# ADPKD

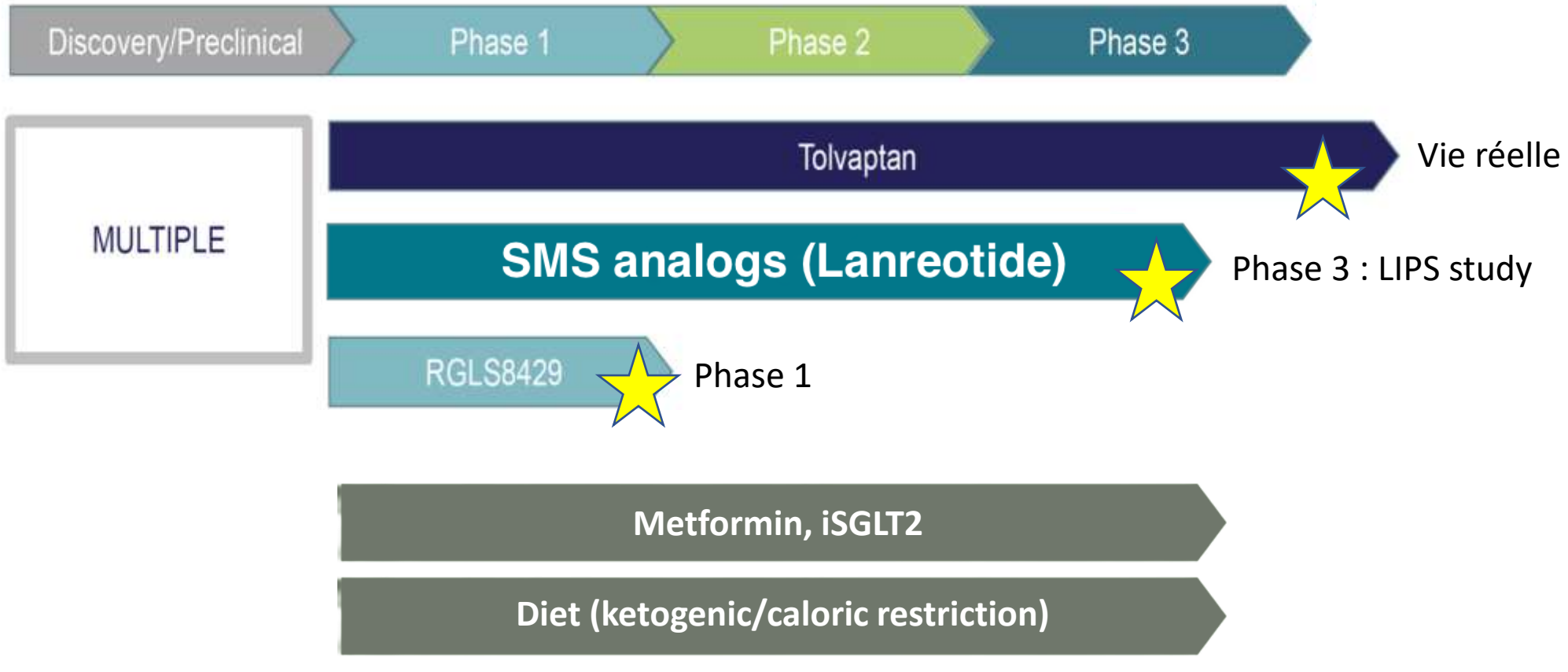
## *therapeutic advances*

Université Paris Cité

Necker ENFANTS MALADES HÔPITAL UNIVERSITAIRE

**Dominique JOLY**

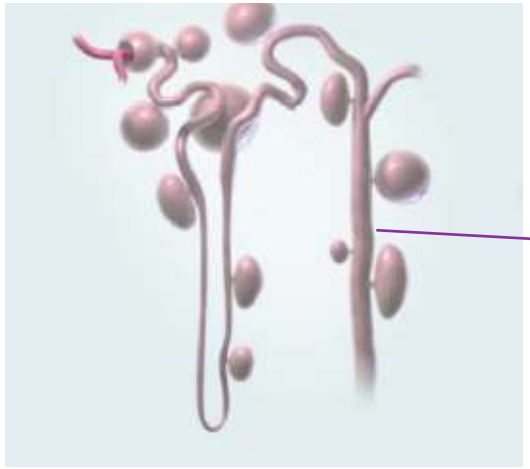
Service de Néphrologie

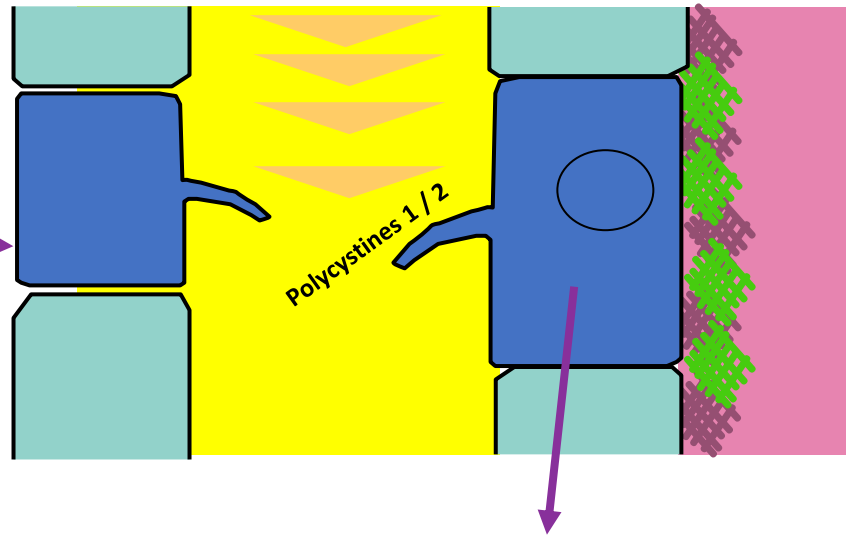



*Venglustat*

*Bardoxolone*

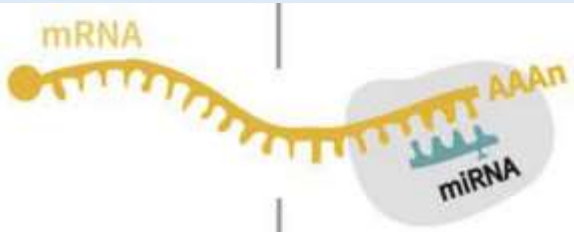
*Lixivaptan*






**Signaling pathways**

## RNA and miRNA

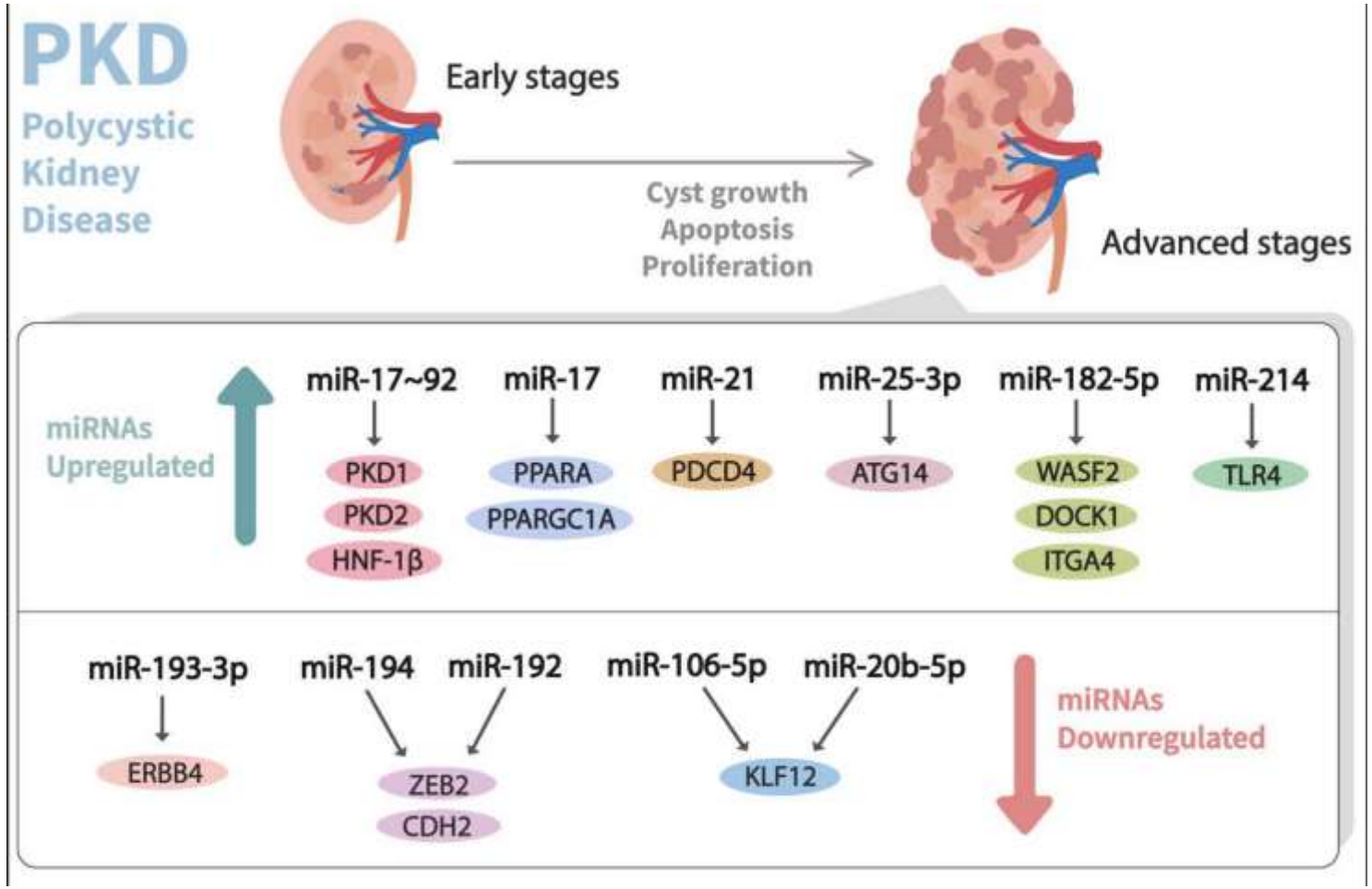



Oligos anti miRNA (ASO)

**RGLS8429**

Degradation of mRNA

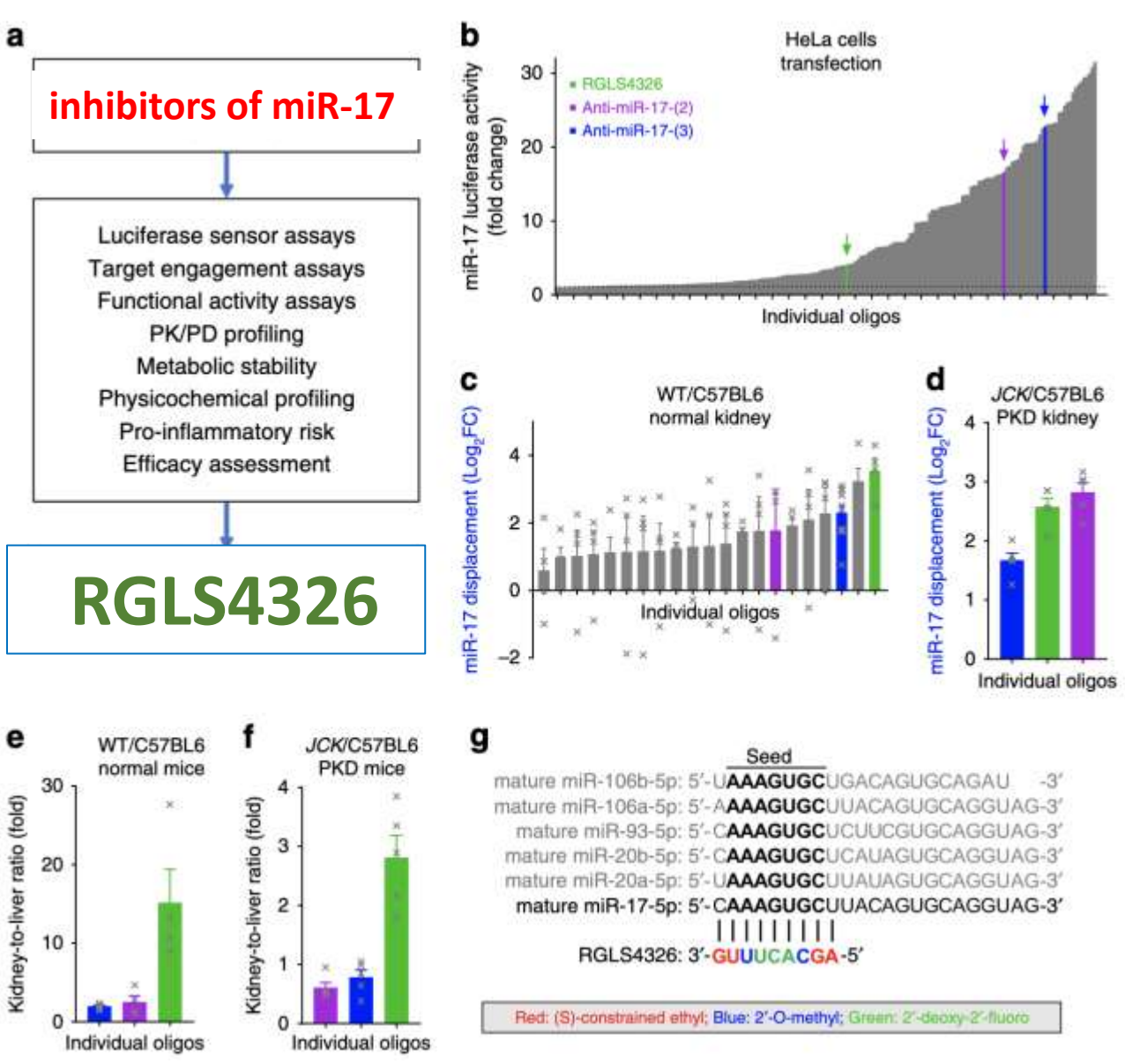
# dysregulation of miRNA expression in PKD




The **miR-17 family** of miRNAs is upregulated in human and mouse forms of ADPKD

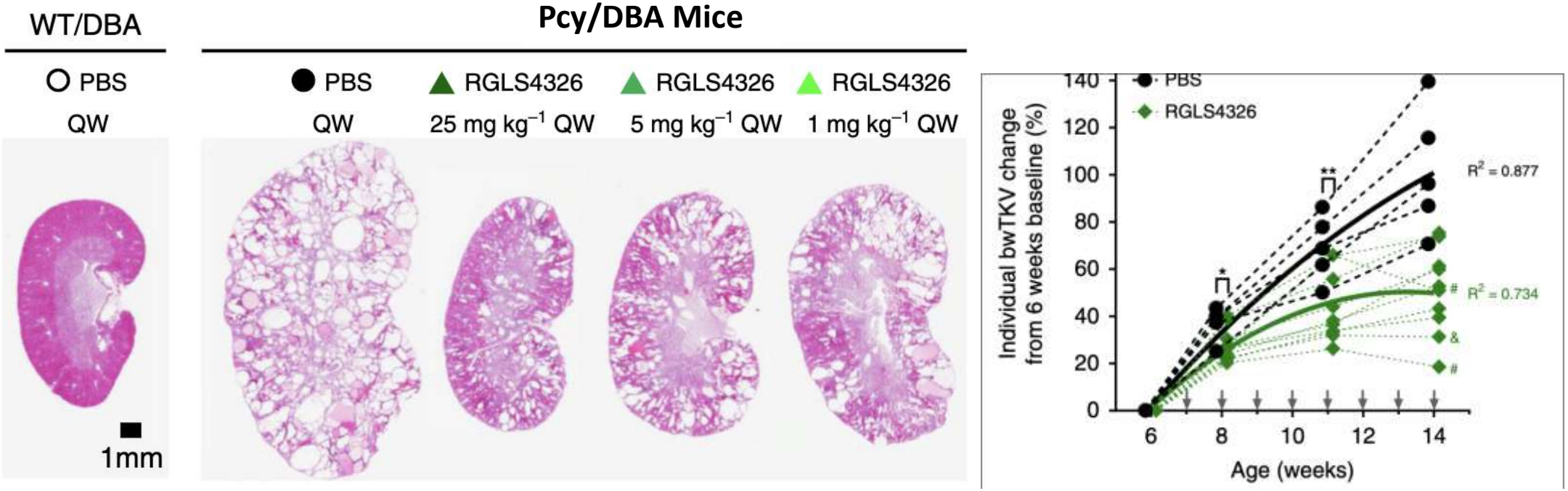
D Li https://doi.org/10.1016/j.xkme.2020.06.013

Screening cascade of 190 oligonucleotides




LEE. NATURE COMMUNICATIONS | (2019) 10:4148

- ✓ preferentially distributes to kidney and collecting duct-derived cysts
- ✓ displaces miR-17 from translationally active polysomes
- ✓ derepresses miR-17 mRNA targets including *Pkd1* and *Pkd2*
- ✓ …




LEE. NATURE COMMUNICATIONS | (2019) 10:4148

REGULUS

RGLS4326

« dose-limiting **CNS toxicity** was observed in mice and monkeys receiving high doses of RGLS4326 in nonclinical toxicity studies off-target inhibition of the neuroreceptor **AMPA-R** »

**RGLS8429**

**inhibitor** of **miR-17**
**Kidney ++**
no affinity for AMPA-R

REGULUS

# RGLS8429

## MAD* study

**Multiple-Ascending Dose*

ADPKD, age: 18 - 70
eGFR 30 - 90 mL/min/1.73m2
BMI 18 - 35 kg/m2
Mayo Class **1C, 1D, or 1E**

**1b** study : RGLS8429 or placebo

3 cohortes 1, 2, 3 mg/kg

**4° cohorte 300 mg**

Subcutaneous injection every other week for 14 weeks (7 doses)

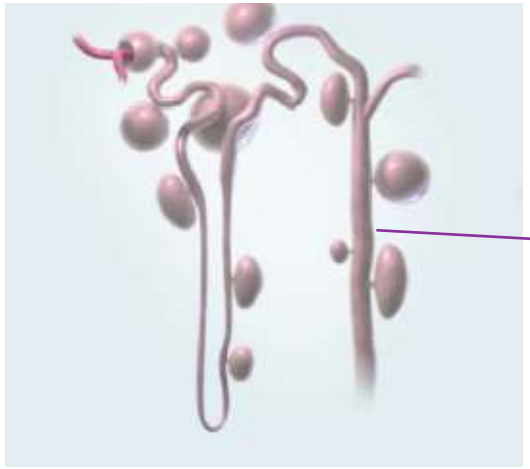
**Outcome measurements : baseline and day 113**

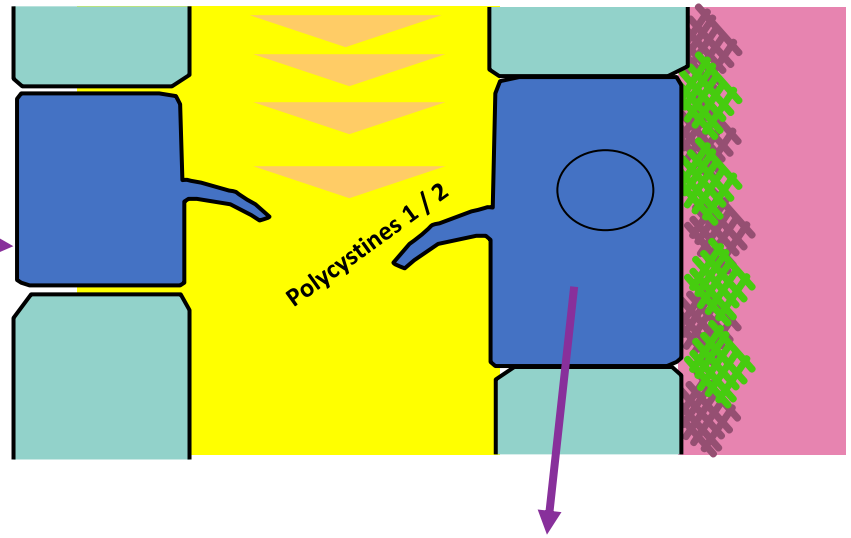
**Safety**

**Tolerability**

**impact on ADPKD biomarkers**

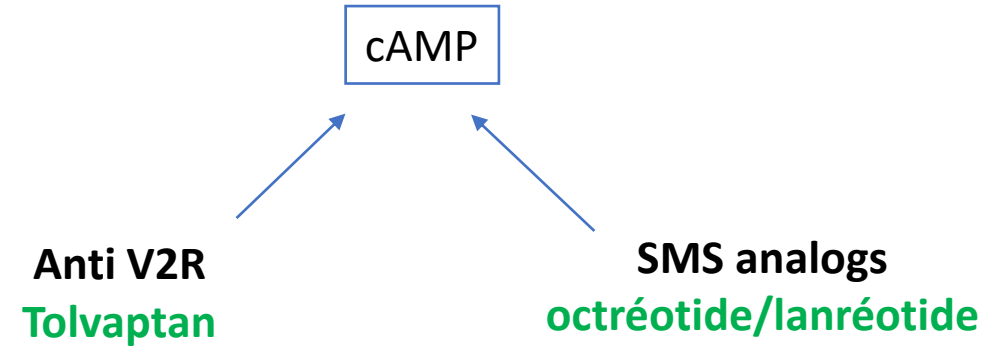
- **changes in urinary polycystins PC1 and PC2**
- **height-adjusted total kidney volume (htTKV)**
- **cyst architecture**
- **and overall kidney function**






**Signaling pathways**

- Involved in proliferation/secretion
- Overexpressed in polycystic disease
- Inhibitable by treatment

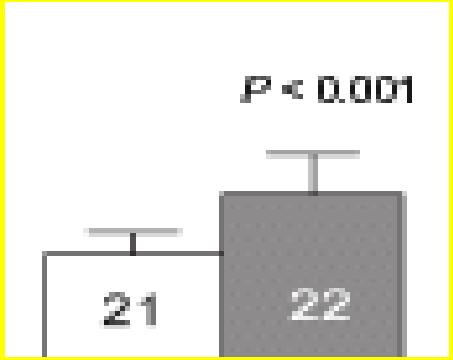


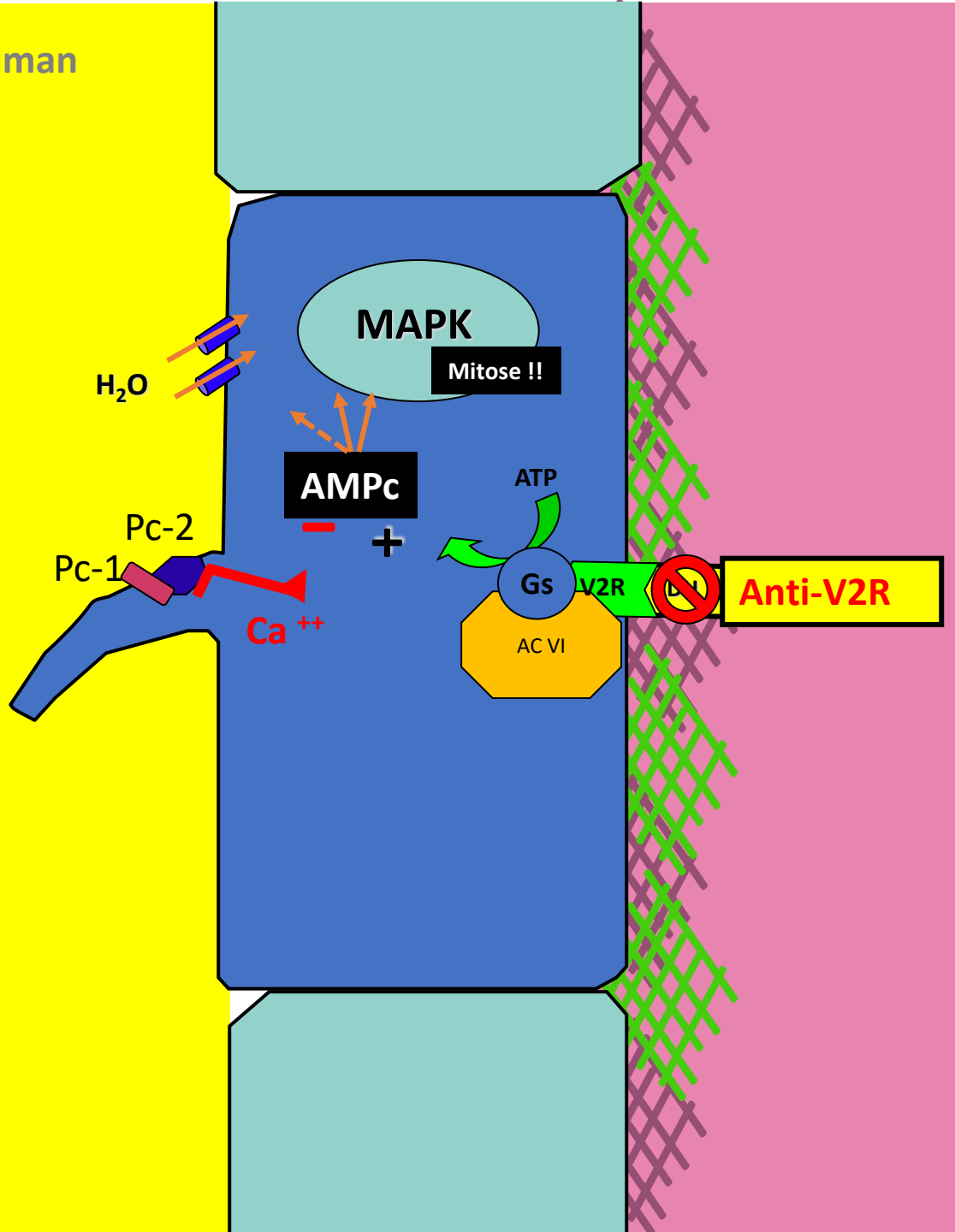
# Cyclic AMP promotes growth and secretion in human polycystic kidney epithelial cells

*Belibi et coll. Kidney Int 2004, 964-973*

*Dr Jared Grantham*

**AMPc**



ORIGINAL ARTICLE

# Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease

Vicente E. Torres, M.D., Ph.D., Arlene B. Chapman, M.D., Olivier Devuyst, M.D., Ph.D., Ron T. Gansevoort, M.D., Ph.D., Jared J. Grantham, M.D., Eiji Higashihara, M.D., Ph.D., Ronald D. Perrone, M.D., Holly B. Krasa, M.S., John Ouyang, Ph.D., and Frank S. Czerwiec, M.D., Ph.D., for the TEMPO 3:4 Trial Investigators*

*N Engl J Med*. 2012;367(25):2407-2418

ndt

*Original Article*

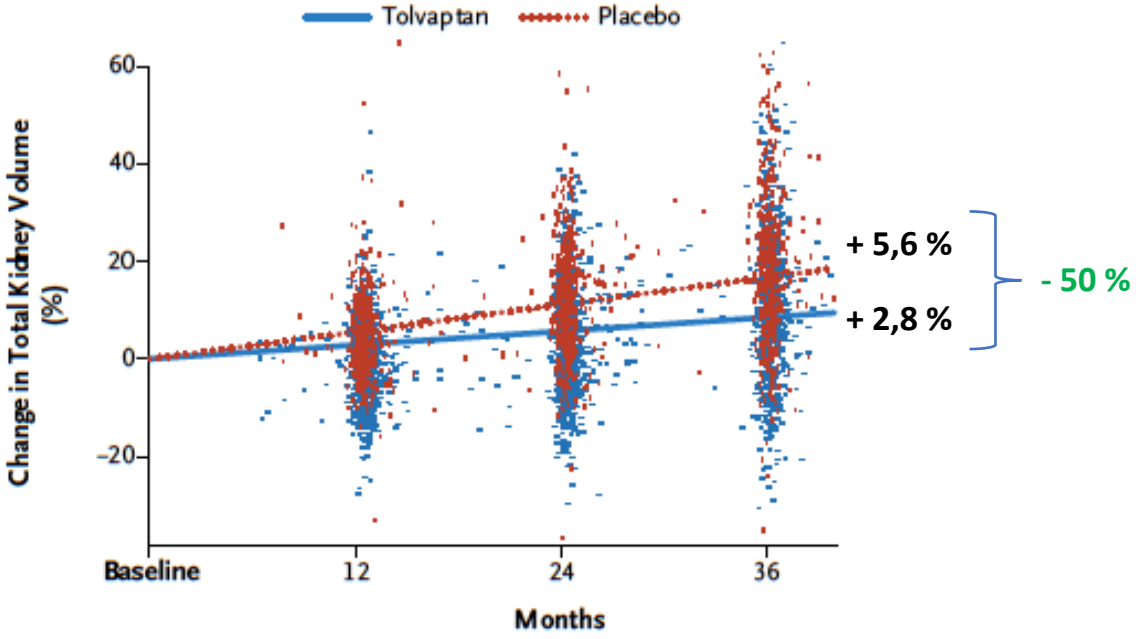
# Multicenter, open-label, extension trial to evaluate the long-term efficacy and safety of early versus delayed treatment with tolvaptan in autosomal dominant polycystic kidney disease: the TEMPO 4:4 Trial

ORIGINAL ARTICLE

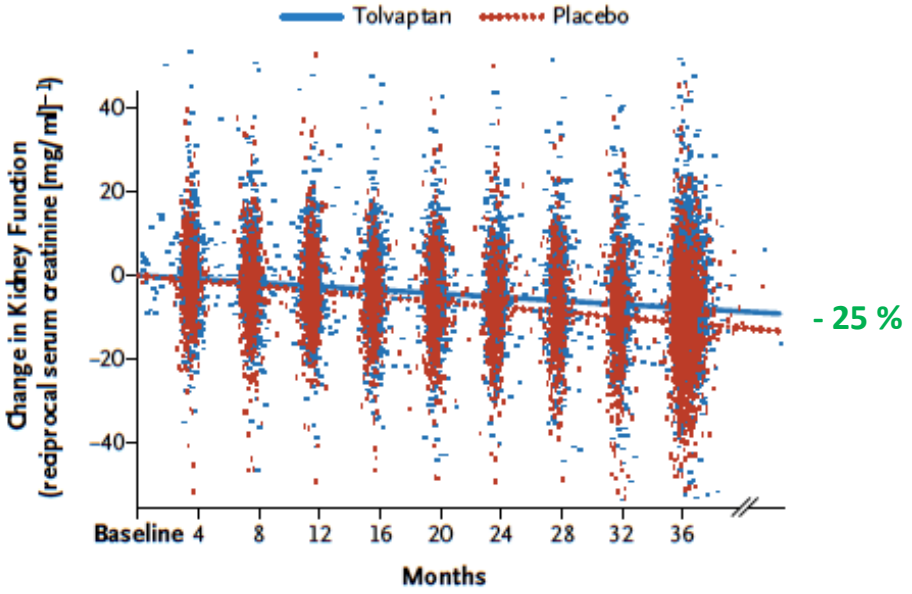
# Tolvaptan in Later-Stage Autosomal Dominant Polycystic Kidney Disease

Vicente E. Torres, M.D., Ph.D., Arlene B. Chapman, M.D., Olivier Devuyst, M.D., Ph.D., Ron T. Gansevoort, M.D., Ph.D., Ronald D. Perrone, M.D., Gary Koch, Ph.D., John Ouyang, Ph.D., Robert D. McQuade, Ph.D., Jaime D. Blais, Ph.D., Frank S. Czerwiec, M.D., Ph.D., and Olga Sergeyeva, M.D., M.P.H., for the REPRISE Trial Investigators*

## Renal Volume




## Renal function




*Tolvaptan : −2.72 ml /mn/1.73 m² /year*
*Placebo : −3.70 ml /mn/1.73 m² /year*

Juillet 2016 => 2019

## Eligibilité

**DFG ≥ 25** ml/mn/1.73 m2

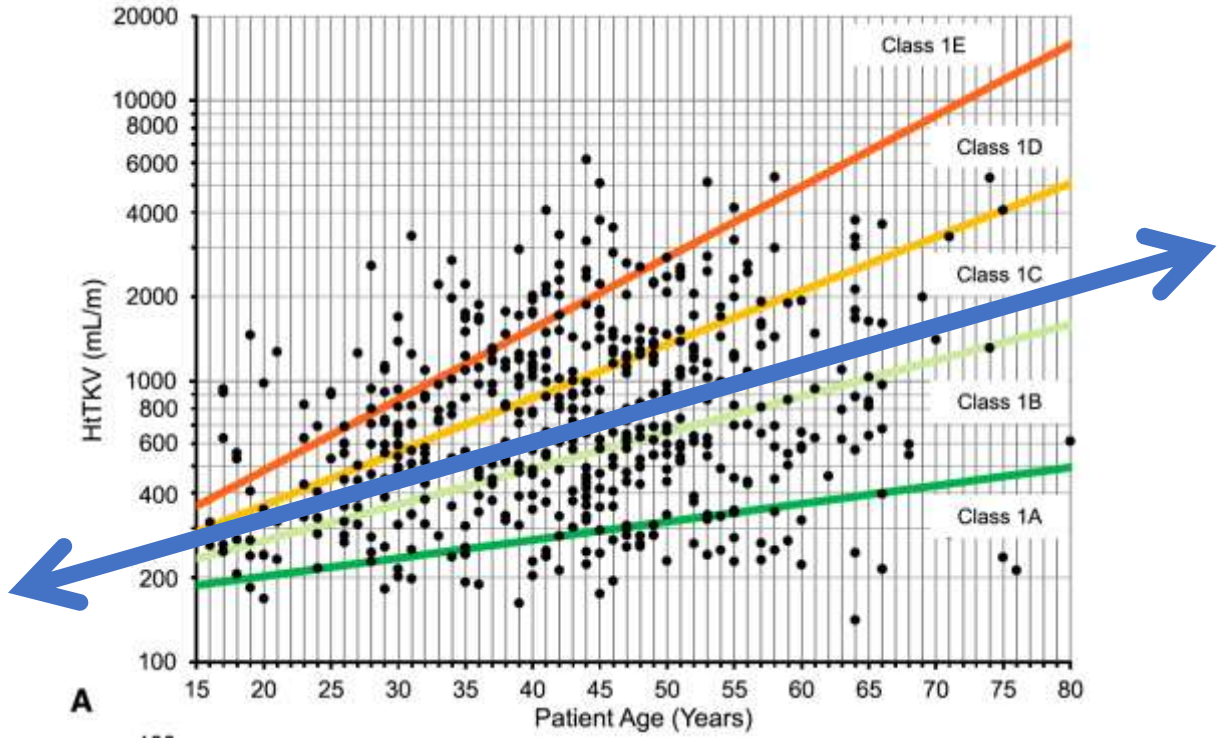
**Néphromégalie** importante

- 600 ml/m IRM > 630/m echo
- > 16.8cm echo > 16,7 cm IRM

**Evolutive**

- Complications uro
- ou déclin > 3.5 ml/mn/an

**Service médical rendu <u>MODERE</u>**




**Age ≤ 55**

**DFG ≥ 25** ml/mn/1.73 m2

**GFR decline ≥ 3 ml/mn/1.73 m2**

**and/or**

**Mayo class 1D or 1E, ± 1C**

# Tolvaptan in « real life »

(preliminary results)

**Eligible** → (no CI) → **Information** → **Start Tolvaptan**

# n=250

**(40 sessions, 2019-2023)**

Collective information session

(preliminary results)

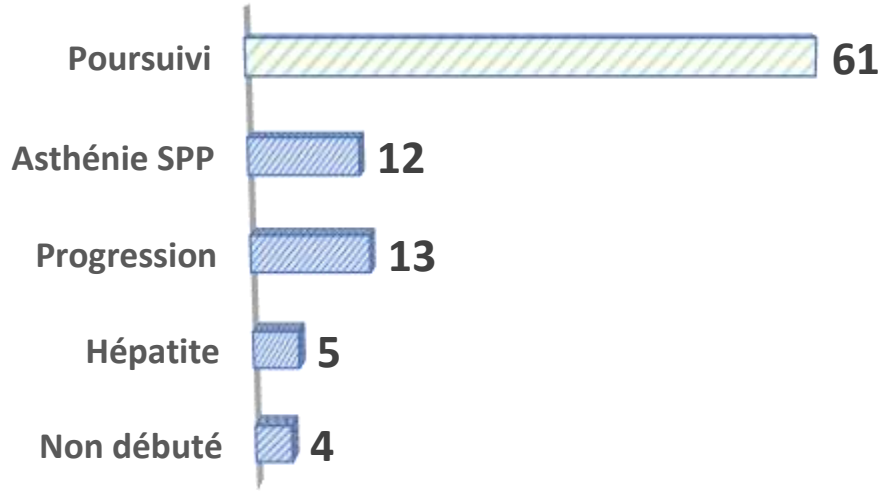
**Eligible** (no CI) **Information** **Start Tolvaptan**

# n=250

**62%**

Younger
Family history -
Higher GFR
Lower GFR decline

**38%**




**Most patients will forego tolvaptan**

**Many patients will stop tolvaptan**

# 1. How to reduce tolvaptan induced polyuria ?

**Reduction in dietary osmole intake**

**DOWNTITRATION**
Minimal dose of tolvaptan needed to maintain urine hypotonicity

**Use a thiazide diuretic**

Amro OW, *AJKD* 2016; **68:** 882-891

# 2. What about efficiency?

**« Low »**

…but comparable to other kidney-protective agents (RASi)

**No long-term results**

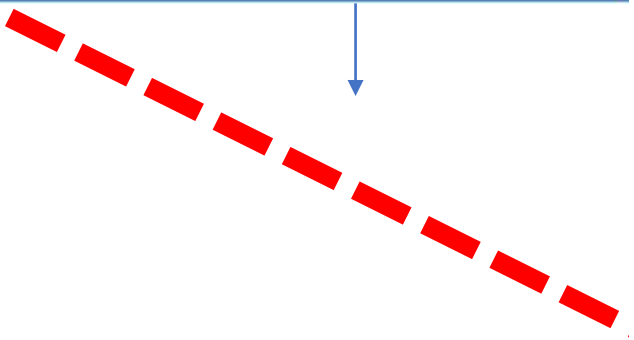
Studies are needed

**Variability**

**INDIVIDUAL ASSESSEMENT OF GFR DECLINE**

# Before tolvaptan

| N dosages | durée avant (s) | Pente avant | r2 avant |
|---|---|---|---|
| 7,0 | 8,5 | -9,1 | 0,90 |

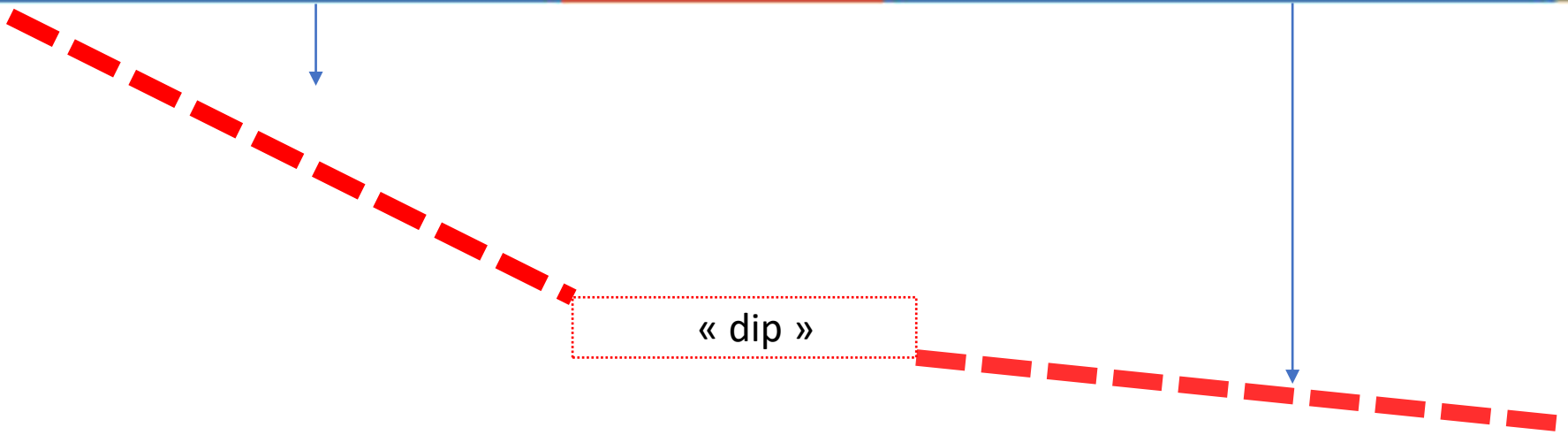


| Avant Tolvaptan | |
|---|---|
| Time to MRC5 | Time to DFG8 |
| -2,9 | -3,7 |
| 41,7 | 42,5 |

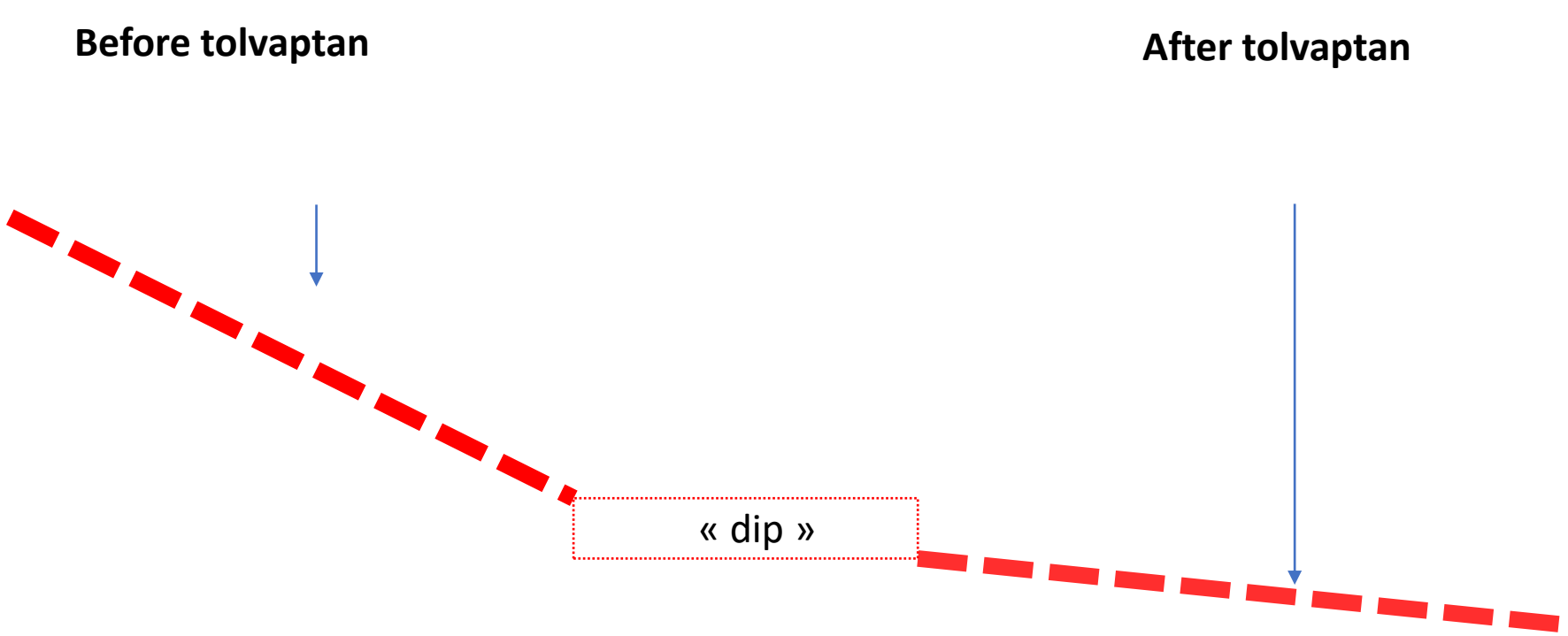
## Before tolvaptan

## After tolvaptan

| N dosages | durée avant (s) | Pente avant | r2 avant | DIP M1 | DIP M1 % | N dosages | durée après | Pente après | r2 après | Réduction du déclin % |
|---|---|---|---|---|---|---|---|---|---|---|
| 7,0 | 8,5 | -9,1 | 0,90 | 1,1 | 2,6 | 12,0 | 3,5 | -4,3 | 0,8 | 52,9 |




| Avant Tolvaptan | | Après tolvaptan | | Gain tolvaptan (si val pos) | |
|---|---|---|---|---|---|
| Time to MRC5 | Time to DFG8 | Time to MRC5 | Time to DFG8 | Time to MRC5 | Time to DFG8 |
| -2,9 | -3,7 | -2,4 | -4,0 | 2,76 | 3,62 |
| 41,7 | 42,5 | 44,5 | 46,1 | | |




**GFR decline reduction**

**-20 %**

(+20 to -80 %)

# Variability

factors driving the response to tolvaptan ?

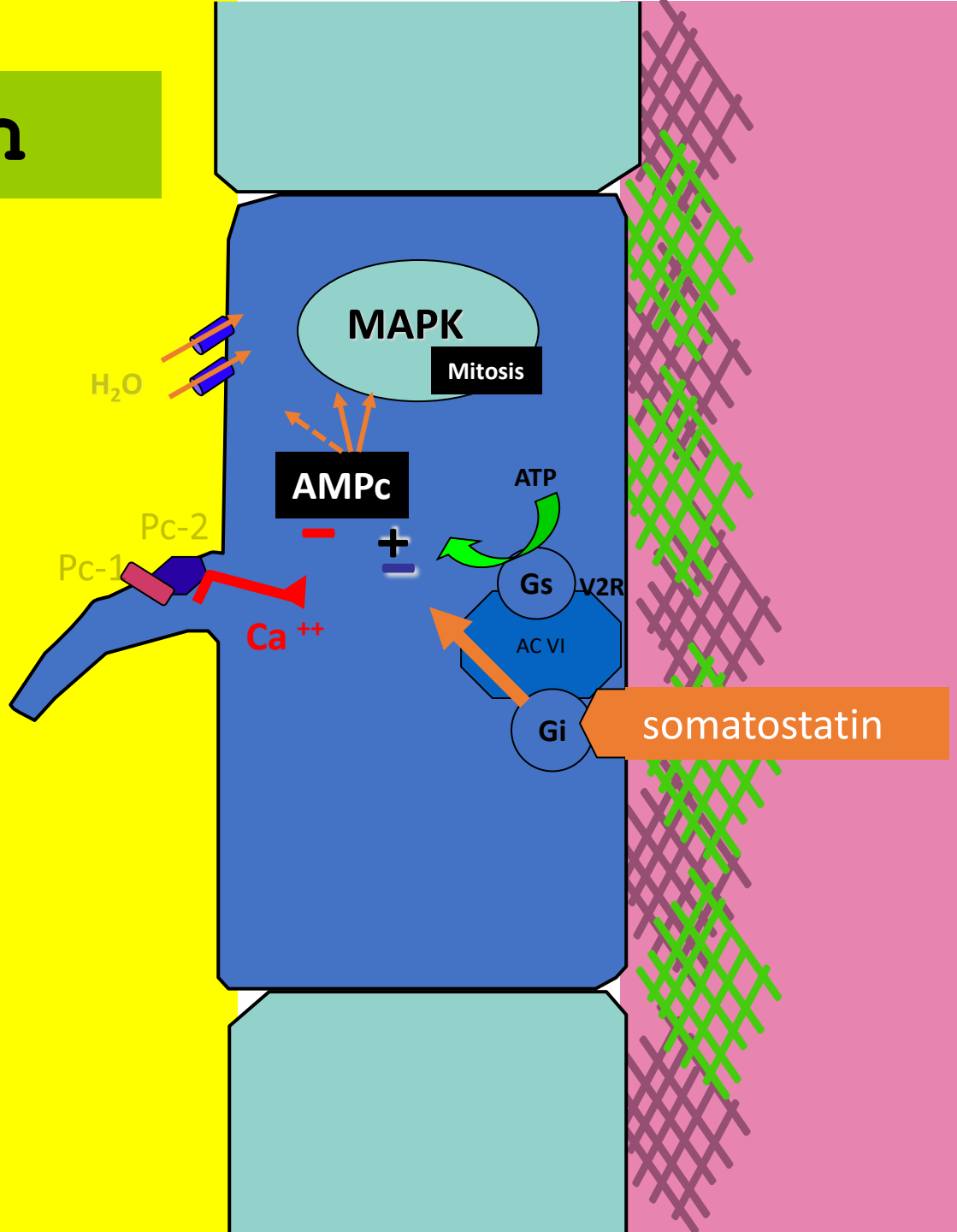
# Tolvaptan in « real life »

**Eligible**

**Motivated**

**Winner**

# Somatostatin



## SMS endogenous peptides


## SMS analogues

- Octreotide (Novartis)
- Pasireotide (Novartis)
- Lanreotide (Ipsen)

## Receptors (SST1-5)


## Physiological inhibition

Endocrine/exocrine secretions
- Hypophysaires (GH, prolactine, TSH, ACTH)
- Thyroïde (T3, T4)
- Pancréas (endocrine & exocrine)
- Estomac (gastrine, acides…)
- Intestin (CCK, VIP…)
- Foie (bile)

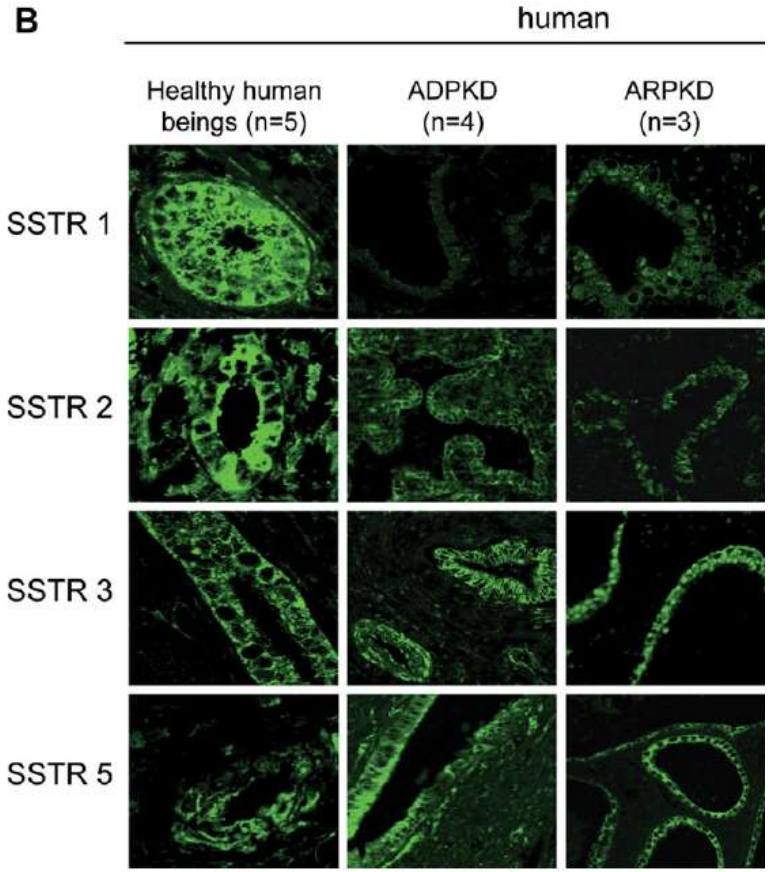
Digestive motility(estomac, vésicule biliaire, intestin)

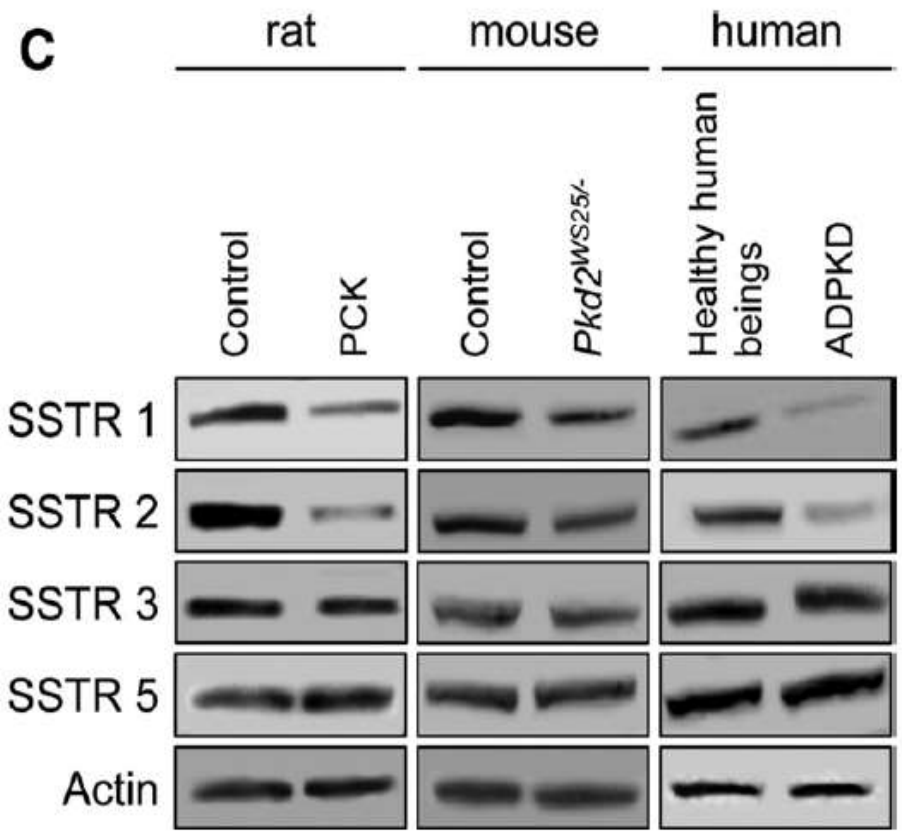
Prolifération /cell growth

## Rare endocrine diseases

- **Carcinoid syndromes**
- **Acromegaly**
- **Thyrotropic adenoma …**

# renal receptors to somatostatin

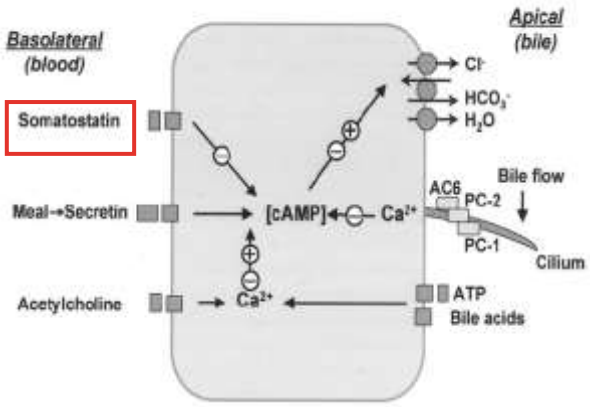


# Cells

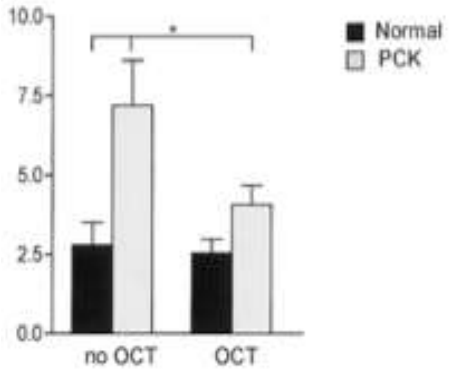
# Animals

## In vitro: cholangiocytes

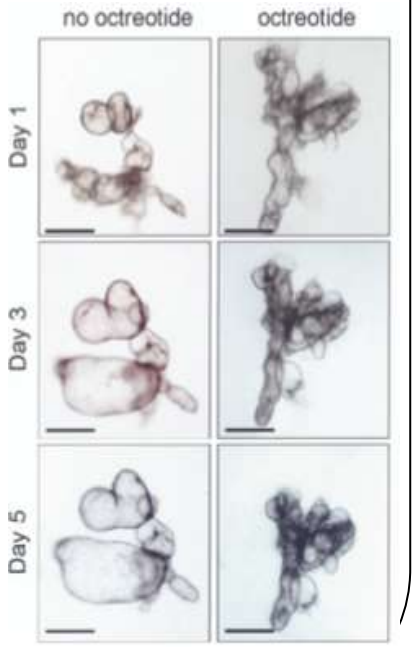



## In vivo: Rat PCK

**Octreotide Inhibits Hepatic Cystogenesis in a Rodent Model of Polycystic Liver Disease by Reducing Cholangiocyte Adenosine 3′,5′-Cyclic Monophosphate**




*Masyuk et al, Gastroenterology 2007*



# Effet of lanreotide on hepatic cysts

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

LOES VAN KEIMPEMA,[1] FREDERIK NEVENS,[2] RAGNA VANSLEMBROUCK,[3] MARTIJN G. H. VAN OIJEN,[1] ASWIN L. HOFFMANN,[1] HELENA M. DEKKER,[1] ROBERT A. DE MAN,[4] and JOOST P. H. DRENTH[4]

[1]Department of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; [2]Department of Hepatology, University Hospital Leuven, Leuven; [3]Department of Radiology, University Hospital Leuven, Leuven, Belgium; [4]Department of Radiation Oncology, Radboud University Nijmegen Medical Centre, Nijmegen; [5]Department of Radiology, Radboud University Nijmegen Medical Centre, Nijmegen; and [6]Department of Gastroenterology and Hepatology, Erasmus Medical Centre, Rotterdam, The Netherlands

GASTROENTEROLOGY 2009;137:1661–1668

- 54 patients with **massive** polycystic liver disease
- Lanreotide 40 mg IM/ mois vs placebo
- Primary criteria : absolute change in liver volume (CT-SCAN) after 6 months.

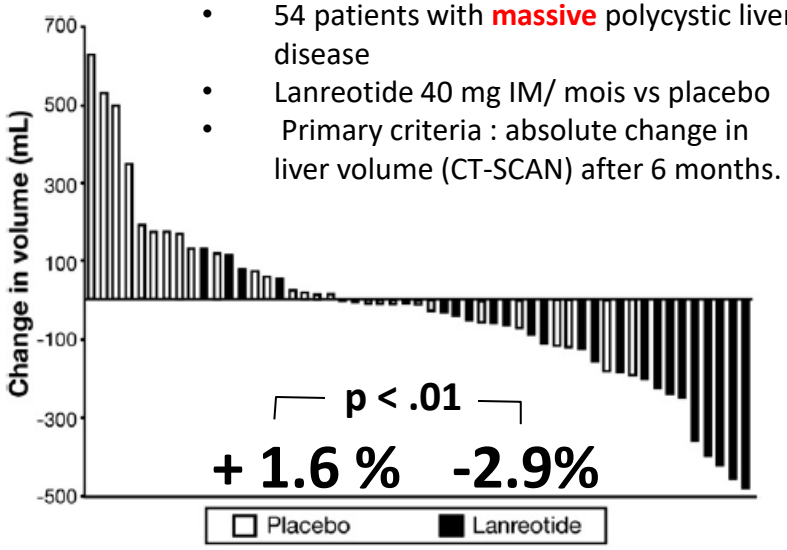



**Figure 2.** Absolute change in liver volume in all patients. Each *bar* represents 1 patient (n = 53).


*Griffiths J, BMJ Open. 2020*
*Suwabe T, PLOS ONE 2021*

# Effet of SMS analogs on hepatic cysts

**Recommendation 5.2.3.1: We suggest prescribing long-acting somatostatin analogues in people with ADPKD and markedly enlarged polycystic liver with severe volume related symptoms (*2B*).**

**Practice Point 5.2.3.3: When long-acting somatostatin analogues are prescribed, the effect on symptom burden and/or volume of polycystic liver and kidneys should be evaluated after 6 months. When beneficial effects of therapy are not observed, somatostatin analogues should be discontinued.**

# Effet of SMS analogs on renal cysts

| Study or Subgroup | Intervention Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|---|---|
| Ruggenenti 2005 | 2.2 | 3.7 | 12 | 5.9 | 5.4 | 12 | 12.4% | -3.70 [-7.40, 0.00] | 2005 |
| van Keimpema 2009 | -1.5 | 31.1 | 27 | 3.4 | 28 | 27 | 1.1% | -4.90 [-20.68, 10.88] | 2009 |
| Hogan 2010 | 0.25 | 7.53 | 28 | 8.61 | 10.07 | 14 | 6.4% | -8.36 [-14.33, -2.39] | 2010 |
| Caroli 2013 | 2.97 | 7.41 | 40 | 6.65 | 5.31 | 39 | 16.5% | -3.68 [-6.52, -0.84] | 2013 |
| Meijer 2018 | 4.15 | 5.2 | 153 | 5.56 | 5.06 | 152 | 26.9% | -1.41 [-2.56, -0.26] | 2018 |
| Perico 2019 | 5.2 | 6.37 | 51 | 8.8 | 6.15 | 49 | 18.7% | -3.60 [-6.05, -1.15] | 2019 |
| Hogan 2020 | -1.4 | 3.5 | 33 | 3.9 | 4.5 | 15 | 18.0% | -5.30 [-7.87, -2.73] | 2020 |
| Total (95% CI) | | | 344 | | | 308 | 100.0% | -3.66 [-5.35, -1.97] | |

Heterogeneity: Tau² = 2.42; Chi² = 13.52, df = 6 (P = 0.04); I² = 56%
Test for overall effect: Z = 4.24 (P < 0.0001)

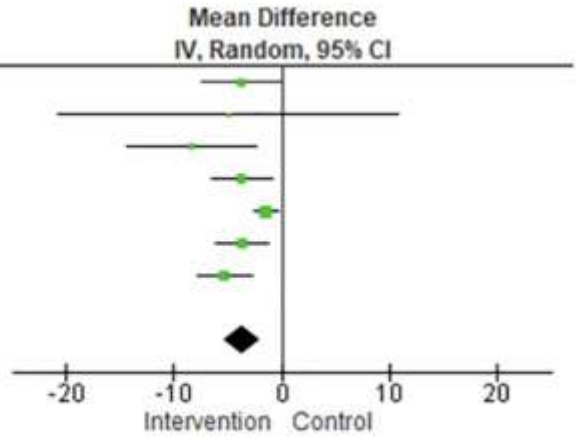
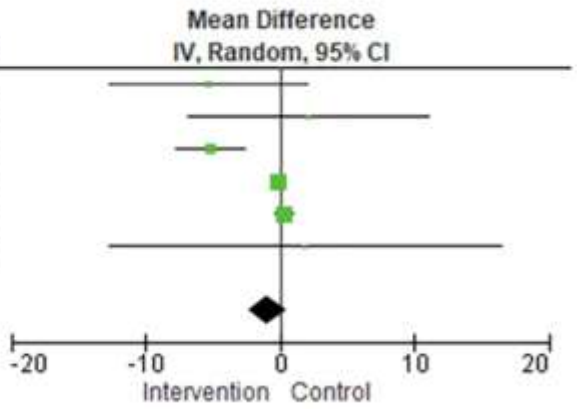



**Fig 3. Meta-analysis of TKV.**

# Effet of SMS analogs on renal function

| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|---|---|
| Ruggenenti 2005 | -5.5 | 10.75 | 12 | -0.2 | 7.33 | 12 | 3.4% | -5.30 [-12.66, 2.06] | 2005 |
| Hogan 2010 | -5.1 | 15.46 | 28 | -7.2 | 13.21 | 14 | 2.4% | 2.10 [-6.88, 11.08] | 2010 |
| Caroli 2013 | -10.82 | 7.03 | 40 | -5.61 | 4.09 | 39 | 17.8% | -5.21 [-7.74, -2.68] | 2013 |
| Meijer 2018 | -3.53 | 2.93 | 153 | -3.46 | 1.39 | 152 | 38.6% | -0.07 [-0.58, 0.44] | 2018 |
| van Aerts 2019 | -6.2 | 2.5 | 51 | -6.5 | 0.8 | 49 | 36.8% | 0.30 [-0.42, 1.02] | 2019 |
| Hogan 2020 | -0.3 | 14 | 19 | -2.2 | 17.7 | 7 | 0.9% | 1.90 [-12.64, 16.44] | 2020 |
| Total (95% CI) | | | 303 | | | 273 | 100.0% | -0.96 [-2.38, 0.46] | |

Heterogeneity: Tau² = 1.29; Chi² = 19.10, df = 5 (P = 0.002); I² = 74%
Test for overall effect: Z = 1.32 (P = 0.19)




*Griffiths J, BMJ Open. 2020*
*Suwabe T, PLOS ONE 2021*

# DIPAK 1 trial

JAMA

JAMA. 2018 Nov 20; 320(19): 2010–2019. PMCID: PMC6246170
Published online 2018 Oct 25. doi: 10.1001/jama.2018.15870 PMID: 30422235

Effect of Lanreotide on Kidney Function in Patients With Autosomal Dominant Polycystic Kidney Disease
The DIPAK 1 Randomized Clinical Trial

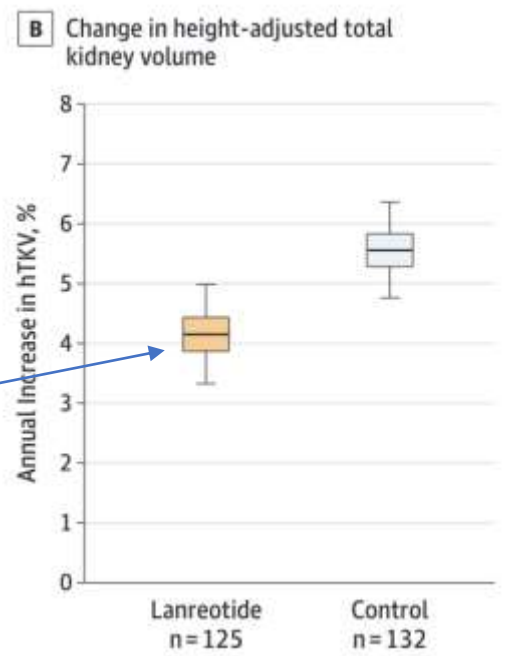
0pen-labeled
Randomized
Lanreotide vs standard care

**CKD3** (eGFR 30-60)

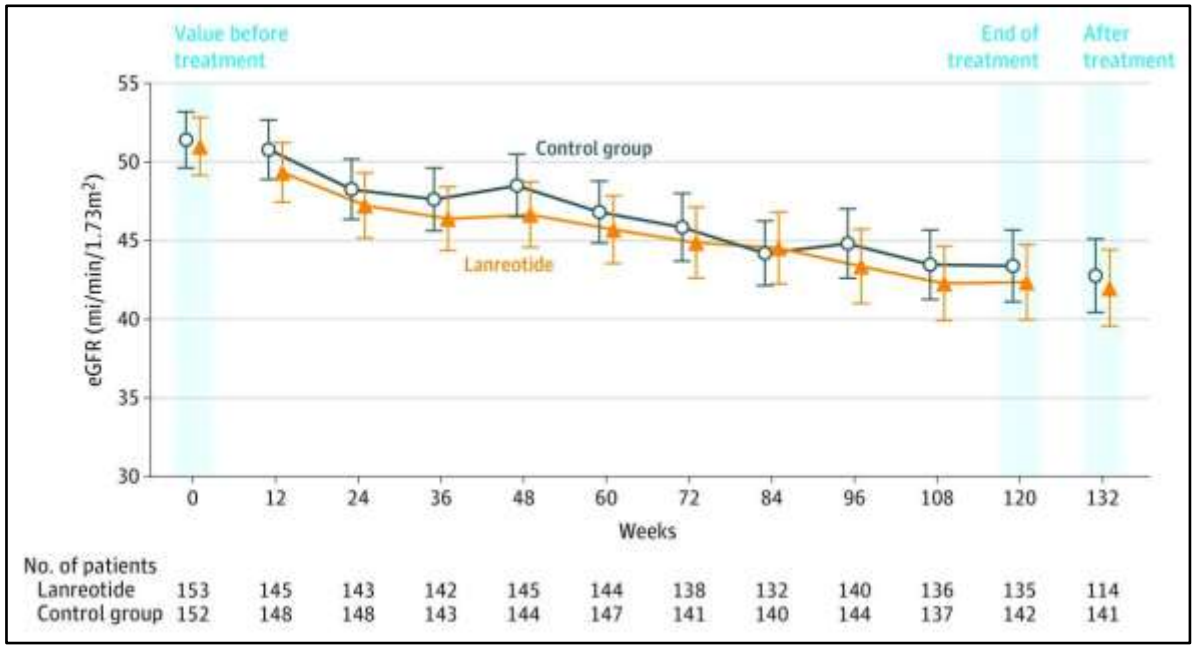
## TKV growth rate

3.55%/year on lanreotide
5.81%/year on control

37% reduction




## eGFR




*Meijer et coll JAMA 2018*

# LIPS

(Lanreotide in Polycystic kidney disease Study)

*(in submission)*

Randomized, double blinded
Lanreotide vs placebo

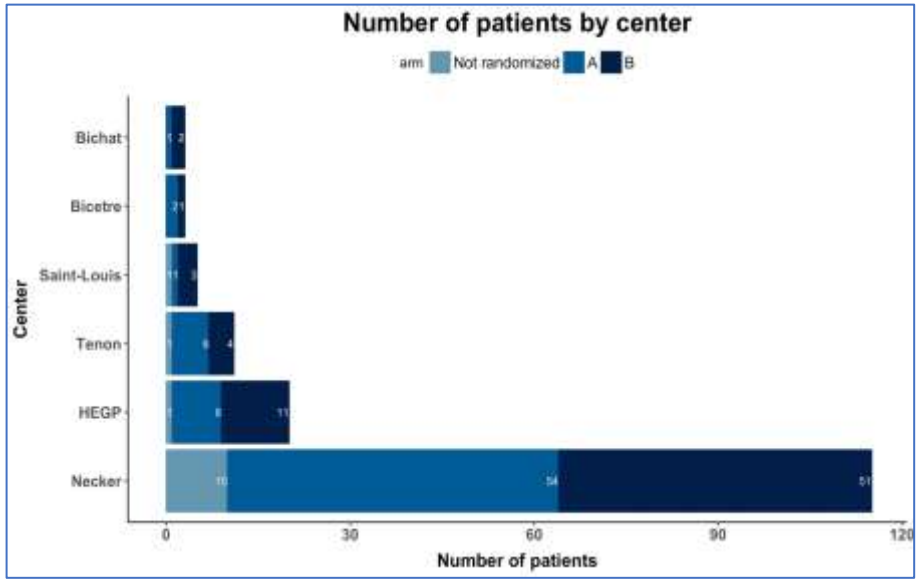
CKD2 + CDK3

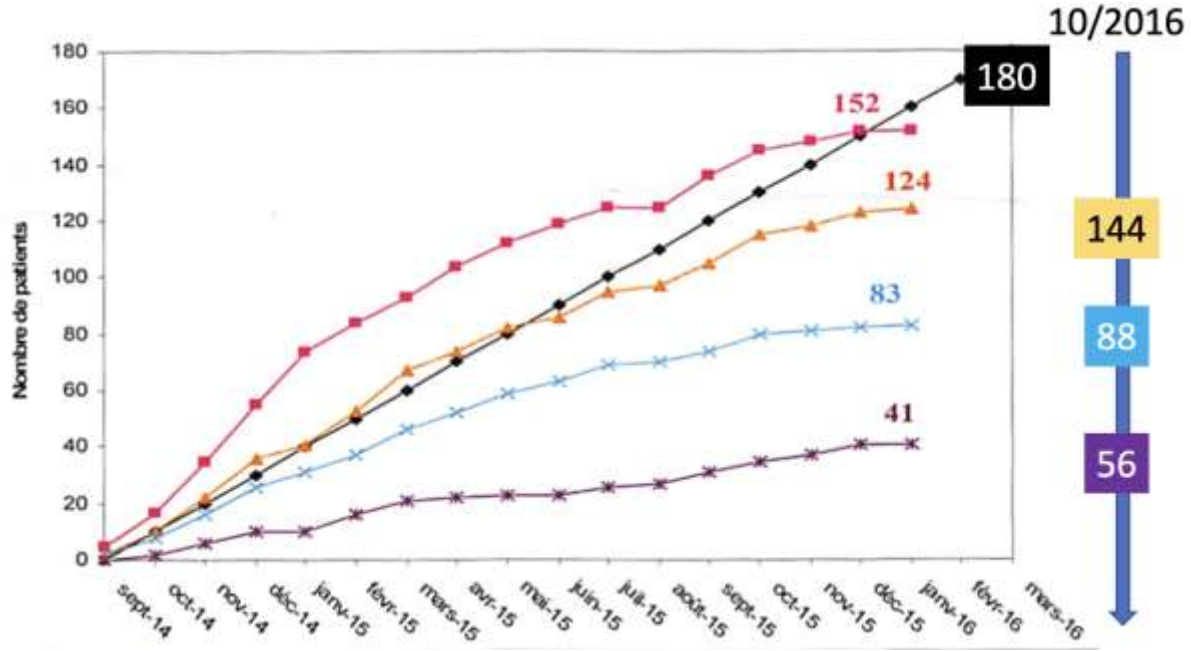
180 patients
stratification
90 CKD2 patients : DFG 89 à 60
90 CKD3 patients : DFG 59 à 30

**Criteria**

**1° ) Δ measured GFR (mGFR)**

2° Δ eGFR, eGFR slope, QOL, safety…



# LIPS

(Lanreotide in Polycystic kidney disease Study)

*(in submission)*

Randomized, double blinded
Lanreotide vs placebo

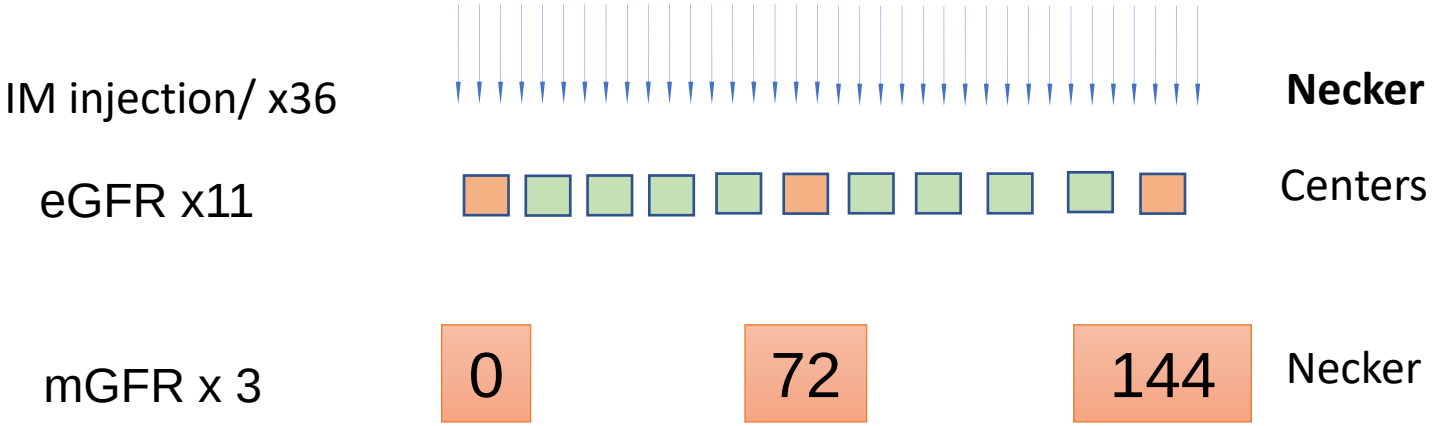
CKD2 + CDK3

180 patients
=> Inclusion + stratification
90 CKD2 patients : DFG 89 à 60
90 CKD3 patients : DFG 59 à 30

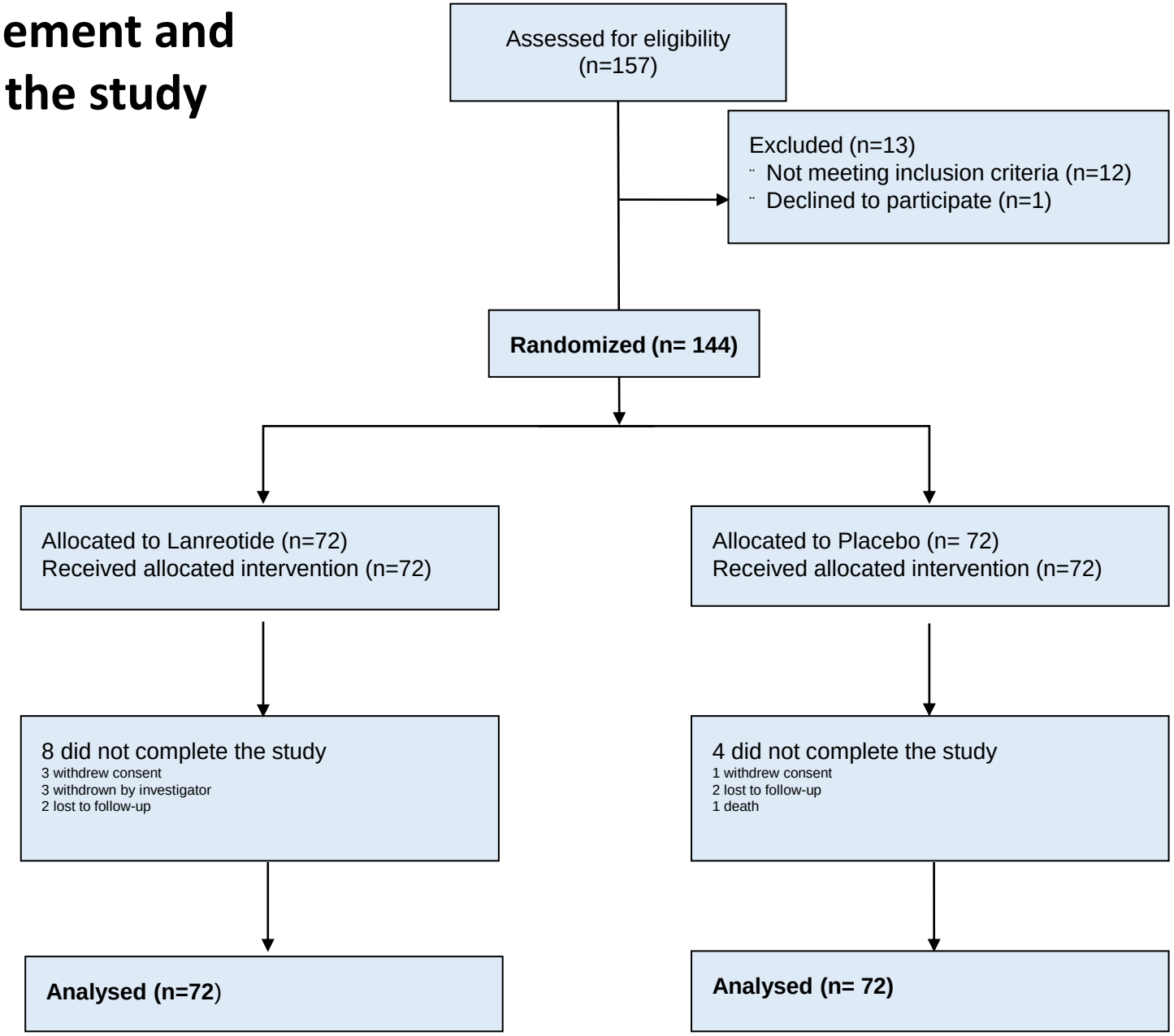
inclusions : 18 months

patients 50% Necker 50 % other centers
< 30 sorties d'étude

**Criteria**
**1° ) Δ measured GFR**
2° Δ eGFR, eGFR slope, QOL, safety…



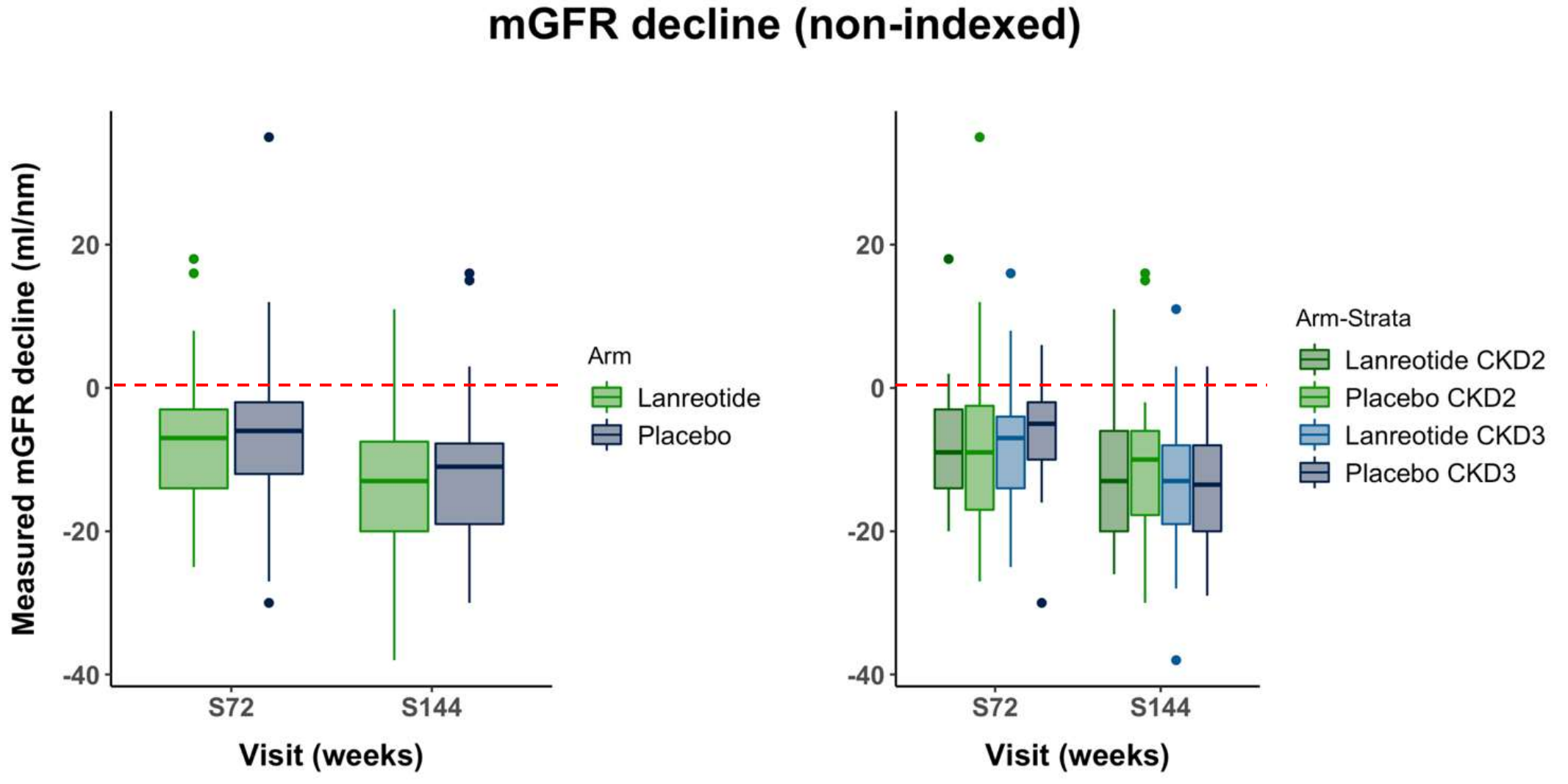
# Patients enrollement and flow chart of the study



144 56 88

| Baseline | Overall | | CKD2 | | CKD3 | |
|---|---|---|---|---|---|---|
| | Lanreotide n = 72 | Placebo n= 72 | Lanreotide n= 28 | Placebo n = 28 | Lanreotide n = 44 | Placebo n = 44 |
| Male gender (%) | 41.7 | 52.8 | 46.4 | 42.9 | 38.6 | 59.1 |
| Age (years) | 47.5 [40.8;54] | 47 [41;52.2] | 43 [37.8;48.2] | 43.5 [36.8;49.2] | 49.5 [45.2;57] | 48 [43;53.2] |
| BMI (kg/m²) | 25.2 [22.2;27.8] | 24.4 [21.6;26.8] | 25.1 [22.6;27.5] | 23.4 [21.4;26.5] | 25.4 [22;28.3] | 24.6 [22.5;27.1] |
| Blood Pressure (mmHg) systolic/diastolic | 127 [116.5;135.5]<br>77 [71;82] | 125 [119.5;135]<br>79 [73.5;84] | 122 [113;132.5]<br>74 [70;80.5] | 122 [118;131]<br>76 [72;82] | 127.5 [119;136]<br>77.5 [72;82.5] | 126.5 [122.8;135.2]<br>79.5 [75;85] |
| Estimated GFR ml/min/1.73 m² | 52 [42;68] | 55.5 [42;66] | 69.5 [65.3;82.2] | 69.5 [61;75.5] | 44.4 [36;49] | 45.5 [38.9;55.2] |
| Measured DFG ml/min/1.73 m² | 56 [42;70] | 54.5 [46;71.2] | 74.5 [69.5;84.5] | 73.5 [69;78] | 43.5 [37.8;53.5] | 49 [42.8;53] |
| | | | | | | |
| Mayo Clinic classification | | | | | | |
| 1B | 6 (8.7%) | 4 (5.7%) | 5 (18.5%) | 3 (11.1%) | 1 (2.4%) | 1 (2.3%) |
| 1C | 29 (42%) | 24 (34.3%) | 11 (40.7%) | 9 (33.3%) | 18 (42.9%) | 15 (34.9%) |
| 1D | 23 (33.3%) | 21 (30%) | 8 (29.6%) | 10 (37%) | 15 (35.7%) | 11 (25.6%) |
| 1E | 5 (7.2%) | 14 (20%) | 1 (3.7%) | 3 (11.1%) | 4 (9.5%) | 11 (25.6%) |
| 2 | 3 (4.3%) | 2 (2.9%) | 1 (3.7%) | 1 (3.7%) | 2 (4.8%) | 1 (2.3%) |
| ND | 3 (4.3%) | 5 (7.1%) | 1 (3.7%) | 1 (3.7%) | 2 (4.8%) | 4 (9.3% |
| | | | | | | |

# mGFR


mGFR decline (non-indexed)
Measured mGFR decline (ml/nm)
20
0
-20
-40
S72
S144
Visit (weeks)
Arm
Lanreotide
Placebo
Arm-Strata
Lanreotide CKD2
Placebo CKD2
Lanreotide CKD3
Placebo CKD3

# mGFR

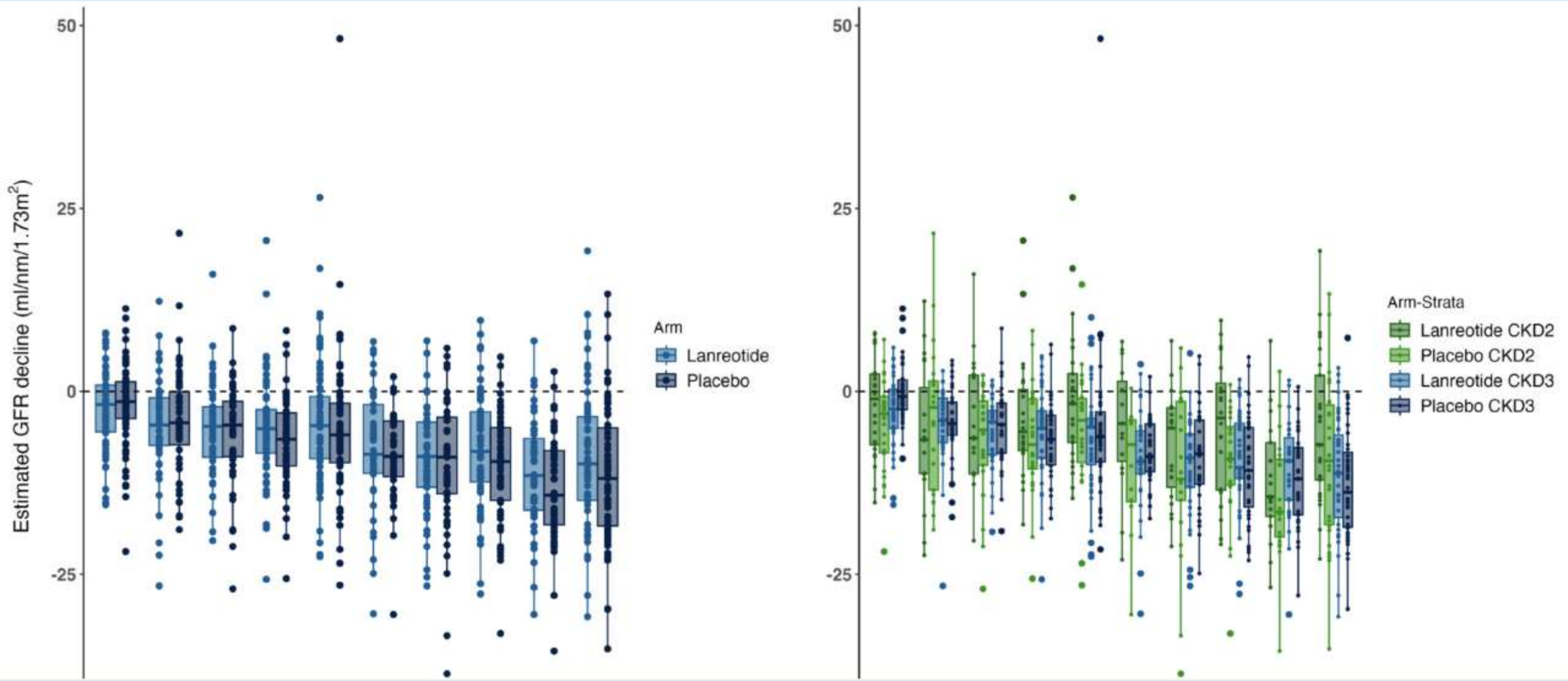
| Variable | Visit | Overall | | CKD2 | | CKD3 | |
|---|---|---|---|---|---|---|---|
| | | Lanreotide n = 72 | Placebo n = 72 | Lanreotide n = 28 | Placebo n = 28 | Lanreotide n = 44 | Placebo n = 44 |
| **mGFR reduction (ml/min) median [Q1;Q3] Missing** | W72 | **-7 [-14;-3] 4** | **-6 [-12;-2] 1** | **-9 [-14;-3] 3** | **-9 [-17;-2.5] 1** | **-7 [-14;-4] 1** | **-5 [-10;-2] 0** |
| | W144 | **-13 [-20;-7.5] 9** | -11 [-19;-7.8] 4 | -13 [-20;-6] 6 | -10 [-17.8;-6] 2 | -13 [-19;-8] 3 | -13.5 [-20;-8] 2 |
| **mGFR slope (ml/min/y) median [Q1;Q3] (min,max) Missing** | W72 | -5 [-10;-2.1] 4 | -4 [-8;-1.4] 1 | -6.4 [-9.3;-1.9] 3 | -6.4 [-12.1;-1.8] 1 | -5 [-10;-2.9] 1 | -3.6 [-7.1;-1.3] 0 |
| | W144 | -4.6 [-7.1;-2.7] 9 | -3.9 [-6.8;-2.7] 4 | -4.6 [-7.1;-2.1] 6 | -3.5 [-6.3;-2.2] 2 | -4.6 [-6.8;-2.9] 3 | -4.7 [-6.9;-2.9] 2 |

linear mixed-effects model

⇒ no significant interaction of the treatment arm with the time (**0.27 95%CI [-2.8, 3.4], p 0.864**)

*adjusted by the time and strata effect*

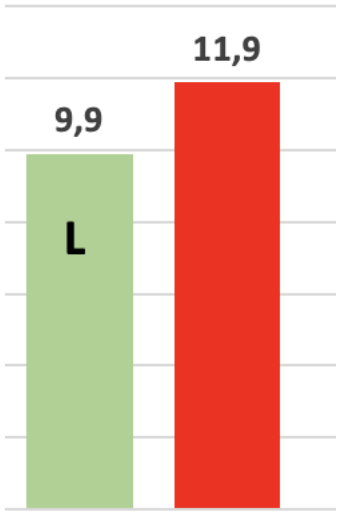
# eGFR reduction

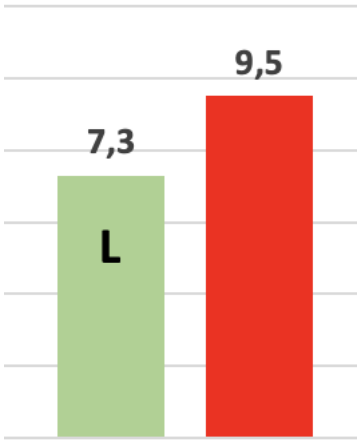


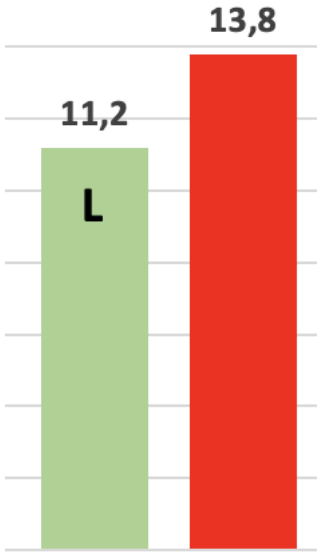
# eGFR

| | Overall | | CKD2 | | CKD3 | |
|---|---|---|---|---|---|---|
| | Lanreotide n = 72 | Placebo n = 72 | Lanreotide n = 28 | Placebo n = 28 | Lanreotide n = 44 | Placebo n = 44 |
| estimated GFR reduction at W 144 median [Q1;Q3] | n= 68 -9.9 [-14.9;-3.5] | n = 69 -11.9 [-18.4;-5] | n = 25 -7.3 [-12.1;2.2] | n = 26 -9.5 [-18.2;-1.9] | n = 43 -11.2 [-17.2;-5.9] | n = 43 -13.8 [-18.6;-8.3] |
| estimated GFR slope at W 144 median [Q1;Q3] | -3.5 [-5.3;-1.2] | -4.1 [-6.5;-1.8] | -2.6 [-4.3;0.8] | -3.4 [-6.5;-0.7] | -4 [-6;-2.1] | -4.9 [-6.4;-3] |

linear mixed-effects model




estimated difference

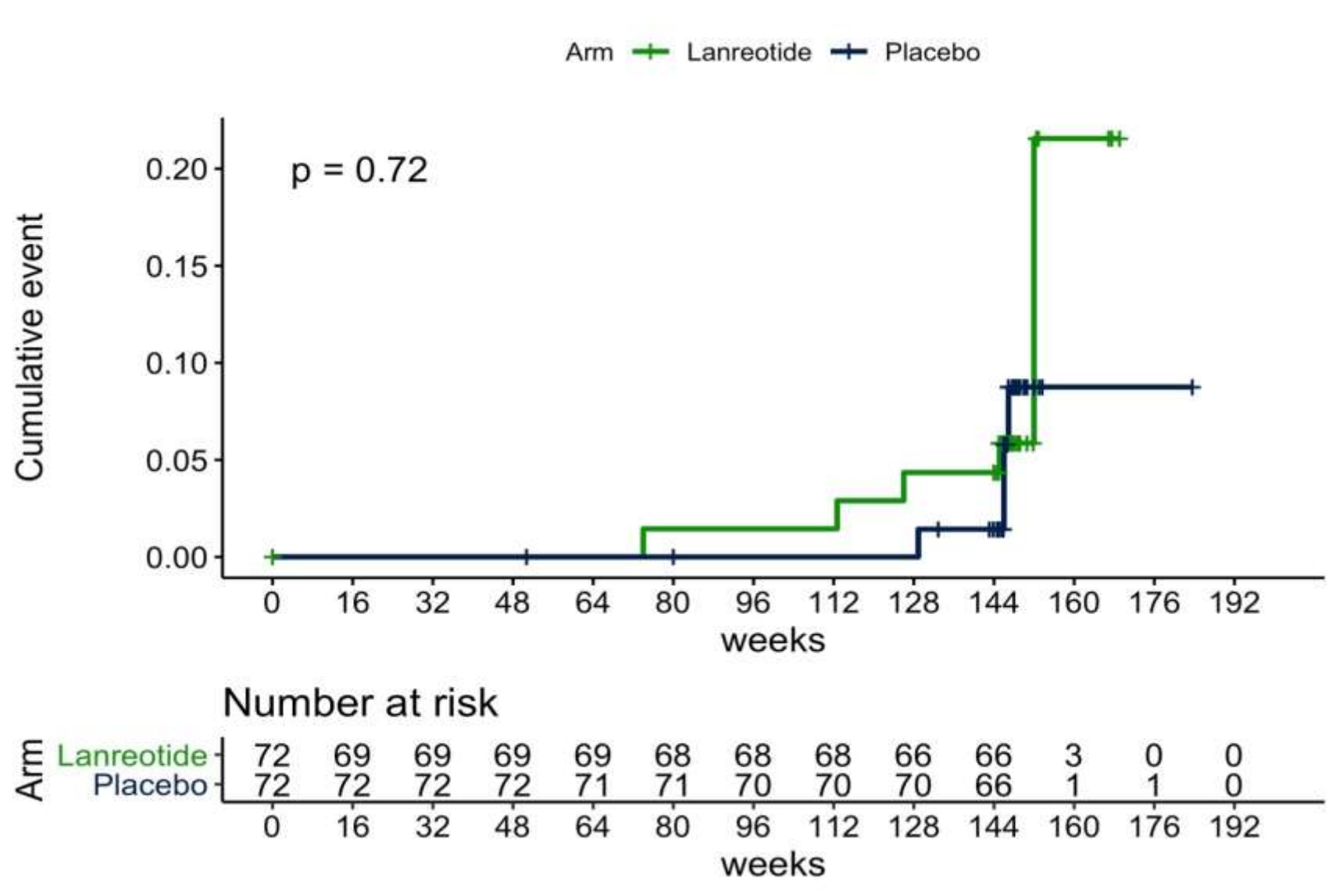
**1.1** (SE 0.39) ml/mn
**p < 0.01**

**1.3** (SE 0.8) ml/mn

**1** (SE 0.4)

# Cumulative event plot for the secondary composite endpoint : time to renal event

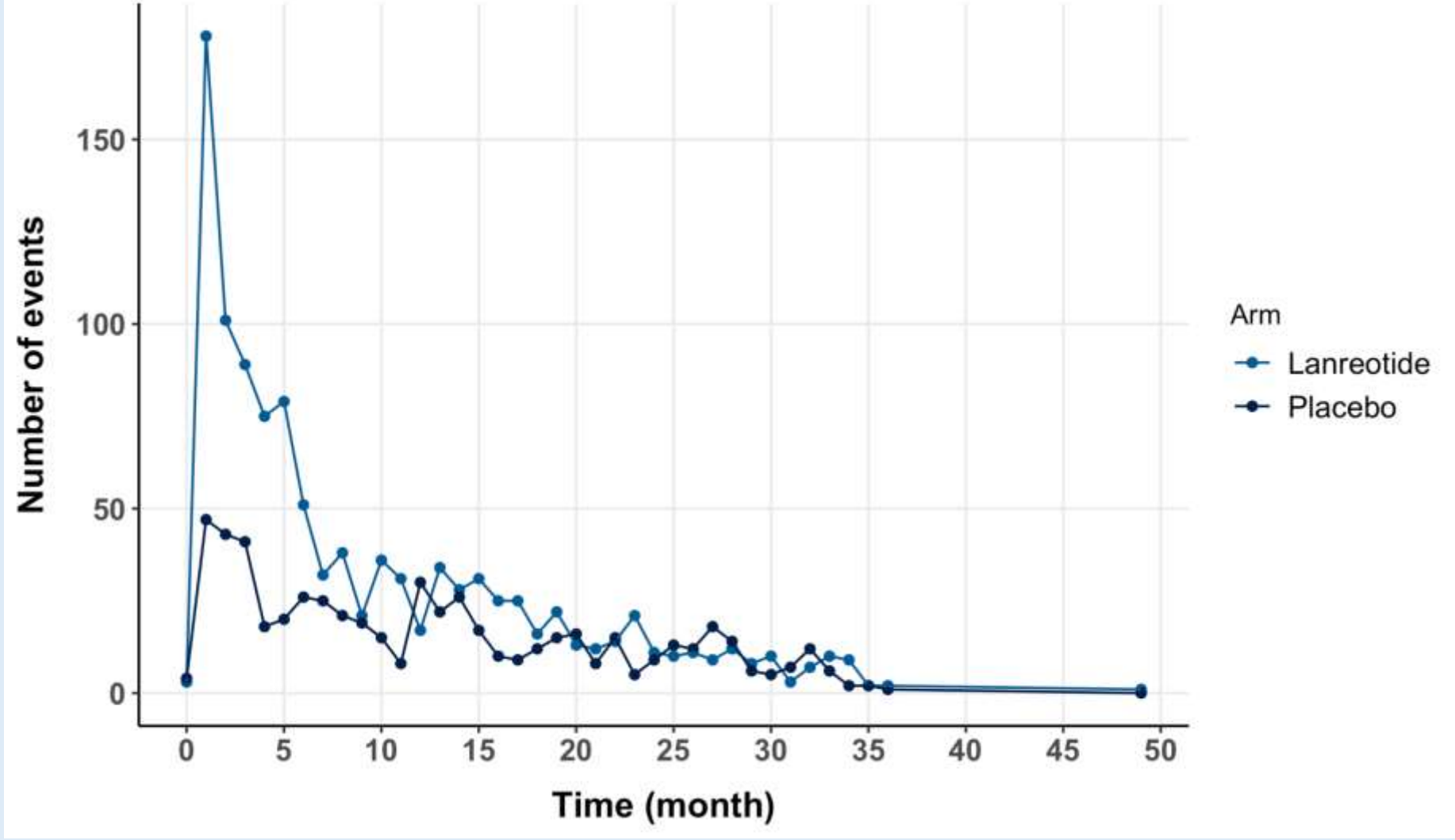
***doubling of serum creatinine or GFR < 15 ml/mn/1.73m2 or being dialyzed or being kidney grafted.***



# Adverse events

| | Number of Adverse events n (% of patients) | |
|---|---|---|
| | Lanreotide, n=72 | Placebo, n=72 |
| Total number of adverse event | 1105 | 584 |
| Selected adverse events | | |
| **Number of diarrhea episodes** | **238 (xx)** | 37 (xx) |
| **Number abdominal pain episodes** | **213 (xx)** | 84 (xx) |
| **Nausea** | **52 (72.2)** | 14 (19.4) |
| **Vomiting** | **23 (31.9)** | 8 (11.1) |
| **Constipation** | **13 (18)** | 4 (5.5) |
| **Flatulence** | **29 (40.3)** | 8 (11.1) |
| **Decreased appetite and weight loss** | **11 (15.3)** | 1 (1.3) |
| **Fatigue** | **37 (51)** | 17 (23.6) |
| **Dizziness** | **17 (23.6)** | 8 (11.1) |
| **Headache** | 34 (47) | 25 (34.7) |
| **Bradycardia** | 4 (5.5) | 1 (1.3) |
| **Hair loss** | 6 (8.3) | 3 (4.1) |
| **Injection site discomfort/nodule** | 41 (56) | 3 (4.1) |
| **Pruritus/skin allergy** | 6 (8.3) | 4 (5.5) |
| **Hypoglycemia** | 21 (29) | 1 (1.3) |
| **Hyperglycemia** | 2 (2.7) | 3 (4.1) |

# Time course of the number of adverse events reported by treatment group



# SAE

| | Patients with SAE, n (%) | |
|---|---|---|
| | Lanreotide (n=72) | Placebo (n=72) |
| Any SAE (% of patients) | 36 (37.5) | 63 (48.6) |
| SAE leading to treatment withdrawal | 3 | 0 |
| Cyst infection : renal /hepatic | 7/0 (9.7) | 6/0 (8.3) |
| Pyelonephritis | 0 (0) | 8 (11.1) |
| Cyst haemorrhage : renal/hepatic | 2/3 (6.9) | 0/0 (0) |
| Epigastric pain | 1 (1.4) | 1 (1.4) |
| Urolithiasis | 0 (0) | 2 (2.8) |
| Cholelithiasis | 4 (5.5) | 2 (2.8) |
| Acute pancreatitis | 0 (0) | 1 (1.4) |
| Acute colitis | 2 (2.8) | 3 (4.2) |
| Hypoglycaemia | 3 (4.2) | 0 (0) |
| Suicide attempt / depression | 3 (4.2) | 3 (4.2) |
| Acute coronary syndrome | 2 (2.8) | 4 (5.5) |
| Subarachnoid hemorrhage | 2 (2.8) | 2 (2.8) |

# mGFR or eGFR ?

**eGFR x 11**

=> Lanreotide **efficient**

**mGFR x 3**

0 72 144

=> Lanreotide **not efficient**

final mGFR
not obtained in all patients

eGFR x3

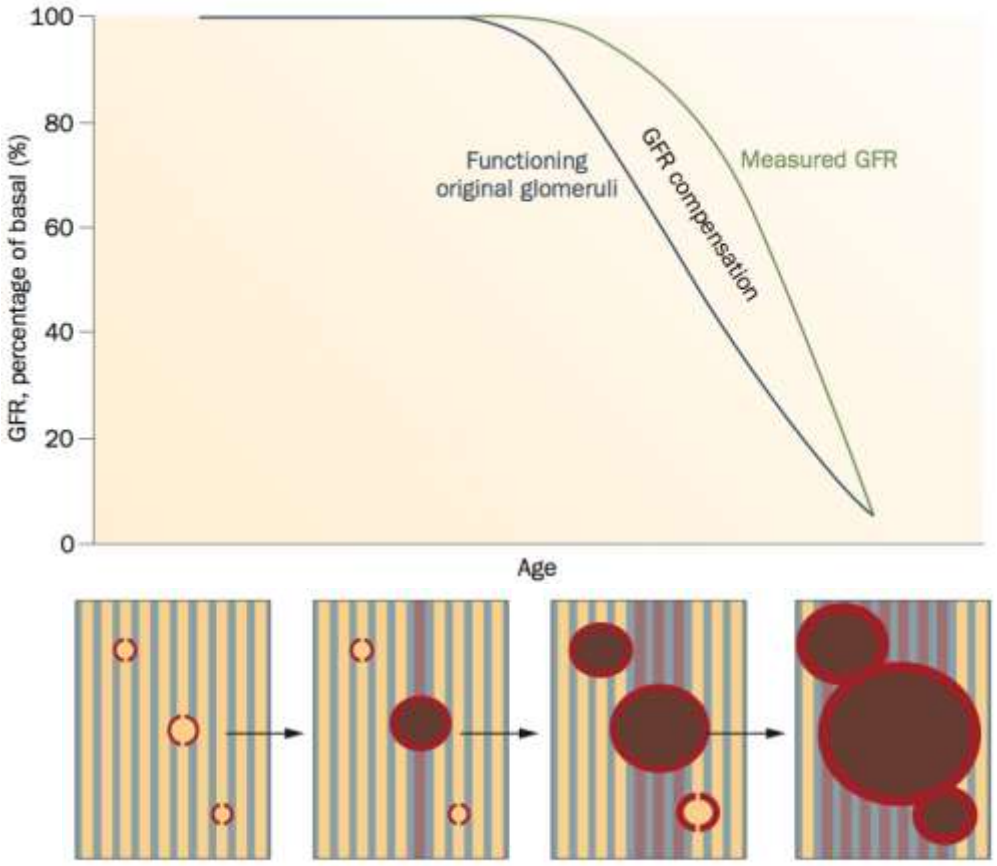
=> Lanreotide **not efficient**

# mGFR or eGFR ?

- eGFR predicts outcomes better than mGFR based slopes
- eGFR total slope from baseline to 3 years is a valid primary endpoint for clinical trials of CKD progression

*Porrini E,. Nat Rev Nephrol. 2019*
*Ku E, J Am Soc Nephrol 2016*
*Inker LA Nat Med. 2023;29(7):1867-1876*

## Cystogenesis : gap between structural and functional changes




## Somatostatin analogs efficient on volume .... but not on renal function ??

(i) somatostatin analogs may induce an initial acute **hemodynamic decline** of GFR

(ii) the benefit on volume will translate **years later** into a benefit on renal function (missed by short term trials)

(iii) inclusion of patients with **later-stage ADPKD**, potentially worse or non-responders to treatment

# Differences between LIPS and DIPAK-1 ?

| | DIPAK1 | LIPS |
|---|---|---|
| **design** | Open labeled/control | Double blind/placebo |
| **n planned randomized** | 300/309 | 180/**144** |
| **duration** | 2.5 | **3** |
| **dosage** | 112 | **120** |
| **CKD stage** | 3 | **2 + 3** |
| **Age** | 48.4 (SD 7.3) | **46.9 (SD 9.0)** |
| **Mayo class 1C/1D/1E** | 77.8 | **84** |
| **GFR loss (control)** | 3.46 | **4.1** |
| **Initial eGFR (control)** | 51 | **55.5** |
| **Primary criteria** | eGFR loss | **mGFR loss** |

# LIPS study

## Lanreodite

- ❑ AE frequent, but limited to the first 2/3 months
- ❑ Reduction of GFR loss ?

only apparent on **eGFR** (11 points vs 3 points-mGFR)

**modest effect** in absolute value

result mostly driven by **CKD2 patients**

# LIPS study

**Results applicable to patients with large liver/kidneys and normal renal function ?**

**4.6. Somatostatin analogues**

**Recommendation 4.6.1: We suggest that somatostatin analogues should be prescribed only in people with ADPKD with severe symptoms due to massively enlarged kidneys to lower the growth rate of kidney cysts when no better options are available(*2B*).**

**Practice Point 5.2.3.4: Somatostatin analogues should not be prescribed for the sole purpose of improving the rate of eGFR loss in people with ADPKD.**

# Remerciements


**Patients**

**Associations**

France Polykystose  AIRG

**Cliniciens**

E Thervet
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MN Peraldi
M Fouchard
B Kneblemann

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**Biostatistiques** M. Ursino (R Debré)
**Explorations fonctionnelles rénales**
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K EL Karoui
F Bienaimé
C Cohen

**INSERM**
F Terzi

**URC**
**CIC**
**DRC**