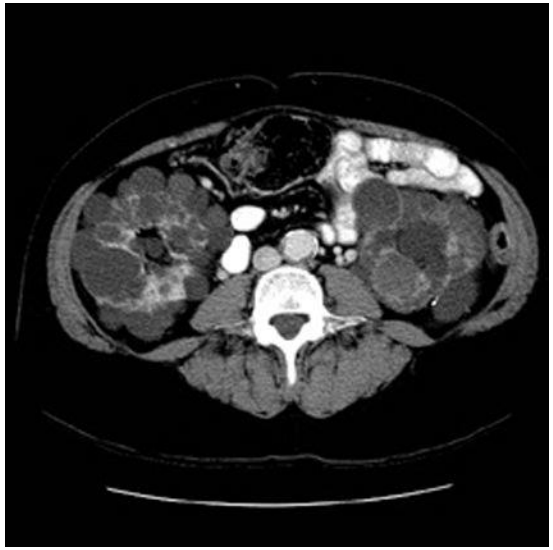
Polykystose Hépato-Rénale Autosomique Dominante



Actualités thérapeutiques

Dominique JOLY
Hôpital Necker
INSERM 845

I. Pression artérielle

(HALT study NEJM)

- PA **< 110/75** si âge 18-50 et DFG > 60
- PA **< 130/85** dans les autres cas

II. Alimentation

- Index de masse corporelle < 24
- NaCl < 6g/j
- apports limités en protides/phosphates
- apports hydriques +++ => **Osm U < 280**

III. Le Tolvaptan

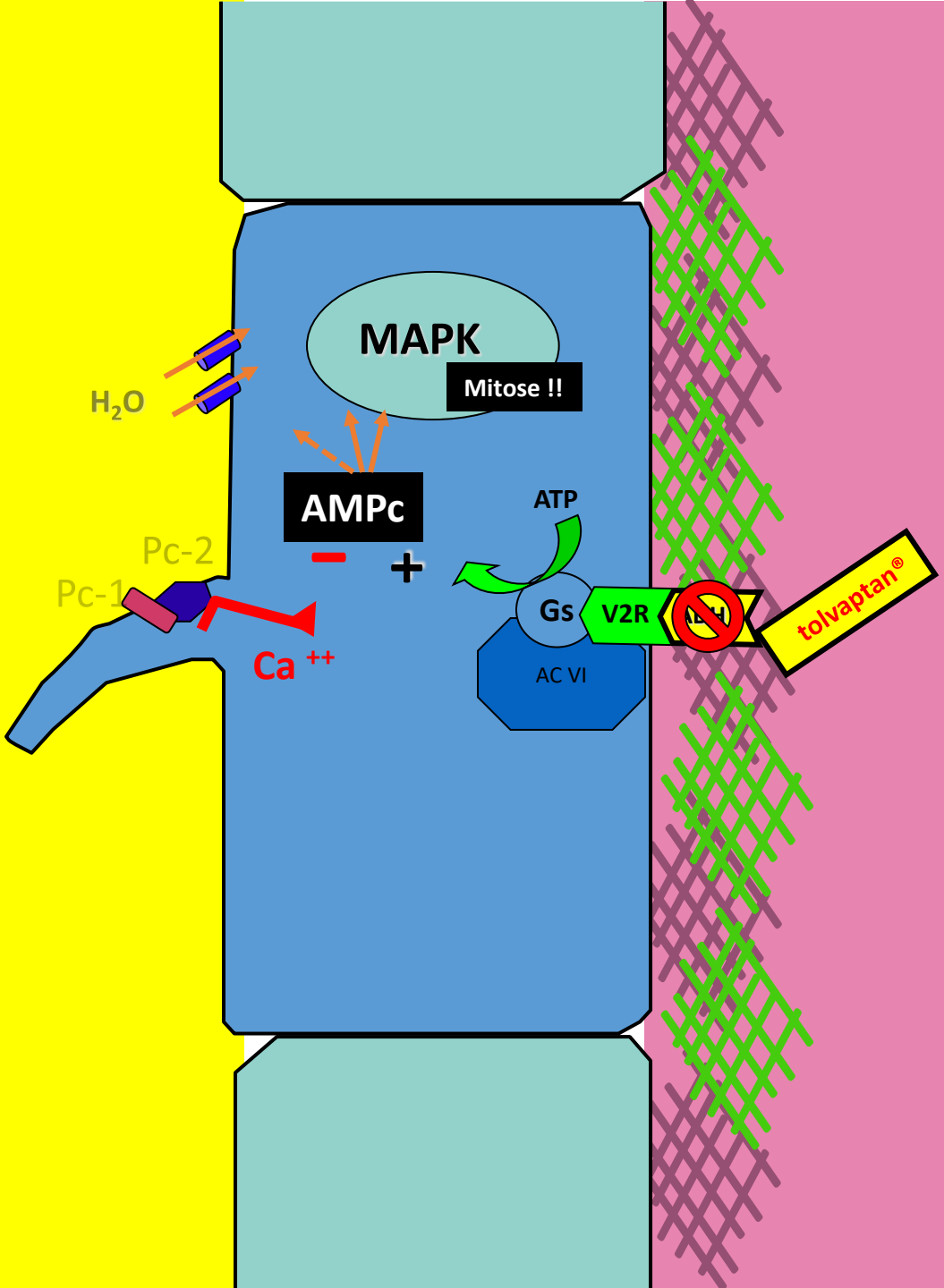
Cellules

Animaux

Hommes

Etude TEMPO

Mise sur le marché



Jinarc® (tolvaptan) disponible depuis > 3 ans

décision concertée patient/néphrologue

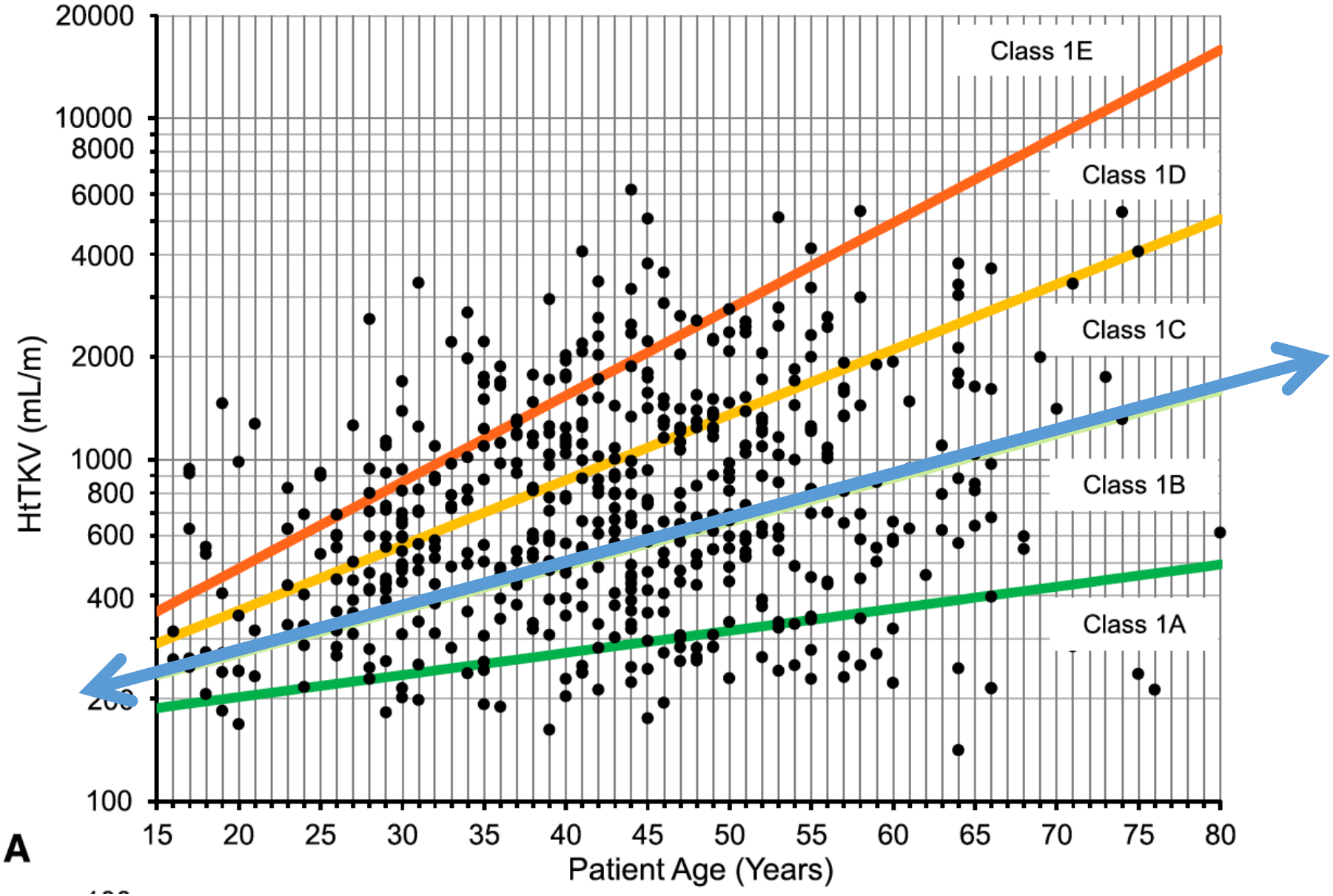
- Eligible
- Motivé

Juillet 2019

Service médical rendu <u>MODERE</u>

- un DFG > 30 ml/min/1,73 m² > 25 ml/mn/1.73 m^2
- et une néphromégalie importante associée à un risque de perte de fonction rénale (un volume rénal ajusté à la taille > 600 ml/m à l'IRM ; ≥ 630 ml/m à l'échographie ou une longueur des reins > 16,7 cm à l'IRM ; > 16,8 cm à l'échographie.) ;
- et des signes d'évolution rapide de la maladie tels que la présence de manifestations cliniques (douleurs rénales, ou hémorragie ou infection intra-kystique, hématurie macroscopique) ou une perte significative du DFG d'au moins 5 ml/min/an (appréciée par les formules du MDRD, CKD-EPI ou par la clairance de la créatinine). > 3,5 ml/mn/1.73 m^2

Mayo clinic : traiter les patients qui sont dans les couloirs de volume C,D et E



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*

✓ **Inclusion =**

- **adultes jeunes ≤ 50 ans**
- **bonne fonction rénale (> 60 ml/mn)**
- **gros reins (Volume Rénal Total > 750 ml)**

✓**Tirage au sort : 1445 patients**

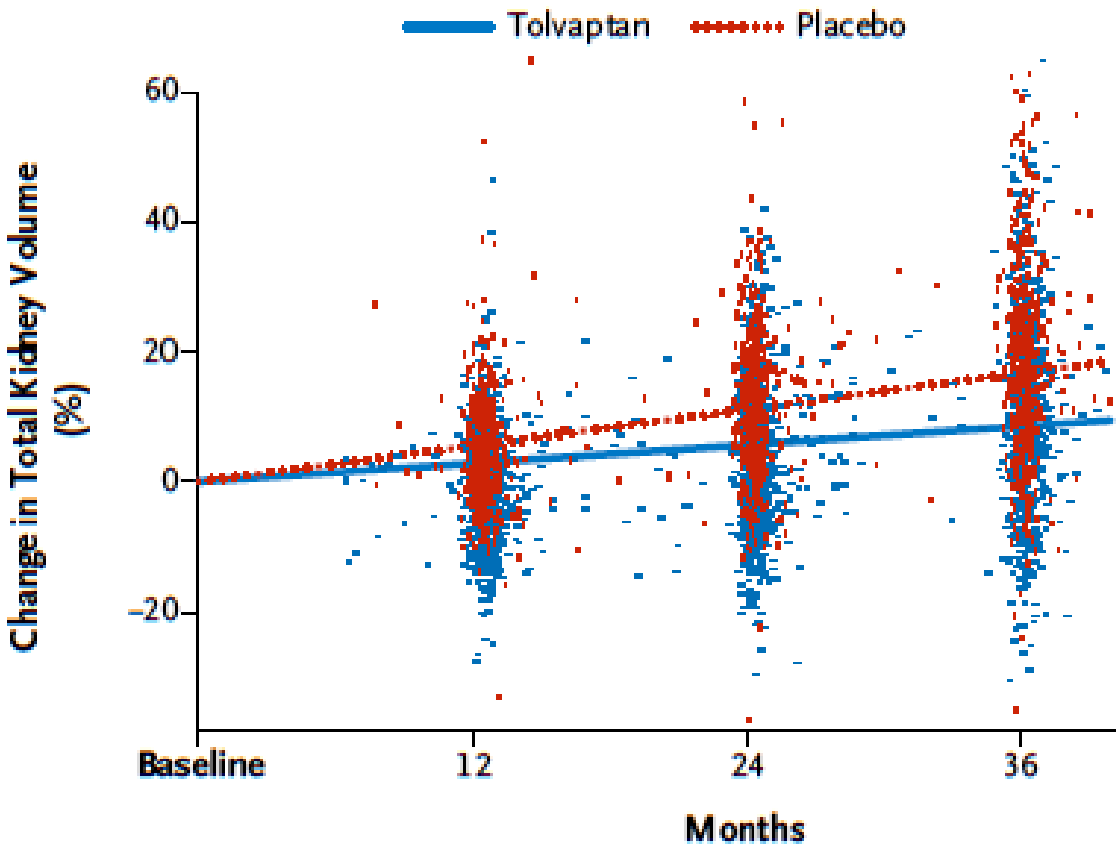
- **tolvaptan ou placebo durant 3 ans**

✓ **Critère Principal :**

- **évolution du Volume Rénal Total (IRM)**

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

Volume rénal



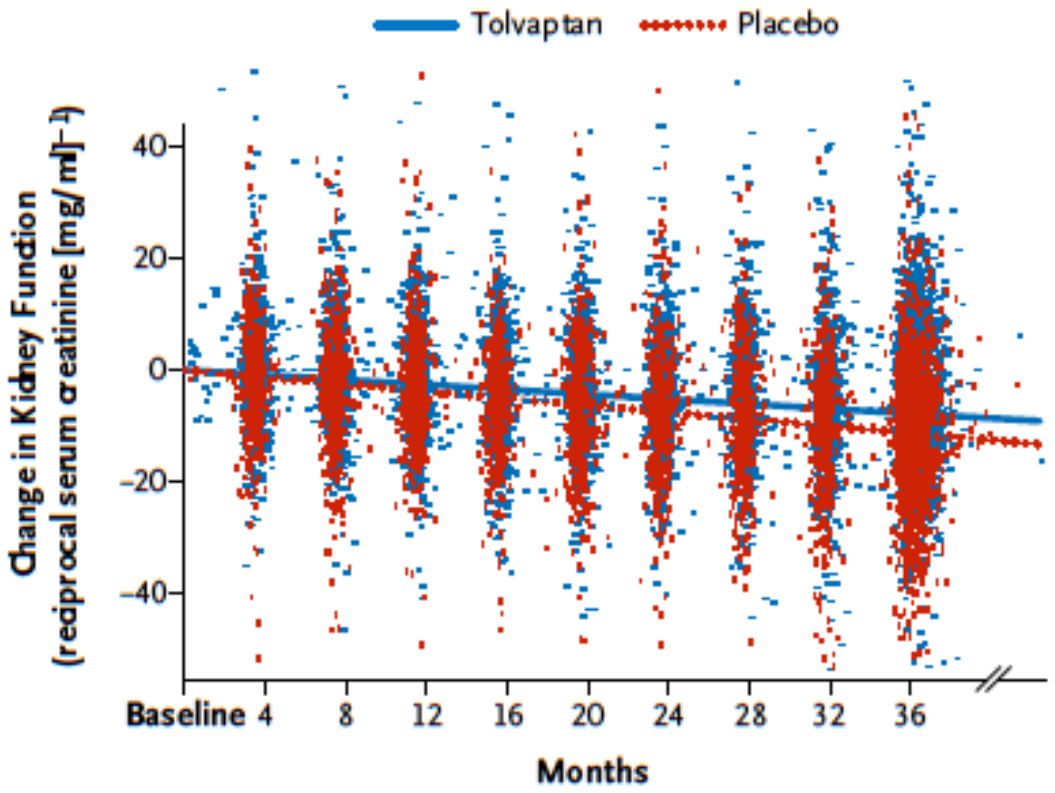
+ 5,6 %

+ 2,8 %

- 50 %

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

Fonction rénale

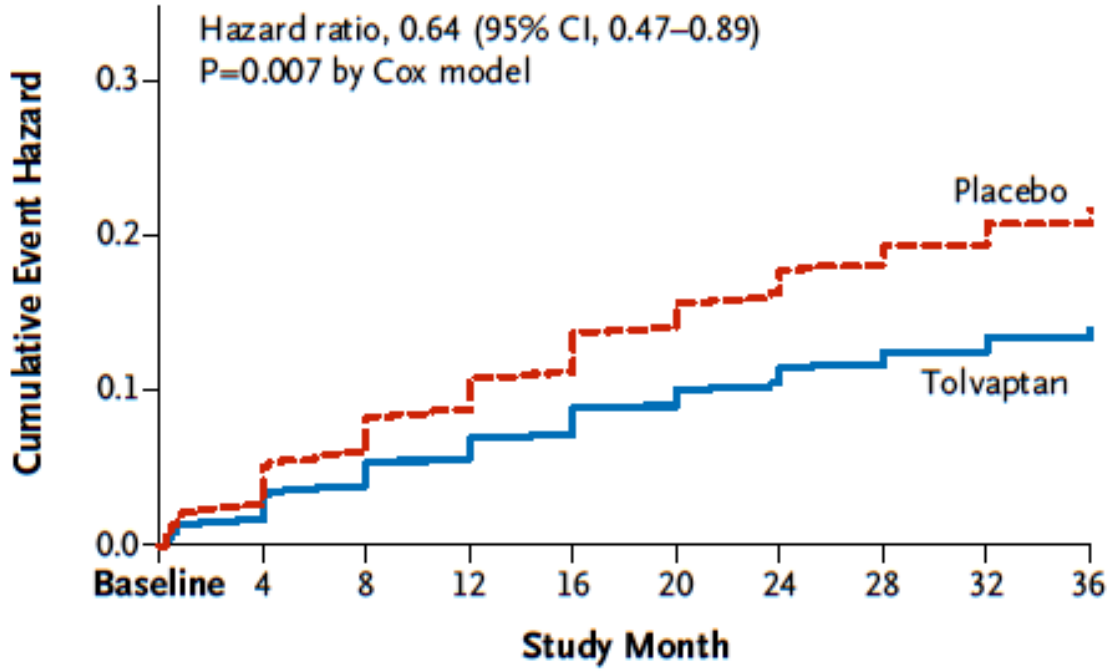


Tolvaptan : −2.72 ml /mn/1.73 m² /an

Placebo : −3.70 ml /mn/1.73 m² /an

- 25 %

Risque de Douleur rénale nécessitant une intervention médicale



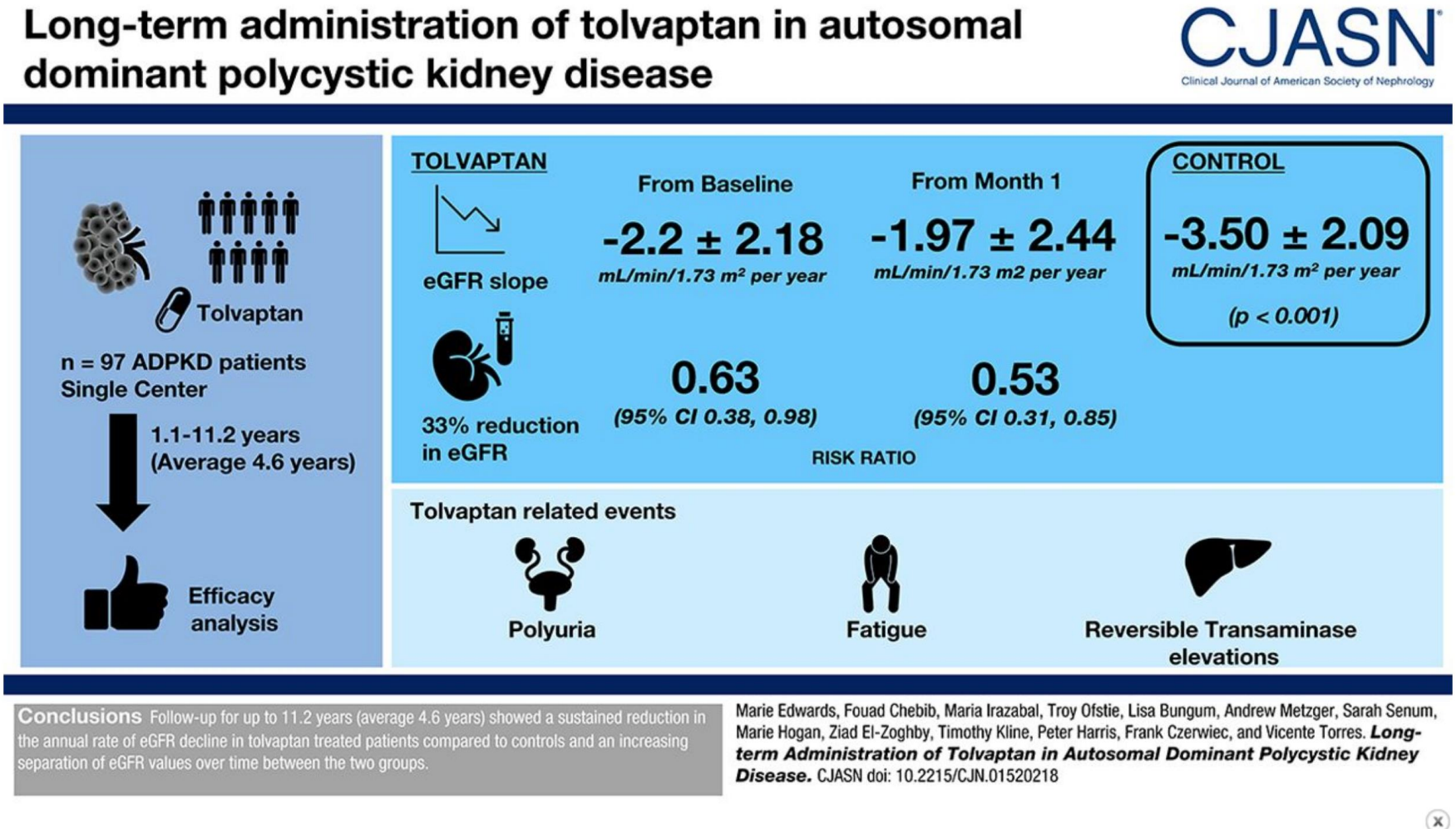
No. at Risk

Tolvaptan	961	870	835	811	792	776	763	752	744	642
Placebo	483	472	463	454	446	438	428	422	418	359

- 36 %

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

Efficacité à l'épreuve du temps ?



Tolvaptan : quelle efficacité chez l'insuffisant rénal ?

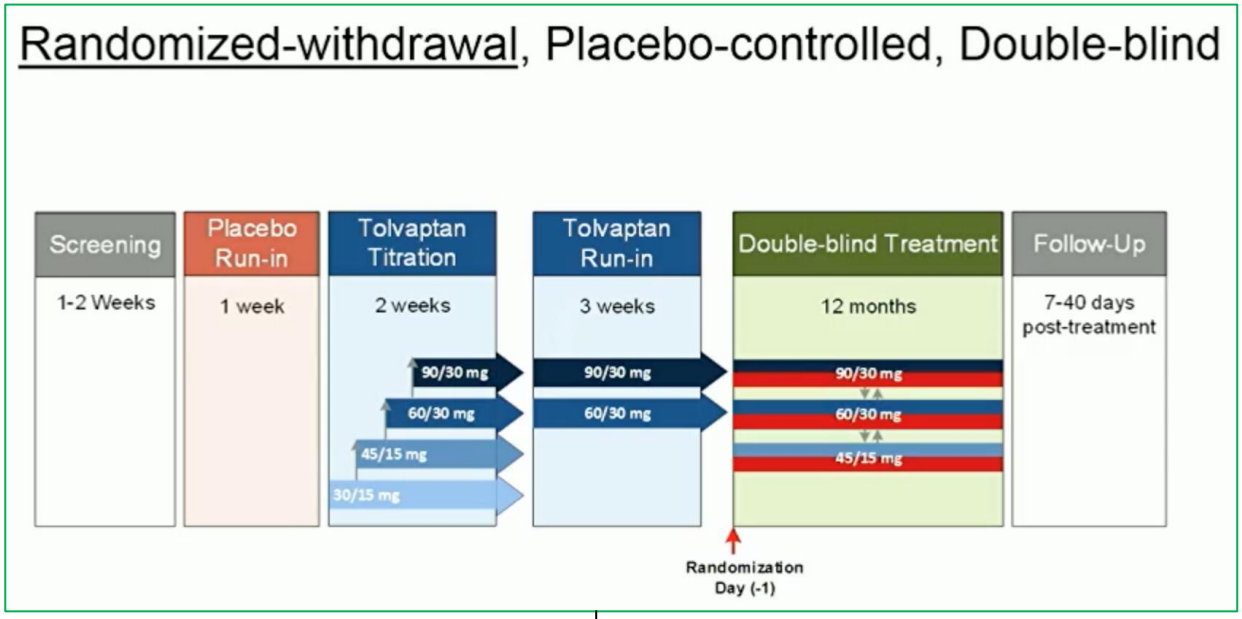
Etude **REPRISE**

- ADPKD
- 18-55 ans DFGe **25 à 65** mL/min/1.73 m^2
- 55-65 ans DFGe **25 à 44** mL/min/1.73 m^2
- Δ DFG > 2.0 mL/min/1.73 m^2 /an

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*



Effectif calculé = 1300 patients pour une différence de 1 ml/mn/1.73m^2 à 1 an

Torres et al. ASN 2017 et NEJM 2017

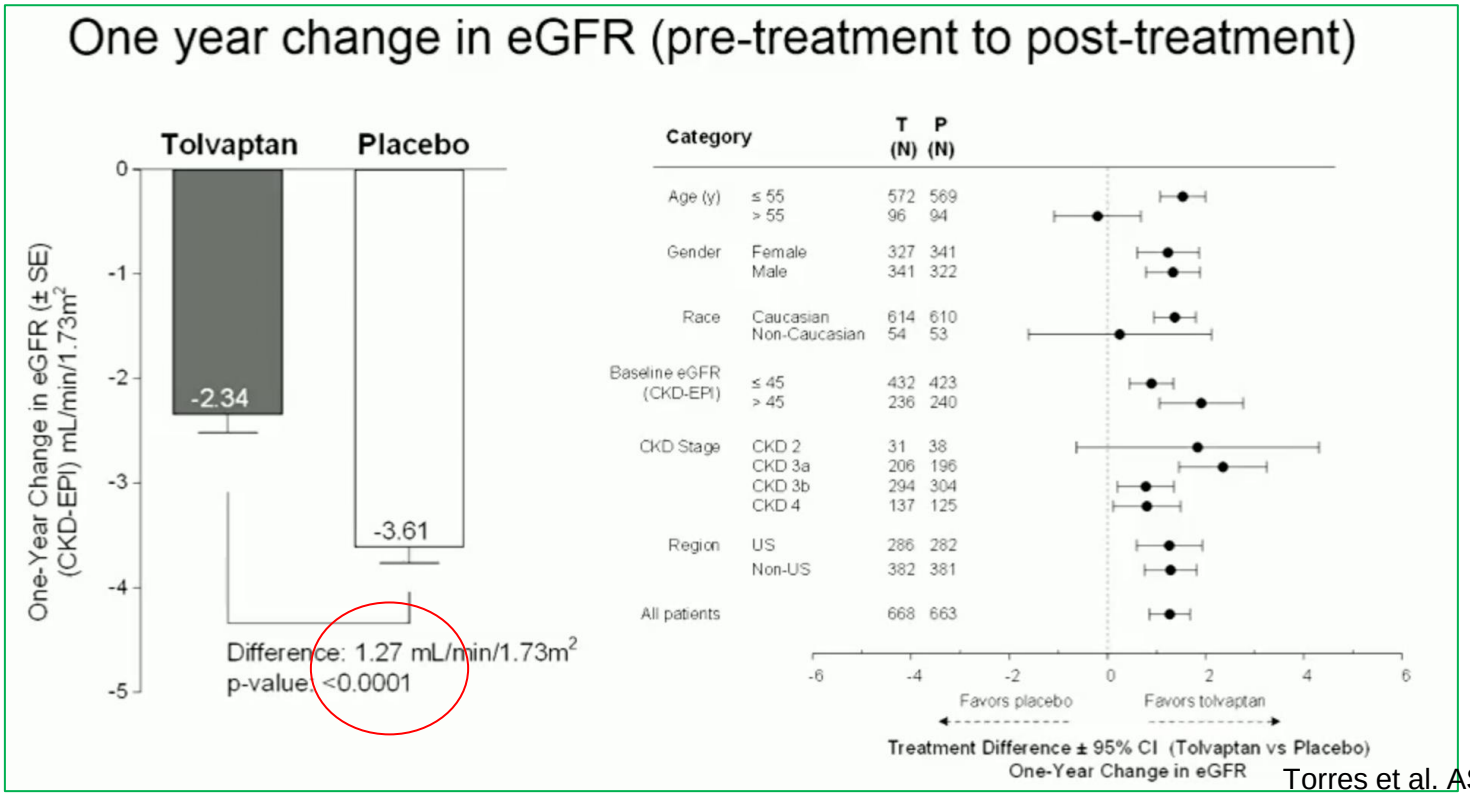
Etude REPRISE

ORIGINAL ARTICLE

Tolvaptan in Later-Stage Autosomal Dominant Polycystic Kidney Disease

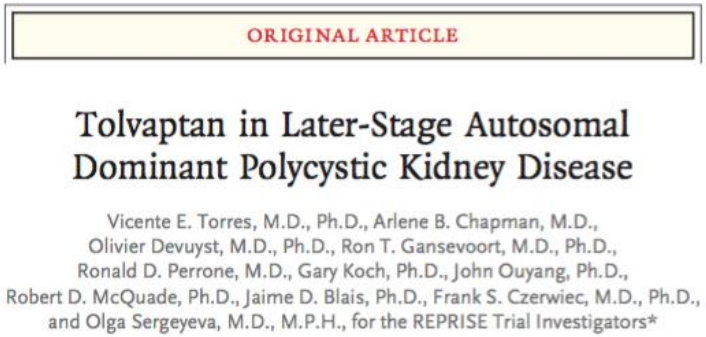
Vicente E. Torres, M.D., Ph.D., Arlene B. Chapman, M.D., Olivier Devuyst, M.D., Ph.D., Ron T. Gansevoort, M.D., Ph.D., Ronald D. Perrone, M.D., Gary Koch, Ph.D., John Ouyang, Ph.D., Robert D. McQuade, Ph.D., Jaime D. Blais, Ph.D., Frank S. Czerwiec, M.D., Ph.D., and Olga Sergeyeva, M.D., M.P.H., for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

- ADPKD
- 18-55 ans DFGe **25 à 65** mL/min/1.73 m^2
- 55-65 ans DFGe **25 à 44** mL/min/1.73 m^2
- ΔDFG > 2.0 mL/min/1.73 m^2 /an



Torres et al. ASN 2017 et NEJM 2017

Etude REPRISE



ORIGINAL ARTICLE

Tolvaptan in Later-Stage Autosomal Dominant Polycystic Kidney Disease

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\+ Le tolvaptan modifie l'histoire de la maladie **y compris en cas d'IRC**

\- **Trop court** … Rien de démontré sur des critères « durs »

Torres et al. ASN 2017 et NEJM 2017

Trois risques à discuter

1 hépatite grave (sur 6000 patients traités)

Atteinte hépatique

- hépatite médicamenteuse : risque < 5%, minimisable
- bilan hépatique mensuel x 18 mois puis trimestriel
- TRANSMETTRE LES RESULTATS

Perte d'eau

- soif, pollakiurie, nycturie
- avoir accès à l'eau
- boire avant d'avoir soif (+ au coucher + après chaque miction nocturne)
- limiter les **apports sodés et protéiques**

Pas de Grossesse ni d'allaitement

- contraception efficace 1 mois avant et 1 mois après son arrêt

IV. Même effet que le tolvaptan : la mambaquarétine

FROM RESEARCH TO INDUSTRY

cea

A snake mamba toxin for renal diseases

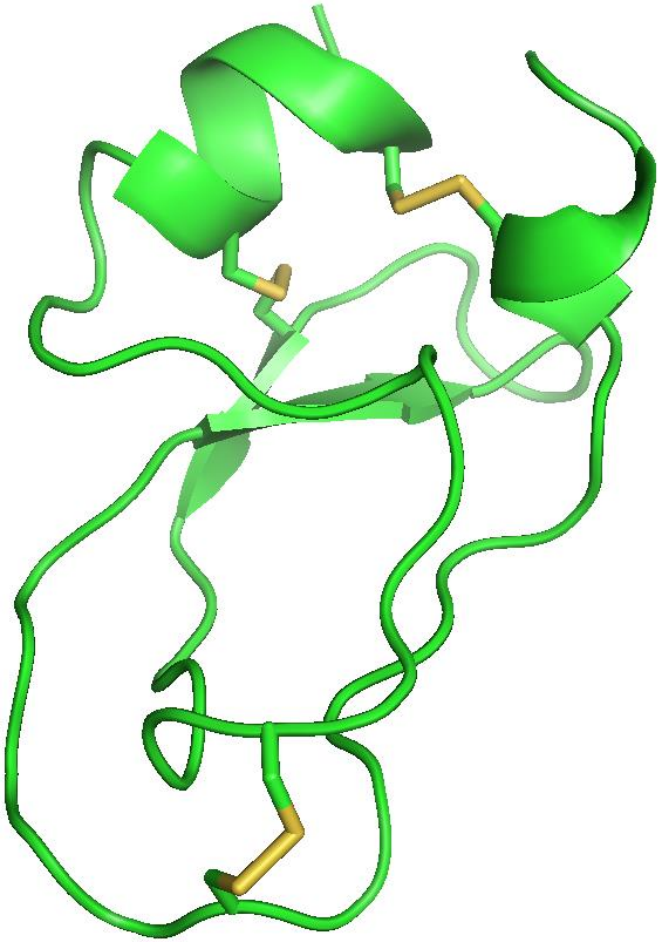
Alternative Energies Atomic Energy Commission

Department of Medicines and Healthcare Technologies

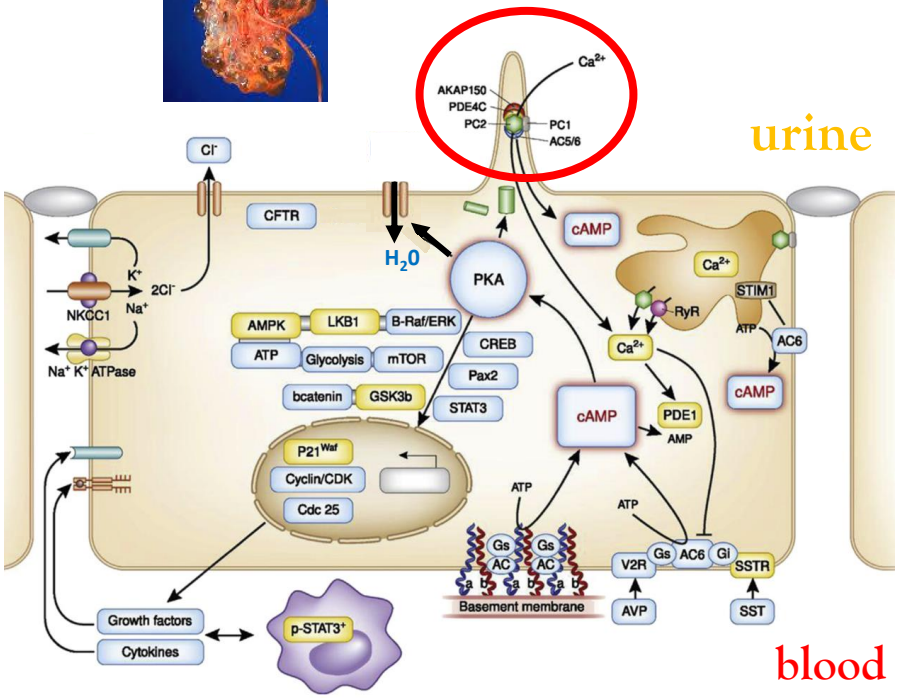
Toxin, Receptors and Channels Team

Nicolas.gilles@cea.fr

Mamba venom : mambaquaretin and V2R



Polycystic Kidney disease and V2R



From Torres's lab, Rochester, Minnesota

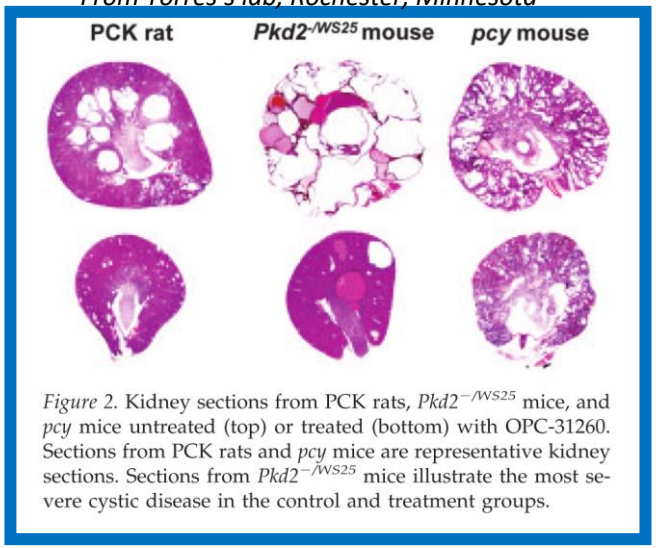
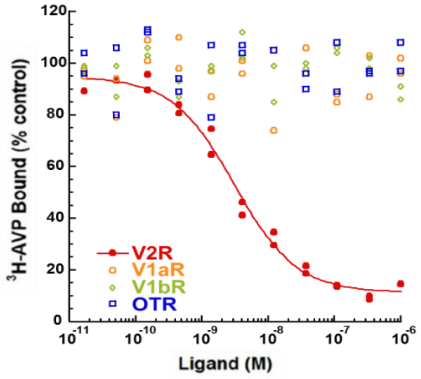


Figure 2. Kidney sections from PCK rats, *Pkd2*$^{-/WS25}$ mice, and *pcy* mice untreated (top) or treated (bottom) with OPC-31260. Sections from PCK rats and *pcy* mice are representative kidney sections. Sections from *Pkd2*$^{-/WS25}$ mice illustrate the most severe cystic disease in the control and treatment groups.

Blockage of the V2R against polycystic kidney diseases

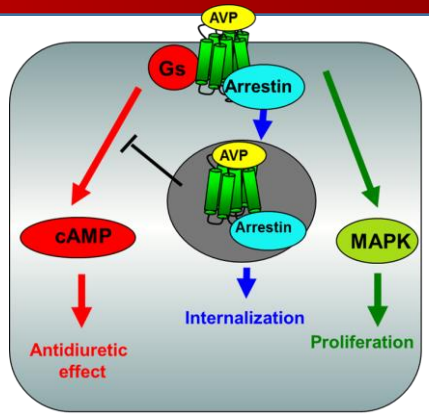
mambaquaretin the most selective antagonist

Binding competition

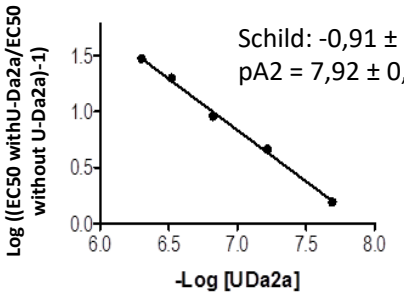


Safety profile

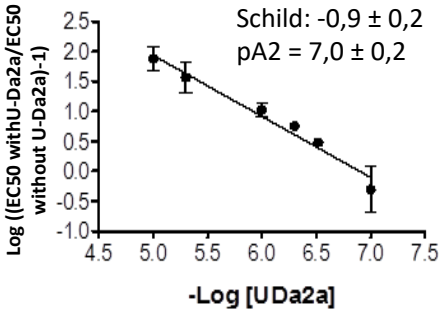
No activity on:
156 GPCRs
15 ionic channels
45 serine proteases



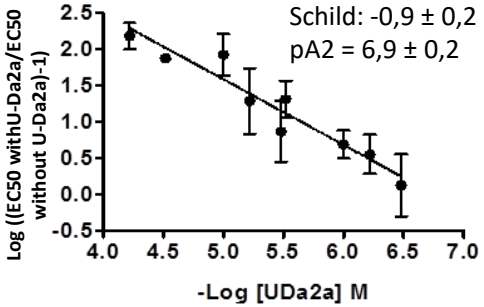
AMPc Production



β-Arrestin mobilisation



MAPK phosphorylation

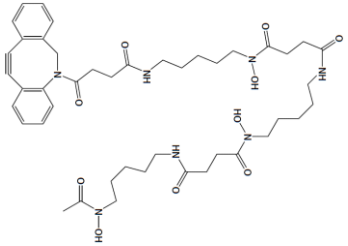


MQ is the most selective antagonist of the V2R

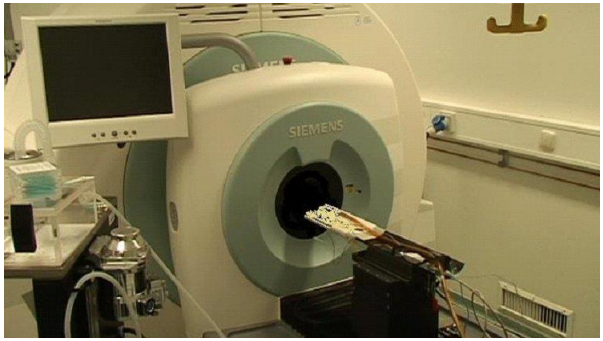
Biodistribution by PET imaging

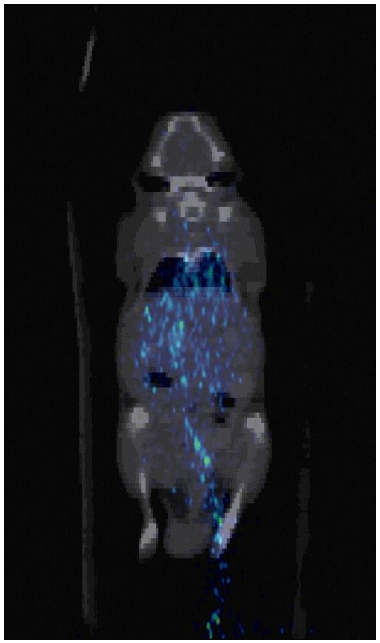
^{89}Zr labelling, Half-live 78 hours

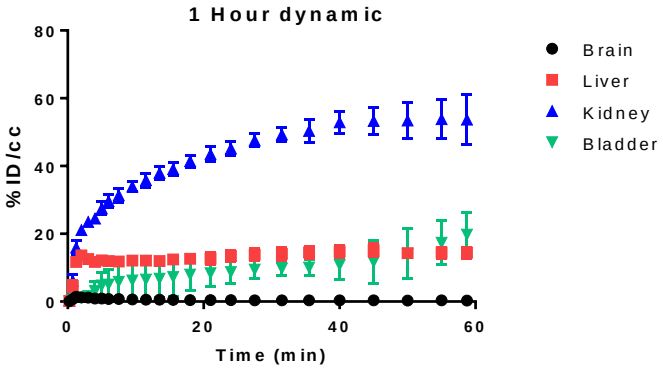
1 µg I.P. injection on mice, n=6



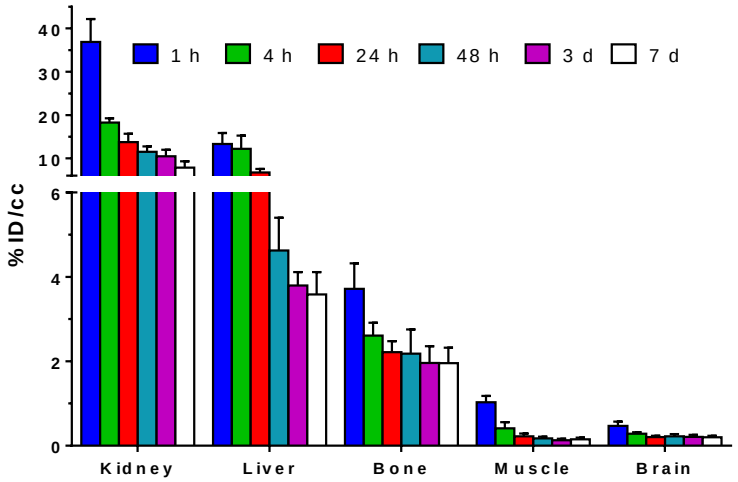
DFO-DBCO (deferoxamine)







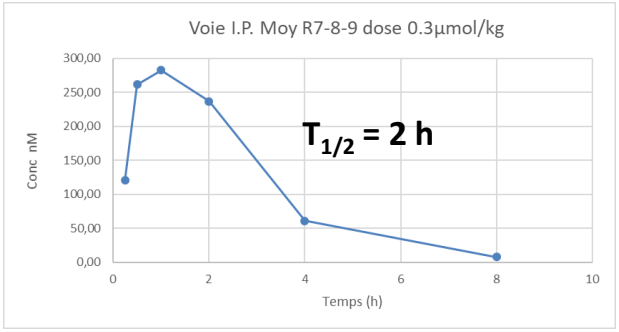
Dynamic distribution of MQ

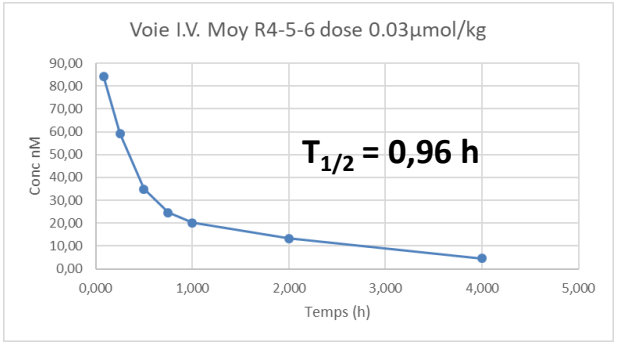


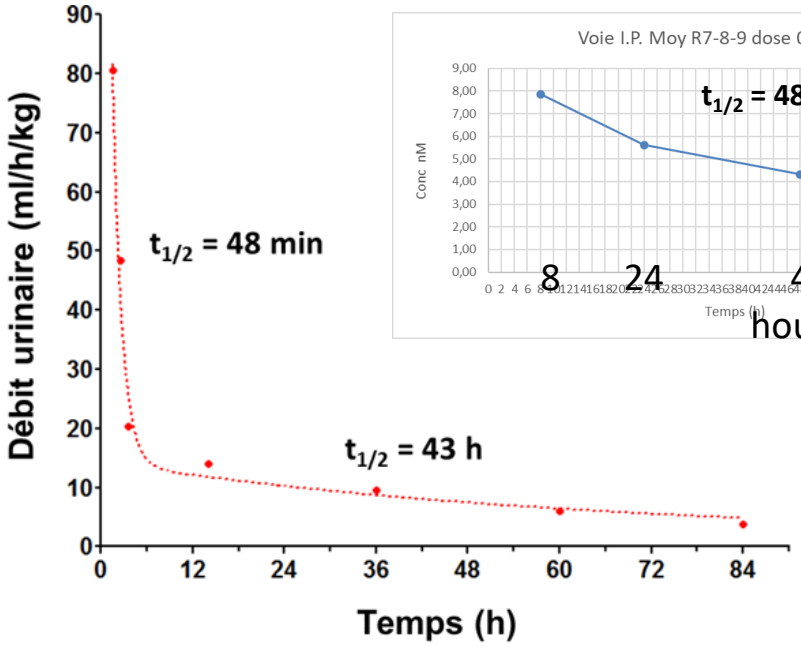
Biodistribution overtime

PK/PD studies

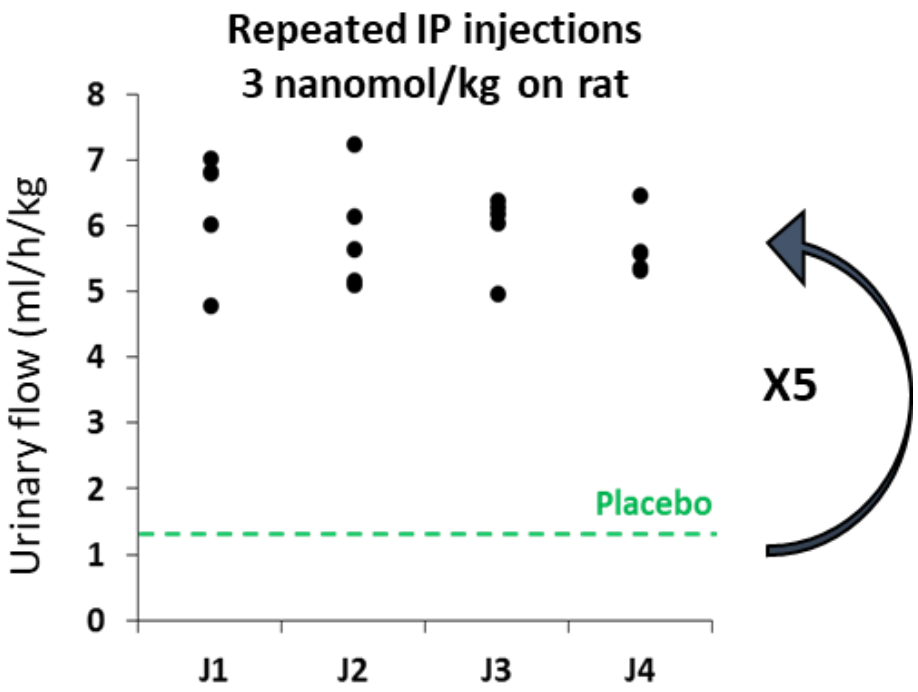
Pharmacokinetics







THERAPEUTIC WINDOW



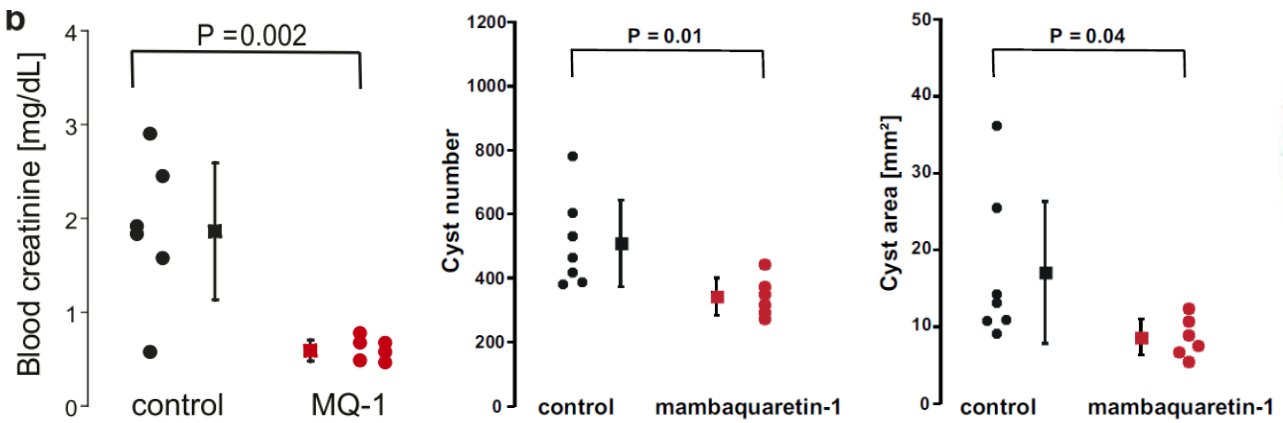
3 nanomol/kg increases 5 times the diuresis and produces hypotonic urines

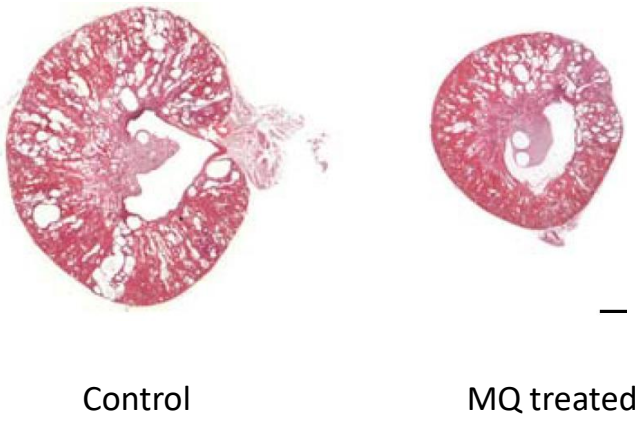
Estimated therapeutic dose
6 µg/rat/day => 200 µg/human/day
GMP manufacturing : 3€/day

Estimated toxic dose
6000 µg/rat
Large therapeutic window

Mambaquaretin against PKD

Universität Regensburg





MQ is a validated drug candidate against PKD
First patent in 2014

PNAS

Green mamba peptide targets type-2 vasopressin receptor against polycystic kidney disease

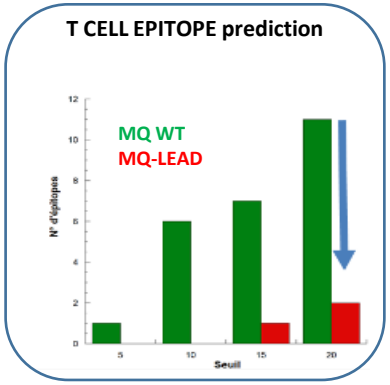
Justyna Ciolek[a,1], Helen Reinfrank[b,1,2], Loïc Quinton[c], Say Viengchareun[d], Enrico A. Stura[a], Laura Vera[a,3], Sabrina Sigismeau[a], Bernard Mouillac[e], Hélène Orcel[e], Steve Peigneur[f], Jan Tytgat[f], Laura Droctové[a], Fabrice Beau[a], Jerome Nevoux[d], Marc Lombès[d], Gilles Mourier[a], Edwin De Pauw[c], Denis Servent[a], Christiane Mendre[e,4], Ralph Witzgall[b,4], and Nicolas Gilles[a,4]

[a]Service d'Ingénierie Moléculaire des Protéines, Institut des Sciences du Vivant Frédéric Joliot, Commissariat à l'Energie Atomique, Université Paris-Saclay, F-91191 Gif sur Yvette, France; [b]Institute for Molecular and Cellular Anatomy, University of Regensburg, 93053 Regensburg, Germany; [c]Laboratoire de Spectrométrie de Masse, Unité de Recherche Molecular Systems, Université de Liège, Liège 4000, Belgium; [d]INSERM U1185, Université Paris Sud, Université Paris-Saclay, F-94276, Le Kremlin-Bicêtre, France; [e]Institut de Génomique Fonctionnelle, CNRS, INSERM, Université Montpellier, F-34094 Montpellier, France; and [f]Laboratory of Toxicology, University of Leuven, Leuven B-3000, Belgium

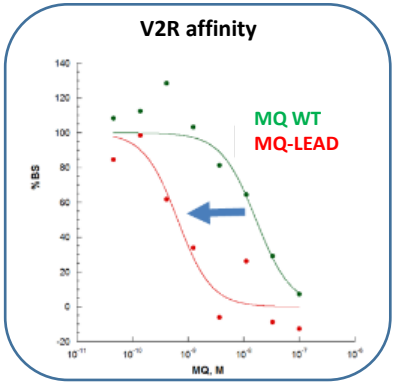
De-immunization of the mambaquaretin

Mambaretin sequence

MQ → **4 mutations** → **MQ LEAD**



Much lower risk of immunogenicity



10 times better affinity

Patent in progress

Tolvaptan

Comprimés

Hépatites

Mambatoxine

Injections

(Immunogènicité)

V. Le Venglustat (GZ402671)

Inhibiteur de la glucosylceramide synthase (GCS)

glucosylceramide (GL-1)

Essai en cours « STAGED PKD »

560 patients ADPKD

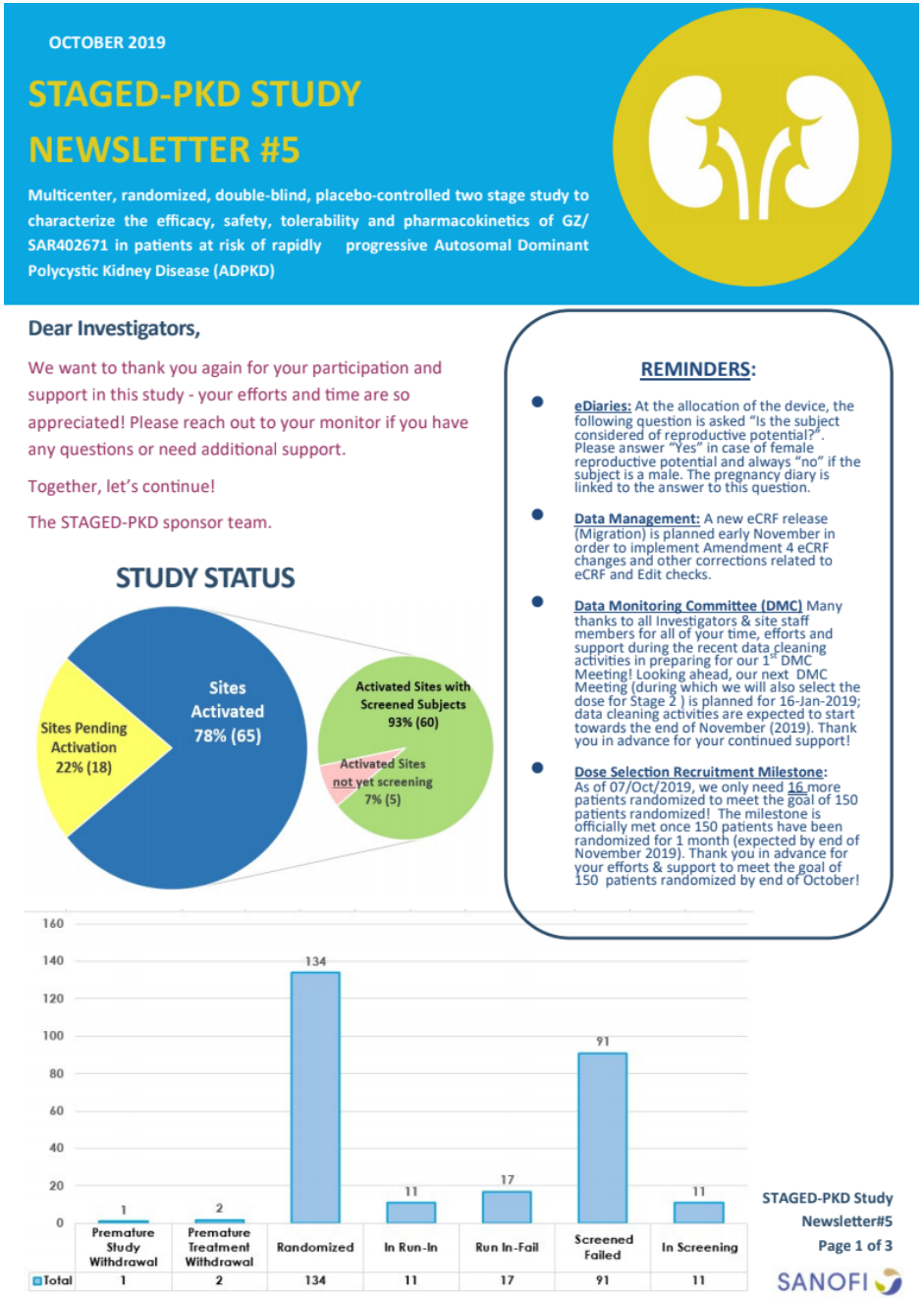
- 18 à 50 ans
- Volume rénal classe C,D,E
- DFG 45 à 90

Tirage au sort

- Dose 1
- Dose 2
- Placebo

Jugement

- Evolution du volume rénal (18m)
- Evolution de la fn rénale (24m)
- Securité etc …



OCTOBER 2019

STAGED-PKD STUDY NEWSLETTER #5

Multicenter, randomized, double-blind, placebo-controlled two stage study to characterize the efficacy, safety, tolerability and pharmacokinetics of GZ/SAR402671 in patients at risk of rapidly progressive Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Dear Investigators,

We want to thank you again for your participation and support in this study - your efforts and time are so appreciated! Please reach out to your monitor if you have any questions or need additional support.

Together, let's continue!

The STAGED-PKD sponsor team.

STUDY STATUS

REMINDERS:

- eDiaries: At the allocation of the device, the following question is asked "Is the subject considered of reproductive potential?". Please answer "Yes" in case of female reproductive potential and always "no" if the subject is a male. The pregnancy diary is linked to the answer to this question.
- Data Management: A new eCRF release (Migration) is planned early November in order to implement Amendment 4 eCRF changes and other corrections related to eCRF and Edit checks.
- Data Monitoring Committee (DMC) Many thanks to all Investigators & site staff members for all of your time, efforts and support during the recent data cleaning activities in preparing for our 1st DMC Meeting! Looking ahead, our next DMC Meeting (during which we will also select the dose for Stage 2) is planned for 16-Jan-2019; data cleaning activities are expected to start towards the end of November (2019). Thank you in advance for your continued support!
- Dose Selection Recruitment Milestone: As of 07/Oct/2019, we only need 16 more patients randomized to meet the goal of 150 patients randomized! The milestone is officially met once 150 patients have been randomized for 1 month (expected by end of November 2019). Thank you in advance for your efforts & support to meet the goal of 150 patients randomized by end of October!

STAGED-PKD Study Newsletter#5 Page 1 of 3

SANOFI

VI. Les analogues de la somatostatine

PLOS MEDICINE

RESEARCH ARTICLE

Octreotide-LAR in later-stage autosomal dominant polycystic kidney disease (ALADIN 2): A randomized, double-blind, placebo-controlled, multicenter trial

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¶ Membership of the ALADIN 2 Study Group is provided in S1 Appendix.
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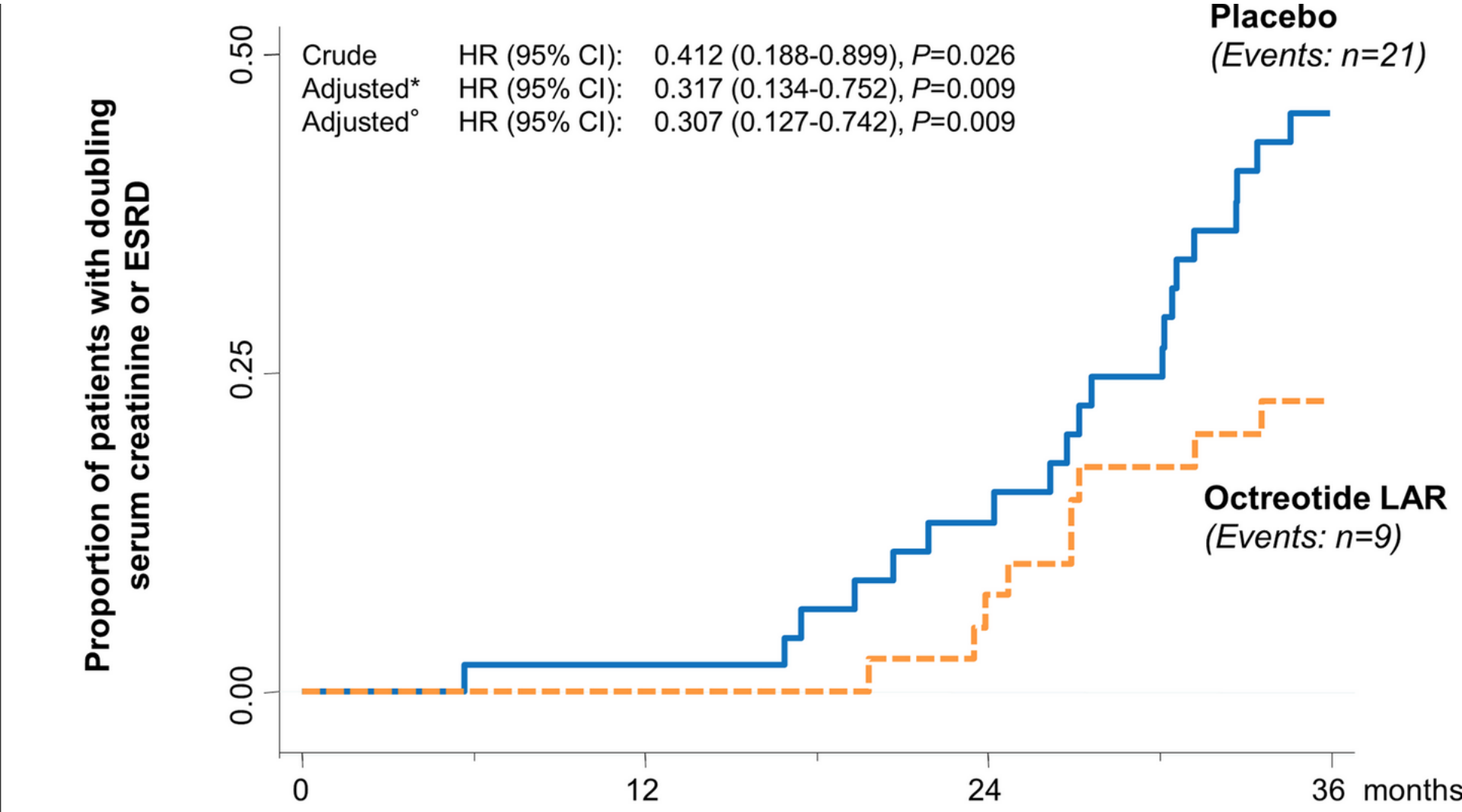
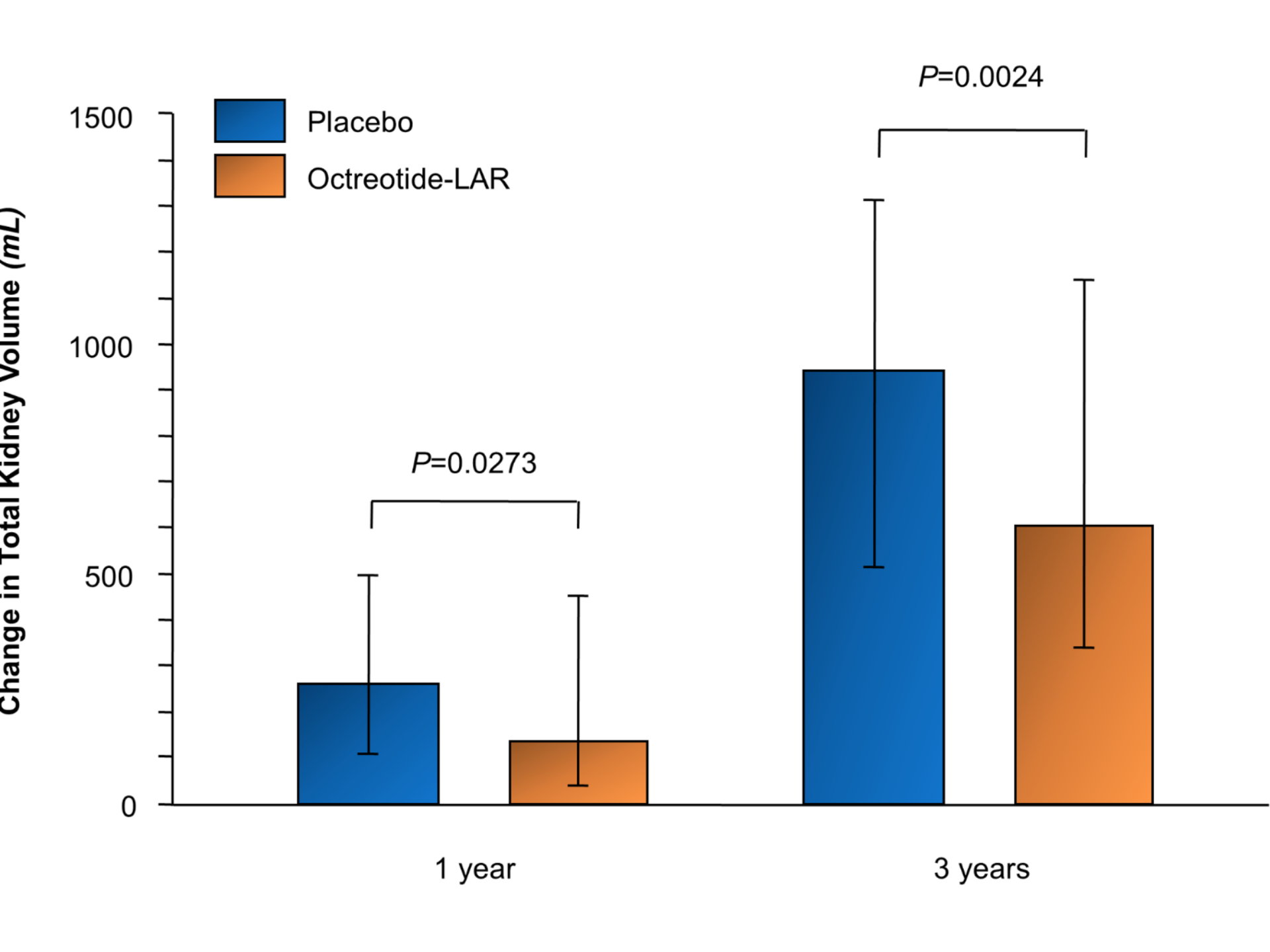


Patients at risk

Placebo	49	46	38	20
Octreotide LAR	51	45	37	23


P=0.0024
Placebo
Octreotide-LAR
1500
1000
500
0
Change in Total Kidney Volume (mL)
P=0.0273
1 year
3 years

JAMA

View Article

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PMID: 30422235

Effect of Lanreotide on Kidney Function in Patients With Autosomal Dominant Polycystic Kidney Disease

The DIPAK 1 Randomized Clinical Trial

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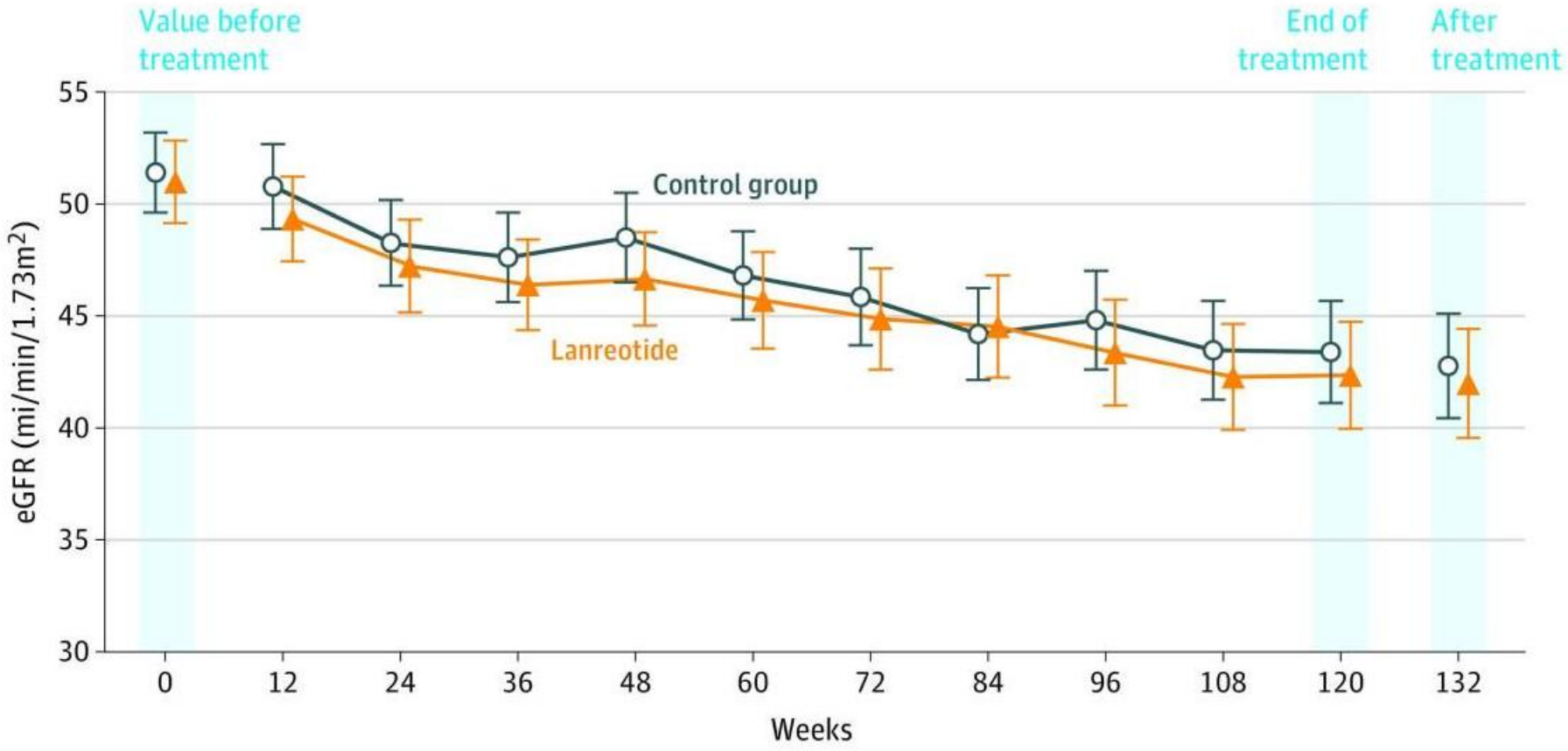


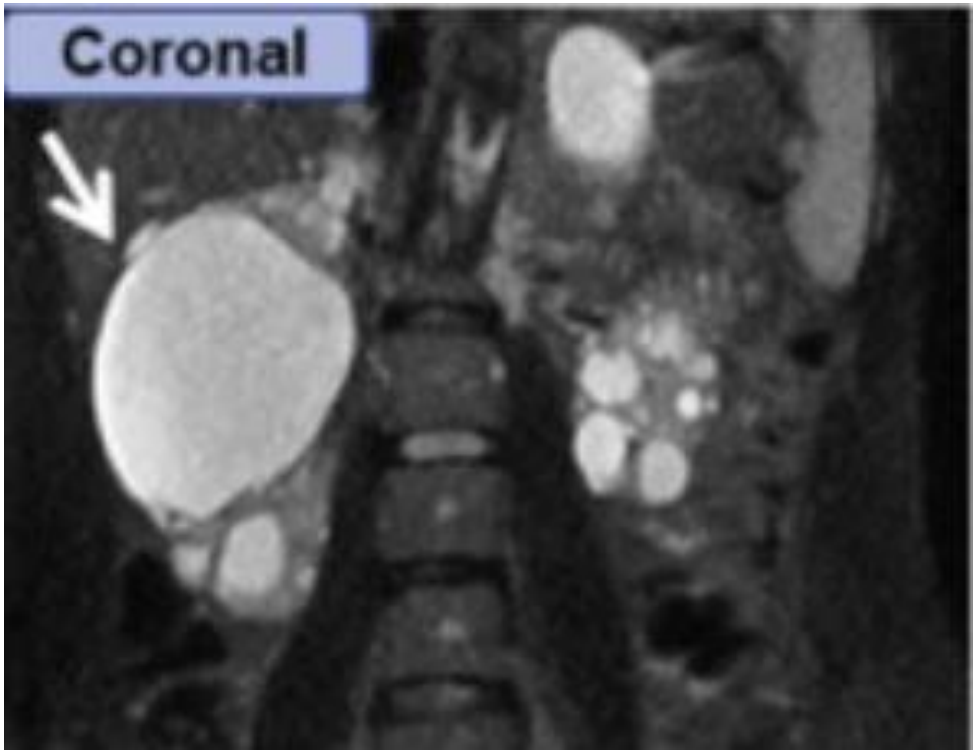
No. of patients												
Lanreotide	153	145	143	142	145	144	138	132	140	136	135	114
Control group	152	148	148	143	144	147	141	140	144	137	142	141

DIPAK-1 (Pays-Bas)

ALADIN-2 (Italie)

LIPS (France)

VII. La sclérothérapie


Coronal

Foam Sclerotherapy for Cyst Volume Reduction in Autosomal Dominant Polycystic Kidney Disease: A Prospective Cohort Study

Kidney Medicine

Methods and Cohort

66 ADPKD patients @ Toronto General Hospital

Mean age 52 yrs
Mean CrCl 84ml/min

≥1 large, non-exophytic cyst (≥5cm)

Foam Sclerotherapy (FS)

US-guided, intra-cystic injection of 3% STS

MRI scan for Total Kidney Volume (TKV)
- baseline
- ≥ 3mo post-FS

Measured CrCl
- Baseline
- 1-3mo
- 4-6mo
- ≥12mo

Findings

21.8% ↓ Volume of **treated** kidneys

Median Before 1138ml

Median After 891ml

CrCl ↑ by ≥ 10ml/min in **4 patients**

Adverse Events

Self-limiting pain (9 patients)

Cyst or urinary tract infection (2 patients)

Conclusion: Foam sclerotherapy is a safe and effective procedure for kidney volume reduction in selected patients with ADPKD. Further studies are needed to assess its effects on kidney blood flow and GFR and to determine the subgroups of patients who are most likely to benefit.

Reference: Foam Sclerotherapy for Cyst Volume Reduction in Autosomal Dominant Polycystic Kidney Disease: A Prospective Cohort Study Iliuta IA, Shi B, Pourafkari M, Akbari P, Bruni G, Hsiao R, Stella SF, Khalili K, Shlomovitz MD, Pei Y. Kidney Medicine, 2019 Visual abstract by Ted Fitzgerald.

Merci pour votre attention