WCN 2021 Overview

By: Shokoufeh Savaj MD

Professor of Iran University of Medical Sciences-Firoozgar Hospital


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Fabry Disease: An Unexpected Cause of RENAL DISEASE
Sunday, April 18, 2021
17:00 CET • Meeting Room 2
MICHAEL MAUER, MD
University of Minnesota Medical School
Minneapolis, MN, USA
ALBERTO ORTIZ, M.D.
Universidad Autónoma de Madrid,
IRSIN, REDINREN
Madrid, Spain
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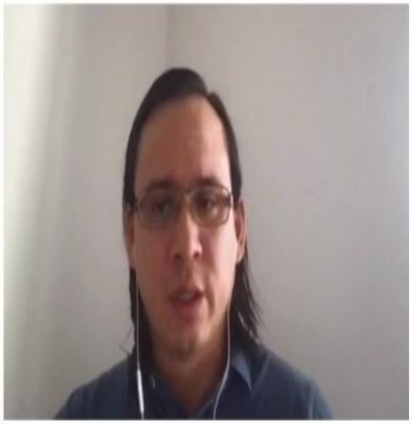

Victor Puelles
(Germany)

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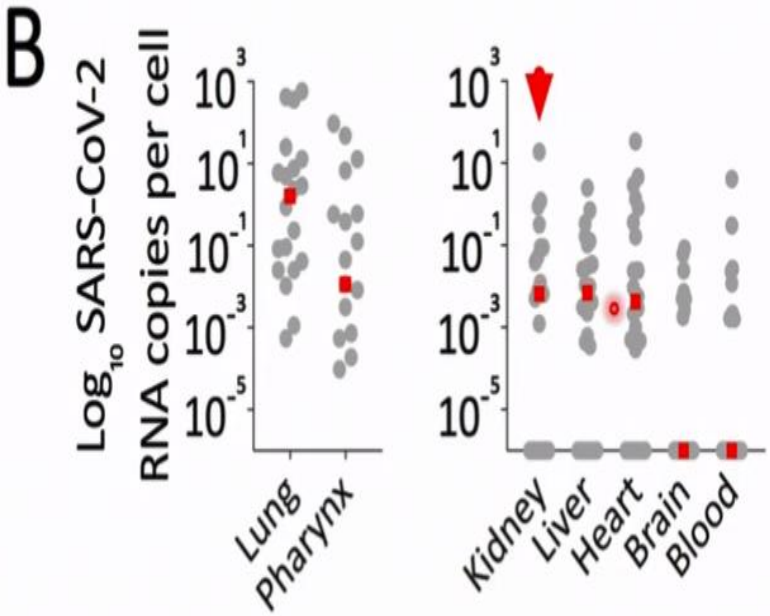
SARS-COV-2 AND THE KIDNEY: DIRECT TARGET OR NOT?

Victor G. Puelles
MD, PhD
III. Department of Medicine, University Medical Centre Hamburg-Eppendorf, Germany

AFTER THE RESPIRATORY TRACT, KIDNEYS SHOWED THE HIGHEST VIRAL LOAD



Puelles et al., NEJM 2020

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Post-Mortem Kidney Pathology Findings in Patients with COVID-19

METHODS

- 42 autopsies of patients who died with COVID-19
- EHR was reviewed for clinical data
- Tissue was evaluated by 2 renal pathologists
- ISH for SARS-CoV-2 was performed in 10 autopsies

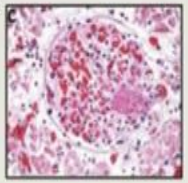
Clinical Characteristics

- Median age 71.5 yrs
- 69% male
- Comorbidities included HTN (73%) & DM (42%)
- 94% developed AKI
- 8 received renal replacement therapy

OUTCOMES

Pathologic Findings

- ATI was the main finding correlating with AKI
- ATI was typically mild
- Focal fibrin thrombi were seen in 6 autopsies
- A single patient had collapsing FSGS
- SARS-CoV-2 not detected by ISH; virions not seen by electron microscopy

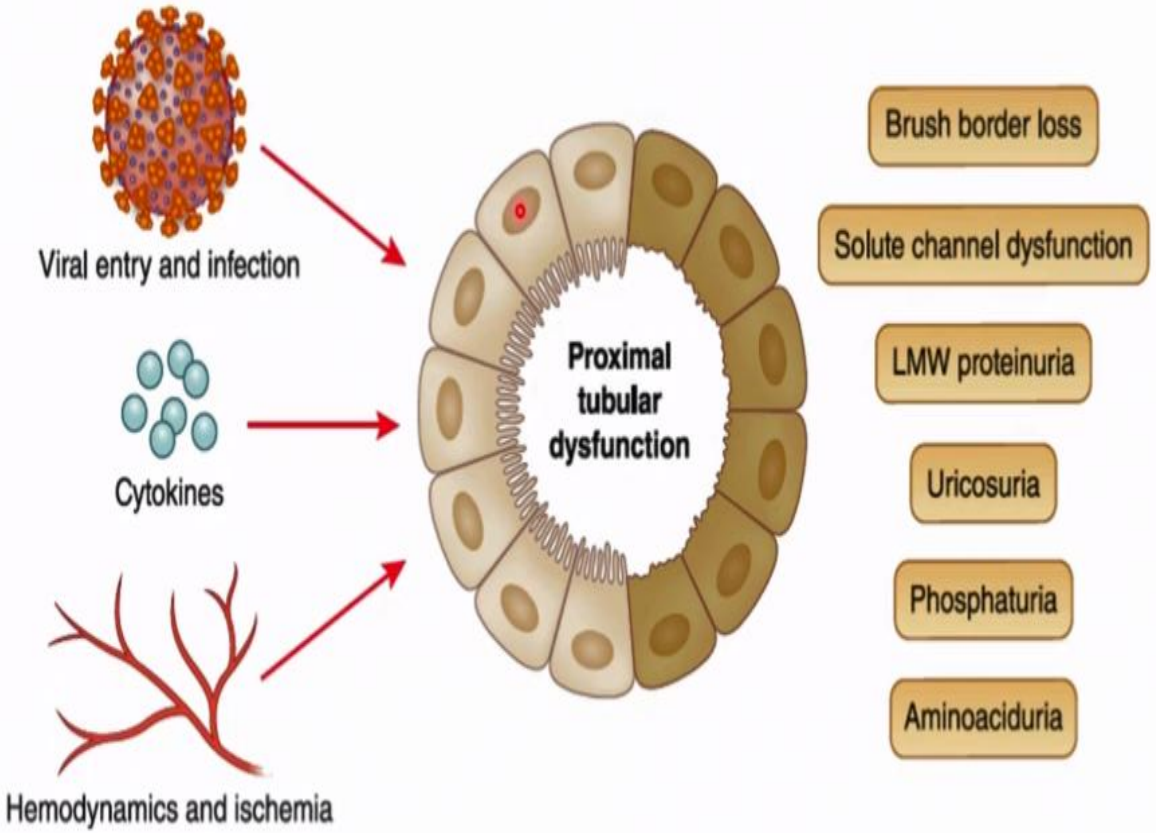


CONCLUSION

Histologic evaluation of the kidneys from autopsies of patients dying with COVID-19 is most notable for the presence of ATI, and the degree of ATI is most commonly mild as compared to the degree of AKI.

doi: 10.1681/ASN.2020050744

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY



Braun et al., Kid Int 2020

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Chandra Theesfeld
(United States)

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SARS-COV-2 RECEPTORS AND THE KIDNEY

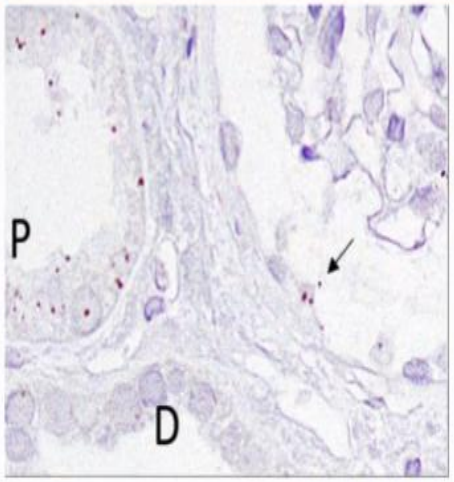
Insight into receptor function from single cell studies

Chandra L Theesfeld, PhD

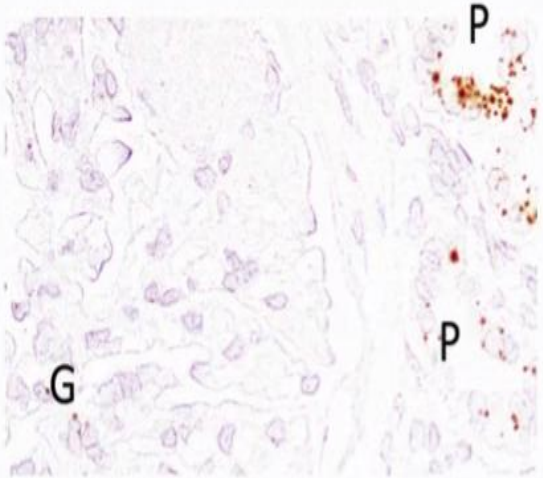
PRINCETON UNIVERSITY

FLATIRON INSTITUTE humanbase MICHIGAN KIDNEY TRANSLATIONAL MEDICINE CORE MICHIGAN MEDICINE UNIVERSITY OF MICHIGAN

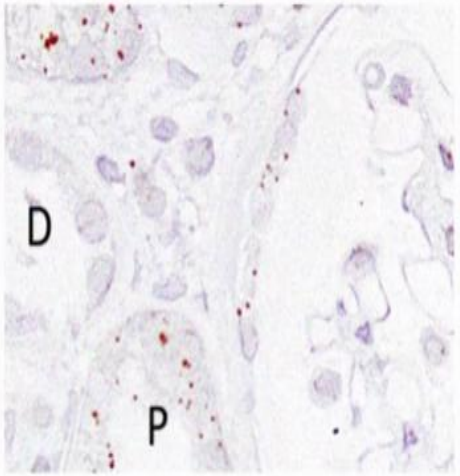
Renal ACE2 Expression in LD and DKD – biopsy in situ



Living Donor Control



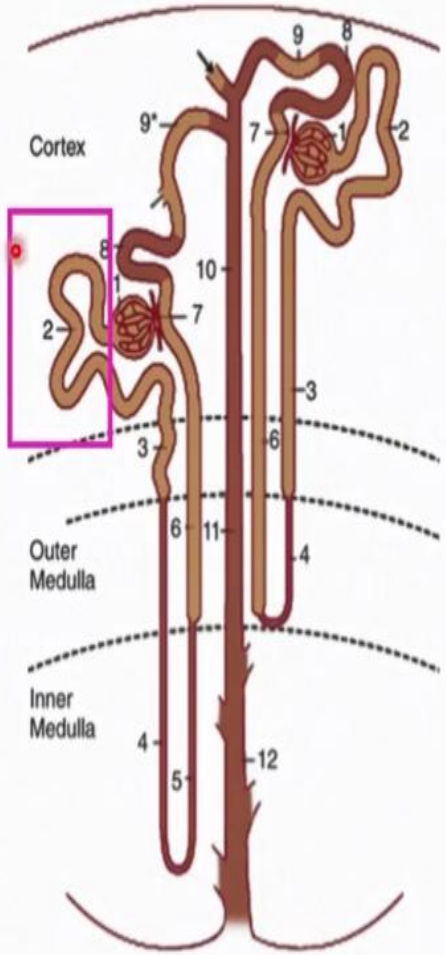
Advanced DKD



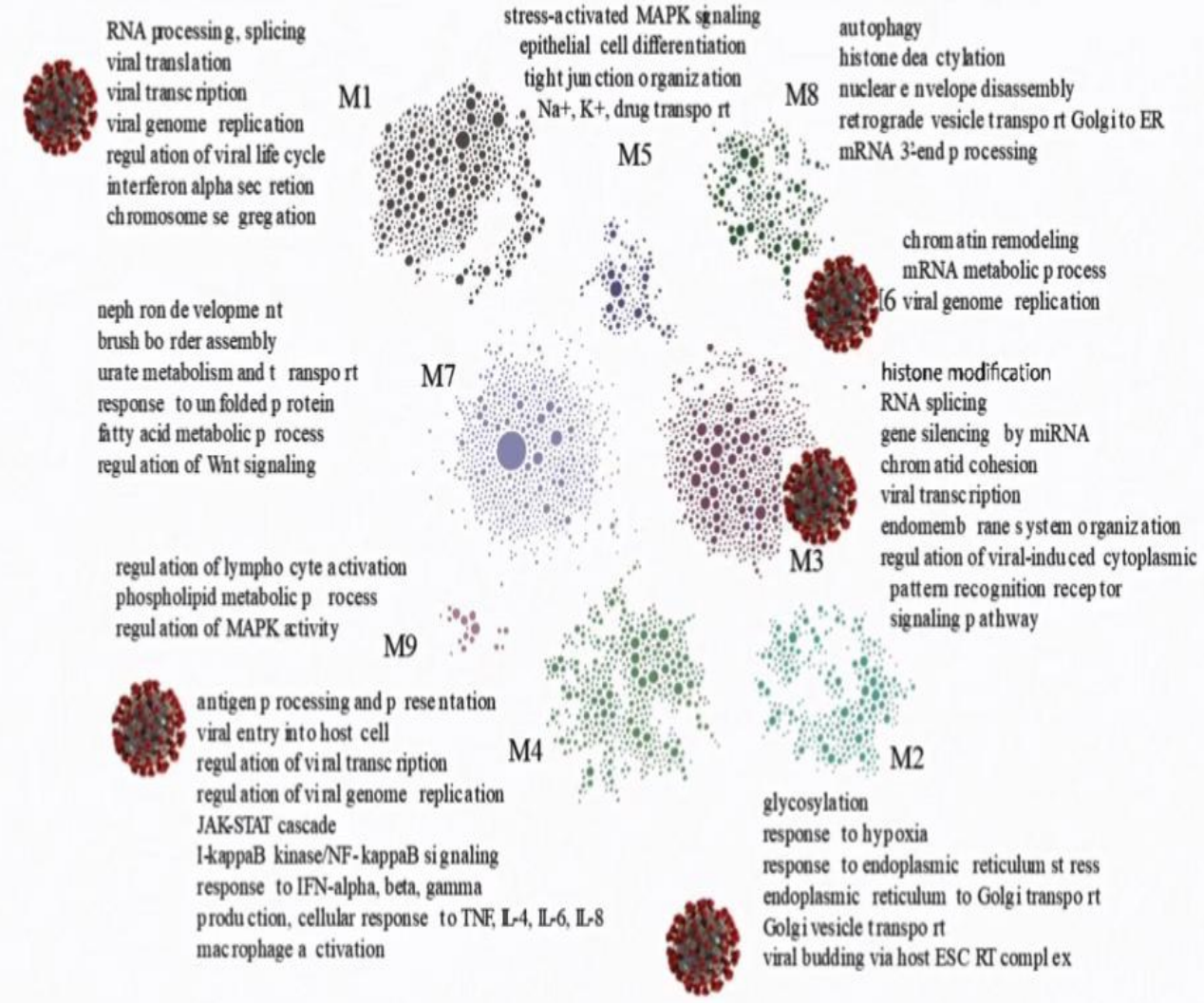
Mild DKD

P Proximal
D Distal
G Glomerulus
↙ Parietal cell

Jeff Hodgin



DKD ACE2+ signature functional summary in PTEC



Enriched immune and viral processes!

Hypothesis: DKD PTEC in a 'primed' state that may make kidneys vulnerable to adverse outcomes

Menon et al., Kidney Int, 2020

Summary

- Molecular network modules induced in ACE2 positive PTEC in DKD (searchable at https://humanbase.flatironinstitute.org/covid19) linked to:
  - viral entry, immune activation, endomembrane reorganization, RNA processing
- Overlap with those seen in cell culture SARS-CoV-2 infected cells.
- ACE2 positive PTEC in COVID-19:
  - consistent ACE2-coregulated expression program:
    - Interaction with the SARS-CoV-2 infection processes likely- recent literature
- The SARS-CoV-2 receptor networks:
  - Starting point for risk stratification and therapeutic strategies for COVID-19 related kidney damage.

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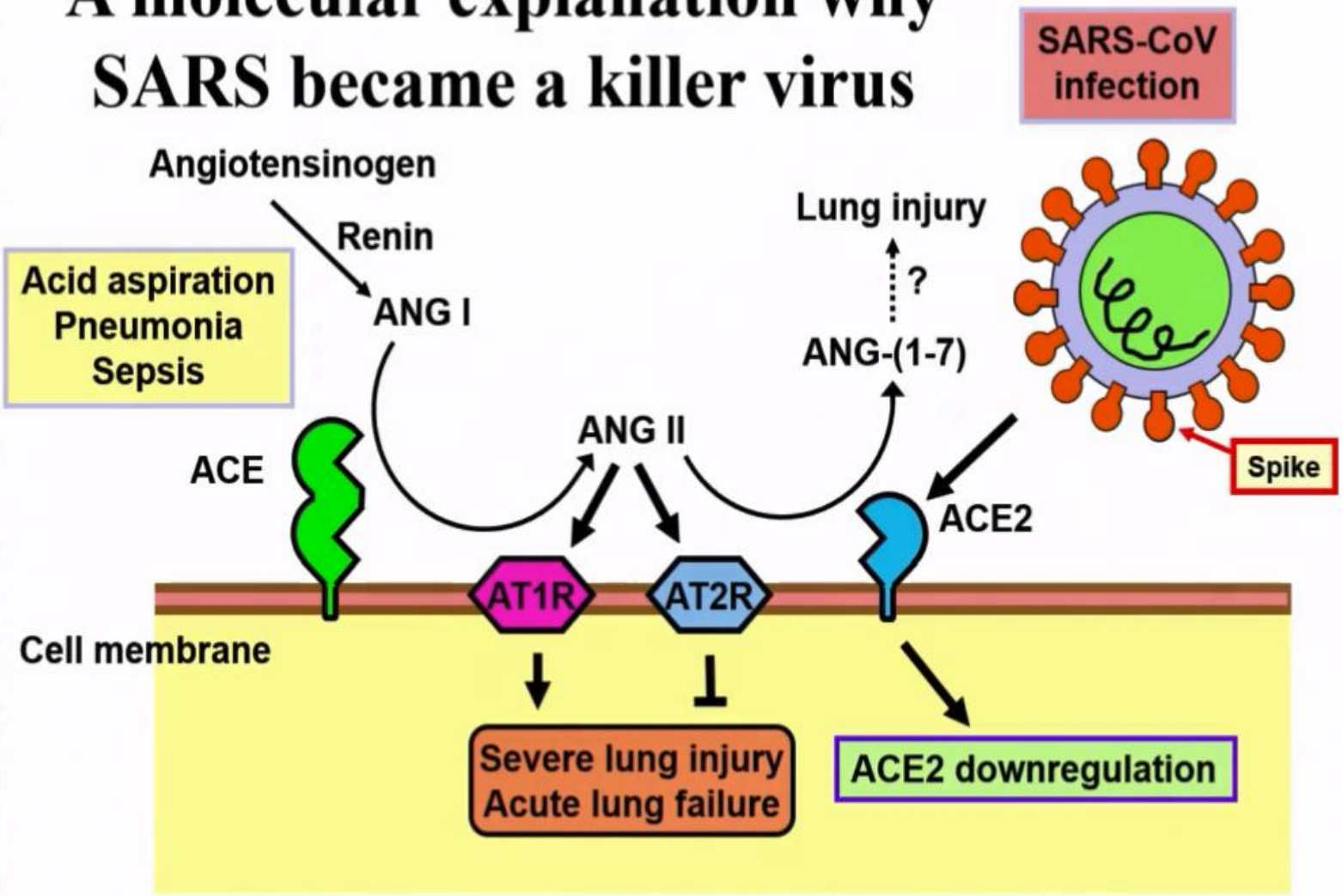
Josef Penninger
(Canada)

ORGANOIDS AS A DRUG SCREENING MODEL FOR COVID-19

Josef Penninger

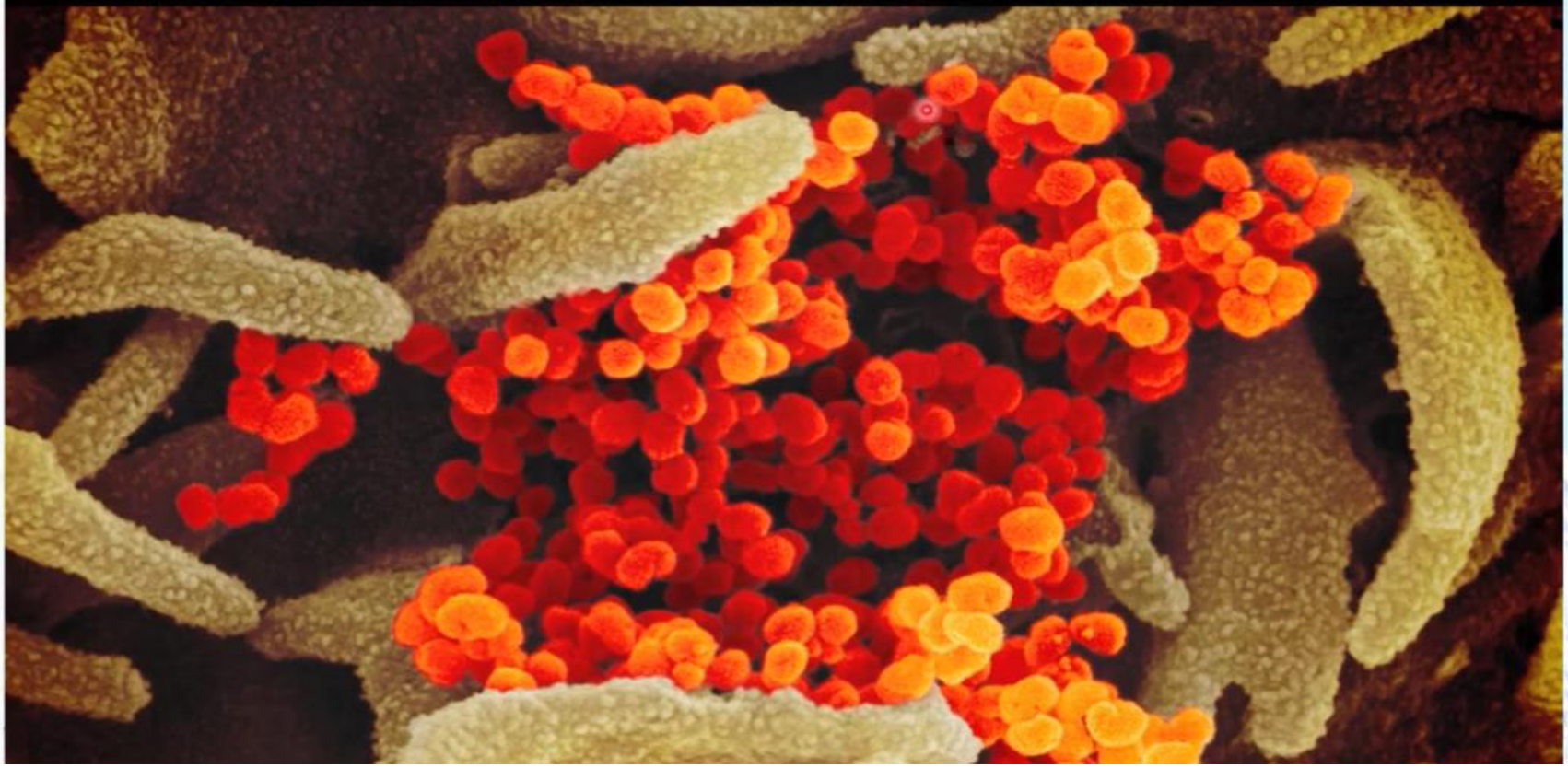
- Thank you so much for
inviting me to this meeting,

A molecular explanation why SARS became a killer virus

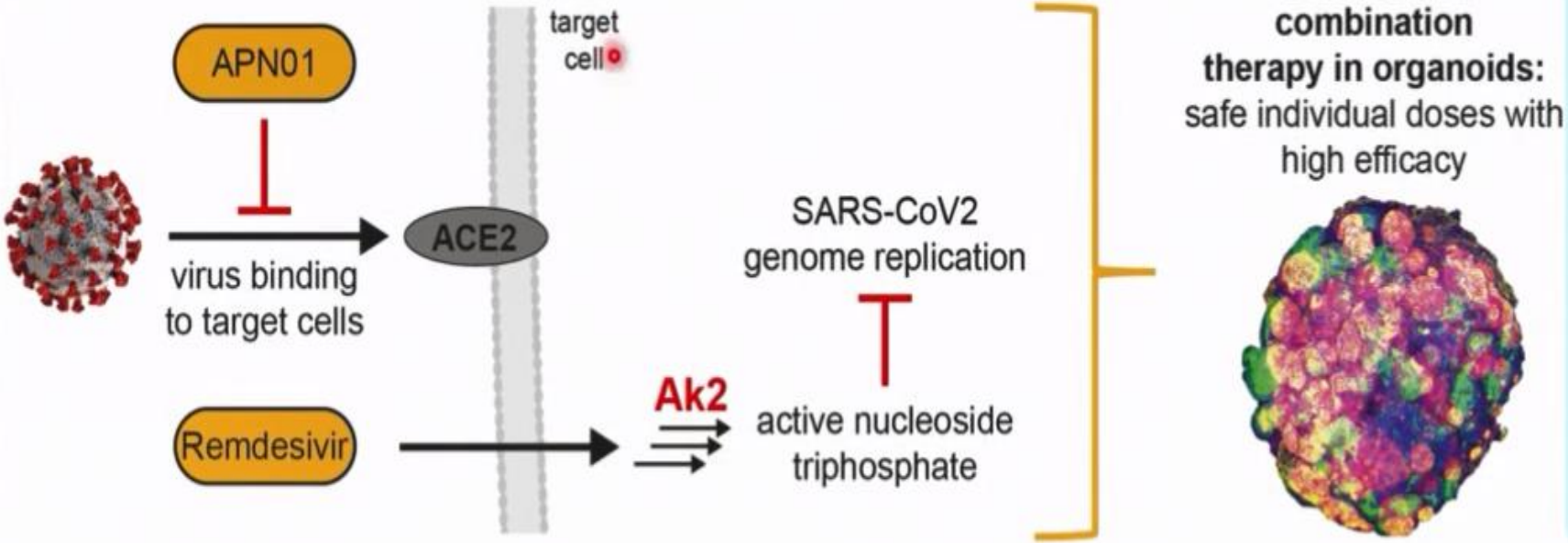


Imai et al Nature; Kuba et al. Nature Med., Imai et al. Cell,
in collaboration with Chengyu Jiang, PUMC, Beijing Art Slutsky, Toronto

Can soluble ACE2 reduce SARS-CoV-2 infections?



Human soluble ACE2 improves the effect of Remdesivir in SARS-CoV2 infection



Monteil et al. EMBO Mol. Med 2020

J. Barratt
(United Kingdom)

NEFECON FOR THE TREATMENT OF IgA NEPHROPATHY IN PATIENTS AT RISK OF PROGRESSING TO END-STAGE RENAL DISEASE: THE NEFIGARD PHASE 3 TRIAL RESULTS

Jonathan Barratt on behalf of the
NefIgArd Study Steering Committee

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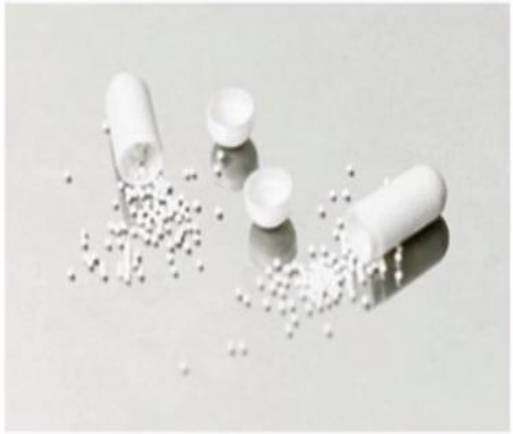
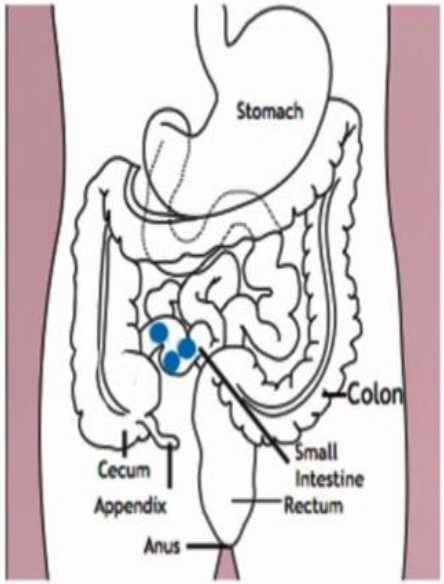
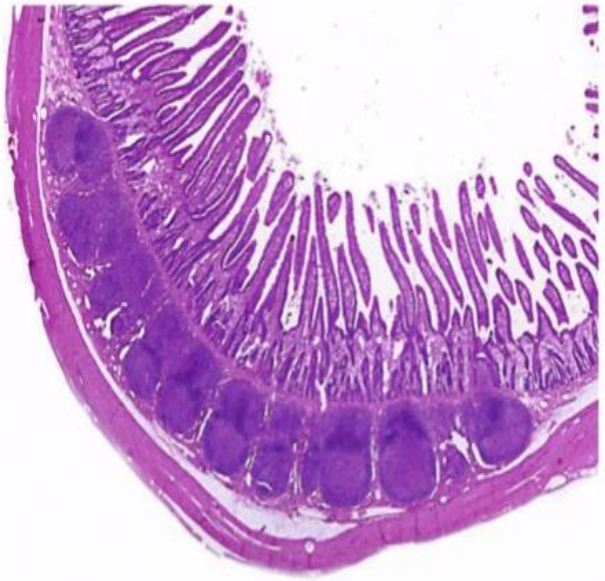
TARGETING THE PEYER'S PATCHES IN THE GALT WITH NEFECON



NEFECON
enteric-coated starch capsules filled with budesonide-coated spheres





NEFECON is an investigational product that has not been approved by regulatory authorities in any jurisdiction. NEFECON is the current proprietary name for the budesonide product candidate from Calliditas; the final proprietary name has not yet been determined

GALT, gut-associated lymphoid tissue. Images taken from Calliditas Therapeutics. Data on File. 2019; http://www.differencebetween.net/science/health/difference-between-jejunum-and-ileum/; Barratt J et al. Kidney Int Rep 020;5:1620

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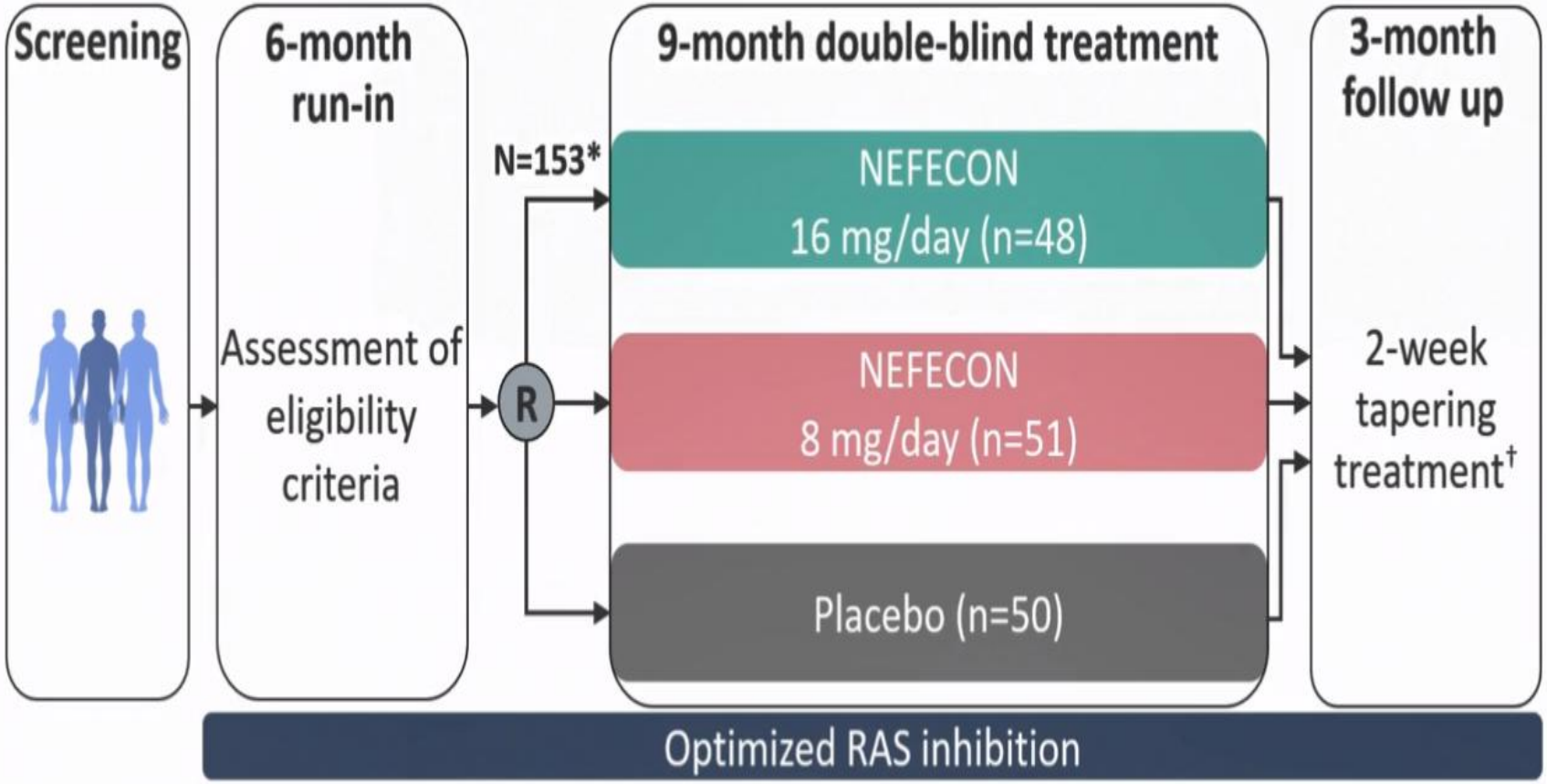
PHASE 2 NEFIGAN TRIAL: TARGETING THE PEYER'S PATCHES IN THE GUT WITH NEFECON IN IgAN



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*Patients were stratified according to baseline UPCR (≤0.9 g/g and >0.9 g/g); †Participants in the Nefecon 16 mg/day group were tapered to 8 mg/day for 2 weeks and participants in the Nefecon 8 mg/day and placebo groups received placebo for 2 weeks

IgAN, immunoglobulin A nephropathy; RAS, renin–angiotensin system; UPCR, urine protein-creatinine ratio

Fellstrom BC *et al. Lancet* 2017;389:2117

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NEFIGARD: KEY INCLUSION AND EXCLUSION CRITERIA

Key inclusion criteria

- Diagnosed IgAN with biopsy verification ≤10 years
- Receiving RAS inhibitor therapy (ACEis and/or ARBs) ≥3 months prior to randomization according to 2012 KDIGO guidelines
- Proteinuria ≥1 g/day or UPCR ≥0.8 g/g (≥90 mg/mmol) in two consecutive measurements
- eGFR 35-90 mL/min/1.73 m^2

Key exclusion criteria

- Recipient of a kidney transplant
- Liver cirrhosis, history of unstable angina, class III or IV congestive HF, clinically significant arrhythmia, unacceptable BP control, poorly controlled T1DM or T2DM
- Taking potent inhibitors of cytochrome P450 3A4 or immunosuppressive medications, other than GCSs, ≤12 months before randomization
- Treated with any systemic GCSs ≤12 months before randomization

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; eGFR, estimated glomerular filtration rate; GCS, glucocorticosteroid; HF, heart failure; IgAN, immunoglobulin A nephropathy; KDIGO, Kidney Disease Improving Global Outcomes; RAS, renin-angiotensin system; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; UPCR, urine protein creatinine ratio

Barratt J, *et al. Kidney Int Rep* 2020;5:1620-1624; Calliditas Therapeutics. Data on File. 2019

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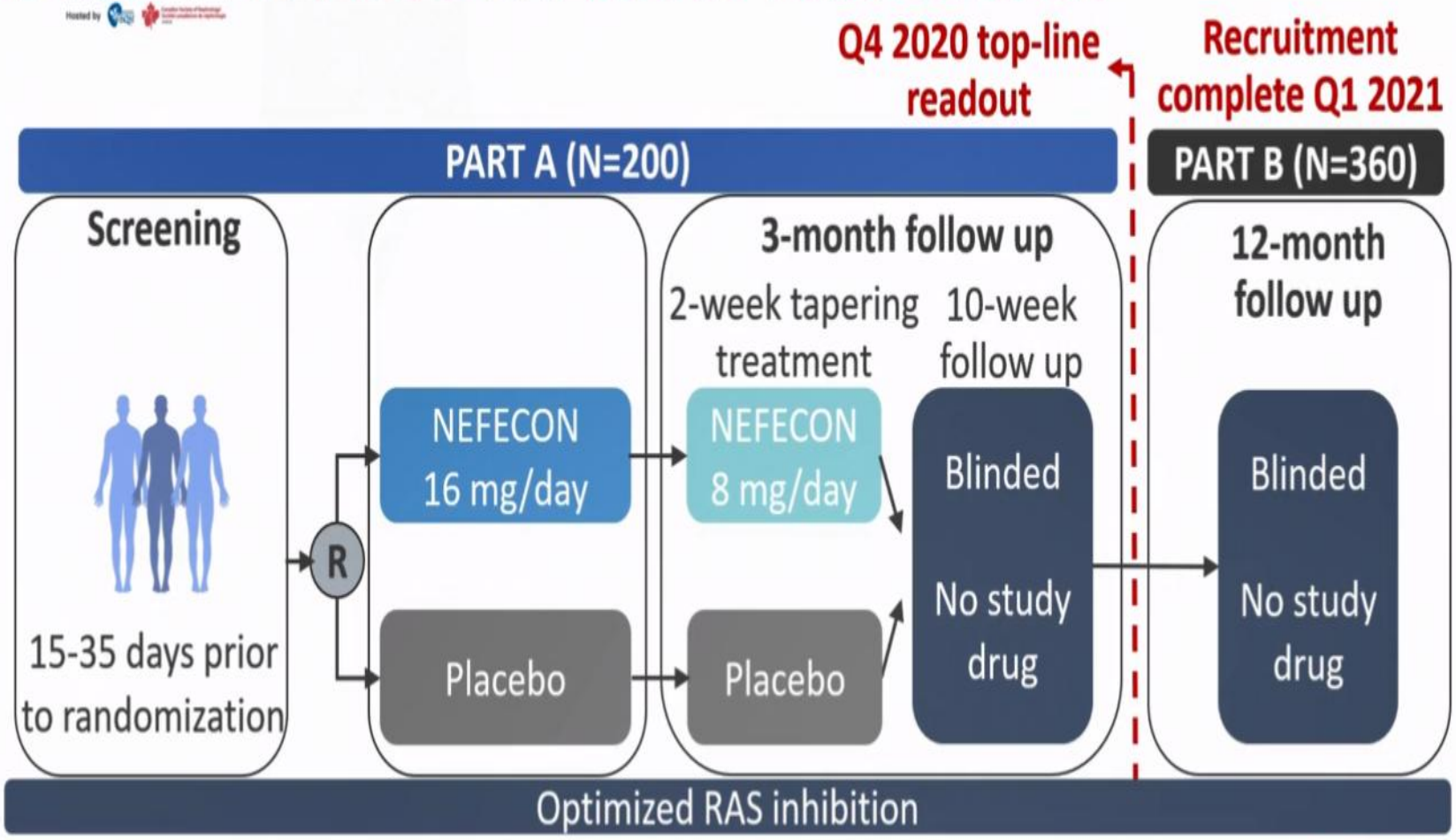
PHASE 3 NEFIGARD TRIAL DESIGN



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eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; IgAN, immunoglobulin A nephropathy; RAS, renin–angiotensin system; UPCR, urine protein-creatinine ratio

Barratt J, *et al. ERA-EDTA* 2020; abstract P0228; Barratt J, *et al. Kidney Int Rep* 2020;5:1620-1624; Calliditas Therapeutics. Data on File. 2019; Calliditas Therapeutics. Press releases. 2017, 2020, 2021.

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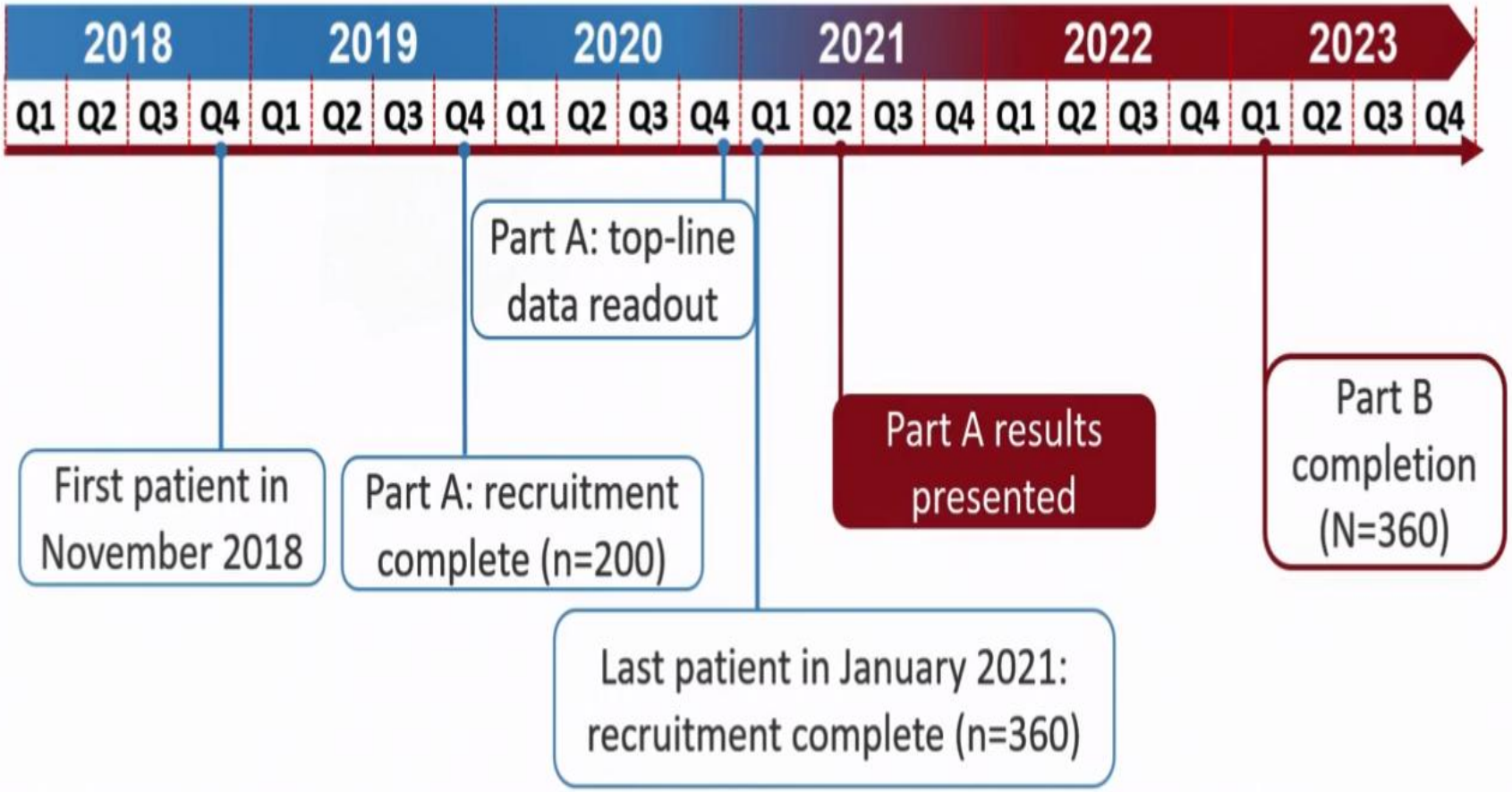
NEFIGARD: TIMELINE



Calliditas Therapeutics. Data on File. 2018. https://www.calliditas.se/en/first-patient-enrolled-in-pivotal-clinical-phase-3-study-nefigard-with-lead-candidate-nefecon-2717/ (accessed Mar 2021); Calliditas Therapeutics. Data on File. 2020. https://www.calliditas.se/en/the-200th-patients-last-visit-completed-in-part-a-of-nefigard-supporting-topline-readout-in-pivotal-phase-3-trial-in-q4-2020-3282/ (accessed Mar 2021); Calliditas Therapeutics. Press release. 2020. https://www.calliditas.se/en/calliditas-therapeutics-to-host-conference-call-on-positive-topline-results-from-pivotal-phase-3-nefigard-trial-3312/ (accessed Mar 2021); Calliditas Therapeutics. Press release. 2021. https://www.calliditas.se/en/calliditas-announces-full-enrollment-of-the-phase-3-nefigard-trial-3385/ (accessed Mar 2021)

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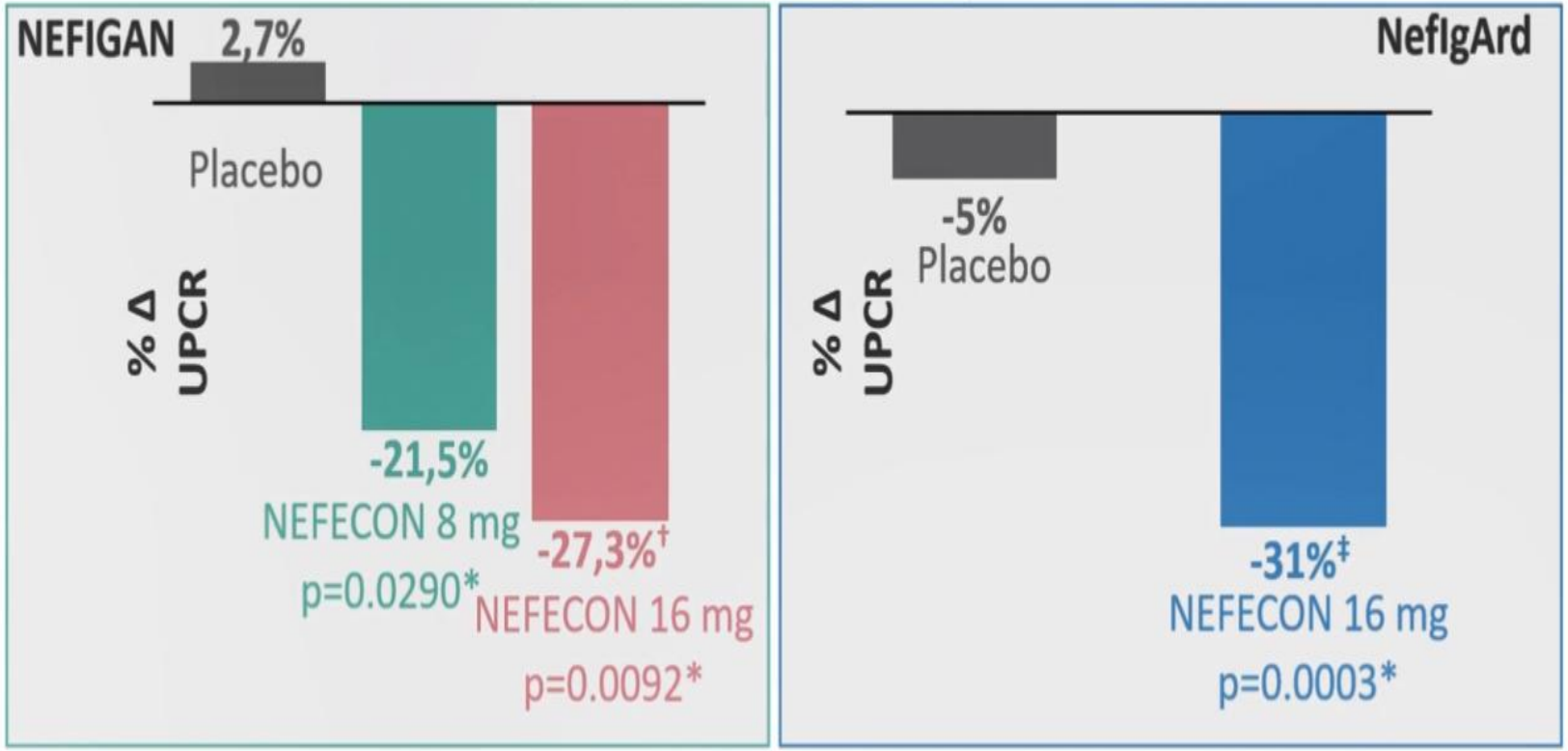
TOP-LINE EFFICACY RESULTS AT 9 MONTHS FROM NEFIGARD CONFIRM FINDINGS FROM NEFIGAN

Primary endpoint: Reduction in proteinuria



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UPCR, urine protein-creatinine ratio. *1-sided p-value; †Compared with placebo, UPCR was reduced by 29.3% in the NEFECON 16 mg/day group after 9 months of treatment; ‡Compared with placebo, UPCR was reduced by 27% in the NEFECON 16 mg/day group after 9 months of treatment

Calliditas Therapeutics. Press release. 2020. https://www.calliditas.se/en/calliditas-therapeutics-to-host-conference-call-on-positive-topline-results-from-pivotal-phase-3-nefigard-trial-3312/ (accessed Jan 2021). Calliditas Therapeutics. Data on File. 2021

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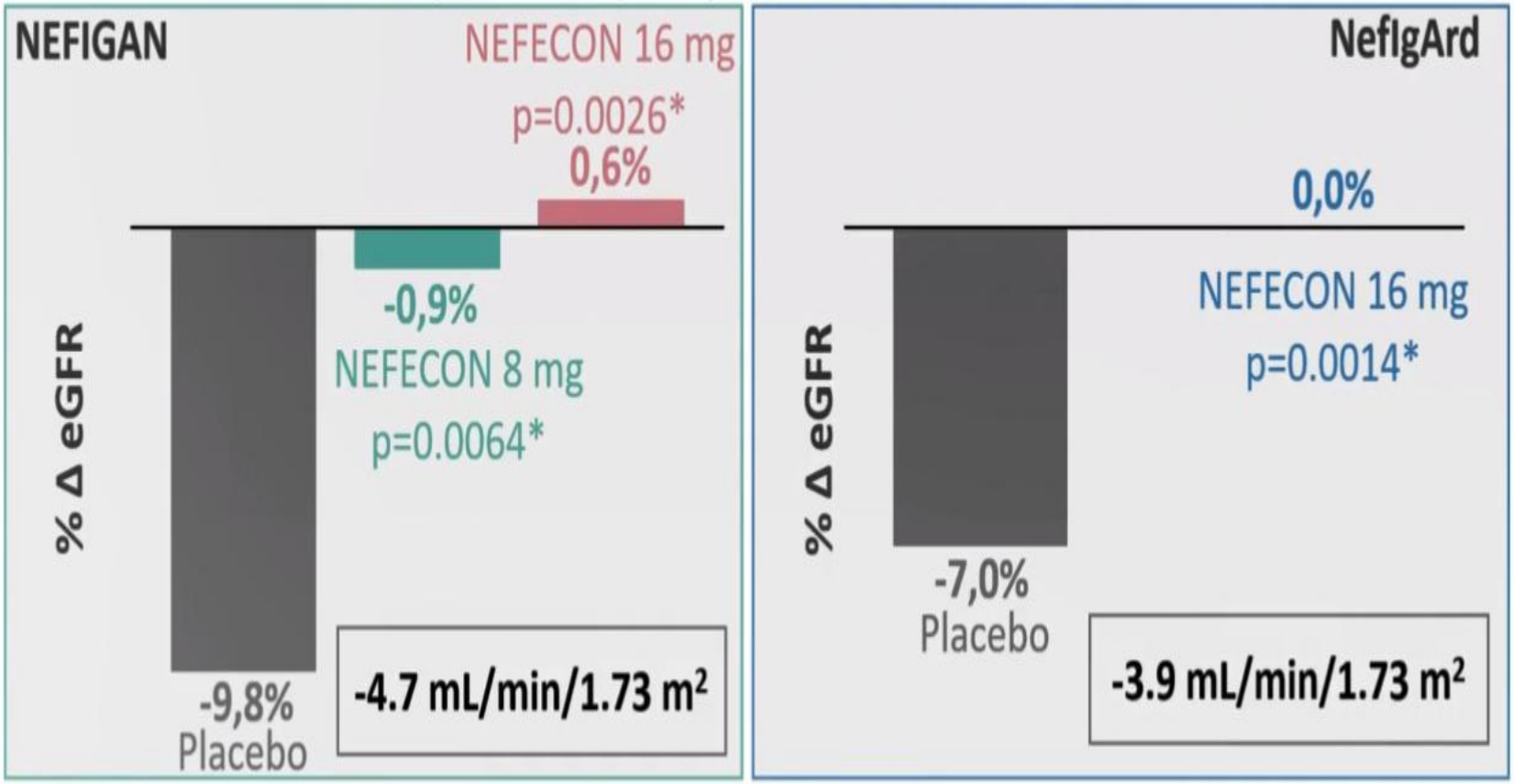
TOP-LINE EFFICACY RESULTS AT 9 MONTHS FROM NEFIGARD CONFIRM FINDINGS FROM NEFIGAN

Key secondary endpoint: Reduction in eGFR



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eGFR, estimated glomerular filtration rate. *1-sided p-value

Calliditas Therapeutics. Press release. 2020. https://www.calliditas.se/en/calliditas-therapeutics-to-host-conference-call-on-positive-topline-results-from-pivotal-phase-3-nefigard-trial-3312/ (accessed Jan 2021). Calliditas Therapeutics. Data on File. 2021

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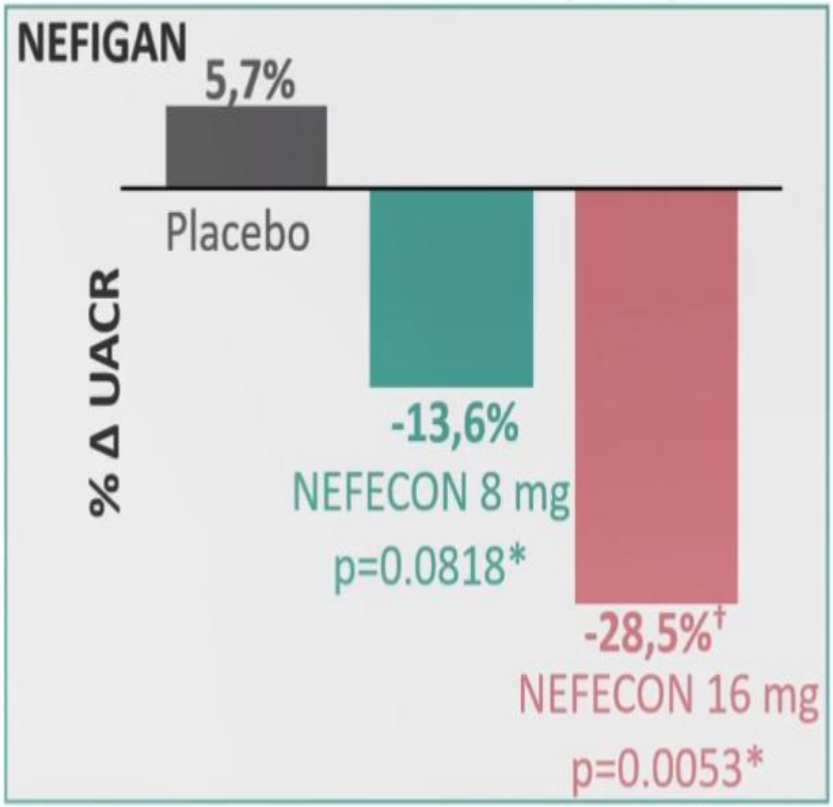
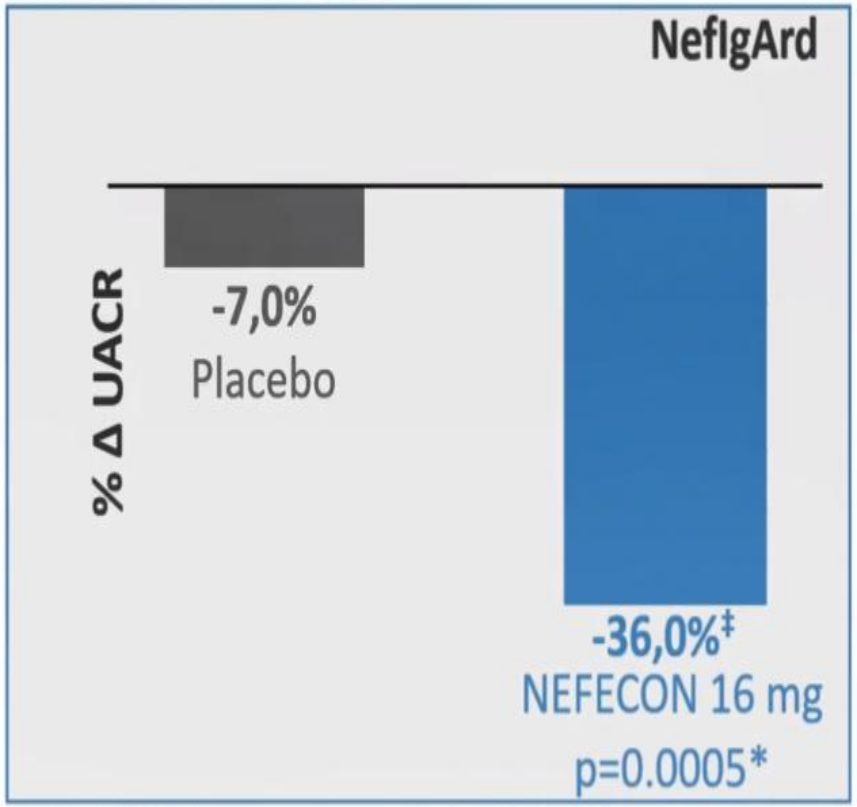
TOP-LINE EFFICACY RESULTS AT 9 MONTHS FROM NEFIGARD CONFIRM FINDINGS FROM NEFIGAN

Secondary endpoint: Reduction in urine albumin





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UACR, urine albumin-to-creatinine ratio. * 1-sided p-value; †Compared with placebo, UACR was reduced by 32% in the NEFECON 16 mg/day group after 9 months of treatment; ‡Compared with placebo, UACR was reduced by 31% in the NEFECON 16 mg/day group after 9 months of treatment

Calliditas Therapeutics. Press release. 2020. https://www.calliditas.se/en/calliditas-therapeutics-to-host-conference-call-on-positive-topline-results-from-pivotal-phase-3-nefigard-trial-3312/ (accessed Jan 2021). Calliditas Therapeutics. Data on File. 2021

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CONCLUSIONS

- The NefIgArd study met its primary endpoint with a favorable safety profile
  - A significant reduction in proteinuria and eGFR stabilization was observed
  - The tolerability and safety profile of Nefecon is consistent with the active ingredient
- The phase 2b and phase 3 clinical trials provide highly consistent evidence of efficacy of Nefecon in a broad range of patients with IgA nephropathy
- This trial will continue in order to verify the clinical benefit of Nefecon and measure long-term renal benefit over 2 years

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eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; IgAN, immunoglobulin A nephropathy; UPCR, urine protein creatinine ratio

Calliditas Therapeutics. Press release. 2020. https://www.calliditas.se/en/calliditas-therapeutics-to-host-conference-call-on-positive-topline-results-from-pivotal-phase-3-nefigard-trial-3312/ (accessed Jan 2021); Calliditas Therapeutics. Data on File. 2019-2021

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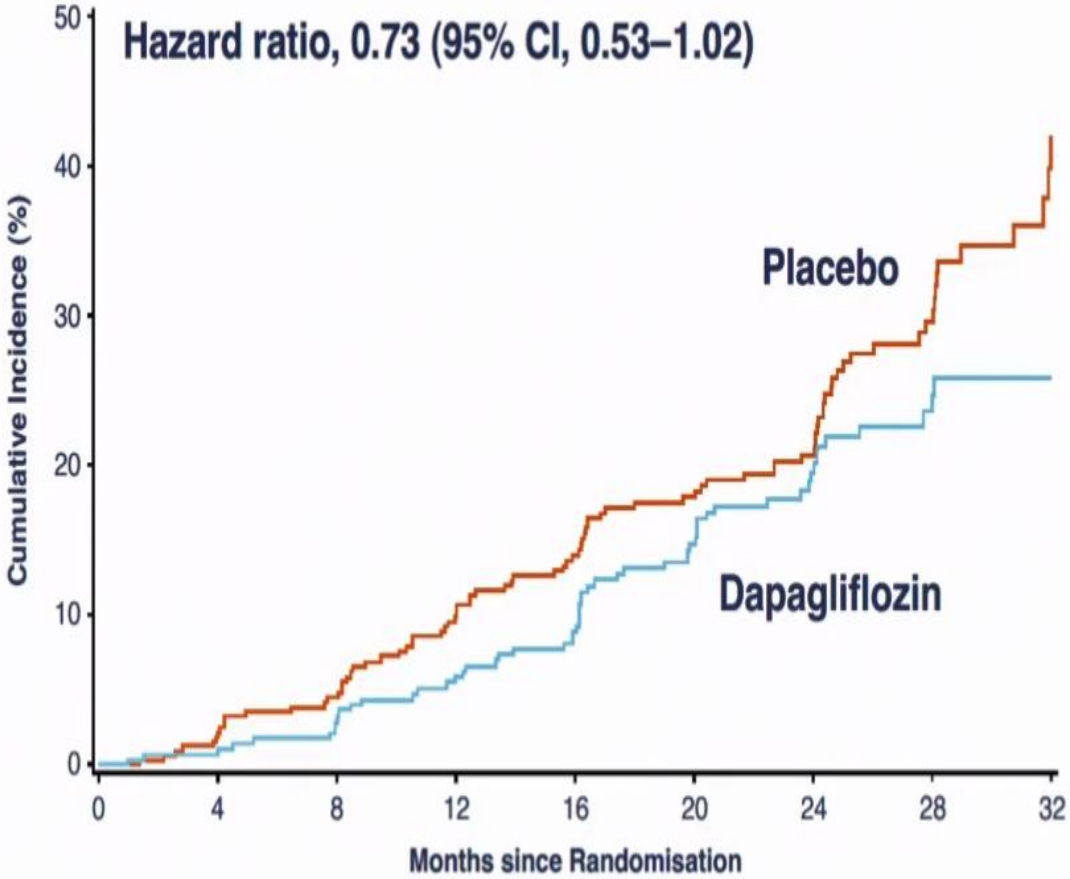
G.M. Chertow
(United States)

Effects of Dapagliflozin in Stage 4 Chronic Kidney Disease: Findings from the DAPA-CKD Trial

Glenn M Chertow, Priya Vart, Niels Jongs, Robert D Toto, Jose Luis Gorriz, Fan Fan Hou, John J V McMurray, Ricardo Correa-Rotter, Peter Rossing, C David Sjöström, Bergur V Stefánsson, Anna Maria Langkilde, David C Wheeler, Hiddo J L Heerspink, for the DAPA-CKD Trial Committees and Investigators

DAPACKD | umcg | UCL DEPARTMENT OF RENAL MEDICINE

Primary composite outcome in Stage 4 CKD



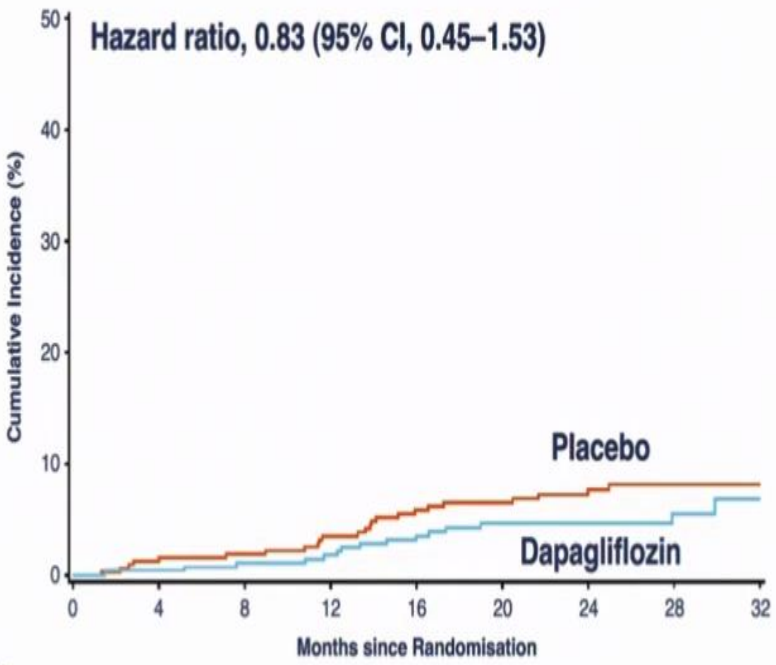
No. at Risk									
Dapagliflozin	293	274	262	249	239	206	135	69	21
Placebo	331	300	285	265	244	223	163	88	29

DAPACKD

Composite outcome of sustained ≥50% eGFR decline, end-stage kidney disease, kidney or cardiovascular death

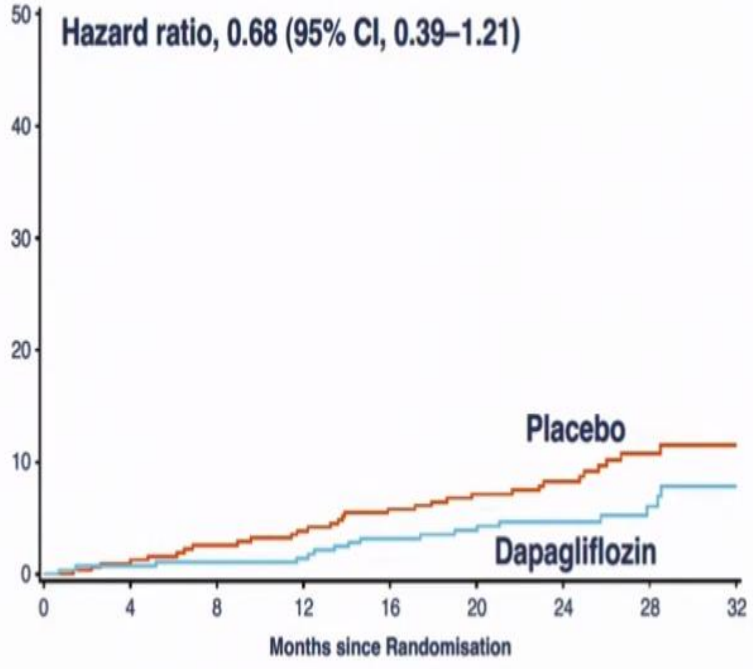
Secondary outcomes in Stage 4 CKD

CV death or heart failure hospitalization



No. at Risk									
Dapagliflozin	293	279	277	275	269	256	194	113	35
Placebo	331	306	300	293	284	270	206	124	43

All-cause death



	293	280	279	278	273	262	198	116	37
	331	307	303	299	293	279	218	129	48

DAPACKD

CV, cardiovascular

Conclusion

- We have already seen that, in patients with CKD with and without type 2 diabetes, dapagliflozin compared to placebo[1]:
  - Reduced the risk of kidney failure
  - Reduced the risk of death from cardiovascular causes or hospitalization for heart failure
  - Prolonged survival

- In this pre-specified analysis, we found that dapagliflozin can safely reduce major kidney and cardiovascular events and attenuate progressive loss of eGFR in patients with stage 4 CKD with and without type 2 diabetes

DAPACKD

1. Heerspink HJL. et al. N Engl J Med. 2020;383:1436-1446.

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H. Lambers Heerspink
(The Netherlands)

Effects of Dapagliflozin on Major Adverse Kidney Events in Patients with IgA Nephropathy

Hiddo J.L. Heerspink, David C. Wheeler, Robert D. Toto, Bergur V. Stefansson, Niels Jongs, Glenn M. Chertow, Tom Greene, Fan Fan Hou, John J. V. McMurray, Roberto Pecoits-Filho, Ricardo Correa-Rotter, Peter Rossing, C. David Sjöström, Kausik Umanath, and Anna Maria Langkilde, for the DAPA-CKD Trial Committees and Investigators

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Objectives – secondary analysis in patients with IgA nephropathy

- In this **pre-specified secondary analysis** from DAPA-CKD, the effect of dapagliflozin versus placebo was assessed for primary and secondary outcomes in those with **IgA nephropathy**

- **Primary outcome**
  - Composite outcome of sustained ≥50% eGFR decline, end-stage kidney disease, kidney or cardiovascular death

- **Secondary outcomes**
  - Composite outcome of sustained ≥50% eGFR decline, end-stage kidney disease, or kidney deat

- **Exploratory outcomes**
  - Rate of eGFR decline (eGFR slope)
  - Urinary albumin:creatinine ratio

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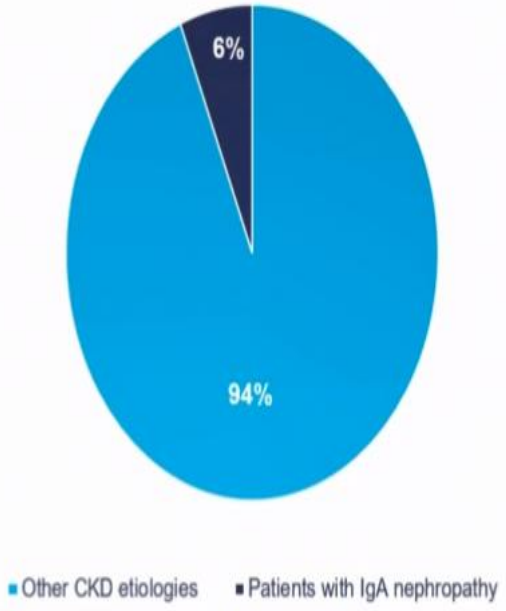
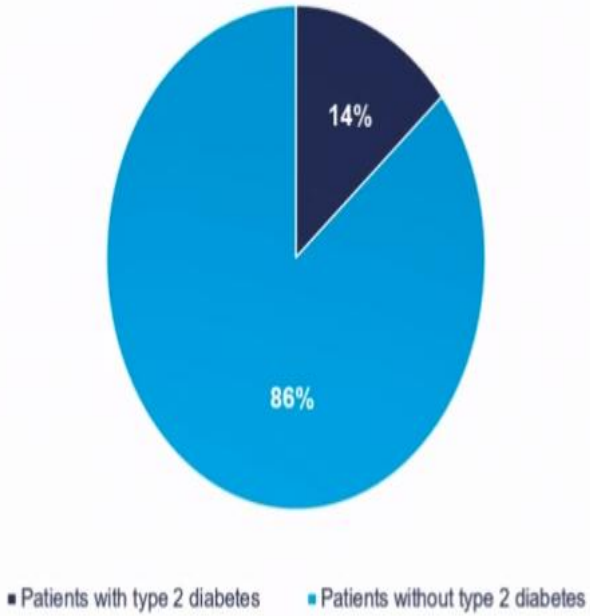
IgA, immunoglobulin A; eGFR, estimated glomerular filtration rate.

Patients with IgA nephropathy in the DAPA-CKD study

Participants with IgA nephropathy in the DAPA-CKD population



Participants with IgA nephropathy: Diabetes status at baseline



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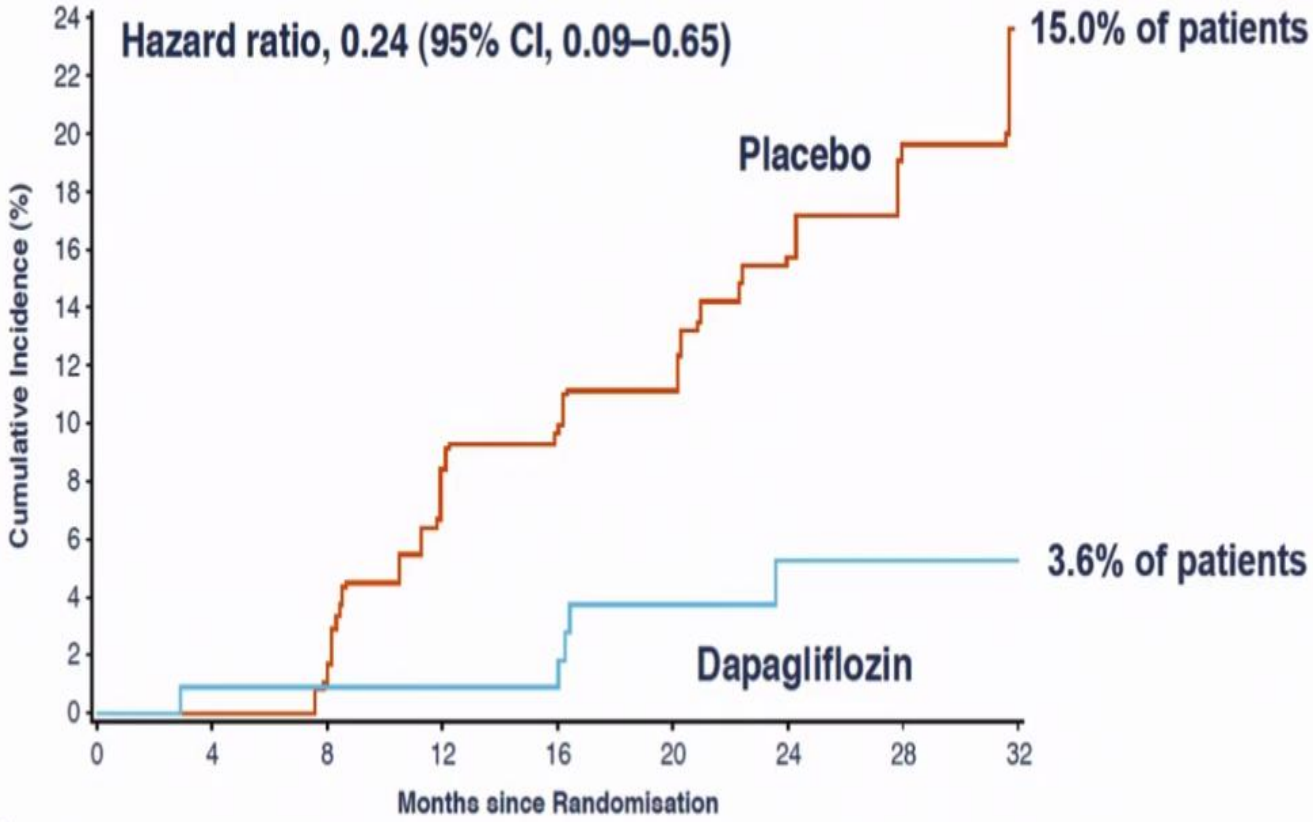
IgA, immunoglobulin A

Kidney-specific outcome in patients with IgA nephropathy



No. at Risk									
Dapagliflozin	137	107	106	105	104	98	61	43	17
Placebo	133	113	108	101	96	92	51	32	19

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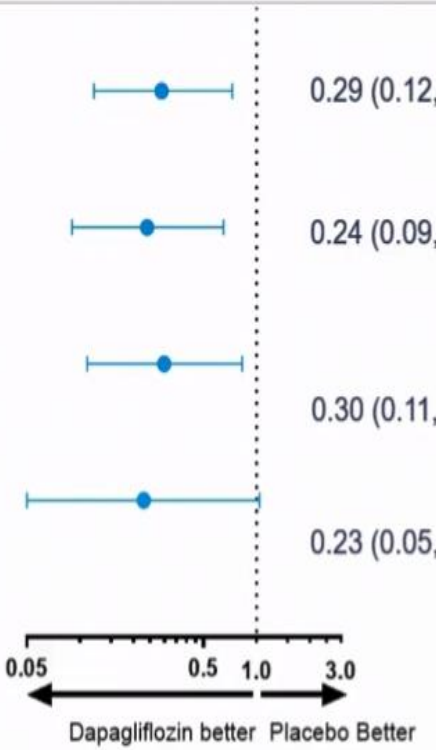
Kidney-specific outcome comprised sustained ≥50% decline in eGFR, onset of end-stage kidney disease, or death from a kidney cause.
IgA, immunoglobulin A; eGFR, estimated glomerular filtration rate

Key endpoints in patients with IgA nephropathy

	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Hazard Ratio (95% CI)	P-value
	No. of participants/total no.		Events/100 patient-years			
Composite primary endpoint	6/137	20/133	2.5	8.8	0.29 (0.12, 0.73)	0.005
Composite kidney-specific endpoint	5/137	20/133	2.1	8.8	0.24 (0.09, 0.65)	0.002
ESKD	5/137	16/133	2.1	6.9	0.30 (0.11, 0.83)	0.014
Composite endpoint of chronic dialysis, kidney transplant and kidney death	2/137	10/133	0.8	4.0	0.23 (0.05, 1.04)	NC



Composite primary endpoint: Composite of sustained ≥50% decline in eGFR, onset of ESKD, or death from a kidney or cardiovascular cause.
Composite kidney-specific endpoint: Composite of sustained ≥50% decline in eGFR, onset of ESKD, or death from a kidney cause.
ESKD: maintenance dialysis for ≥28 days, kidney transplantation, or eGFR <15 mL/min/1.73 m^2 confirmed by a second measurement after 28 days
ESKD, end-stage kidney disease

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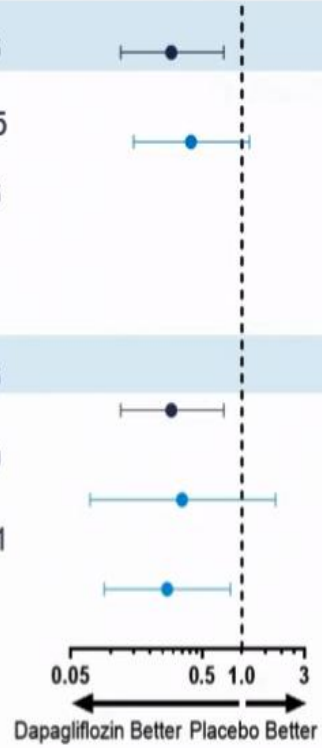
Primary composite endpoint by pre-specified baseline eGFR and UACR subgroups in patients with IgA nephropathy

	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Hazard Ratio	Absolute risk difference
	No. of participants/total no.		Events/100 patient years		(95% CI)	(95% CI)
eGFR						
Overall	6/137	20/133	2.5	8.8	0.29 (0.12, 0.73)	-10.7 (-17.6, -3.7)
<45 mL/min/1.73m^2	6/76	12/70	4.8	11.5	0.41 (0.15, 1.14)	-9.2 (-20.0, 1.5)
≥45 mL/min/1.73m^2	0/61	8/63	0.0	6.6	0.0 (0.0, ∞)	NC
UACR						
Overall	6/137	20/133	2.5	8.8	0.64 (0.50, 0.82)	-10.7 (-17.6, -3.7)
≤1000 mg/g	2/77	5/73	1.5	3.9	0.72 (0.50, 1.04)	-4.3 (-11.0, 2.5)
>1000 mg/g	4/60	15/60	4.0	15.1	0.64 (0.46, 0.89)	-18.3 (-31.0, -5.7)



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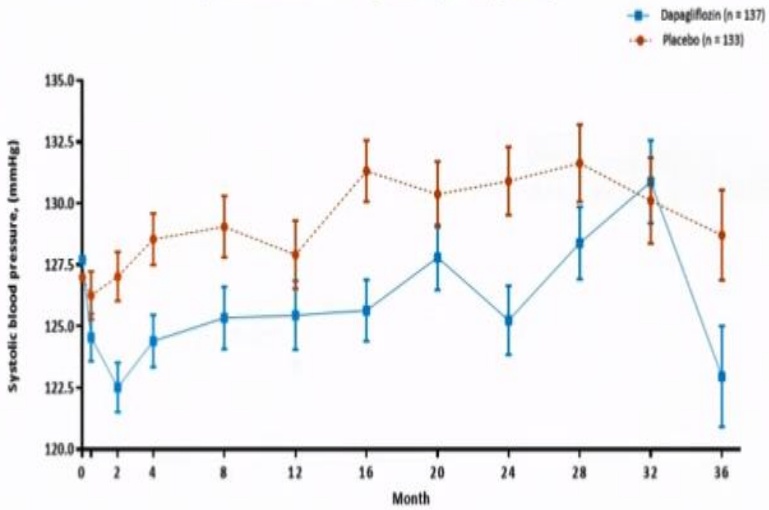
eGFR, estimated glomerular filtration rate; NC, not calculable; UACR, urinary albumin-to-creatinine ratio

Changes over time in blood pressure in patients with IgA nephropathy

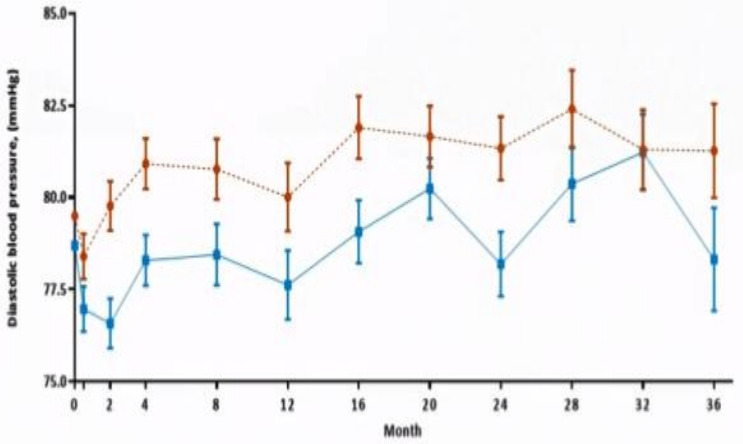
Change in systolic blood pressure over time in patients with IgA nephropathy



Participants per timepoint												
Dapagliflozin	137	131	122	122	105	103	103	102	86	59	39	14
Placebo	133	129	128	126	110	106	105	100	90	51	35	21

Mean treatment effect (95%CI): 3.5 (5.7, 1.3)

Change in diastolic blood pressure over time in patients with IgA nephropathy



Participants per timepoint												
Dapagliflozin	137	131	122	122	105	103	103	102	86	59	39	14
Placebo	133	129	128	126	110	106	105	100	90	51	35	21

Mean treatment effect (95%CI): 2.2 (3.7, 0.8)

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Error bars represent standard error.
eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio

Conclusion

- This pre-specified analysis of the DAPA-CKD trial demonstrated that in patients with IgA nephropathy and when added to RAAS therapy dapagliflozin:
  - Reduced the risk of the primary outcome
  - Reduced the rate of eGFR decline
  - Decreased UACR over time
  - Was safe and well tolerated

- Dapagliflozin may be a novel therapeutic option to slow kidney function decline in patients with IgA nephropathy

1. *Heerspink HJL. et al. N Engl J Med. 2020;383:1436-1446.*

IgA, immunoglobulin A; CKD, chronic kidney disease; RAAS, renin-angiotensin-aldosterone system

DAPACKD

Proteinuria Targets in Focal Segmental Glomerulosclerosis (FSGS)

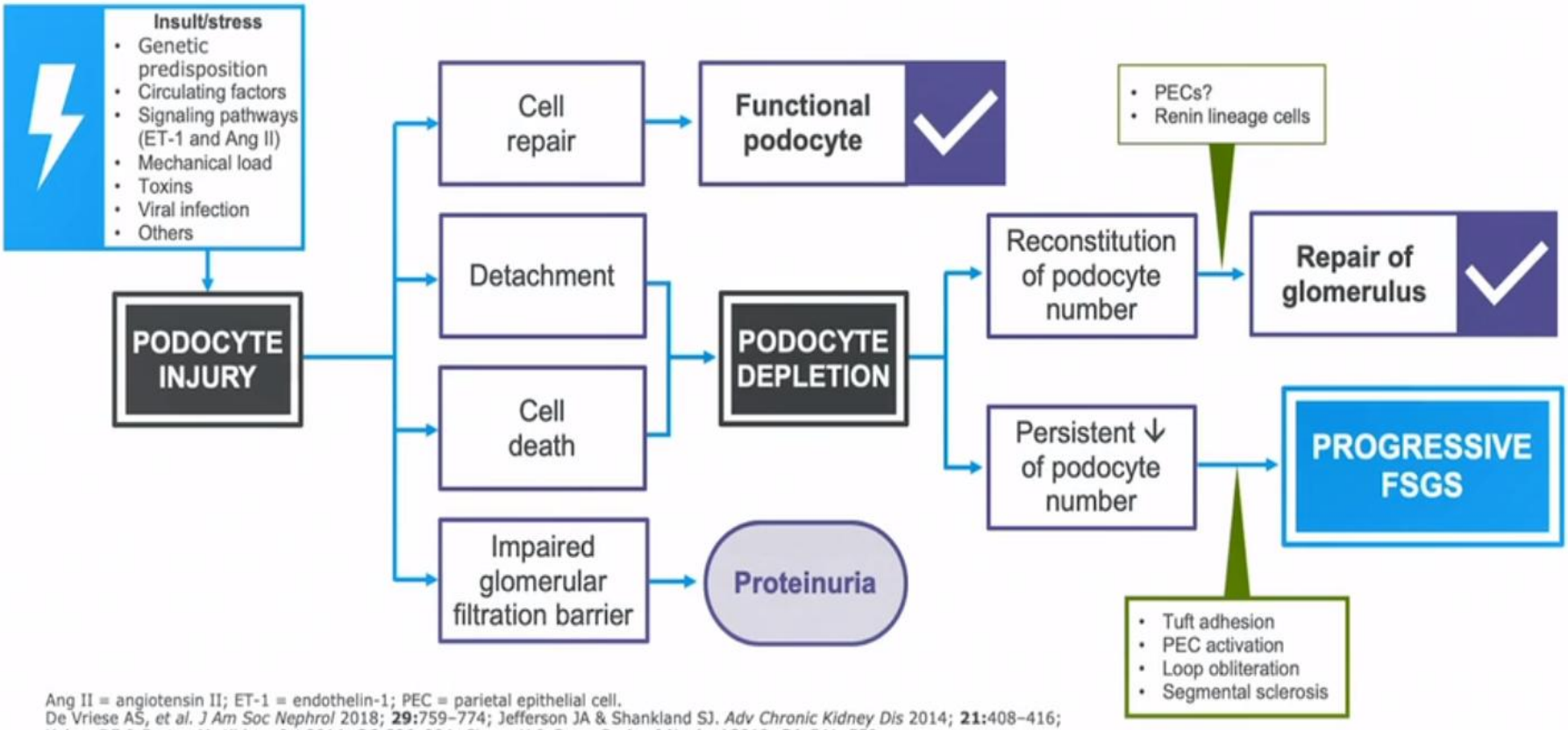
Dr. Laura Mariani, MD, MSCE

TRAVERE THERAPEUTICS

MA-368

TRAVERE THERAPEUTICS

FSGS Is Caused by a Continuous and Sustained Podocyte Injury



Ang II = angiotensin II; ET-1 = endothelin-1; PEC = parietal epithelial cell.

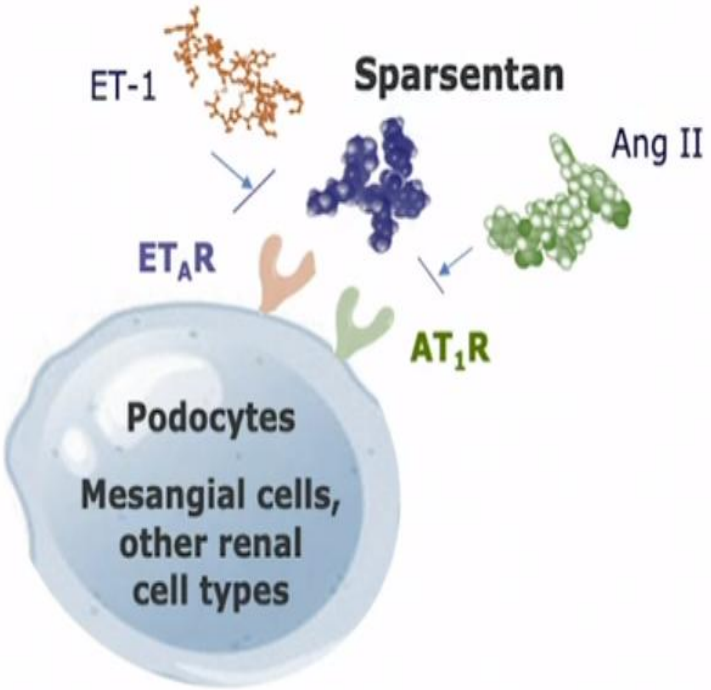
De Vriese AS, *et al. J Am Soc Nephrol* 2018; **29**:759–774; Jefferson JA & Shankland SJ. *Adv Chronic Kidney Dis* 2014; **21**:408–416; Kohan DE & Barton M. *Kidney Int* 2014; **86**:896–904; Siragy H & Carey R. *Am J Nephrol* 2010; **31**:541–550; Wickman L, *et al. J Am Soc Nephrol* 2013; **24**:2081–2095.

TRAVERE THERAPEUTICS

Incorporating the Modified Partial Remission Endpoint into Clinical Trial Design: The Effectiveness and Safety of Sparsentan Is Being Evaluated in Patients with FSGS*

Sparsentan dual mechanism of action[1–3]*

High-affinity antagonist of both the endothelin type A (ET_AR) and angiotensin II type 1 (AT_1R) receptors



- **ET_AR:** emerging evidence of protective effects in kidney and CV system in patients with type 2 diabetes and CKD (atrasentan, SONAR clinical trial)[4,5]
- **ARB:** established evidence of protective effects in kidney and CV system, particularly in patients with diabetic nephropathy[5,6]

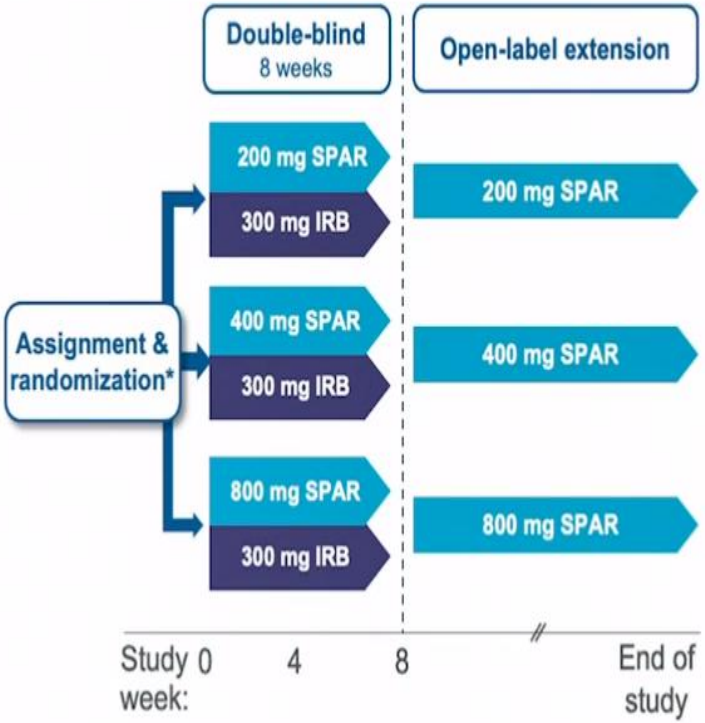
* Sparsentan is an investigational compound for treatment of primary or genetic FSGS and IgAN. It is not approved by any regulatory agency.

Ang II = angiotensin II; ARB = angiotensin receptor blocker; AT_1R = angiotensin II receptor type 1; CV = cardiovascular; ET_AR = endothelin receptor type A; ET-1 = endothelin 1.

1. Kowala MC, *et al. J Pharmacol Exp Ther* 2004; **309:**275–284; 2. Komers R & Plotkin H. *Am J Physiol Regul Integr Comp Physiol* 2016; **310:**R877–R884; 3. Trachtman H, *et al. J Am Soc Nephrol* 2018; **29:**2745–2754; 4. Heerspink HJL, *et al. Lancet* 2019; **393:**1937–1947; 5. Palmer SC *et al. Lancet* 2015; **385:**2047–2056; 6. Dezsi CA. *Am J Cardiovasc Drugs* 2016; **16:**255–266.

The DUET Study Utilized the Modified Partial Remission Endpoint to Evaluate the Efficacy of Sparsentan in FSGS

Phase 2 trial evaluating the efficacy and safety of sparsentan, compared with an angiotensin receptor blocker (irbesartan), to reduce proteinuria in patients with primary or genetic FSGS



Primary endpoint

Change in UP/C from baseline to Week 8

Secondary endpoint

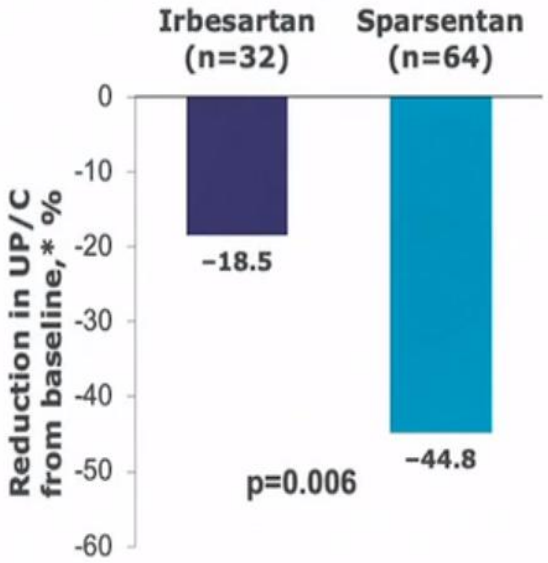
Proportion of patients achieving FSGS partial remission **utilizing the modified partial remission endpoint** (UP/C: ≤1.5 g/g and >40% reduction)

* After 2 weeks' RAAS inhibitor washout.
IRB = irbesartan; RAAS = renin-angiotensin-aldosterone system; SPAR = sparsentan; UP/C = urinary protein-to-creatinine ratio.
Trachtman H, *et al. J Am Soc Nephrol* 2018; **29:**2745–2754.

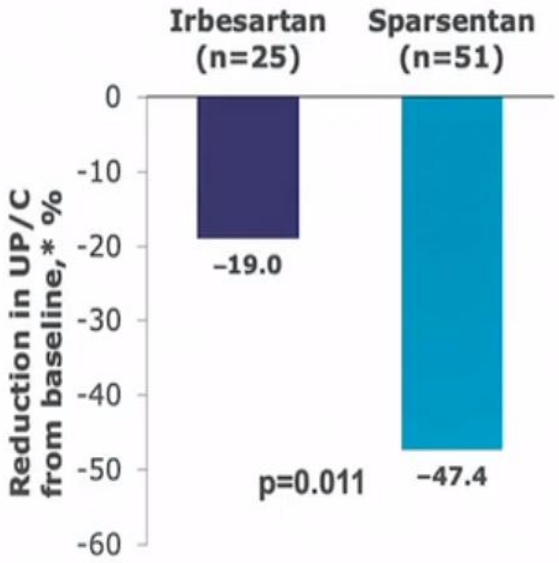
Sparsentan Versus Irbesartan Achieved a Greater Reduction in UP/C from Baseline to Week 8

Primary endpoint

All sparsentan doses, EES population (200 mg, 400 mg, 800 mg)



Pooled 400 mg and 800 mg sparsentan doses, EES population

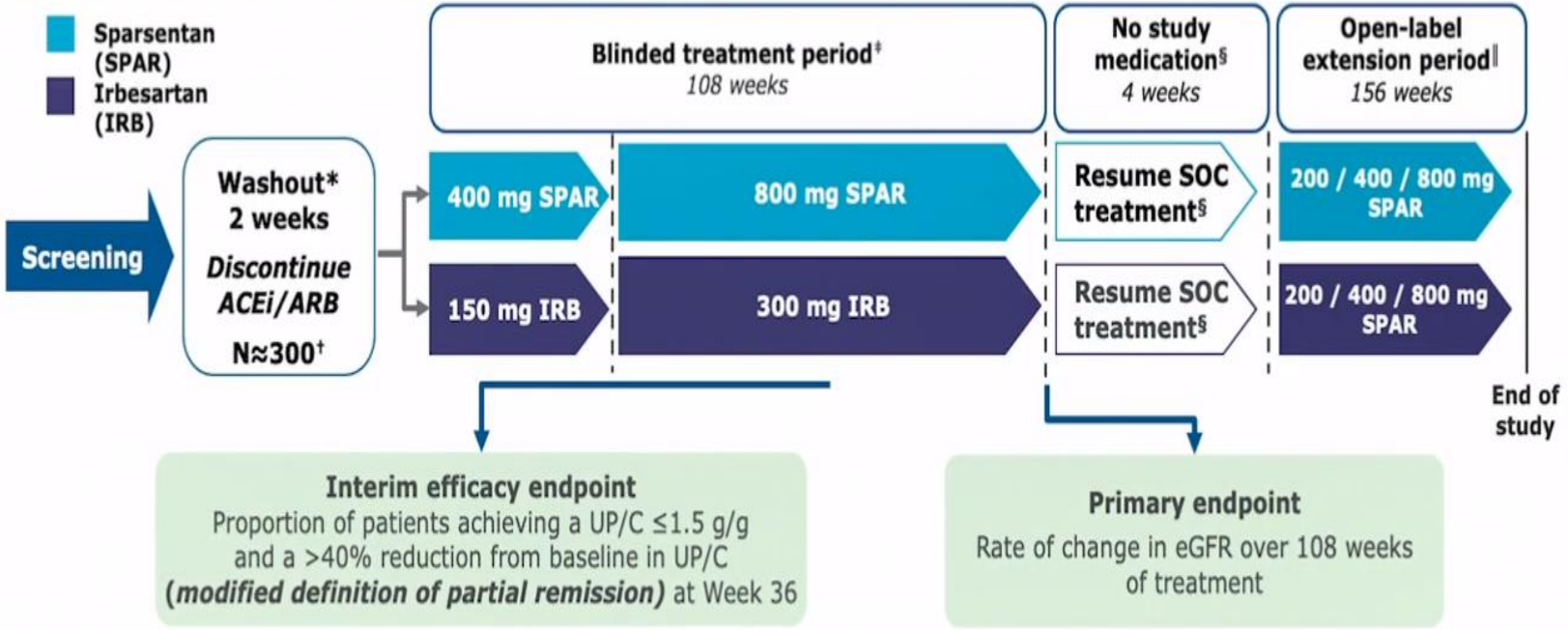


Analyses based on the EES. UP/C based on 24-hour urine. p-values from analysis of covariance.
* Geometric least-squares mean reduction.
EES = efficacy evaluable set; UP/C = urinary protein-to-creatinine ratio.
Images reproduced with permission: Trachtman H, *et al. J Am Soc Nephrol* 2018; **29:**2745–2754.

TRAVERE THERAPEUTICS

The Phase 3 DUPLEX Trial Continues to Use the Modified FSGS Endpoint

Phase 3 trial to determine the long-term nephroprotective potential of treatment with sparsentan compared with irbesartan in patients with primary or genetic FSGS[1-3]



* For patients who are undergoing washout from RAASis; † Patients randomized 1:1 to SPAR or IRB;
‡ Patients whose body weight is ≤50 kg at screening will receive half the otherwise specified doses of either SPAR or IRB;
§ Patients will resume SoC treatment including RAASis with the exception of IRB;
‖ Starting dose and maximum maintenance dose of SPAR for the open-label extension will be based on the percentage of target dose at the end of the blinded treatment period.
ACEi, = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; IRB = irbesartan; RAASis = renin-angiotensin-aldosterone system inhibitors; SPAR = sparsentan; SOC = standard of care; UP/C = urinary protein-to-creatinine ratio.

1. Komers R, *et al. Kidney Int Rep* 2020; **5**:494–502; 2. DUPLEX clinicaltrials.gov ID: NCT03493685; 3. DUPLEX Protocol ID: 021FSGS16010.

Key Findings from the DUET Trial

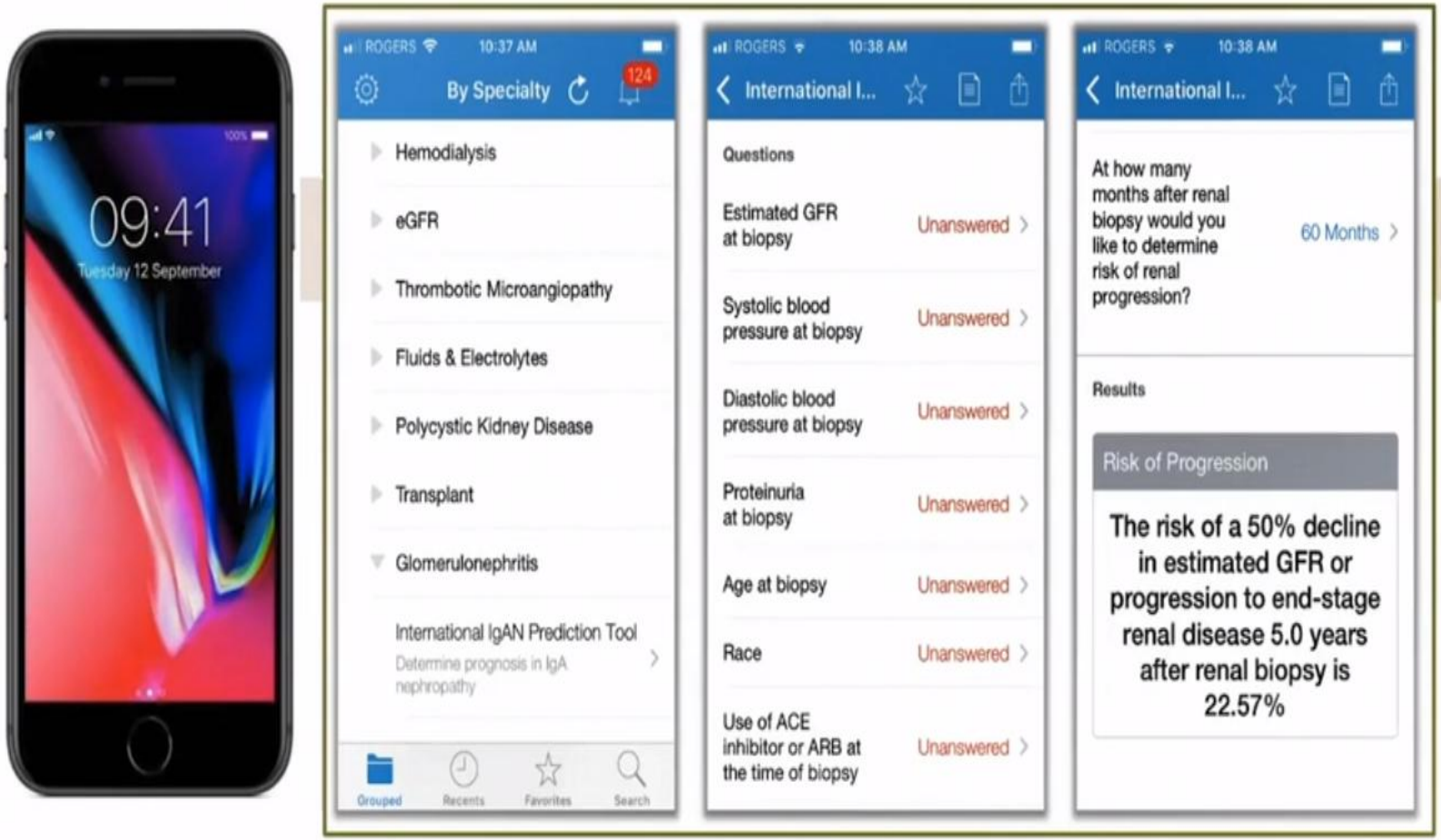
- Sparsentan-treated FSGS patients achieved a significant reduction in proteinuria compared with irbesartan-treated patients
- Significantly more patients achieved the FPRE with sparsentan than with irbesartan
- Patients saw a significantly greater reduction in blood pressure with sparsentan* than with irbesartan
- eGFR remained stable and similar with sparsentan or irbesartan in the 8-week period
- Sparsentan was generally safe and well tolerated during the double-blind period
- The Phase 3 DUPLEX study is further evaluating these findings, **utilizing the modified FSGS endpoint as a surrogate endpoint**

* In the 400 mg plus 800 mg pooled cohort and the 800 mg cohort.
FPRE = FSGS partial remission endpoint; eGFR = estimated glomerular filtration rate.
Trachtman H, *et al. J Am Soc Nephrol* 2018; **29:**2745–2754.

Conclusions

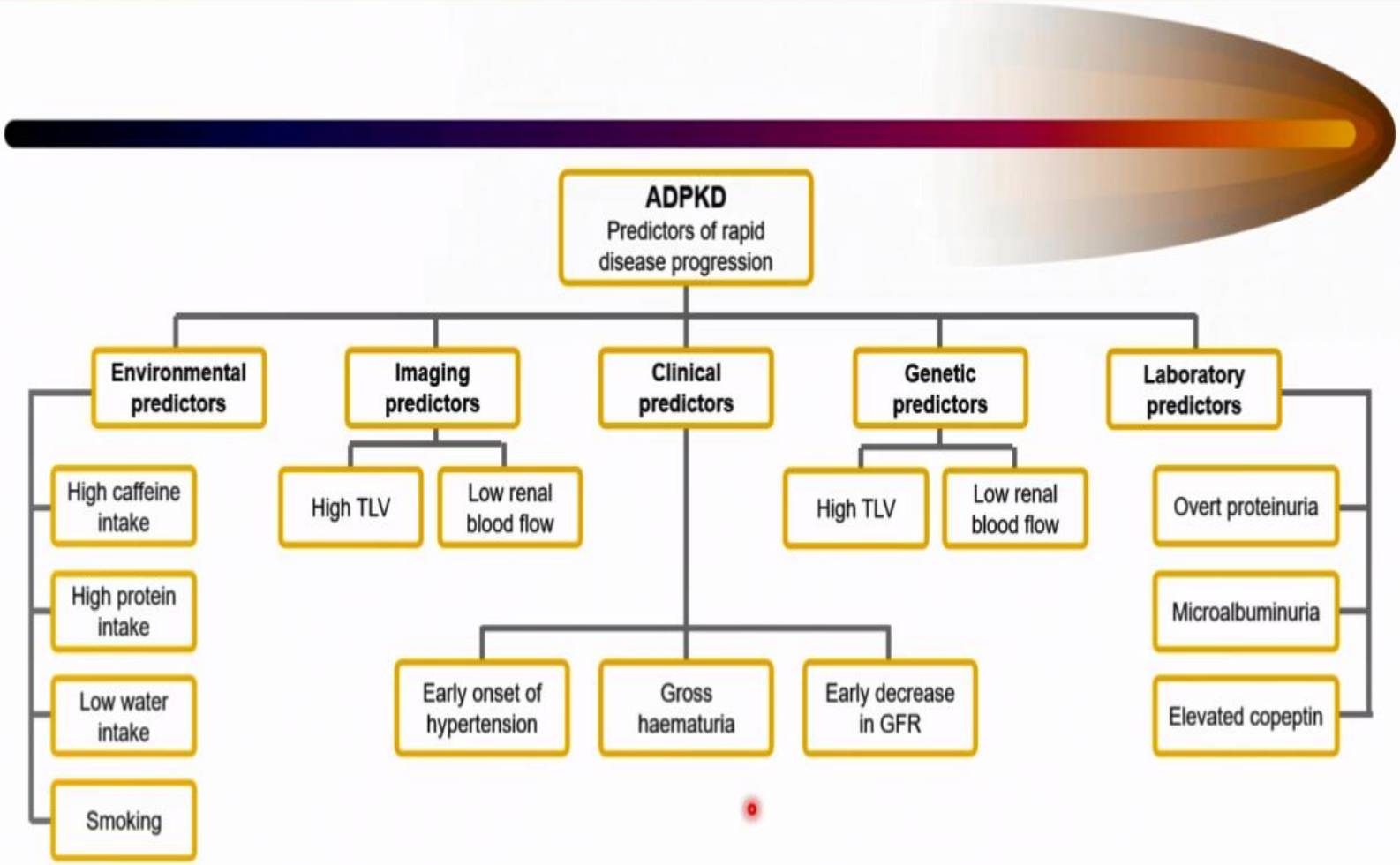
- FSGS is a histologic pattern associated with glomerular disease caused by podocyte injury, which ultimately results in impaired glomerular filtration barrier function and proteinuria
- Patients with FSGS and persistent proteinuria are at increased risk of progressive CKD and CV morbidity/mortality
- The goal of therapy is to induce sustained remission of proteinuria, which is pivotal to slowing progression to kidney failure
- A modified definition of partial remission seems to be associated with earlier prediction of kidney survival versus the conventional definition and may be useful for investigational clinical trials
- The DUET study utilizes the modified FSGS endpoint to evaluate the efficacy of sparsentan in FSGS – a greater percentage of patients reached partial remission at Week 8 with sparsentan versus irbesartan
- Phase 3 DUPLEX study is ongoing and is utilizing the modified FSGS endpoint as an interim analysis to evaluate efficacy of sparsentan versus irbesartan

QxMD mobile-app calculator



BCRenal

Risk Assessment - Integral Feature of Management of ADPKD



ADPKD, autosomal dominant polycystic kidney disease; GFR, glomerular filtration rate; TLV, total kidney volume

Gansevoort RT, *et al. Nephrol Dial Transplant.* 2016;31:337–48

TKV, but not GFR, is a Sensitive Marker of Disease Progression

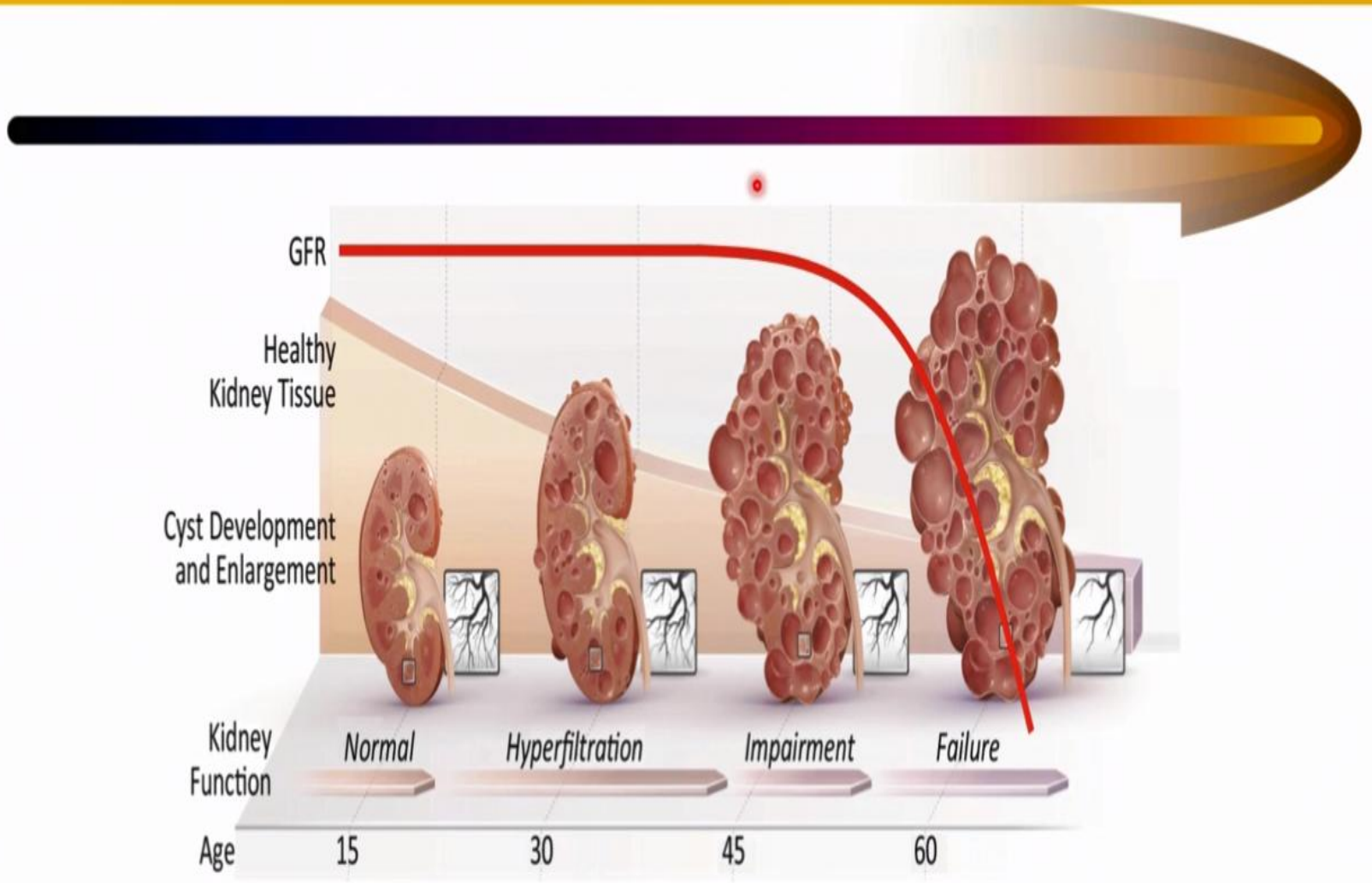
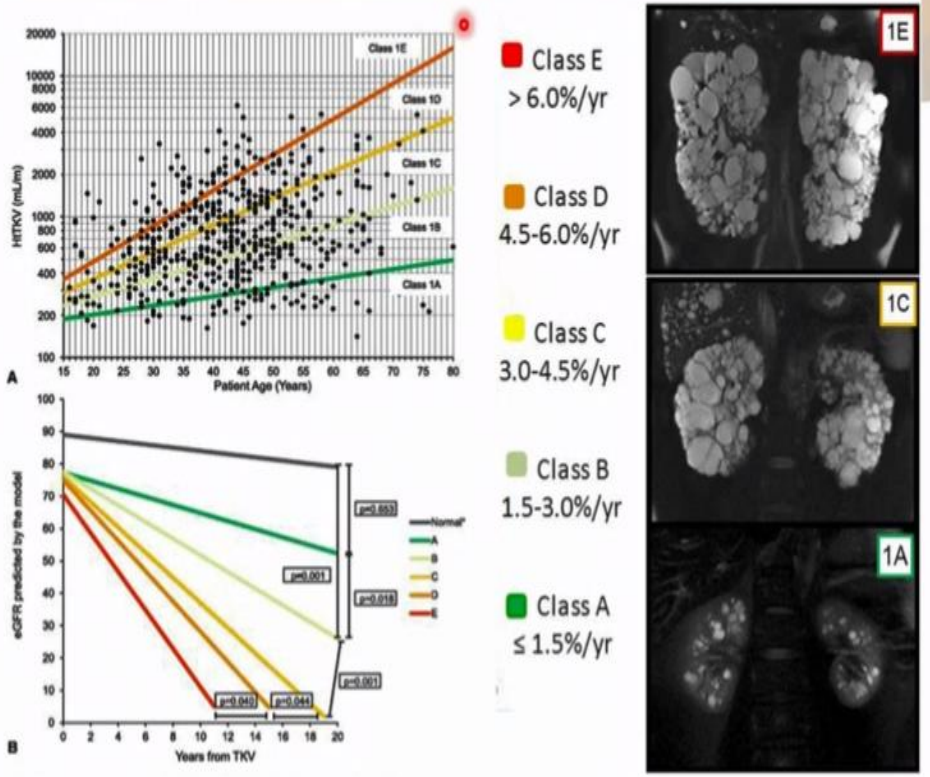


Figure adapted from Antignac C, *et al. J Am Soc Nephrol.* 2015;26:2081–95

Mayo Clinic Imaging Classification for Risk Assessment in ADPKD



Class E
> 6.0%/yr

Class D
4.5-6.0%/yr

Class C
3.0-4.5%/yr

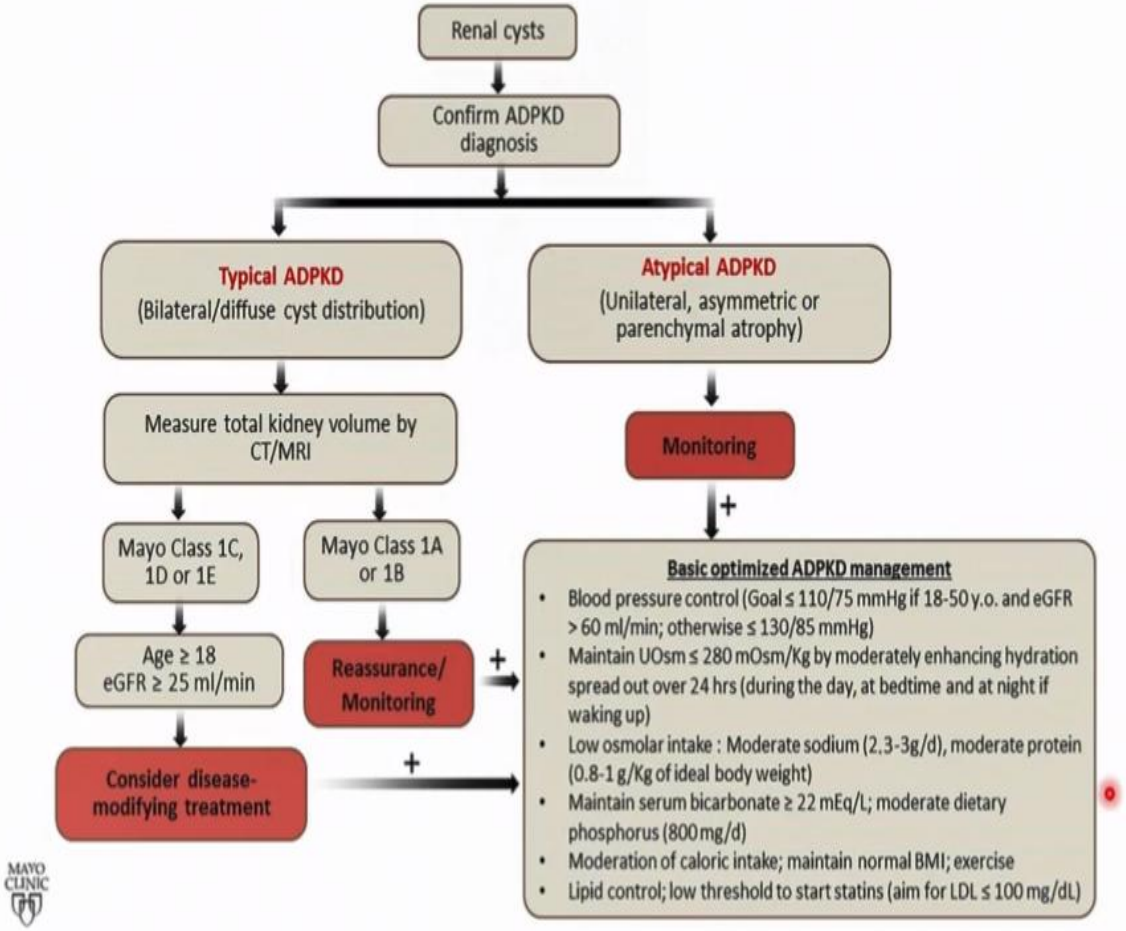
Class B
1.5-3.0%/yr

Class A
≤ 1.5%/yr

ADPKD, autosomal dominant polycystic kidney disease

Adapted with permission: 1. Irazabal MV, *et al. J Am Soc Nephrol.* 2015;26:160–172; 2. Chebib, T, Torres VE. *Clin J Am Soc Nephrol.* 2018;13:1–12

Current Management of ADPKD



ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; CT, computed tomography; eGRF, estimated glomerular filtration rate; LDL, low-density lipoprotein; MRI, magnetic resonance imaging

Adapted with permission: Chebib FT, Torres VE. *Clin J Am Soc Nephrol.* 2018;13(11):1765–76

APRIL 15-19, 2021
ISN VIRTUAL WORLD CONGRESS OF NEPHROLOGY

M. Maski
(United States)

Novel Disease Mechanisms in ADPKD

Dr. Manish Maski, MD, MMSc
Global Head, Rare Nephrology
Sanofi Genzyme Medical Affairs

SANOFI GENZYME

MAT-GLB-2100498 v1.0
Approval 03/2021

ADPKD Pathophysiology: Possible Targets for ADPKD Therapies

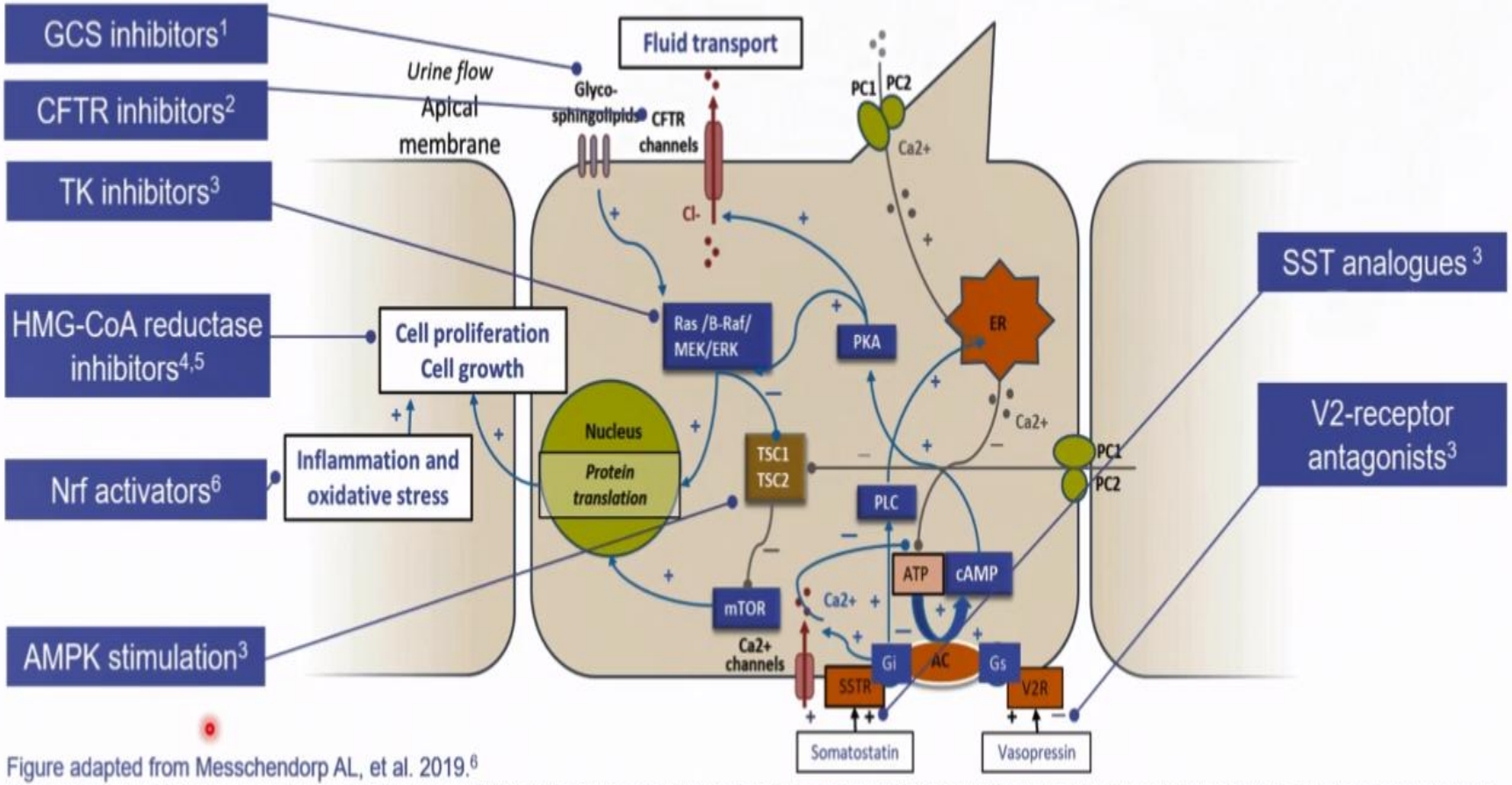
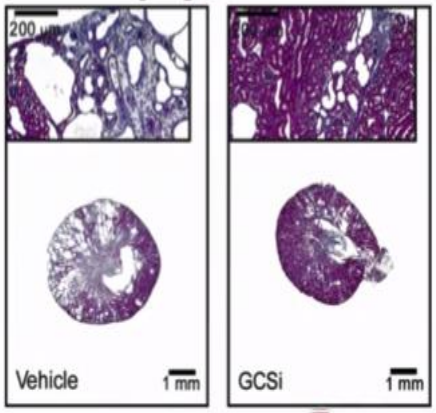


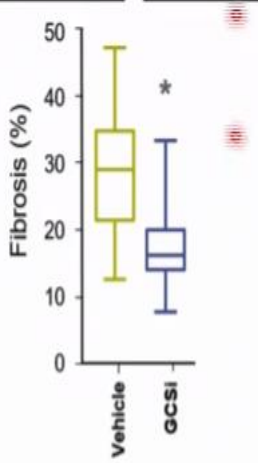
Figure adapted from Messchendorp AL, et al. 2019.[6]

AC, adenylyl cyclase; ADPKD, autosomal dominant polycystic kidney disease; AMPK, AMP-activated protein kinase; ATP, adenosine triphosphate; B-Raf, v-raf murine sarcoma viral oncogene homolog B1; cAMP, cyclic adenosine monophosphate; CFTR, cystic fibrosis transmembrane conductance regulator; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; GCS, glucosylceramide synthase; Gi, Gi protein alpha subunit; Gs, Gs alpha subunit; HMG-COA, 3-hydroxy-3-methyl-glutaryl-CoA reductase; MEK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; PC1/PC2, polycystin 1/2; Nrf, nuclear factor erythroid 2-related factor; PKA, protein kinase A; PLC, phospholipase C; SST(R), somatostatin (receptor); TK, tyrosine kinase; TSC1/2, tuberous sclerosis 1/2;
V2(R), vasopressin 2 (receptor). 1. Cornec-Le Gall E et al. *Lancet*. 2019;393:919–35; 2. Jouret F and Devuyst O. *Cell Sig*. 2020;73:109703; 3. Salvadori M & Tsalouchos A. *J Kidney Hepatic Disord*. 2017;1(1):35–49; 4. Ecder T. *Nephrol Dial Transplant*. 2016;31:1194–6; 5. Belibi F et al. *Expert Opin Investig Drugs*. 2010;19(3):315–28; 6. Yamawaki K et al. *Toxicol Appl Pharmacol*. 2018;360:30–7; 7. Messchendorp AL et al. *Nephrol Dial Transplant*. 2019;pii:gfz054

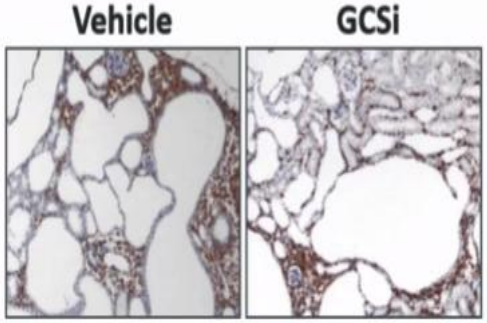
GCSi Treatment Reduces Kidney Fibrosis, Inflammation and Total Kidney Volume in Mouse Models of PKD

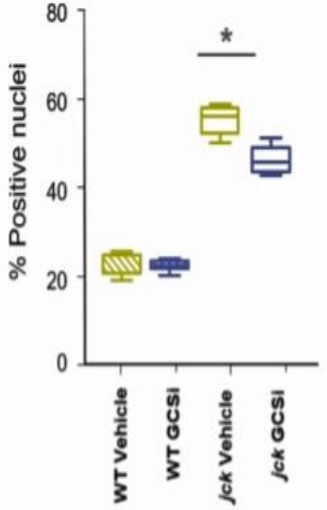
pcy mice



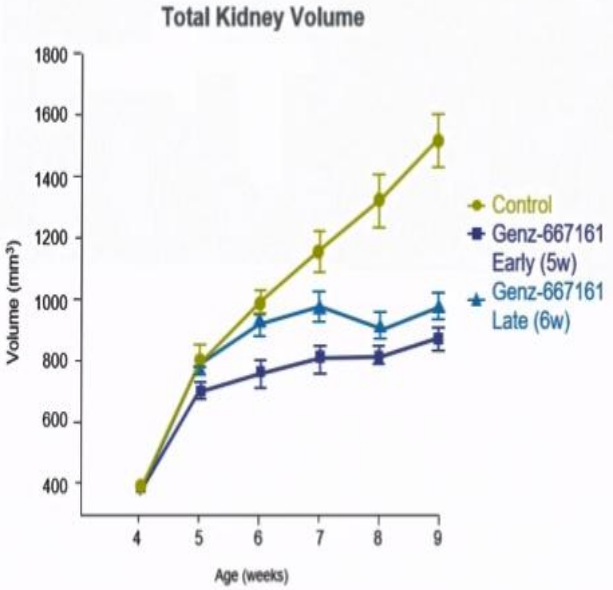


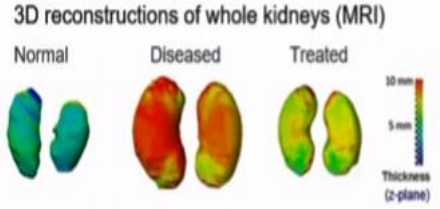
jck mice





GCSi treatment of *jck* mice

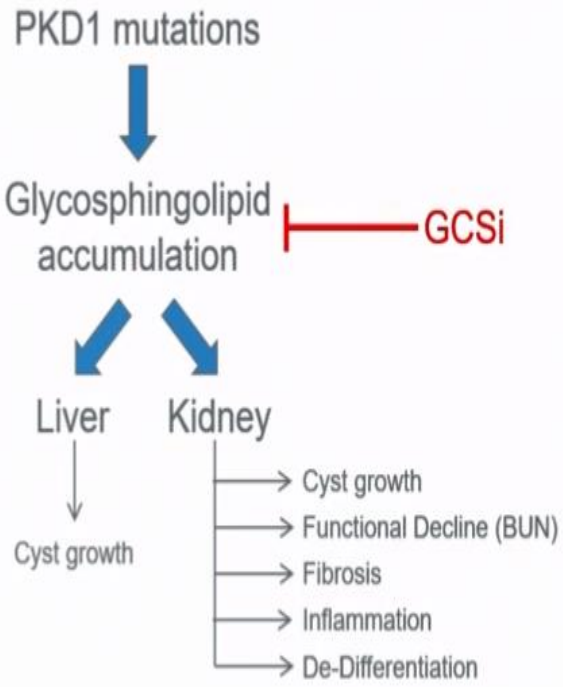




BUN, blood urea nitrogen; GSCi, Glucosylceramide Synthase Inhibitor; *jck*; juvenile cystic kidney; MRI, magnetic resonance imaging; *pcy*; polycystic kidney disease; PKD, polycystic kidney disease; Vol, volume; wt, wildtype

Natoli TA, *et al. Nat Med.* 2010;16(7):788–92; Natoli TA, *et al.* 2019; Clinical trial of Venglustat, a glucosylceramide synthase (GCS) inhibitor, in ADPKD is supported by preclinical and Phase 1 study data. ISN World Congress of Nephrology

Summary



- Several cellular mechanisms have been implicated in the development and growth of cysts in ADPKD
- Current and investigational treatment options target a wide range of disease pathways e.g. vasopressin V2 receptor blockade or reduction of GSL accumulation
- Pharmacological inhibition of GSL accumulation slows liver and kidney cystogenesis, reduces kidney inflammation, fibrosis, and de-differentiation in multiple mouse models of PKD

ADPKD, autosomal dominant polycystic kidney disease; BUN, blood urea nitrogen; GSCi, Glucosylceramide Synthase Inhibitor; GSL, Glycosphingolipids; PKD, polycystic kidney disease

Figure adapted from Natoli TA, *et al.* 2019; Clinical trial of Venglustat, a glucosylceramide synthase (GCS) inhibitor, in ADPKD is supported by preclinical and Phase 1 study data. ISN World Congress of Nephrology; Speaker's own opinion and experience