NHS England Evidence Review:

Lanreotide for polycystic liver disease

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Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost-effectiveness of lanreotide (a somatostatin), with or without supportive treatment, compared to current supportive treatment alone (including placebo control), octreotide (another somatostatin) or liver transplant in patients with polycystic liver disease (PLD).

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from treatment with lanreotide more than others, as well as the criteria used by the included studies to confirm a diagnosis of PLD.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost-effectiveness of lanreotide (a somatostatin) compared with current supportive treatment alone (including placebo control), octreotide (another somatostatin) or liver transplant in patients with polycystic liver disease (PLD).

The searches for evidence published since January 2014 were conducted on the 3rd and 4th December 2024 and identified 199 references. References were screened by title and abstract and 29 full text papers were obtained for full text assessment for relevance.

Overall, 5 study papers were identified for inclusion. Two of these studies were systematic reviews and meta-analyses. However, due to the systematic reviews having limited relevant outcomes, additional data on other outcomes have been extracted from 3 other study papers (2 from the same randomised controlled trial (RCT) and 1 observational study) that also met the inclusion criteria for this review.

The 2 systematic reviews and meta-analyses (Griffiths et al. 2020 and St Pierre et al. 2024) contain outcomes in relation to a few critical, important and safety outcomes relevant to this review. The Griffiths et al. (2020) systematic review included the LOCKCYST RCT which compared lanreotide with placebo and both systematic reviews included the DIPAK-I RCT which compared lanreotide to 'standard of care'. Further evidence for lanreotide on other relevant outcomes was obtained from a randomised controlled trial (the DIPAK-I RCT) reported in 2 papers (Aapkes et al. 2021 and van Aerts et al. 2019) and a prospective observational study (Temmerman et al. 2015) which had no comparator. No studies were identified comparing lanreotide with octreotide or to liver transplantation. No evidence was identified for the outcomes of liver transplant or cost-effectiveness of lanreotide.

In terms of clinical effectiveness:

Critical outcomes

- Total liver volume. A meta-analysis (Griffiths et al. 2020) of 2 RCT provided high certainty evidence that lanreotide statistically significantly reduced total liver volume compared with control (placebo and 'standard of care') at treatment end (6 months in 1 RCT and 120 weeks in the other RCT), mean difference −0.14 litre (L) (95% CI −0.26 to −0.02; p=0.02). However, the reduction is not likely to be clinically meaningful using the default minimal clinically important difference (MCID) for continuous outcomes.
- Symptom control. The DIPAK-I RCT (van Aerts et al. 2019, n=175) provided low certainty evidence that there was no statistically significant difference between lanreotide and 'standard of care' for median symptom scores at baseline (p=0.1) or follow-up (p=0.9) at treatment end (120 weeks). An observational study (Temmerman et al. 2015, n=59) provided very low certainty evidence that the following Polycystic Liver Disease-complaint-specific assessment (POLCA) severity scores were statistically significantly reduced from baseline to follow-up at 18 months: perceived illness (p<0.0001), gastroesophageal reflux disease related complaints (p=0.001), impact on food intake (p=0.04), and perception of enlarged liver volume (p=0.008).

  In the observational study very low certainty evidence for nutritional status was also reported and the mean weight of participants was statistically significantly lower (p=0.01) from baseline 72 [2.2] Kg compared to 70 [2.3] Kg at 18 months. Very low certainty evidence was also reported for the proportion (%) of participants with severe skeletal muscle depletion or sarcopenia which increased from baseline (27%) to 18 months follow-up (38%), but the increase was not statistically significantly different.

- Quality of life. One systematic review (St Pierre et al. 2024) provided moderate certainty evidence from 1 RCT (DIPAK-I RCT, n=305) that there was no statistically significant mean difference in quality of life −0.02 (95% CI −0.12 to 0.08, p=0.69) between lanreotide and 'standard of care' at treatment end (120 weeks).

Important outcomes

- Imaging changes. The DIPAK-I RCT (Aapkes et al. 2021, n=249) provided moderate certainty evidence that at treatment end there was a statistically significant increase ($p<0.05$) in the number of participants with gallstones in the lanreotide group compared with 'standard of care'. The difference remained statistically significant ($p<0.0001$) when adjusted for baseline presence of gallstones. The RCT provided moderate certainty evidence of a statistically significant increase in new incident gallstones in the lanreotide group compared with 'standard of care' in both univariate (odds ratio [OR] 22.5, 95% CI 2.96 to 171, $p<0.01$) and multivariate logistic regression analysis (OR 25.9, 95% CI 3.37 to 199, $p<0.01$). The RCT provided moderate certainty evidence that lanreotide statistically significantly increased the number of incident gallstones for each participant compared to gallstones at baseline ($p=0.004$). However, the new incident gallstones were statistically significantly smaller than those present at baseline ($p=0.001$). Only p values were presented for this outcome, so it is not clear if these are clinically meaningful differences.
- Treatment adherence. The DIPAK-I RCT (van Aerts et al. 2019, n=175) provided low certainty evidence from the intervention group only as the comparator was 'standard of care' and no statistical analysis was performed. In the study, lanreotide was titrated down from 120 mg in 23 of 93 participants during the study period (to 90 mg in 20 participants and to 60 mg in 3 participants). 8 participants were titrated down due to eGFR reaching <30 mL/min/1.73m^2. Fifteen participants were titrated down due to adverse events. In 6 out of 7 participants who were titrated down due to gastrointestinal complaints, the adverse effects were tolerable at the lower dose.
- Liver transplantation. No evidence was identified for liver transplantation.
- Renal function. A systematic review (Griffiths et al. 2020) provided moderate certainty evidence from 1 RCT (DIPAK-I RCT, n=290) that there was no statistically significant difference in estimated glomerular filtration rate (eGFR), mean difference −0.60 mL/min/1.73m^2 (95% CI −3.65 to 2.45, p=0.70) between lanreotide and 'standard of care' at the treatment end (120 weeks).

  One systematic review (St Pierre et al. 2024) provided low certainty evidence from 1 RCT (DIPAK-I RCT, n=305) that there was no statistically significant difference between lanreotide and 'standard of care' for a composite outcome of 30% or more decrease in GFR or kidney failure, relative risk (RR) 0.72 (95% CI 0.43 to 1.20, p=0.21) at treatment end (120 weeks).

  A meta-analysis (Griffiths et al. 2020) of 2 RCTs provided moderate certainty evidence that lanreotide was statistically significantly associated with a reduction in total kidney volume compared with placebo or 'standard of care', mean difference −0.15 L (95% CI −0.21 to −0.10, $p<0.00001$). However, the reduction was not likely to be clinically meaningful using the default MCID for continuous outcomes.

In terms of safety:

- Mortality. A systematic review (St Pierre et al. 2024) provided very low certainty evidence from 1 RCT (DIPAK-I RCT, n=305) that there was no statistically significant

difference in risk of death between lanreotide (1 death) compared with 'standard of care' (0 deaths), RR 3.02 (95% CI 0.12 to 73.55, p=0.50) during follow-up (120 weeks).

- Number of people with serious adverse events. One RCT (van Aerts et al. 2019, DIPAK-I RCT, n=175) provided very low certainty evidence on the number of participants with serious adverse events, in the lanreotide group 28 out of 93 (30.1%) had a serious adverse event compared with 10 out of 82 (12.2%) in 'standard of care' group. No statistical analysis was presented.
- Serious adverse events considered related to lanreotide. One RCT (van Aerts et al. 2019, DIPAK-I RCT, n=175) provided very low certainty evidence on serious adverse events considered related to treatment with lanreotide. Thirteen of the serious adverse events were thought to be related to the study medicine compared with n=3 in the 'standard of care' group. No statistical analysis was presented.
- Serious adverse events leading to study withdrawal. One RCT (van Aerts et al. 2019, DIPAK-I RCT, n=175) provided very low certainty evidence on the number of serious adverse events leading to study withdrawal. The number of participants with a serious adverse event leading to study withdrawal in the lanreotide group was 4 out of 93 (4.3%) compared with 1 out of 82 (1.2%) in the 'standard of care' group. No statistical analysis was presented.

In terms of cost-effectiveness:

- No evidence was identified for cost-effectiveness.

In terms of subgroups:

- Total liver volume subgroup by sex measured from baseline to follow-up. One RCT (van Aerts et al. 2019, DIPAK-I RCT, n=175) provided evidence on total liver volume sub-grouped by sex. The study population included 40 males in each group, representing 43.0% of the lanreotide group and 48.9% of the 'standard of care' group. At baseline height-adjusted liver volume was significantly higher in females than males (p<0.001). At treatment end (120 weeks) liver growth was similar in men and women. At treatment end (120 weeks) there was a statistically significant mean percentage reduction in height-adjusted liver volume in women in the lanreotide group (−7.68%, p=0.001) compared with women in the 'standard of care' group. At treatment end (120 weeks) there was a non-statistically significant mean percentage reduction in height-adjusted liver volume in men in the lanreotide group (−4.05%, p=0.09) compared with men in the 'standard of care' group. The subgroup analysis provides evidence that gender does not appear to be an effect modifier for change in height-adjusted total liver volume (p=0.3).
- Symptom control (nutritional status). A prospective observational study (Temmerman et al. 2015, n=59) provided evidence related to symptom control measured from baseline to treatment end, 18 months. The intervention was lanreotide 90 mg subcutaneously every 4 weeks, with potential escalation in dose (to 120 mg), depending on response (non-responders had a liver volume decrease of <100 mL) at 6 months. In the subgroup of responders (n=21), those with a liver volume decrease of >100 mL in the first 6 months, the mean weight statistically significantly decreased from baseline to 18 months by 3 Kg, p=0.006. The mean skeletal mass index in the responder subgroup also statistically significantly decreased from baseline to 18 months from 44.5 cm^2/h^2 [SE 1.6 cm^2/h^2] to 42.5 cm^2/h^2 [SE1.6 cm^2/h^2], p=0.001. In the subgroup of non-responders (n=22) the mean weight remained stable (data not reported). The mean skeletal mass index reduced in the subgroup of non-responders, but the reduction was not statistically significant, p=0.13.

Frequency, dose, formulation and route of administration of lanreotide in the included studies

- For the LOCKCYST trial (included in the Griffiths et al. 2020 systematic review) lanreotide was given every 28 days, the dose was 120 mg (long-acting release [LAR]) subcutaneously.
- For the DIPAK-I trial included in both systematic reviews (Griffiths et al. 2020 and St Pierre et al. 2024) and reported in the DIPAK-I study papers (Aapkes et al. 2021 and van Aerts et al. 2019) lanreotide was given every 28 days, the dose was 120 mg (LAR) subcutaneously.
- In the prospective observational study (Temmerman et al. 2015) lanreotide was given every 28 days, the dose was 90 mg subcutaneously, with a dose escalation to 120 mg subcutaneously (every 28 days) for non-responders (reduction in liver volume of less than 100 mL at 6 months follow-up).

See the results table (section 5) in the review for further details of outcomes and definitions.

Limitations

This review found no evidence for using lanreotide in children or young people aged less than 18 years and this medicine is not licensed for this indication in children (for details see the summary of product characteristics). The review also found no evidence for lanreotide compared with octreotide or liver transplantation for any outcome, or for liver transplantation as an outcome in any of the included studies. There was no evidence of cost-effectiveness for lanreotide.

Both included systematic reviews were assessed as being of high quality, although the Griffiths et al. (2020) study does have some methods reporting limitations including the lack of a published protocol, some ambiguity around the diagnostic criteria reported by the studies, no additional methods of identifying studies beyond database searching was reported, and no information was reported on how studies were identified for inclusion (sifting). The outcomes in the St Pierre et al. (2024) systematic review which include the DIPAK-I RCT have been downgraded due to the risk of bias of this trial. The main risk of bias in the DIPAK-I RCT (also reported in Aapkes et al. 2021 and van Aerts et al. 2019) relate to its open-label design and standard of care comparator which place it at high risk of open-label study bias.

The main limitations of the prospective observational study of lanreotide by Temmerman et al. (2015) is the lack of description of the diagnostic criteria used for inclusion, and insufficient information is given about the recruitment of the cohort to allow for proper assessment of the method. No information was provided on exclusions, or adjustment, for other treatments that may have been used during the study period that could cause confounding of the study outcomes. It was quality assessed using the CASP tool for cohort studies and found to be very low quality.

Conclusion

Results from one systematic review (Griffiths et al. 2020) provides high certainty evidence that, in meta-analysis, treatment with lanreotide statistically significantly reduces total liver volume (critical outcome) measured at different time points from 6 months to 120 weeks, but the reduction is not likely to be clinically meaningful compared with placebo or ‘standard of care’.

Low certainty evidence from van Aerts et al. 2019 (DIPAK-I) RCT showed that there was no statistically significant difference in symptom control measured using a 7-point scale compared

with ‘standard of care’ at 120 weeks. However, very low certainty evidence from the Temmerman et al. 2015 observational study indicates that treatment with lanreotide statistically significantly improves symptom control at 18 months compared with baseline scores using the validated POLCA score.

The Temmerman et al. 2015 study found very low certainty evidence that treatment with lanreotide resulted in a statistically significant decrease in weight at 18 months compared with baseline.

The DIPAK-I RCT, reported in St Pierre et al. 2024, found with moderate certainty that treatment with lanreotide does not statistically significantly affect the critical outcome of quality of life compared with ‘standard of care’ at 120 weeks.

Aapkes et al. 2019 (DIPAK-I) provides moderate certainty evidence that treatment with lanreotide statistically significantly increases the odds of new incident gallstones and increased the number of new gallstones typically seen in participants at 120 weeks follow-up. However, the new incident gallstones seen at treatment end were statistically significantly smaller than those seen in participants at baseline.

The important outcome of adherence was assessed in the van Aerts et al. 2019 (DIPAK-I) RCT, which provided low certainty evidence that 18 out of 93 (19%) participants discontinued treatment with lanreotide, and 23 out of 93 (21.4%) required the dose being taken to be titrated down. The main cause of lack of adherence to lanreotide (either the dose being titrated down or discontinuation) was due to deteriorating renal function and adverse events. Titration down may be preferrable to discontinuation for certain adverse events, such as gastrointestinal effects.

In terms of the important outcome of renal function, moderate and low certainty evidence from 2 systematic reviews (Griffiths et al. 2020 and St Pierre et al. 20204) found that treatment with lanreotide has no statistically significant effect on eGFR or the composite outcome of a 30% or more decrease in eGFR or kidney failure at treatment end. Pooled data in the Griffiths et al. (2020) systematic review provides moderate certainty evidence that lanreotide treatment is associated with a statistically, but not clinically, significant reduction in total kidney volume at treatment end.

Very low certainty evidence from the St Pierre et al. 2024 systematic review found that treatment with lanreotide had no statistically significant effect on mortality, but this was based on a single death in the lanreotide group during the 120 weeks follow-up. The van Aerts et al. 2019 (DIPAK-I) RCT provides very low certainty evidence that, over 120 weeks, around a third of participants treated with lanreotide experienced a serious adverse event.

In subgroup analysis in the van Aerts et al. 2019 (DIPAK-I) RCT, for treatment with lanreotide, gender does not appear to be an effect modifier for total liver volume. In a subgroup analysis of the Temmerman et al. 2015 study, participants who responded to a lower dose (90 mg SC every 4 weeks) had statistically significant weight loss and lower skeletal muscle index at treatment end compared with baseline, whilst non-responders’ (those who required dose escalation to 120 mg SC every 4 weeks) weight and skeletal mass index remained stable.

People with PLD for whom lanreotide treatment might be considered often have few treatment options left, other than consideration for liver transplant. The findings of this review are important as they suggest that there are small statistically significant differences for both critical (TLV) and important (TKV) outcomes with lanreotide. While these differences might not be clinically meaningful using the default minimal clinically important differences (MCIDs), it might bring into question the appropriateness of default MCID. Smaller clinical differences in these outcomes might be important if other treatment options have been exhausted and lanreotide

delays the need for higher cost invasive treatments such as liver transplant. However, treatment with lanreotide is also associated with adverse outcomes including increasing the risk of new gallstones and potentially a negative effect on nutritional status.

3. Methodology

Review questions

The review question(s) for this evidence review are:

1. In patients experiencing symptomatic PLD, what is the clinical effectiveness of lanreotide compared with supportive treatment, octreotide or liver transplant?
2. In patients experiencing symptomatic PLD, what is the safety of lanreotide compared with supportive treatment, octreotide or liver transplant?
3. In patients experiencing symptomatic PLD, what is the cost-effectiveness of lanreotide compared with supportive treatment, octreotide or liver transplant?
4. From the evidence selected, are there any subgroups of patients that may benefit from lanreotide more than the wider population of interest?
5. From the evidence selected, what was the treatment dose and frequency of lanreotide in the population of interest?
6. From the evidence selected, what was the route and formulation of lanreotide in the population of interest?

See Appendix A for the full PICO document.

Review process

The methodology to undertake this review is specified by NHS England in its 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO documents and were conducted on the 3rd and 4th December 2024.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full text of potentially relevant studies were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE profiles.

4. Summary of included studies

Five study papers were identified for inclusion (Aapkes et al. 2021, Griffiths et al. 2020, St Pierre et al. 2024, Temmerman et al. 2015 and van Aerts et al. 2019). Two of these studies are systematic reviews and meta-analyses (Griffiths et al. 2020 and St Pierre et al. 2024) and contain outcomes in relation to a few critical, important and safety outcomes relevant to this review. However, due to the systematic reviews having limited relevant outcomes, additional data on other outcomes has have been extracted from other studies that also met the inclusion criteria for this review.

Further evidence for lanreotide on other relevant outcomes was obtained from a randomised controlled trial (the DIPAK-I RCT, which is also included in the systematic reviews) reported in 2 papers (Aapkes et al. 2021 and van Aerts et al. 2019) and a prospective observational study (Temmerman et al. 2015).

Table 1: Summary of included studies for lanreotide

Study	Population	Intervention and comparison	Outcomes reported
Aapkes et al. (2021) Open-label randomized clinical trial (DIPAK-I paper). Multicentre (Groningen, Leiden, Nijmegen and Rotterdam) study conducted in the Netherlands.	249 participants aged 18 to 60 years with autosomal-dominant polycystic kidney disease (ADPKD) (diagnosed according to the modified Ravine criteria). • 124 participants were randomised to lanreotide • 125 were randomised to standard of care (control group) • The mean ±SD age of participants was 48±7 years (lanreotide group) and 49±7.0 years (control group). • There was n=58/124 (47%) females in the lanreotide group and 62/125 (50.0%) in the control group. There were no statistically significant differences in most of the baseline characteristics apart from polycystic liver disease classification (mild, moderate or severe) with a greater proportion of moderate and severe in the lanreotide group (p=0.02).	**Intervention** • Lanreotide 120 mg subcutaneously every 4 weeks, dosage titrated down to 90 mg every 4 weeks if eGFR <30 mL/min/1.73m^2 or if significant side effects (could be decreased further to 60 mg or stopped if necessary). Plus, standard care. **Comparator** Standard care alone, consisting of: • Blood pressure control (<140/90 mmHg), if required by sodium-restricted diet and anti-hypertensives (angiotensin-converting enzyme inhibitors, or in case of intolerance for angiotensin-converting enzyme inhibitors, with angiotensin receptor blockers). • Use of oestrogens and oral contraceptives was discouraged (but not an exclusion criterion). • Dietary advice was given at the discretion of the treating physician.	**Critical outcomes** N/A **Important outcomes** • Imaging changes assessed at treatment end (120 weeks) **Safety** N/A
Griffiths et al. (2020) Systematic review and meta-analysis UK systematic review and meta-analysis including 6 trials from Italy, the Netherlands and USA. Three secondary analyses of the same studies were also included.	The review included 2 trials of lanreotide, both were conducted in the Netherlands. • One trial included people with ADPKD alone, the other included people with PLD and ADPKD. • Excluding the number of people in the secondary analysis, a total of n=363 participants of lanreotide studies were included. • Both included studies recruited both male (n=149) and female (n=214) participants who were over the age of 18 years. • Clinical and radiological diagnosis of ADPKD (according to the Ravine Criteria in most studies).	**Intervention** In the 2 trials the interventions used were: • lanreotide long-acting release 120 mg administered subcutaneously every 28 days Duration of treatment in each study is not reported; the study follow-up periods were: • 6 months in 1 study • 120 weeks in 1 study Concomitant treatments are not reported. **Comparison** In the 2 trials the comparators used were: • Placebo in 1 double blind study • Standard of care in 1 open-label study	**Critical outcomes** • Total liver volume (in PLD) **Important Outcomes** • Renal function (eGFR decline and total kidney volume in ADPKD) **Safety** N/A **Outcomes assessment varied by individual study included within the meta-analyses.**

St Pierre et al. (2024) Systematic review and meta-analysis International Cochrane collaboration review incorporating (n=57) studies that had been conducted around the world, but mainly in Europe and the United States.	8016 adults or children with a clinical diagnosis of ADPKD (by MRI or echo tomography) meeting the Ravine criteria, confirmed or not by genetic test • Participants had CKD stages 1 to 4 (according to US National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDQOI) guidelines).	**Interventions** • lanreotide was given every 28 days, the dose was 120 mg (long-acting release [LAR]) subcutaneously The review found evidence for 18 different pharmacological interventions. This comprised: • somatostatin analogues (lanreotide and octreotide) • other interventions vasopressin 2 receptor (V2R) antagonists, antihypertensive therapy, mammalian target of rapamycin (mTOR) inhibitors, antiplatelet agents, eicosapentaenoic acids, statins, kinase inhibitors, diuretics, anti-diabetic agents, water intake, dietary intervention, and supplements. **Comparators** Eligible comparators included in the review were: • Placebo • Intervention plus octreotide • Standard care	**Critical outcomes** • Health-related Quality of life **Important outcomes** • Renal outcomes **Safety** • Mortality **Outcomes assessment varied by individual study included within the meta-analyses**.
Temmerman et al. (2015) Prospective observational study Two tertiary medical centres in Belgium (University Hospitals KU Leuven and the Université Catholique de Louvain in Brussels).	59 adults (≥18 years) with either ADPKD or ADPLD (ADPKD diagnostic criteria not reported) • Participants had symptomatic PLD (Mayo classification C or D) with hepatomegaly • The median age at baseline was 51 years (IQR 47 to 57 years). • The study participants comprised 52 women and 7 men. • Median liver volume was 5163 mL (IQR 3953 to 7238 mL). • Median weight was 68.6 Kg (IQR 61 to 81 Kg) • Median mid-upper arm circumference in women was 25 cm (IQR 23.4 to 26.4 cm) and men was 27 cm (IQR 26 to 29 cm). • Median albumin 46 g/L (IQR 44.8 to 48.3 g/L). • Skeletal muscle mass in women was 41.4 cm^2/h^2 (SE 37.8 to 45) and men was 53.4 (SE 50.4 to 57.8). • The proportion of participants with sarcopenia (defined as the skeletal muscle index less than 38.5 cm^2/h^2 in females and less than 52.4 cm^2/h^2 in men) was 30%. • Median subcutaneous adipose tissue was 144 cm^2 (IQR 92 to 240 cm^2). • Median visceral adipose tissue was 53.4 cm^2 (IQR 29 to 98 cm^2).	**Interventions** • Lanreotide (90 mg subcutaneously every 4 weeks) for 6 months. • Patients with reductions in liver volume of more than 100 mL (classed as responders, primary end point) continued to receive lanreotide (90 mg) for an additional year (18 months total). • Non responders were offered increased doses, up to 120 mg lanreotide, until 18 months. Concomitant treatments were not reported. **Comparator** No comparator, observational study.	**Critical outcomes** • Symptom control **Important outcomes** N/A **Safety** N/A Outcomes were assessed at treatment end (18 months)

van Aerts et al. (2019) Open-label randomised clinical trial (DIPAK-I paper) Multicentre (Groningen, Leiden, Nijmegen and Rotterdam) study conducted in the Netherlands.	175 participants (aged 18 to 60 years) with ADPKD diagnosed according to the modified Ravine criteria and • an eGFR (MDRD) of 30 to 60 mL/min/1.73m^2 • only those with ADPKD with PLD and hepatomegaly (*a priori* definition) of ≥2000 mL at baseline. • N=93 randomised to lanreotide plus standard care • N=82 randomised to standard care alone. • The mean ±Standard deviation (SD) age of participants was 48.3±6.2 years (lanreotide group) and 48±7.0 years (control group). • There was n=40 males in each group (representing 43.0% of the lanreotide group and 48.9% of the control group). • There were no statistically significant differences in height, weight or BMI between the lanreotide and control group, respectively. • There were also no statistically significant differences in baseline blood results alkaline phosphatase, Gamma-glutamyl transferase, serum creatinine, eGFR or CKD stages. • There was a statistically significant difference in height-adjusted total liver volume at baseline; 1528 mL/m (lanreotide) versus 1376 mL/m (control), p=0.04 (Mann-Whitney U test).	**Intervention** • Lanreotide 120 mg subcutaneously every 4 weeks, dosage titrated down to 90 mg every 4 weeks if eGFR <30 mL/min/1.73m^2 or if significant side effects (could be decreased further to 60 mg or stopped if necessary). Plus, standard care. **Comparator** Standard care alone, consisting of: • Blood pressure control (<140/90 mmHg), if required by sodium-restricted diet and anti-hypertensives **(**angiotensin-converting enzyme inhibitors, or in case of intolerance for angiotensin-converting enzyme inhibitors, with angiotensin receptor blockers**)**. • Use of oestrogens and oral contraceptives was discouraged (but not an exclusion criterion). • Dietary advice was given at the discretion of the treating physician.	**Critical outcomes** • Total liver volume - subgroup by sex • Symptom control **Important outcomes** • Adherence to treatment **Safety** • Serious adverse events

Abbreviations

ADPKD, autosomal-dominant polycystic kidney disease; ADPLD, autosomal-dominant polycystic liver disease; BMI, Body mass index; CKD, Chronic kidney disease; eGFR, Estimated glomerular filtration rate; IQR, Interquartile range; MDRD, Modification of Diet in Renal Disease; MRI, Magnetic resonance imaging; PLD, Polycystic liver disease; SD, Standard deviation.

5. Results

In patients experiencing symptomatic PLD, what is the clinical effectiveness and safety of lanreotide compared with supportive treatment, octreotide or liver transplant?

Outcome	Evidence statement
Clinical effectiveness	
Critical outcomes	
Total liver volume	*Total liver volume is important to patients as it is used to determine treatment success and requirement for further treatment. It might not be expected to reduce, and stabilisation may indicate treatment has successfully limited disease progression.*
Certainty of evidence: High	**Lanreotide versus placebo or standard of care** One systematic review and meta-analysis (Griffiths et al. 2020) provided pooled evidence from 2 RCTs (pooled n=210), on total liver volume measured at treatment end (6 months in 1 RCT and 120 weeks in the other RCT). The intervention (lanreotide 120 mg intramuscularly every 28 days) was the same in both RCTs, but the comparators were placebo in one RCT and 'standard of care' in the other. One study assessed participants using CT and the other MRI. At treatment end lanreotide statistically significantly reduced total liver volume, mean difference was −0.14 L (95% CI −0.26 to −0.02; p=0.02). However, the reduction was not likely to be clinically meaningful using the default MCID for continuous outcomes. (**HIGH**) **The data from 2 RCTs, pooled in the systematic review and meta-analysis by Griffiths et al. (2020) provides high certainty evidence that treatment with lanreotide statistically significantly reduces total liver volume at 6 months to 120 weeks, but the reduction is not likely to be clinically meaningful compared with placebo or 'standard of care'.**
Certainty of evidence: not applicable (N/A)	**Lanreotide versus octreotide** No evidence available
Certainty of evidence: N/A	**Lanreotide versus liver transplantation** No evidence available
Symptom control	*Symptom control is important to patients because reduction of symptoms directly improves the patient's quality of life. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment.*
Certainty of evidence: Low and Very Low	**Lanreotide versus standard of care or no comparator** One RCT (van Aerts et al. 2019; DIPAK-I RCT) and one prospective observational study (Temmerman et al. 2015) provided evidence related to symptom control measured from baseline to treatment end (120 weeks) in the RCT and at 18 months for the observational study. The intervention in the RCT was lanreotide 120 mg subcutaneously every 4 weeks, the comparator was 'standard of care'. In the observational study the intervention was lanreotide 90 mg subcutaneously every 4 weeks, with potential escalation in dose (to 120 mg), depending on response at 6 months. In the RCT symptoms were assessed using a 7-point Likert-like scale, ranging from 1 (none) to 7 (very severe). These were partially derived from the Gastrointestinal Symptom Score (modified on expert opinion for PLD symptoms). It is unclear if this symptom score was validated for use once modified. In the observational study

	which is at an increased risk of bias compared with the RCT, symptom control was assessed using the validated POLCA score domains (severity of perceived illness, gastroesophageal reflux disease related complaints, impact on food intake and perception of enlarged liver) and nutritional status (mean weight and Skeletal Mass Index (SMI)). In the RCT there was no statistically significant difference (p=0.1) between the baseline median symptom scores in the lanreotide (n=93) group (9.1, IQR 3.0 to 18.6) compared with 'standard of care' (n=82) group (6.1, IQR 1.5 to 15.5). At treatment end (120 weeks), median scores had increased in both the lanreotide group by 2.7 (95% CI 0.7 to 4.7) and in the 'standard of care' group by 2.6 (95% CI 0.5 to 4.7). There was no statistically significant difference between median symptom scores in the lanreotide group compared with the 'standard of care' at follow-up (p=0.9). (**LOW**) In the observational study (n=43) the mean [SE] severity score of POLCA (perceived illness) statistically significantly reduced (p<0.0001) from baseline 15.9 [0.9] to 9.8 [0.72] at 18 months. (**VERY LOW**) In the observational study (n=43) the mean [SE] severity score of POLCA (gastroesophageal reflux disease related complaints) statistically significantly reduced (p=0.001) from baseline 3.18 [0.6] to 1.67 [0.34] at 18 months. (**VERY LOW**) In the observational study (n=43) the mean [SE] severity score of POLCA (impact on food intake) statistically significantly reduced (p=0.04) from baseline 3.6 [0.38] to 3.0 [0.3] at 18 months. (**VERY LOW**) In the observational study (n=43) the mean [SE] severity score of POLCA (perception of enlarged liver volume) statistically significantly reduced (p=0.008) from baseline 6.8 [0.4] to 5.5 [0.5] at 18 months. (**VERY LOW**) In the observational study (n=53) the mean weight (figure in brackets not defined) of participants was statistically significantly lower (p=0.01) from baseline 72 [2.2] Kg to 70 [2.3] Kg at 18 months. (**VERY LOW**) In the observational study (n=37) the proportion (%) of participants with severe skeletal muscle depletion or sarcopenia increased from baseline (27%) to 18 months (38%) but the increase was not statistically significantly different (p not reported). (**VERY LOW**) **Data from 1 observational study (Temmerman et al. 2015) provided very low certainty evidence that treatment with lanreotide statistically significantly improved symptom control at 18 months compared with baseline scores. However, findings from 1 RCT (van Aerts et al. 2019) provide low certainty evidence that there is no improvement in symptom control compared with 'standard of care' at 120 weeks.** **Data from the observational study by Temmerman et al. (2015) provides very low certainty evidence that treatment with lanreotide results in a statistically significantly increase in the proportion of people experiencing weight loss.**
Certainty of evidence: N/A	**Lanreotide versus octreotide** No evidence available
Certainty of evidence: N/A	**Lanreotide versus liver transplantation** No evidence available
Quality of life	*Quality of life is important to patients as it provides a holistic evaluation of an individual's general health and self-perceived well-being and their ability to*

	participate in activities of daily living. Quality of life can inform patient centred shared decision making.
Certainty of evidence: Moderate	***Lanreotide versus standard of care*** One systematic review and meta-analysis (St Pierre et al. 2024) provided evidence from 1 RCT (DIPAK-I, n=305) relating to quality of life measured from baseline to treatment end (120 weeks). The intervention in the RCT was lanreotide 120 mg subcutaneously every 4 weeks, the comparator was 'standard of care'. Quality of life was assessed using the 18-question ADPKD Impact Scale. At treatment end there was no statistically significant mean difference in quality of life −0.02 (95% CI −0.12 to 0.08, p=0.69) between lanreotide and 'standard of care'. (**MODERATE**) **Data from a systematic review and meta-analysis by St Pierre et al. (2024) provides moderate certainty evidence from a single RCT (DIPAK-I) that treatment with lanreotide does not statistically significantly improve quality of life compared with 'standard of care' at 120 weeks.**
Certainty of evidence: N/A	**Lanreotide versus octreotide** No evidence available
Certainty of evidence: N/A	**Lanreotide versus liver transplantation** No evidence available
Important outcomes	
Imaging changes	*Imaging changes are important to patients as they are used to help determine treatment success and requirement for further treatment. Imaging results might not be expected to return to normal, however, stabilisation may indicate treatment has successfully limited disease progression and may be associated with improvement in clinical features (see also the sections on total liver volume and total kidney volume which were undertaken using CT or MRI in the included systematic reviews and RCTs).*
Certainty of evidence: Moderate	**Lanreotide versus standard of care** One RCT (Aapkes et al. 2021, DIPAK-I, n=249) provided evidence related to imaging changes (presence, number and size of gallstones) measured at baseline and at treatment end (120 weeks). The intervention in the RCT was lanreotide 120 mg subcutaneously every 4 weeks, the comparator was 'standard of care'. The outcome was assessed using MRI according to a standard protocol. At treatment end there was a statistically significant increase (p<0.05) in the number of participants with gallstones in the lanreotide group (18.5%) compared with the standard care group (8.8%). The difference remained statistically significant (p<0.0001) when adjusted for baseline presence of gallstones (number of participants with new incident gallstones) in the lanreotide group (15.3%) compared with the 'standard of care' group (0.8%). (**MODERATE**) The RCT reported that the statistically significant increase in new incident gallstones in the lanreotide group compared with 'standard of care' was seen in both univariate (OR 22.5, 95% CI 2.96 to 171, p<0.01) and multivariate logistic regression analysis (OR 25.9, 95% CI 3.37 to 199, p<0.01). (**MODERATE**) The RCT also found that lanreotide statistically significantly increased the number of incident gallstones for each participant compared to gallstones at baseline (p=0.004). However, the new incident gallstones were statistically significantly smaller than those present at baseline (p=0.001). (**MODERATE**)

	The DIPAK-I RCT (Aapkes et al. 2021) provides moderate certainty evidence that treatment with lanreotide statistically significantly increases the odds of developing gallstones and increases the number of gallstones present (per participant). However, the new gallstones seen at treatment end were statistically significantly smaller than those seen in participants at baseline.
Certainty of evidence: N/A	**Lanreotide versus octreotide** No evidence available
Certainty of evidence: N/A	**Lanreotide versus liver transplantation** No evidence available
Patient adherence to treatment	*Patient adherence to treatment is important to patients as it provides an indication of how satisfied patients are with treatment and how well they adhere to the treatment regimen.*
Certainty of evidence: Low	**Lanreotide versus standard of care** One RCT (DIPAK-I, van Aerts et al. 2019) provided evidence for a group of participants (n=93) with ADPKD with PLD and hepatomegaly in the DIPAK-I RCT who were assigned to lanreotide 120 mg subcutaneously every 4 weeks. As the comparator was 'standard of care' there is no comparable control group data, and no statistical analysis was performed. The outcome was assessed as the number of participants requiring titration down or who discontinued the study medicine during the study period at baseline and at treatment end (120 weeks). In the RCT, lanreotide was titrated down in 23 of the 93 participants during the study period (to 90 mg in 20 participants and to 60 mg in 3 participants). Of these participants, 8 participants were titrated down due to eGFR reaching <30 mL/min/1.73m^2. Fifteen participants were titrated down due to adverse events (7 gastrointestinal complaints; 3 fatigue or malaise; 2 due to bradycardia; 1 hypoglycaemia; 1 hair loss and 1 liver cyst infection). Of the 15, 6 discontinued treatment with lanreotide due to continued adverse events despite titration down, 1 due to nephrectomy and 1 due to loss of confidence in the study medicine. In 6 out of 7 participants titrated down due to gastrointestinal complaints, the adverse effects were tolerable at the lower dose. (**LOW**) In total 18 patients (19%) stopped lanreotide at once, of whom 14 (15%) did so because of adverse events (4 due to fatigue/malaise, 2 due to renal cyst bleeding, 6 due to liver cyst infection and 2 due to gastrointestinal symptom. However, these data are uncertain due to inconsistent reporting. (**LOW**) **The van Aerts et al. (2019) study found that in a group of participants with ADPKD with PLD and hepatomegaly assigned to lanreotide in the DIPAK-I RCT, 23 out of 93 (21.4%) participants required the dose to be titrated down being taken during follow-up (120 weeks) and in total 18 out of 93 (19%) discontinued lanreotide. The main cause of lack of adherence to lanreotide (either the dose being titrated down or discontinuation) was due to deteriorating renal function and adverse events. Titration down of the dose may be preferrable to discontinuation for certain adverse events; however, this is non-comparative data and of low certainty.**
Certainty of evidence: N/A	**Lanreotide versus octreotide** No evidence available
Certainty of evidence: N/A	**Lanreotide versus liver transplantation** No evidence available

Liver transplant Certainty of evidence: N/A	*Liver transplant is important to patients as it identifies whether the intervention has been effective in the management of PLD and therefore the treatment burden associated with liver transplant is avoided.* **No evidence was identified for this outcome.**
Renal function	*Renal function is important as some patients may have liver cysts as a result of ADPKD. Renal function may indicate an incidental systemic improvement beyond the liver.*
Certainty of evidence: Low and moderate	**Lanreotide versus standard of care or placebo** Two systematic reviews and meta-analyses (Griffiths et al. 2020 and St Pierre et al. 2024) provided evidence on different outcomes for renal function, using data from 2 RCTs (DIPAK-I and LOCKCYST). The intervention (lanreotide 120 mg subcutaneously every 28 days) was the same in both RCTs, but the comparators were placebo in one RCT (LOCKCYST) and 'standard of care' in the other (DIPAK-I). The follow-up period was 6 months in the LOCKCYST study and 120 weeks in the DIPAK-I RCT. One systematic review (Griffiths et al. 2020) provided pooled evidence, from 2 RCTs (n=304) on the mean difference in total kidney volume at treatment end. Treatment with lanreotide was statistically significantly associated with a reduction in total kidney volume compared with placebo or 'standard of care' at follow-up, mean difference −0.15 L (95% CI −0.21 to −0.10, p<0.00001). However, the reduction was not likely to be clinically meaningful using the default MCID for continuous outcomes. (**MODERATE**) One systematic review (Griffiths et al. 2020) provided evidence on the mean difference in estimated glomerular filtration rate (eGFR) at treatment end from 1 RCT (n=290). Treatment with lanreotide was not statistically significantly different from 'standard of care' at follow-up, mean difference −0.60 mL/min/1.73m^2 (95% CI −3.65 to 2.45, p=0.70). (**MODERATE**) One systematic review (St Pierre et al. 2024) provided evidence on the relative risk of a 30% or more decrease in GFR or kidney failure at the treatment end from 1 RCT (n=305). Treatment with lanreotide was not statistically significantly different from 'standard of care' at follow-up RR 0.72 (95% CI 0.43 to 1.20, p=0.21). (**LOW**) **The pooled data from both the DIPAK-I and LOCKCYST RCTs in the Griffiths et al. (2020) systematic review provides moderate certainty evidence that lanreotide treatment is associated with a statistically significant reduction in total kidney volume at treatment end, but this is not likely to be a clinically meaningful difference. Data from DIPAK-I RCT used in both systematic reviews (Griffiths et al. 2020 and St Pierre et al. 2024) provide low and moderate certainty evidence that lanreotide has no statistically significant effect on renal function at treatment end.**
Renal function **Certainty of evidence:** N/A	**Lanreotide versus octreotide** No evidence available
Renal function **Certainty of evidence:** N/A	**Lanreotide versus liver transplantation** No evidence available
Safety	
Safety	*The safety of lanreotide is important to patients as it informs treatment decisions and allows comparison of interventional approaches.*
Risk of death	**Lanreotide versus standard of care**

Certainty of evidence: Very low	One systematic review (St Pierre et al. 2024) provided evidence from 1 RCT (DIPAK-I) on the relative risk of death at the treatment end. The intervention was lanreotide 120 mg intramuscularly every 28 days compared with 'standard of care'. The follow-up period was 120 weeks. Treatment with lanreotide (1 death, n=154) was not statistically significantly different to 'standard of care' (0 deaths, n=155) RR 3.02 (95% CI 0.12 to 73.55, p=0.50). (**VERY LOW**) **The DIPAK-I RCT (included within the St Pierre et al. 2024 systematic review) provides very low certainty evidence that treatment with lanreotide has no statistically significant effect on mortality. However, this is based on only 1 death in the intervention group and none in the control group over a 120-week follow-up period.**
Number of serious adverse events **Certainty of evidence:** Very low	**Lanreotide versus standard of care** One RCT (van Aerts et al. 2019, DIPAK-I) provided evidence on the number and type of serious adverse events, and withdrawals due to serious adverse events for a subset of participants (n=175) with ADPKD with PLD and hepatomegaly in the DIPAK-I RCT. The intervention was lanreotide 120 mg intramuscularly every 28 days compared with 'standard of care'. The follow-up period was 120 weeks. In the lanreotide group 28 out of 93 (30.1%) had a serious adverse event compared with 10 out of 82 (12.2%) in 'standard of care' group. No statistical analysis is presented. (**VERY LOW**) **The van Aerts et al. (2019) study provides very low certainty evidence that, over 120 weeks, around a third of participants treated with lanreotide experienced a serious adverse event.**
Serious adverse events considered possibly related to lanreotide **Certainty of evidence:** Very low	**Lanreotide versus standard of care** One RCT (van Aerts et al. 2019, DIPAK-I) provided evidence on serious adverse events considered related to treatment with lanreotide, in a subset of participants (n=175) with ADPKD with PLD and hepatomegaly in the DIPAK-I RCT. The intervention was lanreotide 120 mg intramuscularly every 28 days compared with 'standard of care'. The follow-up period was 120 weeks. Thirteen of the serious adverse events were thought to be related to the intervention (hepatic cyst infection n=6 (6.5%), renal cyst infection n=2 (2.2%), pyelonephritis n=1 (1.1%), epigastric pain 1 (1.1%), fever n=1 (1.1%), urinary tract infection n=1 (1.1%) and cholelithiasis n=1 (1.1%)). This is compared to n=2 (2.4%) renal cyst infections and n=1 (1.2%) pyelonephritis in the 'standard of care' group. No statistical analysis is presented. (**VERY LOW**) **The DIPAK-I RCT provides very low certainty evidence that, over 120 weeks, hepatic cyst infection is the most common serious adverse event possibly related to lanreotide.**
Serious adverse events leading to study withdrawal **Certainty of evidence:** Very low	**Lanreotide versus standard of care** One RCT (van Aerts et al. 2019, DIPAK-I) provided evidence on the number of serious adverse events leading to study withdrawal in a subset of participants (n=175) with ADPKD with PLD and hepatomegaly in the DIPAK-I RCT. The intervention was lanreotide 120 mg subcutaneously every 28 days compared with 'standard of care'. The follow-up period was 120 weeks. The number of participants with a serious adverse event leading to study withdrawal in the lanreotide group was 4 out of 93 (4.3%) compared with 1 out of 82 (1.2%) in the 'standard of care' group. No statistical analysis is presented. (**VERY LOW**)

	The DIPAK-I RCT provides very low certainty evidence that, over 120 weeks, very few of the serious adverse events led to withdrawal of the intervention.
Safety **Certainty of evidence:** N/A	**Lanreotide versus octreotide** No evidence available
Safety **Certainty of evidence:** N/A	**Lanreotide versus liver transplantation** No evidence available

Abbreviations

ADPKD, Autosomal-dominant polycystic kidney disease; CT, Computerised tomography; eGFR, Estimated glomerular filtration rate; IQR, Interquartile range; MCID, Minimally important clinical difference; MRI, Magnetic resonance imaging; P, Probability value; PLD, Polycystic liver disease; POLCA, Polycystic Liver Disease-complaint-specific assessment; RCT, Randomised controlled trial; RR, Relative risk.

In patients experiencing symptomatic PLD, what is the cost-effectiveness of lanreotide compared with supportive treatment, octreotide or liver transplant?

Outcome	Evidence statement
Cost-effectiveness	**No evidence was identified regarding the cost-effectiveness of lanreotide compared with supportive treatment, octreotide or liver transplant in patients experiencing symptomatic PLD**

Abbreviations

PLD, Polycystic liver disease.

From the evidence selected, are there any subgroups of patients that may benefit from lanreotide more than the wider population of interest?

Outcome	Evidence statement
Total liver volume	*Total liver volume is important to patients as it is used to determine treatment success and requirement for further treatment. It might not be expected to reduce, and stabilisation may indicate treatment has successfully limited disease progression.*
Total liver volume subgroup by sex	**Lanreotide versus standard of care** One RCT (van Aerts et al. 2019, DIPAK-I) provided evidence on total liver volume by sex in a subset of participants (n=175) with ADPKD with PLD and hepatomegaly in the DIPAK-I RCT. The intervention was lanreotide 120 mg subcutaneously every 28 days compared with 'standard of care'. The follow-up period was 120 weeks. The study population included 40 males in each group, representing 43.0% of the lanreotide group and 48.9% of the 'standard of care' group. At baseline height-adjusted liver volume was statistically significantly higher in females (1654 mL/m) than males (1283 mL/m) ($p<0.001$). At treatment end (120 weeks) liver growth in the control group was similar in both men and women and there was no statistically significant difference in the percentage change in height-adjusted liver volume between males and females in the 'standard of care' group (no p value reported).

	At treatment end (120 weeks) there was a statistically significant mean percentage reduction in height-adjusted liver volume in women in the lanreotide group (−7.68%, p=0.001) compared with women in the 'standard of care' group. At treatment end (120 weeks) there was a non-statistically significant mean percentage reduction in height-adjusted liver volume in men in the lanreotide group (−4.05%, p=0.09) compared with men in the 'standard of care' group. The authors report that subgroup analysis provides evidence that gender did not appear to be an effect modifier for change in height-adjusted total liver volume (p=0.3). **The DIPAK-I RCT provides evidence that despite differences between genders in the percentage reduction in height-adjusted total liver volume between lanreotide and 'standard of care', gender does not appear to affect the effectiveness of treatment with lanreotide.**
Symptom control	*Symptom control is important to patients because reduction of symptoms directly improves the patient's quality of life. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment.*
Symptom control **Subgroup by responder status**	**Lanreotide versus no comparator** One prospective observational study (Temmerman et al. 2015) provided evidence related to symptom control measured from baseline to treatment end at 18 months. The intervention in the observational study was lanreotide 90 mg subcutaneously every 4 weeks, with potential escalation in dose (to 120 mg), depending on response (a liver volume decrease of <100 mL) at 6 months (non-responders). Liver volumetry was assessed using CT scan. In the subgroup of responders (n=21), those with a liver volume decrease of >100 mL in the first 6 months, the mean weight statistically significantly decreased from baseline to 18 months from 72 Kg [SE 3.4] to 69 Kg [SE 3.4], p=0.006. The mean skeletal mass index in the responder subgroup also statistically significantly decreased from baseline to 18 months from 44.5 cm^2/h^2 [SE 1.6 cm^2/h^2] to 42.5 cm^2/h^2 [SE1.6 cm^2/h^2], p=0.001. In the subgroup of non-responders (n=22), those with <100 mL liver volume decrease at 6 months who were offered increased [120 mg] dose up to 18 months, the mean weight remained stable (data not reported). The mean skeletal mass index reduced in the subgroup of non-responders, but the reduction was not statistically significant, from baseline to 18 months from 42.5 cm^2/h^2 [SE 1.8 cm^2/h^2] to 41.6 cm^2/h^2 [SE 1.6 cm^2/h^2], p=0.13. **The prospective observational trial (Temmerman et al. 2015) provides evidence that participants in their study who responded to a lower dose (90 mg SC every 4 weeks) as assessed by a >100 mL reduction in total liver volume at 6 months had statistically significant decreases in weight and skeletal muscle index at treatment end compared with baseline, whilst in non-responders weight and skeletal mass index remained stable.**

Abbreviations

ADPKD, Autosomal-dominant polycystic kidney disease; CT, Computerised tomography; P, Probability value; RCT, Randomised controlled trial; SE, Standard error of the means.

6. Discussion

This review found no evidence for lanreotide in children or young people aged less than 18 years and lanreotide is not licensed for this indication in children (it is not recommended for use in children and adolescents due to lack of data on safety and efficacy, for details see the summary of product characteristics). The review also found no evidence for lanreotide compared with octreotide or compared with liver transplantation for any outcome. Additionally, no evidence was found for liver transplantation as an outcome in any of the included studies. No studies of cost-effectiveness for lanreotide were identified.

This evidence review includes 2 systematic reviews and meta-analyses (Griffiths et al. 2020 and St Pierre et al. 2024). Griffiths et al. (2020) included participants with both autosomal-dominant polycystic kidney disease (ADPKD) and autosomal-dominant polycystic liver disease (ADPLD) but had only a small number of outcomes of relevance to this review. The more recent St Pierre et al. (2024) review focussed on ADPKD only, and therefore lacked outcomes associated specifically to polycystic liver disease (PLD), but contains useful additional outcome data, for example on quality of life and additional renal outcomes.

Both systematic reviews were assessed as being of high quality, although Griffiths et al. (2020) does have some methods reporting limitations including the lack of a published protocol, some ambiguity around the diagnostic criteria reported by the studies. All participants were reported to have had a clinical and radiological diagnosis of ADPKD. In most, but not all, the included studies this was according to the Ravine criteria. The systematic review does not give further details of which studies used the Ravine criteria, or what diagnostic criteria were used in the remaining studies. No additional methods of identifying studies beyond database searching was reported, and no information was reported on how studies were identified for inclusion (sifting).

Data for lanreotide comes from 2 RCTs versus placebo or ‘standard of care’ included in the systematic review and meta-analysis (Griffith et al. 2020). The larger (n=309) study RCT of lanreotide (DIPAK-I) had a follow-up of 120 weeks but is limited as it is open-label and used a standard care comparator leading to potential open-label bias, particularly for more subjective outcomes. The smaller (n=54) LOCKCYST RCT was placebo-controlled but had a follow-up period of just 6 months.

Due to the outcome limitations of the 2 systematic reviews, supplementary data on other outcomes has been extracted from 2 studies reported in 3 papers that also met the inclusion criteria for this review, (Aapkes et al. 2021 and van Aerts et al. 2019) report additional outcomes from the DIPAK-I RCT, and a prospective observational study (Temmerman et al. 2015).

The Griffiths et al. (2020) review assessed the outcome of total liver volume (TLV). The meta-analysis for lanreotide of 2 studies found a statistically significant reduction in the lanreotide group. This reduction was mainly driven by data from the large (n=157) DIPAK-I RCT which had an overall 85% of the weight in the meta-analysis. However, the result of the meta-analysis did not reach the default minimally important clinical difference and so is not likely to be a clinically meaningful reduction. A similar, though lesser, effect from the DIPAK-I was seen for the outcome of total kidney volume (TKV). Lanreotide had no statistically significant effect on estimated glomerular filtration rate (eGFR).

Two papers (Aapkes et al. 2021 and van Aerts et al. 2019) report outcomes from the DIPAK-I RCT of lanreotide. The Aapkes et al. (2021) paper reported imaging outcomes addressing baseline and incident gallstones in the DIPAK-I RCT (n=305) which was undertaken in those with ADPKD, whilst the van Aerts et al. (2019) reported a relevant subpopulation of the DIPAK-I trial RCT which focussed on those with ADPKD and PLD (n=175) and had additional critical

outcomes of total liver volume sub-grouped by sex, and symptom control. The main risks of bias in the DIPAK-I RCT relate to its open-label design and standard care comparator which place it at high risk of bias. In subgroup analysis the van Aerts et al. (2019) paper reported that despite differences between genders in the percentage reduction in height-adjusted total liver volume between lanreotide and 'standard of care', gender does not appear to affect the effectiveness of treatment with lanreotide. The prospective observational study of lanreotide by Temmerman et al. (2015) did not describe the diagnostic criteria used for inclusion, and insufficient information is given about the recruitment of the cohort to allow for proper assessment of the method. There were also no exclusion or adjustment for other treatments that may have been used that could cause confounding of the study outcomes. It was quality assessed using the CASP tool for cohort studies and found to be very low quality.

The DIPAK-I RCT (Aapkes et al. 2021and van Aerts et al. 2019) and Temmerman et al. (2015) both assessed lanreotide for the outcome of symptom control. While the Temmerman et al. (2015) study found a reduction in symptoms using the validated POLCA score at 18 months follow-up, the DIPAK-I RCT found no reduction in symptoms at 120 weeks follow-up. The DIPAK-I RCT used a modified Gastrointestinal Symptom Score, the validity of which is unknown.

Temmerman et al. (2015) found that participants continued to lose weight and muscle mass, with those responsive to a lower dose (90 mg subcutaneously every 4 weeks) appearing to most affected. However, this was in a small study population (n=53) and whilst not an exploratory outcome of the study the authors discussed that more investigation into these findings was required.

The paper by van Aerts et al. (2019) found the main causes of lack of adherence to lanreotide (either the dose being titrated down or discontinuation) in a subset of participants with ADPKD with PLD and hepatomegaly in the DIPAK-I RCT were deteriorating renal function and adverse events. Titration down of the dose may be preferrable to discontinuation for certain adverse events; however, the adverse event data is non-comparative data, inconsistently and poorly reported and therefore of low certainty.

7. Conclusion

Overall, 5 study papers provided evidence on the clinical effectiveness and safety of lanreotide for people with polycystic liver disease (PLD). Two of these studies were high quality systematic reviews and meta-analyses. One of the systematic reviews (Griffiths et al. 2020) provides high certainty evidence from a meta-analysis that treatment with lanreotide statistically significantly reduces the critical outcome of total liver volume (critical outcome) measured at different time points from 6 months to 120 weeks. However, the reduction is not likely to be clinically meaningful compared with placebo or 'standard of care'.

The Griffiths et al. (2020) systematic review also provides moderate certainty evidence for the important outcome of renal function. Lanreotide treatment demonstrates a statistically significant reduction in total kidney volume at treatment end at 120 weeks compared with standard of care, but the reduction is not likely to be clinically meaningful. The systematic review also found that treatment with lanreotide has no statistically significant effect on eGFR at 120 weeks compared with standard of care.

The DIPAK-I RCT, reported in the St Pierre et al. (2024) systematic review, found with moderate certainty that treatment with lanreotide does not statistically significantly improve the critical outcome of quality of life compared with 'standard of care' at 120 weeks. This systematic review also provides low certainty evidence that treatment with lanreotide has no statistically significant effect on the composite outcome of a 30% or more decrease in eGFR or kidney failure at treatment end at 120 weeks compared with standard of care.

For the critical outcome of symptom control, there is uncertainty about the treatment effect of lanreotide. Low certainty evidence from van Aerts et al. (2019) DIPAK-I RCT showed that there was no statistically significant difference in symptom control measured using a 7-point scale compared with 'standard of care' at 120 weeks, however the validity of the scale used is not known. Very low certainty evidence from the Temmerman et al. (2015) observational study indicates that treatment with lanreotide statistically significantly improves symptom control at 18 months compared with baseline scores using the validated POLCA score. However, this study is at high risk of bias. The difference in results between the 2 studies could be explained by differences in study design, the outcome measure used or be reflective of symptom scores at different time points.

While weight change is not a symptom usually associated with PLD, abdominal bloating and discomfort due to an enlarged liver may affect weight or appetite. The Temmerman et al. (2015) study found very low certainty evidence that treatment with lanreotide resulted in a statistically significant decrease in weight at 18 months compared with baseline.

Aapkes et al. 2019 (DIPAK-I) was the only study to report on the important outcome of imaging changes (beyond the CT and MRI scans used for liver and kidney volumetry) and provides moderate certainty evidence that treatment with lanreotide statistically significantly increases the odds of new incident gallstones and increased the number of new gallstones typically seen in participants at 120 weeks follow-up compared with standard of care. However, the new incident gallstones seen at treatment end were statistically significantly smaller than those seen in participants at baseline.

The important outcome of adherence was assessed in the van Aerts et al. (2019) DIPAK-I RCT, which provided low certainty, non-comparative, evidence that 18 out of 93 (19%) participants discontinued treatment with lanreotide, and 23 out of 93 (21.4%) required the dose being taken to be titrated down. The main cause of lack of adherence to lanreotide (either the dose being titrated down or discontinuation) was due to deteriorating renal function and adverse events.

Titration down of the dose may be preferrable to discontinuation for certain adverse events, such as gastrointestinal effects.

In subgroup analysis in the Temmerman et al. (2015) study, participants who responded to a lower dose (90 mg SC every 4 weeks) had statistically significant weight loss and lower skeletal muscle index at treatment end compared with baseline, whilst non-responders' (those who required dose escalation to 120 mg SC every 4 weeks) weight and skeletal mass index remained stable. In a subgroup analysis of the DIPAK-I RCT (van Aerts et al. 2019) gender did not appear to be an effect modifier on total liver volume for treatment with lanreotide.

In terms of safety, very low certainty evidence from the St Pierre et al. (2024) systematic review found that treatment with lanreotide has no statistically significant effect on mortality, but this was based on a single death in the lanreotide group during the 120 weeks follow-up. The van Aerts et al. (2019) DIPAK-I RCT provides very low certainty evidence that, over 120 weeks, around a third of participants treated with lanreotide experienced a serious adverse event.

People with PLD for whom lanreotide treatment might be considered often have few treatment options left, other than consideration for liver transplant. The findings of this review are important as they suggest that there are small statistically significant differences for both critical (TLV) and important (TKV) outcomes with lanreotide. While these are not likely to be clinically meaningful this does bring into question whether default minimal clinically important differences (MCIDs) are appropriate. Smaller differences in these outcomes might also be clinically meaningful if other treatment options have been exhausted and lanreotide delays the need for higher cost invasive treatments such as liver transplant. However, whether treatment with lanreotide does delay the need for such treatments is also unclear as no evidence was found for lanreotide and whether it affects liver transplantation as an outcome, as it was not an outcome reported in the evidence. Treatment with lanreotide is associated with adverse outcomes including increasing the risk of new gallstones and potentially a negative effect on nutritional status.

No cost-effectiveness studies were identified so the balance of benefit, harms and comparative costs is unclear. No conclusion could be drawn about the effectiveness of lanreotide treatment compared with octreotide or liver transplantation as no evidence was found that compared these interventions.

Appendix A PICO document

The review questions for this evidence review are:

1. In patients experiencing symptomatic PLD, what is the clinical effectiveness of lanreotide compared with supportive treatment, octreotide or liver transplant?
2. In patients experiencing symptomatic PLD, what is the safety of lanreotide compared with supportive treatment, octreotide or liver transplant?
3. In patients experiencing symptomatic PLD, what is the cost-effectiveness of lanreotide compared with supportive treatment, octreotide or liver transplant?
4. From the evidence selected, are there any subgroups of patients that may benefit from lanreotide more than the wider population of interest?
5. From the evidence selected, what was the treatment dose and frequency of lanreotide in the population of interest?
6. From the evidence selected, what was the route and formulation of lanreotide in the population of interest?

P-Population and Indication	Patients experiencing symptomatic PLD. [The disease may also be referred to in the literature as: • autosomal-dominant polycystic kidney disease (ADPKD) • autosomal-dominant polycystic liver disease (ADPLD)] Subgroups of interest: • Though principally interested in multiple diffuse cyst distribution, all cyst distribution and size should be reviewed [These may be communicated descriptively or via standardised classification such as Qian's classification, Gigot's classification and Schnelldorfer's classification in which all types of each classification should be reviewed] • Premenopausal women [Hormone oestrogen could be involved in PLD. Most people who present early and develop severe polycystic liver disease are women. The condition can stabilise after the menopause, when oestrogen levels go down] • Hormonal oestrogen levels • Autosomal-dominant polycystic liver disease (ADPLD) versus autosomal-dominant polycystic kidney disease (ADPKD)
I-Intervention	Lanreotide with or without supportive treatment [Treatment with lanreotide would be initiated as monotherapy] [Supportive treatment would include analgesia, nutritional support, antibiotics, medication for blood pressure control and stopping oestrogen treatments.]

C-Comparator	1. Supportive treatment 2. Octreotide 3. Liver transplant [The above treatment options represent standard care. Supportive treatment includes, but is not limited to, analgesia, nutritional support, antibiotics, medication for blood pressure control and stopping oestrogen treatments.]
O-Outcomes	**Clinical Effectiveness** Minimally clinically important differences (MCIDs) are not known unless stated; outcome measurement at 6 months with long term follow-up (up to 24 months) are of particular interest. *Critical to decision-making:* • **Total liver volume** *This outcome is important to patients as it is used to determine treatment success and requirement for further treatment. It might not be expected to reduce, and stabilisation may indicate treatment has successfully limited disease progression*. [Total liver volume may also be described in literature as height-adjusted total liver volume and can be measured directly by computed tomography or estimated based on correlation existing with the body surface area] • **Symptom control** *This outcome is important to patients because reduction of symptoms directly improves the patient's quality of life. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment.* [Commonly reported symptoms can be broadly classified into two categories: mass effect resulting from the enlarged liver and those which are complications of the cysts (such as, but not limited to, infection, torsion, rupture, and haemorrhage). Mass effect can result in symptoms including, but not limited to, abdominal distention, early satiety, postprandial fullness, gastro-oesophageal reflux, malnutrition dyspnoea, hepatic venous-outflow obstruction (Budd-Chiari syndrome), inferior vena cava syndrome, portal-vein compression and bile-duct compression. Standardised disease-specific questionnaires such as PLD-Q and POLCA may also be used] • ***Quality of life*** *This outcome is important to patients as it provides a holistic evaluation of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. Quality of life can inform patient centred shared decision making.* [Quality of life questionnaires include but are not limited to validated questionnaires such as EQ-5D & SF 36 which can provide information regarding improvement in symptoms. Disease specific quality of life questionnaires can provide information regarding improvement in symptoms.] *Important to decision-making:*

	• ***Imaging changes*** *This outcome is important to patients as imaging changes are used to help determine treatment success and requirement for further treatment. Imaging results might not be expected to return to normal, however, stabilisation may indicate treatment has successfully limited disease progression and may be associated with improvement in clinical features.* [Imaging refers to magnetic resonance imaging or computed tomography.] • ***Patient adherence to treatment*** *This outcome is important to patients as it provides an indication of how satisfied patients are with treatment and how well they adhere to the treatment regimen.* • ***Liver transplant*** *This outcome is important to patients as it identifies whether the intervention has been effective in the management of PLD and therefore the treatment burden associated with liver transplant is avoided.* • ***Renal function*** *This outcome is important as some patients may have liver cysts as a result of ADPKD. Renal function may indicate an incidental systemic improvement beyond the liver.* [This may also be recorded as, but not limited to, estimated glomerular filtration rate (eGFR)] ***Safety*** *The safety of lanreotide is important to patients as it informs treatment decisions and allows comparison of interventional approaches.* [Examples of measures include, but are not limited to: • Frequency of adverse events • Frequency of grade 3 or 4 adverse events • Adverse events leading to discontinuation or reduction in dosage • Treatment related adverse events – e.g., cholelithiasis or cholecystitis, diarrhoea, urinary tract infections and hepatic or renal cyst infection.] ***Cost-effectiveness***
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher-level quality evidence is found, case series can be considered.
Language	English only

Patients	Human studies only
Age	All ages
Date limits	2014 - 2024
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-prints and guidelines
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase, Central (Cochrane Library – incorporating Cochrane Database of Systematic Reviews) were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, commentaries, letters, editorials and case reports were excluded.

Search dates: 3rd and 4th December 2024

Example of search terms used (Medline)

Specific search

1 Liver Diseases/ and Cysts/ (3158)

2 (polycyst* adj (liver or hepatic)).tw. (1003)

3 (multicyst* adj (liver or hepatic)).tw. (17)

4 (cyst* adj (liver or hepatic)).tw. (556)

5 PLD.tw. (6024)

6 PCLD.tw. (125)

7 ADPLD.tw. (39)

8 ARPLD.tw. (0)

9 ADPCLD.tw. (0)

10 ARPCLD.tw. (0)

11 exp Polycystic Kidney Diseases/ (11090)

12 (polycyst* adj (kidney* or renal)).tw. (11013)

13 (multicyst* adj (kidney* or renal)).tw. (572)

14 (cyst* adj (kidney* or renal)).tw. (3127)

15 PKD.tw. (3091)

16 PCKD.tw. (43)

17 ADPKD.tw. (4069)

18 ARPKD.tw. (580)

19 ADPCKD.tw. (3)

20 ARPCKD.tw. (2)

21 or/1-20 (27690)

22 lanreotide*.tw. (1069)

23 angiopeptin*.tw. (80)

24 bim 23014*.tw. (56)

25 bim23014*.tw. (19)

26 bm 23014*.tw. (0)

27 bm23014*.tw. (0)

28 dc 13116*.tw. (0)

29 dc13116*.tw. (0)

30 ipstyl*.tw. (2)

31 somatuli*.tw. (81)

32 or/22-31 (1225)

33 21 and 32 (31)

34 limit 33 to english language (30)

35 limit 34 to yr="2014 -Current" (20)

36 animals/ (7554994)

37 exp Animals, Laboratory/ (980170)

38 exp Animal Experimentation/ (10617)

39 exp Models, Animal/ (667349)

40 exp Rodentia/ (3663461)

41 (rat or rats or mouse or mice or rodent*).ti. (1514119)

42 or/36-41 (7684362)

43 42 not humans/ (5368781)

44 35 not 43 (20)

45 limit 44 to (comment or congress or editorial or guideline or letter or preprint) (1)

46 44 not 45 (19)

Drug class search

1 Liver Diseases/ and Cysts/ (3158)

2 (polycyst* adj (liver or hepatic)).tw. (1003)

3 (multicyst* adj (liver or hepatic)).tw. (17)

4 (cyst* adj (liver or hepatic)).tw. (556)

5 PLD.tw. (6024)

6 PCLD.tw. (125)

7 ADPLD.tw. (39)

8 ARPLD.tw. (0)

9 ADPCLD.tw. (0)

10 ARPCLD.tw. (0)

11 exp Polycystic Kidney Diseases/ (11090)

12 (polycyst* adj (kidney* or renal)).tw. (11013)

13 (multicyst* adj (kidney* or renal)).tw. (572)

14 (cyst* adj (kidney* or renal)).tw. (3127)

15 PKD.tw. (3091)

16 PCKD.tw. (43)

17 ADPKD.tw. (4069)

18 ARPKD.tw. (580)

19 ADPCKD.tw. (3)

20 ARPCKD.tw. (2)

21 or/1-20 (27690)

22 somatostatin*.tw. (33570)

23 exp Somatostatin/ (20246)

24 or/22-23 (37133)

25 21 and 24 (161)

26 limit 25 to english language (149)

27 limit 26 to yr="2014 -Current" (93)

28 animals/ (7554994)

29 exp Animals, Laboratory/ (980170)

30 exp Animal Experimentation/ (10617)

31 exp Models, Animal/ (667349)

32 exp Rodentia/ (3663461)

33 (rat or rats or mouse or mice or rodent*).ti. (1514119)

34 or/28-33 (7684362)

35 34 not humans/ (5368781)

36 27 not 35 (90)

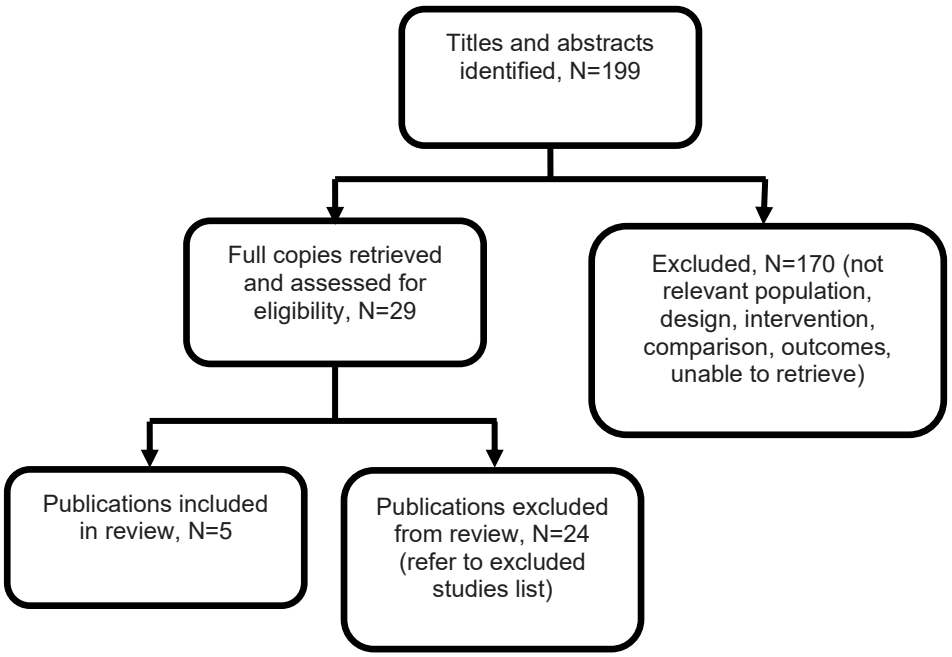
37 limit 36 to (comment or congress or editorial or guideline or letter or preprint) (4)

38 36 not 37 (86)

Appendix C Evidence selection

The literature searches identified 199 references. These were screened using their titles and abstracts and 29 references were obtained in full text and assessed for relevance. Of these, 5 references are included in the evidence summary. The remaining 24 references were excluded and are listed in Appendix D.

Figure 1 – Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection - decision and rationale if excluded
van Aerts RMM, Kievit W, D'Agnolo HMA, Blijdorp CJ, Casteleijn NF, Dekker SEI, de Fijter JW, van Gastel M, Gevers TJ, van de Laarschot LFM, Lantinga MA, Losekoot M, Meijer E, Messchendorp AL, Neijenhuis MK, Pena MJ, Peters DJM, Salih M, Soonawala D, Spithoven EM, Visser FW, Wetzels JF, Zietse R, Gansevoort RT, Drenth JPH; DIPAK-1 Investigators. Lanreotide Reduces Liver Growth In Patients With Autosomal Dominant Polycystic Liver and Kidney Disease. Gastroenterology. 2019 Aug;157(2):481-491.e7. doi: 10.1053/j.gastro.2019.04.018. Epub 2019 Apr 22. PMID: 31022403	This paper is included within this review.
Suwabe T, Barrera FJ, Rodriguez-Gutierrez R, Ubara Y, Hogan MC. Somatostatin analog therapy effectiveness on the progression of polycystic kidney and liver disease: A systematic review and meta-analysis of randomized clinical trials. PLoS One. 2021 Sep 24;16(9):e0257606. doi: 10.1371/journal.pone.0257606. PMID: 34559824; PMCID: PMC8462725	This study was deprioritised as it does not present the results for each somatostatin (lanreotide and octreotide) separately, it also includes a study of a somatostatin (pasireotide) in its pooled analyses which is excluded from this review.
Neijenhuis MK, Gevers TJ, Nevens F, Hogan MC, Torres VE, Kievit W, Drenth JP. Somatostatin analogues improve health-related quality of life in polycystic liver disease: a pooled analysis of two randomised, placebo-controlled trials. Aliment Pharmacol Ther. 2015	This study was deprioritised as it does not present the results for each somatostatin (lanreotide and octreotide) separately, it is also unclear if this is a systematic review as no details of searching, study selection or quality assessment are presented and therefore it represents a high risk of selection bias.

Sep;42(5):591-8. doi: 10.1111/apt.13301. Epub 2015 Jul 1. PMID: 26129925	

Appendix D Excluded studies table

Study reference	Reason for exclusion
Billiet, Antoon, Temmerman, Frederik, Coudyzer, Walter et al. (2023) Questionnaire PLD-complaint-specific assessment identifies need for therapy in polycystic liver disease: A multi-centric prospective study. United European gastroenterology journal 11(7): 633-641	No relevant outcomes (derivation and validation of POLCA scores).
Bolignano, D., Palmer, S.C., Ruospo, M. et al. (2015) Interventions for preventing the progression of autosomal-dominant polycystic kidney disease. Cochrane Database of Systematic Reviews 2015(7): cd010294	There is an updated version of this Cochrane review (St Pierre et al. 2024) which is included within this review.
Dekker, Shosha E I, Bierau, Jorgen, Giera, Martin et al. (2024) Serum bile acids associate with liver volume in polycystic liver disease and decrease upon treatment with lanreotide. European journal of clinical investigation 54(4): e14147	No relevant outcomes (post hoc exploratory analysis of bile acids).
Duijzer, R., Barten, T.R.M., Staring, C.B. et al. (2022) Treatment of Polycystic Liver Disease: Impact on Patient-reported Symptom Severity and Health-related Quality of Life. Journal of Clinical Gastroenterology 56(9): 731	A narrative review of treatments (including somatostatins) and their effect on health-related quality of life, does not present the results for each somatostatin (lanreotide and octreotide) separately.
Garofalo, Carlo, Capuano, Ivana, Pennino, Luigi et al. (2021) The effects of somatostatin analogues on liver volume and quality of life in polycystic liver disease: a meta-analysis of randomized controlled trials. Scientific reports 11(1): 23500	This study does not present the results for each somatostatin (lanreotide and octreotide) separately, it also includes a study of a somatostatin (pasireotide) in its pooled analyses which is excluded from this review.
Gevers, Tom J G, Hol, Jeroen C, Monshouwer, Rene et al. (2015) Effect of lanreotide on polycystic liver and kidneys in autosomal-dominant polycystic kidney disease: an observational trial. Liver international: official journal of the International Association for the Study of the Liver 35(5): 1607-14	Higher quality randomised trial evidence is included for the outcomes reported in this study.
Gevers, Tom J G, Nevens, Frederik, Torres, Vicente E et al. (2016) Alkaline phosphatase predicts response in polycystic liver disease during somatostatin analogue therapy: a pooled analysis. Liver international: official journal of the International Association for the Study of the Liver 36(4): 595-602	No relevant outcomes (individual patient data meta-analysis to identify factors associated with response to somatostatin).
Jones, T.R., Tingle, S.J., Thompson, E.R. et al. (2022) Transplantation versus other therapies for patients with polycystic liver disease. Cochrane Database of Systematic Reviews 2022(6): cd015279	Study review protocol only.
Khan, S; Dennison, A; Garcea, G (2016) Medical therapy for polycystic liver disease. Annals of the Royal College of Surgeons of England 98(1): 18-23	A narrative review of treatment trials and case series involving somatostatins, no meta-analyses presented. Newer, better-quality reviews are available including more studies.
Lantinga, Marten A, D'Agnolo, Hedwig M A, Casteleijn, Niek F et al. (2017) Hepatic Cyst Infection During Use of the Somatostatin Analog Lanreotide in Autosomal-Dominant Polycystic Kidney Disease: An Interim Analysis of the Randomized Open-Label Multicenter DIPAK-1 Study. Drug safety 40(2): 153-167	An interim analysis of the data from the DIPAK-I trial, for which full data are now available and included within this review.
Meijer, Esther, Drenth, Joost P H, d'Agnolo, Hedwig et al. (2014) Rationale and design of the DIPAK 1 study: a randomized controlled clinical trial assessing the efficacy of lanreotide to Halt disease progression in autosomal-dominant polycystic kidney disease. American journal of kidney diseases: the official journal of the National Kidney Foundation 63(3): 446-55	Study protocol only.
Meijer, Esther, Visser, Folkert W, van Aerts, Rene M M et al. (2018) Effect of Lanreotide on Kidney Function in	Presents data from the DIPAK-I study in ADPKD, the data from this trial which is relevant to the population

Patients With Autosomal-Dominant Polycystic Kidney Disease: The DIPAK 1 Randomized Clinical Trial. JAMA 320(19): 2010-2019	(those with ADPKD and PLD) is included within the systematic reviews and RCT papers in this review.
Messchendorp, A Lianne, Kramers, Bart J, Spithoven, Edwin M et al. (2019) Effect of a Somatostatin Analogue on the Vasopressin Pathway in Patients With ADPKD. Kidney international reports 4(8): 1170-1174	No relevant outcomes (vasopressin levels and renal water handling).
Messchendorp, A Lianne, Meijer, Esther, Visser, Folkert W et al. (2019) Rapid Progression of Autosomal-Dominant Polycystic Kidney Disease: Urinary Biomarkers as Predictors. American journal of nephrology 50(5): 375-385	No relevant outcomes (serum markers) and no intervention (no use of somatostatin).
Messchendorp, A Lianne, Spithoven, Edwin M, Casteleijn, Niek F et al. (2018) Association of plasma somatostatin with disease severity and progression in patients with autosomal-dominant polycystic kidney disease. BMC nephrology 19(1): 368	No relevant outcomes (association between endogenous plasma somatostatin concentration and disease severity and progression).
Myint, Thida M; Rangan, Gopi K; Webster, Angela C (2014) Treatments to slow progression of autosomal-dominant polycystic kidney disease: systematic review and meta-analysis of randomized trials. Nephrology (Carlton, Vic.) 19(4): 217-26	Does not present the results for each somatostatin (lanreotide and octreotide) separately. Newer, better-quality reviews are available including more studies.
Neijenhuis, M K, Gevers, T J G, Nevens, F et al. (2015) Somatostatin analogues improve health-related quality of life in polycystic liver disease: a pooled analysis of two randomised, placebo-controlled trials. Alimentary pharmacology & therapeutics 42(5): 591-8	Does not present the results for each somatostatin (lanreotide and octreotide) separately, it is also unclear if this is a systematic review as no details of searching, study selection or quality assessment are presented and therefore it represents a high risk of selection bias.
Neijenhuis, Myrte K, Wijnands, Titus F M, Kievit, Wietske et al. (2019) Symptom relief and not cyst reduction determines treatment success in aspiration sclerotherapy of hepatic cysts. European radiology 29(6): 3062-3068	Incorrect intervention (aspiration sclerotherapy).
Santoro, Domenico, Pellicano, Vincenzo, Visconti, Luca et al. (2015) An overview of experimental and early investigational therapies for the treatment of polycystic kidney disease. Expert opinion on investigational drugs 24(9): 1199-218	Narrative systematic review, no meta-analysis. Newer, better-quality reviews are available including more studies.
Suwabe, Tatsuya, Barrera, Francisco J, Rodriguez-Gutierrez, Rene et al. (2021) Somatostatin analog therapy effectiveness on the progression of polycystic kidney and liver disease: A systematic review and meta-analysis of randomized clinical trials. PloS one 16(9): e0257606	Does not present the results for each somatostatin (lanreotide and octreotide) separately, it also includes a study of a somatostatin (pasireotide) in its pooled analyses which is excluded from this review.
Temmerman, Frederik, Dobbels, Fabienne, Ho, Thien Anh et al. (2014) Development and validation of a polycystic liver disease complaint-specific assessment (POLCA). Journal of hepatology 61(5): 1143-50	No intervention and no relevant outcomes (derivation of POLCA score).
Treille, S, Bailly, J M, Van Cauter, J et al. (2014) The use of lanreotide in polycystic kidney disease: a single-centre experience. Case reports in nephrology and urology 4(1): 18-24	Small (n=6) case series. Higher quality randomised trial evidence is included for the outcomes reported in this study.
Tsukamoto, Shunichiro, Urate, Shingo, Yamada, Takayuki et al. (2022) Comparative Efficacy of Pharmacological Treatments for Adults With Autosomal-Dominant Polycystic Kidney Disease: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials. Frontiers in pharmacology 13: 885457	Does not present the results for each somatostatin (lanreotide and octreotide) separately, it also includes a study of a somatostatin (pasireotide) in its pooled analyses which is excluded from this review.
van Aerts, Rene M M, Kolkman, Marieke, Kievit, Wietske et al. (2018) Drug holiday in patients with polycystic liver disease treated with somatostatin analogues. Therapeutic advances in gastroenterology 11: 1756284818804784	Intervention not relevant (drug holiday).
Wijnands, T.F.M., Neijenhuis, M.K., Kievit, W. et al. (2014) Evaluating health-related quality of life in patients	No intervention is assessed.

with polycystic liver disease and determining the impact of symptoms and liver volume. Liver International 34(10): 1578	

Appendix E Evidence table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Full citation Griffiths J, Mills MT, Ong AC (2020) Long-acting somatostatin analogue treatments in autosomal-dominant polycystic kidney disease and polycystic liver disease: a systematic review and meta-analysis. BMJ Open. Jan 9;10(1):e032620. **Study location** UK systematic review (University of Sheffield) including 6 trials from Italy, the Netherlands and USA. Three secondary analyses of the included studies (2 Italian and 1 Netherlands studies) were also included. **Study type** Systematic review and meta-analysis **Study aim** "To evaluate all available RCTs investigating the efficacy of somatostatin analogues treatment in ADPKD and PLD." **Study dates** No search dates are reported in the paper or supplementary material online. No registration with PROSPERO database is declared.	**Inclusion criteria** • Randomised control trials (RCT) with appropriate control subjects. • Adults with a clinical and radiological diagnosis of ADPKD or PLD. • Intervention with an appropriate long-acting somatostatin analogue administered monthly at any dose in any formulation. • Relevant reported outcomes to the authors (TKV, TLV, eGFR, BP, AE, progression to ESRF, mortality and hospital admissions). **Exclusion Criteria** • Non-English language reports. • Interventions that included another treatment (for example combination with tolvaptan). • Observational trials and pooled analysis studies were excluded. • People with liver or kidney transplants were excluded from TKV, and eGFR or TLV analysis, respectively. People with Chronic Kidney Disease Stage 5 (CKD5) or receiving dialysis were also excluded. **Total sample size**	**Interventions** In the 2 trials the intervention used was: • lanreotide long-acting release 120 mg administered intramuscularly (IM) every 28 days Duration of treatment in each study is not reported, the study follow-up periods were: • 6 months in 1 study • 120 weeks in 1 study Concomitant treatments are not reported. **Comparators** In the 2 trials the comparators used were: • Placebo was the comparator in 1 double blind study. • Standard of care was the comparator in 1 open-label study.	**Critical outcomes** The authors report that the imaging modality used (TKV/TLV) was computed tomography scan in 1 RCT and magnetic resonance imaging in 1 RCT. *Total liver volume at treatment end (lanreotide versus control)* • Data from 2 studies pooled (meta-analysis) n=210, mean difference compared with control −0.14 L (95% CI −0.26 to −0.02; p=0.02) Random Effects model, I^2=0%. **Important outcomes** **Renal function** *Estimated glomerular filtration rate (eGFR) at treatment end (lanreotide versus control)* • Data from 1 study n=290, mean difference compared with standard of care at 120 weeks −0.60 mL/min/1.73m^2 (95% CI −3.65 to 2.45, p=0.70) Random Effects model, I^2=N/A. *Total kidney volume at treatment end (lanreotide versus control)* • Data from 2 studies pooled (meta-analysis) n=304, mean difference compared with control −0.15 L (95% CI −0.21 to −0.10, p<0.00001) Random Effects model, I^2=0%.	This study was appraised using ROBIS: Tool to assess risk of bias in systematic reviews DOMAIN 1: STUDY ELIGIBILITY CRITERIA 1.1 Probably yes 1.2 Yes 1.3 Probably yes 1.4 Yes 1.5 Yes Concerns regarding specification of study eligibility criteria: LOW DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES 2.1 Yes 2.2 No 2.3 Probably yes 2.4 No 2.5 No Information Concerns regarding the identification and selection of studies: HIGH DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL 3.1 Yes 3.2 Yes 3.3 Yes 3.4 Yes 3.5 Yes

	• Excluding the number of people in the secondary analysis, a total of n=363 participants were included for lanreotide studies. • All included studies recruited both male (n=149) and female (n=214) participants. **No. of participants in each treatment group** Varies by outcome in the meta-analysis, however the overall maximum number in the lanreotide group was n=146 and in the control n=158. **Baseline characteristics** The authors of the review only report the baseline characteristics of eGFR, TKV and TLV. The most significant variation in inclusion criteria between studies was baseline renal function, which appears reflective of the renal function criteria of each of the studies.			Concerns regarding data collection and study appraisal: Low DOMAIN 4: SYNTHESIS AND FINDINGS 4.1 Yes 4.2 Probably yes 4.3 Yes 4.4 Probably yes 4.5 Probably yes 4.6 No Concerns regarding the synthesis and findings: Low Overall Risk of Bias: Low risk. **Other comments:** "Patients with liver or kidney transplants were excluded from TKV and eGFR or TLV analysis, respectively. Patients with Chronic Kidney Disease Stage 5 (CKD5) or receiving dialysis were also excluded." **Source of funding:** "The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors. Publications charges were funded by the Sheffield Kidney Research Foundation."
Full citation St Pierre_K, Cashmore_BA, Bolignano_D et al. (2024) Interventions for preventing the progression of autosomal-dominant polycystic kidney disease. Cochrane Database of Systematic Reviews 2024, Issue 10. Art. No.: CD010294. **Study location** International Cochrane collaboration review incorporating (n=57) studies that had been conducted around the world, but mainly in Europe and the United States.	**Inclusion criteria** • Adults or children with a clinical diagnosis of ADPKD (by MRI or echo tomography meeting the Ravine criteria), confirmed or not by genetic test • Participants had kidney and cyst volumes of any dimension • Participants had CKD stages 1 to 4 (according to US National Kidney Foundation's Kidney Disease Outcomes Quality	**Interventions** The review found evidence for 18 different pharmacological interventions. This comprised vasopressin 2 receptor (V2R) antagonists, antihypertensive therapy, mammalian target of rapamycin (mTOR) inhibitors, somatostatin analogues, antiplatelet agents, eicosapentaenoic acids, statins, kinase inhibitors, diuretics, anti-diabetic agents, water intake, dietary intervention, and supplements. **Comparators** Eligible comparators included in the review were:	**Critical outcomes** *Health-related Quality of life* • Data from 1 study (DIPAK-1) assessed HRQoL, n=305, lanreotide plus standard care was not statistically significantly different to standard care alone from baseline to treatment end (120 weeks), mean difference −0.02 (95% CI −0.12 to 0.08, p=0.69). In the DIPAK=1, trial the measure used to assess quality of life was the 18-question ADPKD Impact Scale (Oberdhan et al. 2018). A minimum score of 1 indicates "not bothered at all" and the maximum score of 5 indicates "extremely bothered".	This study was appraised using ROBIS: Tool to assess risk of bias in systematic reviews DOMAIN 1: STUDY ELIGIBILITY CRITERIA 1.1 Yes 1.2 Yes 1.3 Yes 1.4 Yes 1.5 Yes Concerns regarding specification of study eligibility criteria: LOW

Study type Systematic review and meta-analysis **Study aim** "To evaluate the benefits and harms of interventions to prevent the progression of ADPKD and the safety based on patient-important endpoints, defined by the Standardised Outcomes in NephroloGy-Polycystic Kidney Disease (SONG-PKD) core outcome set, and general and specific adverse effects." **Study dates** The review search from database inception to 13 August 2024	Initiative (KDQOI) guidelines). **Exclusion Criteria** • Participants with ADPKD and CKD stage 5 (GFR <15 mL/min /1.73 m^2), receiving kidney dialysis or who had undergone kidney transplantation. • Diagnosis of autosomal recessive polycystic kidney disease (or other liver or kidney cystic diseases). **Total sample size** The total number of patients randomised was n=8016 randomised to 18 different treatments. **No. of participants in each treatment group** Varies by outcome in the meta-analysis, overall number for somatostatin studies not reported. **Baseline characteristics** As per included studies, not detailed separately for somatostatin studies	• Placebo • Intervention plus octreotide • Standard care	**Important outcomes** **Renal function** • Data from 1 study (DIPAK-1) assessed a 30% or more decrease in GFR or kidney failure, n=305, lanreotide plus standard care was not statistically significantly different to standard care alone from baseline to treatment end (120 weeks), RR 0.72 (0.43 to 1.20, p=0.21). **Safety** • Data from 1 study (DIPAK-1) assessed the outcome of death, n=309, lanreotide plus standard care was not statistically significantly different to standard care alone from baseline to treatment end (120 weeks), RR 3.02 (95% CI 0.12 to 73.55, p=0.50).	DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES 2.1 Yes 2.2 Yes 2.3 Yes 2.4 Yes 2.5 Yes Concerns regarding the identification and selection of studies: Low DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL 3.1 Yes 3.2 Yes 3.3 Yes 3.4 Yes 3.5 Yes Concerns regarding data collection and study appraisal: Low DOMAIN 4: SYNTHESIS AND FINDINGS 4.1 Yes 4.2 Yes 4.3 Yes 4.4 Probably yes 4.5 Yes 4.6 Yes Concerns regarding the synthesis and findings: Low Overall Risk of Bias: Low risk. **Other comments: N/A**

				Source of funding: Cochrane review, Cochrane do not accept commercial or conflicted funding. Funding and support comes from institutes and Governmental sources around the world such as the NIHR.
Full citation Temmerman F, Ho TA, Vanslembrouck R et al (2015) Lanreotide Reduces Liver Volume, But Might Not Improve Muscle Wasting or Weight Loss, in Patients With Symptomatic Polycystic Liver Disease. Clin Gastroenterol Hepatol. Dec;13 (13):2353-9. e1. **Study location** Two tertiary medical centres in Belgium (University Hospitals KU Leuven and the Université Catholique de Louvain in Brussels). **Study type** Prospective observational study **Study aim** To investigate the efficacy of a lower dose of lanreotide and its effects on nutritional status. **Study dates** January 2011 and August 2012 (18 months)	**Inclusion criteria** • Adults aged 18 years or older with either ADPKD or ADPLD (ADPKD diagnostic criteria not reported) • Participants had symptomatic PLD (Mayo classification C or D) with hepatomegaly **Exclusion Criteria** • Intake of hormone replacement or hormonal contraception • Pregnancy or breast feeding • Planned to undergo non-liver transplant liver or kidney surgery during the study period • Known allergy to somatostatin or analogues • Somatostatin use within 6 months of study inclusion **No. of participants** This study included n=59 participants **Baseline characteristics** • The median age at baseline was 51 years (IQR 47 to 57 years).	**Interventions** • Lanreotide (90 mg subcutaneously every 4 weeks) for 6 months. • Patients with reductions in liver volume of more than 100 mL (classed as responders, primary end point) continued to receive lanreotide (90 mg) for an additional year (18 months total). • Non responders were offered increased doses, up to 120 mg lanreotide, until 18 months. Concomitant treatments were not reported. **Comparator** No comparator, observational study.	**Critical outcomes** **Symptom control** Outcome was assessed using the Polycystic Liver Disease-complaint-specific assessment (POLCA) score after 18 months of treatment (n=43). Mean [SE] severity of perceived illness at baseline 15.9 [0.9] and at 18 months 9.8 [0.72], p<0.0001 (score range 0 to 35) Mean [SE] gastroesophageal reflux disease related complaints at baseline 3.18 [0.6] and at 18 months 1.67 [0.34], p=0.001 (score range 0 to 20) Mean [SE] impact on food intake at baseline 3.6 [0.38] and at 18 months 3.0 [0.3], p=0.04 (score range 0 to 10) Mean [SE] perception of enlarged liver volume at baseline 6.8 [0.4] and at 18 months 5.5 [0.5], p=0.008 (score range 0 to 15) **Nutritional status** Mean weight of participants at baseline was 72 [2.2, not reported if SE or SD] Kg, which was statistically significantly reduced to 70 [2.3] Kg at follow-up, p=0.01 The mean skeletal mass index of participants at baseline was 43.076 cm^2/h^2 [1.1, not reported if SE or SD], which was statistically significantly reduced to 42.02 [1.1] cm^2/h^2 at follow-up (p<0.001). The proportion (%) of participants with sarcopenia at baseline was 27% (n=10/37) which increased at follow-up to 38% (14/37), not statistically significantly different (p not reported).	This study was appraised using the Critical Appraisal Skills Programme Cohort Study Checklist Section A: Are the results valid? 1. Yes 2. Yes 3. Yes 4. Yes 5a. No 5b. No 6a. No 6b. Yes. Section B: What are the results? 7. See Study outcomes. 8. No 9. Can't Tell Section C: Will the results help locally? 10. Can't Tell 11. Yes 12. Yes Overall quality assessment: Low Other comments: This author discloses the following: Frederik Nevens received an unrestricted grant from Ipsen Pharma (2012-2637). The remaining authors disclose no conflicts." Source of funding:" This study was sponsored in part by Ipsen Pharma, who supported the

	• The study participants comprised 52 women and 7 men. • Median liver volume was 5163 mL (IQR 3953 to 7238 mL). • Median weight was 68.6 Kg (IQR 61 to 81 Kg) • Median mid-upper arm circumference in women was 25 cm (IQR 23.4 to 26.4 cm) and men was 27 cm (IQR 26 to 29 cm). • Median albumin 46 g/L (IQR 44.8 to 48.3 g/L). • Skeletal muscle mass in women was 41.4 cm^2/h^2 (SE 37.8 to 45) and men was 53.4 (SE 50.4 to 57.8). • The proportion of participants with sarcopenia (defined as the skeletal muscle index less than 38.5 cm^2/h^2 in females and less than 52.4 cm^2/h^2 in men) was 30%. • Median subcutaneous adipose tissue was 144 cm^2 (IQR 92 to 240 cm^2). • Median visceral adipose tissue was 53.4 cm^2 (IQR 29 to 98 cm^2).		**Subgroup responders** (liver volume decrease >100 mL at 6 months) n=21 Mean weight statistically significantly decreased from baseline to 18 months from 72 Kg [SE 3.4] to 69 Kg [SE 3.4], p=0.006. Mean skeletal mass index statistically significantly decreased from baseline to 18 months from 44.5 cm^2/h^2 [SE 1.6 cm^2/h^2] to 42.5 cm^2/h^2 [SE1.6 cm^2/h^2], p=0.001 **Subgroup non responders** (those with <100 mL liver volume decrease at 6 months who were offered increased [120 mg] dose up to 18 months) n=22 Mean weight data not reported, but authors state weight remained stable. Mean skeletal mass index reduced, but the reduction was not statistically significant, from baseline to 18 months from 42.5 cm^2/h^2 [SE 1.8 cm^2/h^2] to 41.6 cm^2/h^2 [SE 1.6 cm^2/h^2], p=0.13.	performance of 2 computed tomographic scans in the study."
Full citation van Aerts RMM, Kievit W, D'Agnolo HMA. et al for the DIPAK-1 Investigators (2019) Lanreotide Reduces Liver Growth In Patients With Autosomal-Dominant Polycystic Liver and Kidney Disease.	**Inclusion criteria** • Aged 18 to 60 years • ADPKD diagnosed according to the modified Ravine criteria	**Interventions** • Lanreotide 120 mg subcutaneously every 4 weeks, dosage titrated down to 90 mg every 4 weeks if eGFR <30 mL/min/1.73m^2 or if significant side effects (could be	**Critical outcomes** **Total liver volume** *Total liver volume - subgroup by sex* • No statistically significant difference in the percentage change in height-adjusted liver	This study was appraised using the Cochran risk of bias tool for randomized trials (RoB 2). Domain 1: Risk of bias arising from the randomization process 1.1 Probably yes

Gastroenterology. 2019 Aug;157(2):481-491.e7. Aapkes SE, de Haas RJ, Bernts LHP, et al. DIPAK consortium. (2021) Incident Gallstones During Somatostatin Analog Treatment are Associated with Acute Biliary Complications Especially After Discontinuation. Drugs R D. 2021 Jun;21(2):179-188. 1. Epub 2021 Mar 29. **Study location** Multicentre (Groningen, Leiden, Nijmegen and Rotterdam) study conducted in the Netherlands. **Study type** Open-label randomised clinical trial. **Study aim** The aim of the **van Aerts et al. 2019** paper was "to determine the effects of lanreotide on height-adjusted liver volume and combined height-adjusted liver and kidney volume in patients with ADPKD." The aim of the **Aapkes et al.2021** paper was to "determine the incidence, number, size, and complications of gallstones in a systematic, prospective way." **Study dates** June 2012 to August 2017	• An eGFR (MDRD) of 30 to 60 mL/min/1.73m^2 • (For **van Aerts et al. 2019** paper) only those with ADPKD with PLD and hepatomegaly (a priori definition) of ≥2000 mL at baseline. **Exclusion Criteria** • Any person who in the opinion of the investigator represented a safety risk. • Those persons unable to comply with trial procedures. • Any person taking other medications or with concomitant illness likely to confound study endpoint assessment, including other experimental therapies. • Anyone who underwent surgical or drainage interventions for cystic kidney disease within 1 year (or likely candidate for such procedure within 2 years of study start) or liver cyst drainage or surgery in the 12 months prior to study entry (can join but not assessed for TLV). • Anyone having taken lanreotide or another somatostatin analogue within 3 months before study commencement (or with a known intolerance for somatostatins). • Women in pregnancy or breastfeeding.	decreased further to 60 mg or stopped if necessary). Plus, standard care. • Administration was by trained nurses on a homecare service. Concomitant treatments as per standard care below. **Comparator** Standard care alone, consisting of: • Blood pressure control (<140/90 mmHg), if required by sodium-restricted diet and anti-hypertensives **(**angiotensin-converting enzyme inhibitors, or in case of intolerance for angiotensin-converting enzyme inhibitors, with angiotensin receptor blockers**)**. • Use of oestrogens and oral contraceptives was discouraged (but not an exclusion criterion). • Dietary advice (reduction in sodium, caffeine, and protein intake and increase in water intake) was given at the discretion of the treating physician.	volume at 120 weeks (treatment end) between males and females in the control group (no p value reported). • In women there was a statistically significant mean percentage reduction in height-adjusted liver volume at 120 weeks in the lanreotide group (−7.68%, p=0.001) compared with those in the control group. • In men there was a non-statistically significant mean percentage reduction in height-adjusted liver volume at 120 weeks in the lanreotide group (−4.05%, p=0.09) compared with those in the control group. • The authors report that subgroup analysis provides evidence that gender was not an effect modifier for change in height-adjusted total liver volume (p=0.3). **Symptom control** • Change in symptom severity score, symptoms were assessed using a 7-point Likert-like scale, ranging from 1 (none) to 7 (very severe) and were partially derived from the Gastrointestinal Symptom Score (modified on expert opinion for PLD symptoms). Symptom severity score was calculated by summing all scores and converting it to a score from 0 to 100 from baseline to follow-up: • Baseline median symptom score in the lanreotide group was 9.1 (IQR 3.0 to 18.6), the baseline median symptom score in the standard care group (6.1, IQR 1.5 to 15.5) was not statistically significantly different to the lanreotide group (p=0.1) • At 120 weeks in the lanreotide group the median symptom score increased by 2.7 (95% CI 0.7 to 4.7) compared with an increase of 2.6 (95% CI 0.5 to 4.7) in the standard care group, again there was no statistically significant difference from the lanreotide group (p=0.9). **Important outcomes**	1.2 No information 1.3 Yes Concerns arising from the risk of bias arising from the randomization process: High Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) 2.1 Yes 2.2 Yes 2.3 Probably No 2.4 N/A 2.5 N/A 2.6 Yes 2.7 N/A Concerns arising from risk of bias due to deviations from the intended interventions (effect of assignment to intervention): Low Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) 2.1 Yes 2.2 Yes 2.3 Yes 2.4 No 2.5 No 2.6 N/A Concerns arising from risk of bias due to deviations from the intended interventions (effect of adhering to intervention): Low Domain 3: Risk of bias due to missing outcome data 3.1 Yes

	• Anyone with a cardiac arrythmia thought to be dangerous in combination with lanreotide. • Anyone with a history of symptomatic gallstones, not having undergone cholecystectomy or a history of pancreatitis or infected liver cysts. • (For **Aapkes et al. 2021** paper) Participants with a history of diabetes mellitus, pancreatitis, known presence of gallstones, prior gall bladder removal or bradycardia. **No. of participants in each treatment group** Participants in the original DIPAK-I study were (block size 6) randomised (1:1) to either lanreotide plus standard care (n=154) or standard care alone (n=155). The **van Aerts et al. 2019** paper included n=93 randomised to lanreotide plus standard care and n=82 randomised to standard care alone. The Aapkes et al. 2021 paper included n=124 randomised to lanreotide and n=125 randomised to standard care. **Baseline characteristics** **van Aerts et al.** • The mean ±SD age of participants was 48.3±6.2 years (lanreotide group) and 48±7.0 years (control group).		**Imaging changes** MRI (before and after treatment) were made according to a standard protocol, including coronal and transversal T2-weighted single shot fast gradient spin-echo with fat saturation. These were independently scored by 2 blinded reviewers. Disagreement was resolved by 3rd party radiologist. **Baseline** • At baseline 15/249 (6%) of participants had gallstones • There was no statistically significant difference between the number with gall stones in the lanreotide group, 4/124 (3.2%), and the standard care group (11/125 [8.8%], p=0.07). **Follow-up** • At treatment end (120 weeks) 34/249 (14%) participants had gallstones • There was a statistically significant difference between the number of participants with gallstones in the lanreotide group (23/124; 18.5%) and the standard care group (11/125; 8.8%, p<0.05). • Accounting for baseline gallstones (new incident gallstones) there was a statistically significant difference between the number of participants with gallstones during the study between the lanreotide group (19/124, 15.3%) and the standard care group (1/125, 0.8%, p<0.0001). • Use of lanreotide was associated with a statistically significant increased odds of incident gallstones in both univariate (OR 22.5, 95% CI 2.96 to 171, p<0.01), and multivariate (OR 25.9, 95% CI 3.37 to 199, p<0.01), logistic regression analysis. • The number of incident gallstones in each of the 19 participants in the lanreotide group was statistically significantly increased compared to baseline (p=0.004),	3.2 N/A 3.3 N/A 3.4 N/A Concerns arising from risk of bias due to missing outcome data: Low Domain 4: Risk of bias in measurement of the outcome 4.1 Probably no 4.2 No 4.3 Yes 4.4 Probably yes 4.5 Probably no Concerns arising from risk of bias in measurement of the outcome: Some concerns Domain 5: Risk of bias in selection of the reported result 5.1 Yes 5.2 No 5.3 No Concerns arising from risk of bias in selection of the reported result: Low Overall risk of bias: High Other comments: The authors state that the cohort was not stratified for baseline liver volume and that this accounts for the imbalance of baseline hTLV. Source of funding:" This study is funded by a Consortium Grant obtained from the Dutch Kidney Foundation (€1.5 million [~$1.9 million]). IPSEN Farmaceutica BV, the company producing lanreotide, is a minor sponsor and provided an unrestricted grant of €240,000 ($310,000). Neither funding party has any role in developing the protocol or performing the study or in the publication process."

	• There was n=40 males in each group (representing 43.0% of the lanreotide group and 48.9% of the control group). • Over 97% of the participants in the 2 groups were white. • There were no statistically significant differences in height (1.78±0.10 cm vs. 1.76±0.10 cm, p=0.45), weight (86.0±17.4 Kg vs. 87.1±20.0 Kg, p=0.69) or BMI (27.2±4.3 Kg/m^2 vs. 27.9±5.4 Kg/m^2, p=0.35) between the lanreotide and control group, respectively. • There were also no statistically significant differences in baseline alkaline phosphatase (p=0.66), Gamma-glutamyl transferase (p=0.35), serum creatinine (p=0.78), eGFR (p=0.71) or CKD stages (p=0.71). • There was a statistically significant difference in height-adjusted total liver volume at baseline; 1528 mL/m (lanreotide) versus 1376 mL/m (control), p=0.04 (Mann-Whitney U test). • At baseline height-adjusted liver volume was statistically significantly higher in females (1654 mL/m) than males (1283 mL/m) (p<0.001) **Aapkes et al. 2021** • The mean ±SD age of participants was 48±7		however, they were typically smaller in size (0 to 10 mm, p=0.001). **Adherence to treatment** • Lanreotide was titrated down in 23 participants (to 90 mg in 20 participants and 60 mg in 3 participants). • 8 participants were titrated down due to eGFR reaching <30 mL/min/1.73m^2 • 15 participants were titrated down due to adverse events (7 gastrointestinal complaints; 3 fatigue or malaise; 2 due to bradycardia; 1 hypoglycaemia; 1 hair loss and 1 liver cyst infection). • 8 participants discontinued lanreotide, 6 due to continued adverse events despite titration down. Two participants discontinued lanreotide for other reasons (1 due to nephrectomy and 1 other due to loss of confidence in the intervention). • 6 out of 7 participants titrated down due to gastrointestinal complaints, the adverse effects were tolerable at the lower dose. • In total 18 patients (19%) stopped lanreotide at once, of whom 14 did so because of adverse events **Safety** • In this cohort, serious adverse events (SAE) occurred in 28 (30.1%) participants in the lanreotide group (n=93), and in 10 (12.2%) participants in the control group (n=82). • Four (4.3%) of the SAE led to study withdrawal in the lanreotide group compared with 1 (1.2%) in the control group. • Thirteen SAE were thought to be related to the intervention; this comprised hepatic cyst infection n=6 (6.5%); renal cyst infection n=2 (2.2%); pyelonephritis n=1 (1.1%); epigastric pain 1 (1.1%); fever n=1 (1.1%); urinary tract infection n=1 (1.1%)	

	years (lanreotide group) and 49±7.0 years (control group). • There was n=58/124 (47%) females in the lanreotide group and 62/125 (50.0%) in the control group. • There were no statistically significant differences in baseline age (p=0.54); BMI (p=0.74); median height-adjusted total liver volume (p=0.06); eGFR (CKD-EPI) (p=0.82); AST (p=0.58); ALT (p=0.15); ALP (p=0.58); GGT (p=0.08) or indirect bilirubin (p=0.57). • There was a statistically significant difference in polycystic liver disease classification (mild moderate and severe) with a greater proportion of moderate and severe in the lanreotide group (p=0.02). • There was a reported statistically significant difference in median direct bilirubin, however, the median and IQR were the same in both groups (3.0 µmol/L, IQR 2.0 to 4.0, p=0.008).		and cholelithiasis n=1 (1.1%). This compared to n=2 (2.4%) renal cyst infections and n=1 (1.2%) pyelonephritis in the control group.	

Abbreviations

AE, Adverse events; ADPKD, Autosomal-dominant polycystic kidney disease; ADPLD, Autosomal-dominant polycystic liver disease; ALT, Alanine transaminase; ALP, Alkaline phosphatase; AST, Aspartate aminotransferase; BMI, Body mass index; BP, Blood pressure; CI, Confidence interval; CKD, Chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, Estimated glomerular filtration rate; ESRF, End stage renal failure; GGT, Gamma-glutamyl transferase; I^2, I^2 statistic for heterogeneity; IQR, Interquartile range; MDRD, Modification of Diet in Renal Disease; N/A, Not applicable; OLE, Open-label extension; P, probability value; PLD, Polycystic liver disease; POLCA, Polycystic Liver Disease-complaint-specific assessment; RCT, Randomised controlled trial; RR, Risk ratio; SD, Standard deviation; SE, Standard error of the means; TLV, Total liver volume; TKV, Total kidney volume.

Appendix F Quality appraisal checklists

ROBIS: Tool to assess risk of bias in systematic reviews

Domain 1: Study eligibility criteria	
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Y/PY/PN/N/NI
1.2 Were the eligibility criteria appropriate for the review question?	Y/PY/PN/N/NI
1.3 Were eligibility criteria unambiguous?	Y/PY/PN/N/NI
1.4 Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Y/PY/PN/N/NI
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Y/PY/PN/N/NI
Concerns regarding specification of study eligibility criteria and rationale for concern	Low /High /Unclear
Domain 2: Identification and selection of studies	
2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Y/PY/PN/N/NI
2.2 Were methods additional to database searching used to identify relevant reports?	Y/PY/PN/N/NI
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Y/PY/PN/N/NI
2.4 Were restrictions based on date, publication format, or language appropriate?	Y/PY/PN/N/NI
2.5 Were efforts made to minimise error in selection of studies?	Y/PY/PN/N/NI
Concerns regarding methods used to identify and/or select studies and rationale for concern	Low /High /Unclear
Domain 3: Data collection and study appraisal	
3.1 Were efforts made to minimise error in data collection?	Y/PY/PN/N/NI
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Y/PY/PN/N/NI
3.3 Were all relevant study results collected for use in the synthesis?	Y/PY/PN/N/NI
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Y/PY/PN/N/NI
3.5 Were efforts made to minimise error in risk of bias assessment?	Y/PY/PN/N/NI
Concerns regarding methods used to collect data and appraise studies and rationale for concern	Low /High /Unclear
Domain 4: Synthesis and findings	
4.1 Did the synthesis include all studies that it should?	Y/PY/PN/N/NI
4.2 Were all pre-defined analyses reported or departures explained?	Y/PY/PN/N/NI

4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Y/PY/PN/N/NI
4.4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Y/PY/PN/N/NI
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Y/PY/PN/N/NI
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Y/PY/PN/N/NI
Concerns regarding the synthesis and findings and rationale for concern	Low /High /Unclear
Overall risk of bias in the review	Low /High /Unclear
Abbreviations: Y/PY/PN/N/NI: Yes/ Probably Yes/ Probably No/ No/ No information	

Cochrane risk of bias tool for randomised trials (RoB 2)

Domain 1: Risk of bias arising from the randomization process	
1.1 Was the allocation sequence random?	Y/PY/PN/N/NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y/PY/PN/N/NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Y/PY/PN/N/NI
Risk of bias judgement	Low / High / Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	
2.1. Were participants aware of their assigned intervention during the trial?	Y/PY/PN/N/NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y/PY/PN/N/NI
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	Y/PY/PN/N/NI
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	Y/PY/PN/N/NI
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	Y/PY/PN/N/NI
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y/PY/PN/N/NI
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Y/PY/PN/N/NI

Risk of bias judgement	Low / High / Some concerns
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	
2.1. Were participants aware of their assigned intervention during the trial?	Y/PY/PN/N/NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y/PY/PN/N/NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	Y/PY/PN/N/NI
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	Y/PY/PN/N/NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	Y/PY/PN/N/NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Y/PY/PN/N/NI
Risk of bias judgement	Low / High / Some concerns
Domain 3: Risk of bias due to missing outcome data	
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y/PY/PN/N/NI
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	Y/PY/PN/N/NI
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Y/PY/PN/N/NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Y/PY/PN/N/NI
Risk of bias judgement	Low / High / Some concerns
Domain 4: Risk of bias in measurement of the outcome	
4.1 Was the method of measuring the outcome inappropriate?	Y/PY/PN/N/NI
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Y/PY/PN/N/NI
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Y/PY/PN/N/NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Y/PY/PN/N/NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Y/PY/PN/N/NI
Risk of bias judgement	Low / High / Some

	concerns
Domain 5: Risk of bias in selection of the reported result	
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y/PY/PN/N/NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...	
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Y/PY/PN/N/NI
5.3 ... multiple eligible analyses of the data?	Y/PY/PN/N/NI
Risk of bias judgement	Low / High / Some Concerns
Overall risk of bias in the review	Low /High /Unclear
Abbreviations: Y/PY/PN/N/NI: Yes/ Probably Yes/ Probably No/ No/ No information	

Critical Appraisal Skills Programme Cohort Study Checklist

Section A: Are the results valid?	
1. Did the study address a clearly focused issue?	Yes/ No/ Can't Tell
2. Was the cohort recruited in an acceptable way?	Yes/ No/ Can't Tell
3. Was the exposure accurately measured to minimise bias?	Yes/ No/ Can't Tell
4. Was the outcome accurately measured to minimise bias?	Yes/ No/ Can't Tell
5. (a) Have the authors identified all important confounding factors?	Yes/ No/ Can't Tell
5. (b) Have they taken account of the confounding factors in the design and/or analysis?	Yes/ No/ Can't Tell
6. (a) Was the follow-up of subjects complete enough?	Yes/ No/ Can't Tell
6. (b) Was the follow-up of subjects long enough?	Yes/ No/ Can't Tell
Section B: What are the results?	
7. What are the results of the study?	Yes/ No/ Can't Tell
8. How precise are the results?	Yes/ No/ Can't Tell
9. Do you believe the results?	Yes/ No/ Can't Tell
Section C: Will the results help locally?	
10.Can the results be applied to the local population?	Yes/ No/ Can't Tell
11.Do the results of this study fit with other available evidence?	Yes/ No/ Can't Tell
12.What are the implications of this study for practice?	Yes/ No/ Can't Tell

Appendix G GRADE profiles

Table 2: Question: In patients experiencing symptomatic PLD, what is the clinical effectiveness of lanreotide compared with supportive treatment, octreotide or liver transplant?

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Lanreotide	Placebo and/or standard of care	Result (95%CI)		
Total liver volume was assessed by meta-analysis of 2 RCTs in 1 systematic review									
Mean difference in total liver volume at follow-up (6 months in 1 RCT, 120 weeks in 1 RCT) Lower is better									
Systematic Review Griffiths et al. (2020)	No serious limitations	No serious indirectness	No serious inconsistency I^2=0%. Random effects model used.	No serious imprecision	N=110	N=100	Mean difference −0.14 L (95% CI −0.26 to −0.02; p=0.02)	Critical	High
Symptom control was assessed by 1 RCT (overall symptom score) and 1 observational study (POLCA)									
Assessed using 7-point Likert-like scale, ranging from 1 (none) to 7 (very severe), sum of all scores converted to a score from 0 to 100 from baseline to follow-up (120 weeks). Lower is better									
1 RCT van Aerts et al. (2019) DIPAK-I	Very serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=93 Baseline median symptom score was 9.1 (IQR 3.0 to 18.6)	N=82 Baseline median symptom score in standard care group 6.1 (IQR 1.5 to 15.5)	Median symptom score: • at follow-up increased by 2.7 (95% CI 0.7 to 4.7) in the lanreotide group • at follow-up increased by 2.6 (95% CI 0.5 to 4.7) in the standard care group • no statistically significant difference between groups at baseline (p=0.1) or follow-up (p=0.9)	Critical	Low
Symptom control was assessed in 1 prospective observational study using the POLCA score after 18 months of treatment (lower score indicates better symptoms)									
Assessed as change in mean [SE] severity of perceived illness (change in POLCA score [range 0 to 35] from baseline to follow-up at 18 months). Lower is better									
1 prospective observational study Temmerman et al. (2015)	Very serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=43	N/A	Mean [SE] severity score of perceived illness: • at baseline 15.9 [0.9] • at follow-up 9.8 [0.72]	Critical	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Lanreotide**	**Placebo and/or standard of care**	**Result (95%CI)**		
							• statistically significantly lower at follow-up (p<0.0001)		
Assessed as change in mean [SE] severity of gastroesophageal reflux disease related complaints (change in POLCA score [range 0 to 20] from baseline to follow-up at 18 months). Lower is better									
1 prospective observational study Temmerman et al. (2015)	Very serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=43	N/A	Mean [SE] gastroesophageal reflux disease related complaints: • at baseline 3.18 [0.6] • at 18 months 1.67 [0.34] • statistically significantly lower at follow-up (p=0.001)	Critical	Very low
Assessed as change in mean [SE] severity of impact on food intake (change in POLCA score [range 0 to 10] from baseline to follow-up at 18 months). Lower is better									
1 prospective observational study Temmerman et al. (2015)	Very serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=43	N/A	Mean [SE] impact on food intake: • at baseline 3.6 [0.38] • at 18 months 3.0 [0.3] • statistically significantly lower at follow-up (p=0.04)	Critical	Very low
Assessed as change in mean [SE] severity of perception of enlarged liver volume (change in POLCA score [range 0 to 15] from baseline to follow-up at 18 months). Lower is better									
1 prospective observational study Temmerman et al. (2015)	Very serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=43	N/A	Mean [SE] perception of enlarged liver volume: • at baseline 6.8 [0.4] • at 18 months 5.5 [0.5] • statistically significantly lower at follow-up (p=0.008)	Critical	Very low
Nutritional status was assessed in 1 prospective observational study using mean weight [not reported if SE or SD] and mean Skeletal Mass Index (SMI) [SE]									
Assessed as change in mean weight [not reported if SE or SD] from baseline to follow-up at 18 months.									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Lanreotide**	**Placebo and/or standard of care**	**Result (95%CI)**		
1 prospective observational study Temmerman et al. (2015)	Very serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=53	N/A	Mean weight [figure in brackets not defined]: • at baseline 72 [2.2] Kg • at follow-up 70 [2.3] Kg • statistically significantly lower at follow-up (p=0.01)	Critical	Very low
Assessed as change in skeletal mass index, cm^2/h^2 [not reported if SE or SD] from baseline to follow-up at 18 months. Higher is better.									
1 prospective observational study Temmerman et al. (2015)	Very serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=37	N/A	Mean skeletal mass index [figure in brackets not defined]: • at baseline 43.076 [1,1] • at follow-up 42.02 [0.95] • statistically significantly lower at follow-up (p<0.001)	Critical	Very low
Assessed as the proportion of those with severe skeletal muscle depletion or sarcopenia (severe skeletal muscle depletion or sarcopenia defined as Skeletal Mass Index (SMI) <38.5 cm^2/h^2 in females and < 52.4 cm^2/h^2 in men). Lower proportion is better.									
1 prospective observational study Temmerman et al. (2015)	Very serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=37	N/A	Proportion (%) of participants with sarcopenia: • at baseline (27%, n=10/37) • at follow-up (38%, 14/37) • not statistically significantly different (p not reported).	Critical	Very low
Quality of life was assessed in 1 systematic review (included data from a single RCT)									
Quality of life was assessed using the 18-question ADPKD Impact Scale (Oberdhan et al. 2018). A minimum score of 1 indicates "not bothered at all" and the maximum score of 5 indicates "extremely bothered", follow-up was at 120 weeks. Lower is better.									
Systematic review	Serious limitations[3]	No serious indirectness	Not applicable	No serious imprecision	N=153	N=152 Standard of care	Mean difference −0.02 (95% CI −0.12 to 0.08, p=0.69).	Critical	Moderate

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Lanreotide**	**Placebo and/or standard of care**	**Result (95%CI)**		
St Pierre et al. (2024) DIPAK-I									
Imaging changes were assessed in 1 RCT									
MRI to determine the number of participants with gallstones (MRI according to a standard protocol), follow-up was at 120 weeks. Lower number is better.									
Randomised controlled trial Aapkes et al. (2021) DIPAK-I	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=124	N=125 Standard of care	The number of participants with gallstones at follow-up: • lanreotide group 23 / 124 (18.5%) • standard care group 11 / 125 (8.8%) • statistically significantly lower in the lanreotide group (p<0.05).	Important	Moderate
MRI to determine the number of participants with gallstones adjusted for presence of gallstones at baseline (MRI according to a standard protocol), follow-up was at 120 weeks. Lower number is better.									
Randomised controlled trial Aapkes et al. (2021) DIPAK-I	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=124	N=125 Standard of care	The number of participants with new incident gallstones at follow-up: • lanreotide group 19 / 124 (15.3%) • standard care group 1 / 125 (0.8%) • statistically significantly lower in the standard care group (p<0.0001).	Important	Moderate
MRI to determine the odds of incident gallstones (MRI according to a standard protocol), follow-up was at 120 weeks. Lower number is better.									
Randomised controlled trial Aapkes et al. (2021) DIPAK-I	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=124	N=125 Standard of care	Lanreotide statistically significantly increased the odds of incident gallstones in both: • univariate logistic regression analysis (OR 22.5, 95% CI 2.96 to 171, p<0.01)	Important	Moderate

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Lanreotide**	**Placebo and/or standard of care**	**Result (95%CI)**		
							• multivariate logistic regression analysis (OR 25.9, 95% CI 3.37 to 199, p<0.01)		
MRI to determine the number of incident gallstones each of the participants with new incident gallstones had (MRI according to a standard protocol), follow-up was at 120 weeks. Lower number is better.									
Randomised controlled trial Aapkes et al. (2021) DIPAK-I	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=19	N/A	• at baseline, of the 14 participants with gallstones 13 (93%) had between 1 and 15 stones • at follow-up, of the 19 participants with new incident gallstones 14 (74%) had between 15 and 30+ incident gallstones • lanreotide statistically significantly increased the number of incident gallstones for each participant compared to gallstones at baseline (p=0.004)	Important	Moderate
MRI to determine the size of incident gallstones each of the participants with new incident gallstones had (MRI according to a standard protocol), follow-up was at 120 weeks. Lower number is better.									
Randomised controlled trial Aapkes et al. (2021) DIPAK-I	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=19	N/A	• 63% of new incident gallstones were ≤3 mm and 37% were between 3 and 10 mm • Only 14% of gallstones at baseline were ≤3 mm, and 43% were ≥10 mm • New incident gallstones were statistically significantly smaller than those present at baseline (p=0.001).	Important	Moderate
Adherence to treatment was assessed in 1 RCT									
Number of participants requiring titration down (from 120 mg, subcutaneously, every 4 weeks to 90 mg or 60 mg, subcutaneously, every 4 weeks) follow-up was 120 weeks. Lower is better.									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Lanreotide**	**Placebo and/or standard of care**	**Result (95%CI)**		
1 RCT van Aerts et al. (2019) DIPAK-I	Very serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=93	N/A	No statistical analysis. Lanreotide was titrated down in 23 participants during study period: • to 90 mg in 20 participants • to 60 mg in 3 participants. Of these participants: • 8 participants were titrated down due to eGFR reaching <30 mL/min/1.73m^2 • 15 participants were titrated down due to adverse events (7 gastrointestinal complaints; 3 fatigue or malaise; 2 due to bradycardia; 1 hypoglycaemia; 1 hair loss and 1 liver cyst infection). • In 6 out of 7 participants titrated down due to gastrointestinal complaints, the adverse effects were tolerable at the lower dose.	Important	Low
Number of participants discontinuing study intervention treatment due to adverse events, follow-up was 120 weeks. Lower is better									
1 RCT van Aerts et al. (2019) DIPAK-I	Very serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=93	N/A	No statistical analysis. Lanreotide was discontinued in 8 participants during the study period: • 6 due to continued adverse events despite titration down. • 1 due to nephrectomy 1 due to loss of confidence in lanreotide. In total 18 patients (19%) stopped lanreotide at once, of whom 14 (15%) did so because of adverse events: • 4 due to fatigue/malaise	Important	Low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Lanreotide**	**Placebo and/or standard of care**	**Result (95%CI)**		
							• 2 due to renal cyst bleeding • 6 due to liver cyst infection • 2 due to gastrointestinal symptoms		
Renal outcomes were assessed in 2 systematic reviews									
Mean difference in estimated glomerular filtration rate (eGFR) at treatment end, follow-up was 120 weeks in 1 randomised controlled trial. Higher is better									
Systematic Review Griffiths et al. (2020) DIPAK-I	Serious limitations[3]	No serious indirectness	Not applicable	No serious imprecision	N=146	N=144 Standard of care	Mean difference −0.60 mL/min/1.73m^2 (95% CI −3.65 to 2.45, p=0.70)	Important	Moderate
Mean difference in total kidney volume at treatment end (lanreotide versus control) in 2 RCTs, follow-up was 24 weeks in 1 RCT and 120 weeks in 1 RCT. Lower is better									
Systematic Review Griffiths et al. (2020) DIPAK-I and LOCKCYST	Serious limitations[3]	No serious indirectness	No serious inconsistency I^2=0%. Random effects model used.	No serious imprecision	N=146	N=158	Mean difference −0.15 L (95% CI −0.21 to −0.10, p<0.00001)	Important	Moderate
Risk of a 30% or more decrease in GFR or kidney failure, follow-up was 120 weeks. Lower is better									
Systematic review St Pierre et al. (2024) DIPAK-I	Serious limitations[3]	No serious indirectness	Not applicable	Serious imprecision[4]	N=21/153	N=29/152 Standard of care	RR 0.72 (95% CI 0.43 to 1.20, p=0.21).	Important	Low

Table 3: Question: In patients experiencing symptomatic PLD, what is the safety of lanreotide compared with supportive treatment, octreotide or liver transplant?

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Lanreotide	Placebo and/or standard of care	Result (95%CI)		
Safety outcomes were addressed in 1 systematic review and 1 RCT									
Risk of death, follow-up was at 120 weeks. Lower is better									
Systematic review St Pierre et al. (2024) DIPAK-I	Serious limitations[3]	No serious indirectness	Not applicable	Very serious imprecision[5]	N=154 1 death	N=155 0 deaths Standard of care	RR 3.02 (95% CI 0.12 to 73.55, p=0.50).	Important	Very low
Number of participants with a serious adverse event, follow-up was at 120 weeks. Lower is better									
1 RCT van Aerts et al. (2019) DIPAK-I	Very serious limitations[1]	No serious indirectness	Not applicable	Not calculable	28/93 (30.1%)	10/82 (12.2%)	No statistical analysis	Safety	Very low
Number of participants with a serious adverse event leading to study withdrawal. Lower is better									
1 RCT van Aerts et al. (2019) DIPAK-I	Very serious limitations[1]	No serious indirectness	Not applicable	Not calculable	4/93 (4.3%)	1/82 (1.2%)	No statistical analysis	Safety	Very low
Specific serious adverse events possibly related to lanreotide. Lower is better									
1 RCT van Aerts et al. (2019) DIPAK-I	Very serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=13/93	N=3/82	No statistical analysis. Thirteen SAE were thought to be related to the intervention: • hepatic cyst infection n=6 (6.5%) • renal cyst infection n=2 (2.2%) • pyelonephritis n=1 (1.1%)	Safety	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Lanreotide	Placebo and/or standard of care	Result (95%CI)		
							• epigastric pain 1 (1.1%) • fever n=1 (1.1%) • urinary tract infection n=1 (1.1%) • cholelithiasis n=1 (1.1%). This compared to n=2 (2.4%) renal cyst infections and n=1 (1.2%) pyelonephritis in the control group.		

Abbreviations

ADPKD, Autosomal-dominant polycystic kidney disease; CI, Confidence interval; eGFR, Estimated glomerular filtration rate; I^2, I^2 statistic for heterogeneity; IQR, Interquartile range; MRI, Magnetic resonance imaging; N, number of participants; N/A, Not applicable; OR, Odds Ratio; P, probability value; PLD, Polycystic liver disease; POLCA, Polycystic Liver Disease-complaint-specific assessment; RCT, Randomised controlled trial; RR, Risk ratio; SAE, Serious adverse events; SD, Standard deviation; SE, Standard error of the means; SMI, Skeletal Mass Index.

Footnotes

1 Downgraded 2 levels – DIPAK-I study is at high risk of bias from randomisation process and some concerns from measurement of outcomes (unclear validity of symptom control measure)
2 Downgraded 2 levels – the study by Temmerman et al. (2015) is at high risk of bias from confounding due to allowing use of other medicines, unexplained loss-to-follow-up, incomplete reporting of data, and lack of reported diagnostic criteria for the cohort
3 Downgraded 1 level – Risk of bias from randomisation process in the included DIPAK-I study
4 Downgraded 1 level – 95% confidence interval crosses the default minimal clinically important difference (MCID) NB default MCID are 0.8 below null and 1.25 above null, or for continuous outcomes 0.5 of the standard deviation of the control group
5 Downgraded 2 levels – 95% confidence interval crosses both default minimal clinically important difference (MCID) NB default MCID are 0.8 below null and 1.25 above null, or for continuous outcomes 0.5 of the standard deviation of the control group

Glossary

Gastrointestinal Symptom Score	The van Aerts et al. 2019 study uses a 7-point Likert-like scale, ranging from 1 (none) to 7 (very severe). These were partially derived from the Gastrointestinal Symptom Score (modified on expert opinion for PLD symptoms). This is based on the Gastrointestinal symptoms' questionnaire (Bovenschen et al. 2006)
Observational study	A retrospective or prospective study in which the investigator observes the natural course of events with or without control groups (for example, cohort studies and case–control studies).
Odds ratio	Compares the odds (probability) of something happening in 1 group with the odds of it happening in another. An odds ratio of 1 shows that the odds of the event happening (for example, a person developing a disease or a treatment working) is the same for both groups. An odds ratio of greater than 1 means that the event is more likely in the first group than the second. An odds ratio of less than 1 means that the event is less likely in the first group than in the second group.
Polycystic Liver Disease-complaint-specific assessment (POLCA) Score	The Temmerman et al. 2015 study uses the 4 subscale Polycystic Liver Disease-complaint-specific assessment (POLCA) score (Temmerman et al. 2014)
Randomised controlled trial	A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug, treatment or other intervention. One group (the experimental group) has the intervention being tested, the other (the comparison or control group) has an alternative intervention, a dummy intervention (placebo) or no intervention at all. The groups are followed up to see how effective the experimental intervention was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
Relative risk	The probability of an event occurring in the study group compared with the probability of the same event occurring in the control group, described as a ratio. If both groups face the same level of risk, the relative risk is 1. If the first group had a relative risk of 2, subjects in that group would be twice as likely to have the event happen. A relative risk of less than 1 means the outcome is less likely in the first group. Relative risk is sometimes referred to as risk ratio. It will be very similar to the odds ratio when events are rare.
Systematic review and meta-analysis	A review that summarises the evidence on a clearly formulated review question according to a predefined protocol, using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, analyse, collate and report their findings. It may or may not use statistical techniques, such as meta-analysis.

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