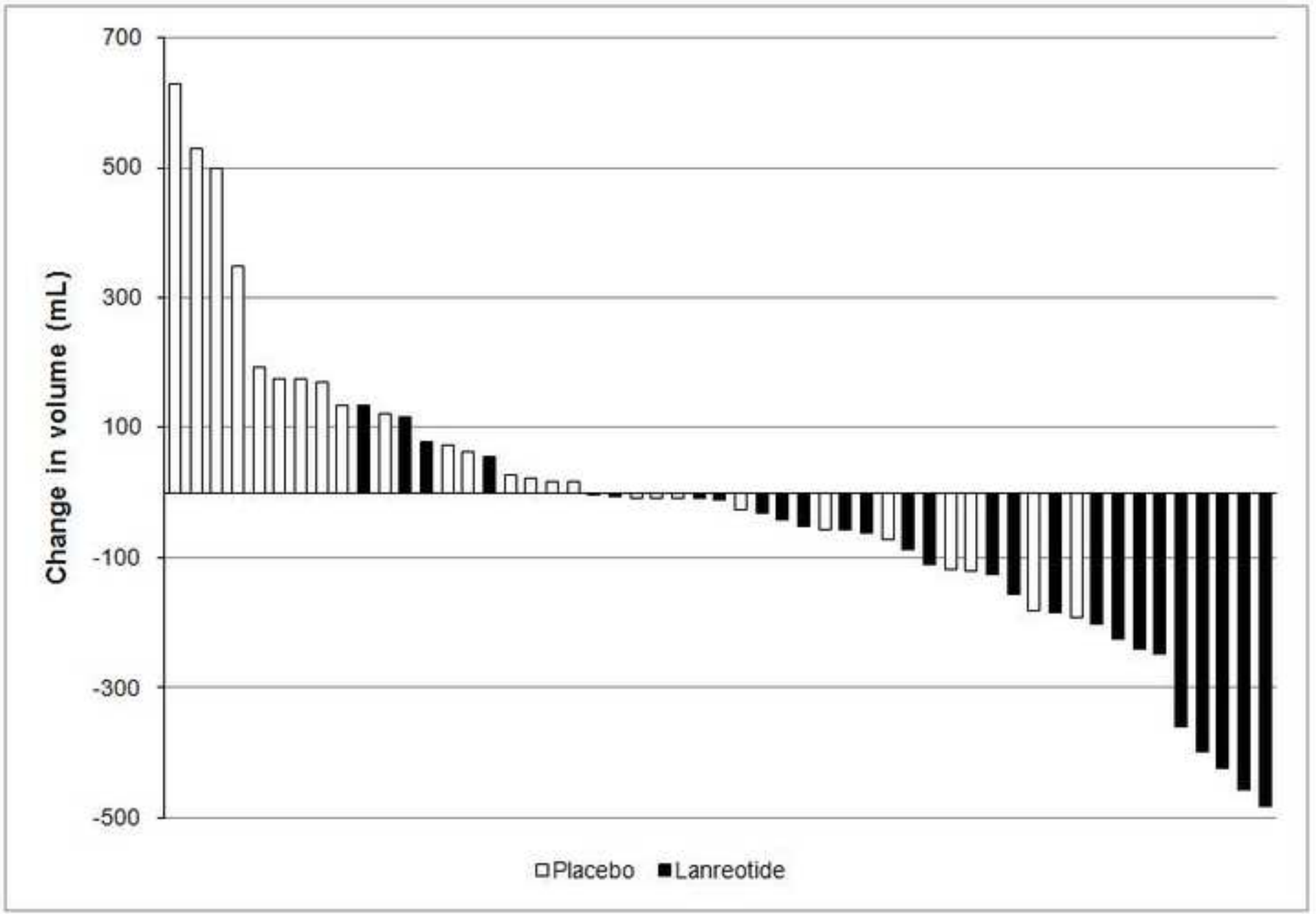
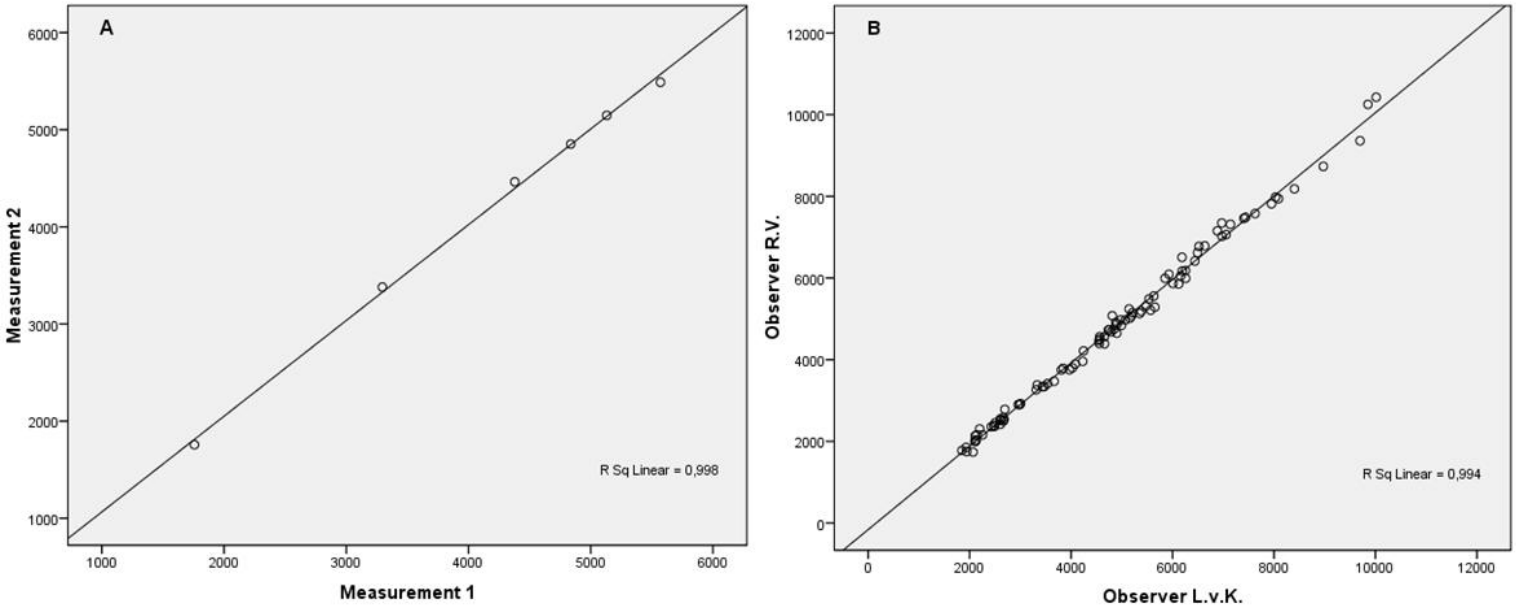


Supplementary figure 1: Scatter-plots showing correlation between intra-observer (A) and interobserver (B).

Briefly, after loading the CT scan into Pinnacle$^{3®}$ v8.0d (Philips Electronics NV, Eindhoven, the Netherlands), the liver outline was manually delineated in transverse slices every 9 or 10 mm, and for the kidney outline every 5 or 6 mm. Software interpolated intermediate slices and after fine tuning of the interpolated contours the indicated circumferences were calculated for total liver and kidney volume.

We validated our results by using a second independent and aselective set of CT scans from PCLD and ADPKD patients. Measurements of liver and kidney volume were performed twice in a blinded manner by the same researcher (L.v.K). We calculated the Pearson's correlation for the intra-observability, which was excellent ($r=0.998$, $p<0.01$) (Supplementary figure 1). Next, another validation step was introduced as a quality measure, and volumes were determined independently by a second observer (R.V.) using Siemens Volume software (Siemens Medical Solutions, Erlangen, Germany). The liver was outlined manually every 3 or 5 mm without inter-slice interpolation of the edges. As the software is based on Hounsfield Units (HU; densities), the following threshold settings were used: -15 HU to + 125 HU for unenhanced CT scans, 15 HU to + 195 HU for contrast-enhanced CT scans. We calculated the interobserver correlation by the Pearson correlation which was excellent as well ($r=0.994$, $p<0.01$) (supplementary figure 1).



***Supplementary table 1: S*everity of abdominal symptoms and mean VAS score**.

	Lanreotide		Placebo	
	Baseline n/N (%)*	**End n/N (%)***	**Baseline n/N (%)***	**End n/N (%)***
Abdominal pain				
In common	10/27 (37)	9/27 (33)	8/26 (31)	6/26 (23)
Postprandial	12/26 (46)	8/27 (30)	9/27 (33)	8/26 (31)
Fasting	8/26 (31)	6/27 (22)	9/27 (33)	5/26 (19)
Unrelated to defecation	6/26 (23)	7/27 (26)	6/27 (22)	6/26 (23)
Epigastric				
In common	13/27 (48)	8/26 (30)	13/26 (50)	13/26 (50)
During daytime	12/26 (46)	10/27 (37)	13/27 (48)	13/26 (50)
At night/asleep	9/26 (35)	4/27 (15)	11/27 (41)	11/26 (42)
Heartburn	9/27 (33)	4/27 (15)	8/27 (30)	4/25 (16)
Regurgitation	12/27 (44)	6/27 (22)	12/27 (44)	9/26 (35)
Nausea	6/27 (22)	6/27 (22)	8/27 (30)	10/26 (38)
Vomiting	4/27 (15)	1/27 (4)	3/27 (11)	2/26 (8)
Loss of appetite	10/27 (37)	9/27 (33)	8/27 (30)	6/26 (23)
Postprandial fullness	15/27 (56)	16/27 (59)	21/27 (78)	19/26 (73)
Shortness of breath	12/27 (44)	14/27 (52)	15/27 (56)	14/26 (54)
Abdominal distension	16/27 (59)	14/25 (56)	18/27 (67)	14/26 (54)
Involuntary weight loss	4/27 (15)	6/27 (22)	4/27 (15)	3/26 (12)
VAS score[†]	21 (-23–66)	22 (-27–71)	20 (-16–57)	25 (-23–73)

* Denominators depend on the number of patients who provided an answer for a specific question in the questionnaire.

[†] Data are mean (95% CI).

Abdominal symptom severity ≥ 2 on a seven-point adjectival scale ranging from 0 to 6.

VAS, visual analogue scale; scored on a range of 0–100 (0=no pain, 100=worst pain)

Supplementary table 2: **Mean health-related quality of life scores.** Data are mean (95% CI).

	Lanreotide		Placebo	
SF-36	**Baseline**	**End**	**Baseline**	**End**
Physical functioning	64 (6–123)	69 (15–123)	64 (21–107)	61 (21–101)
Social functioning	75 (24–126)	78 (27–129)	74 (20–128)	77 (29–125)
Physical role functioning	54 (-33–140)	65 (-21–151)	55 (-30–139)	51 (-40–142)
Emotional role functioning	86 (31–142)	74 (-4–152)	78 (7–150)	80 (9–151)
Mental health	75 (43–107)	72 (36–108)	74 (42–107)	74 (40–109)
Vitality	54 (8–100)	55 (17–93)	50 (7–93)	50 (15–86)
Bodily pain	22 (-4–49)	24 (4–45)	24 (3–45)	22 (-2–46)
Change in health perception	42 (-11–94)	62 (18–106) *†	43 (-4–90)	41 (4–78)
General health perception	53 (12–94)	59 (20–97)	48 (4–93)	48 (11–84)
Physical component summary	54 (12–95)	58 (14–97)	53 (14–92)	52 (4–78)
Mental component summary	69 (35–102)	67 (26–109)	66 (23–108)	66 (15–88)

Scored on a range of 0–100 (0=worst imaginable, 100=best imaginable).
*$p<0.01$ vs baseline; †$p<0.01$ vs placebo