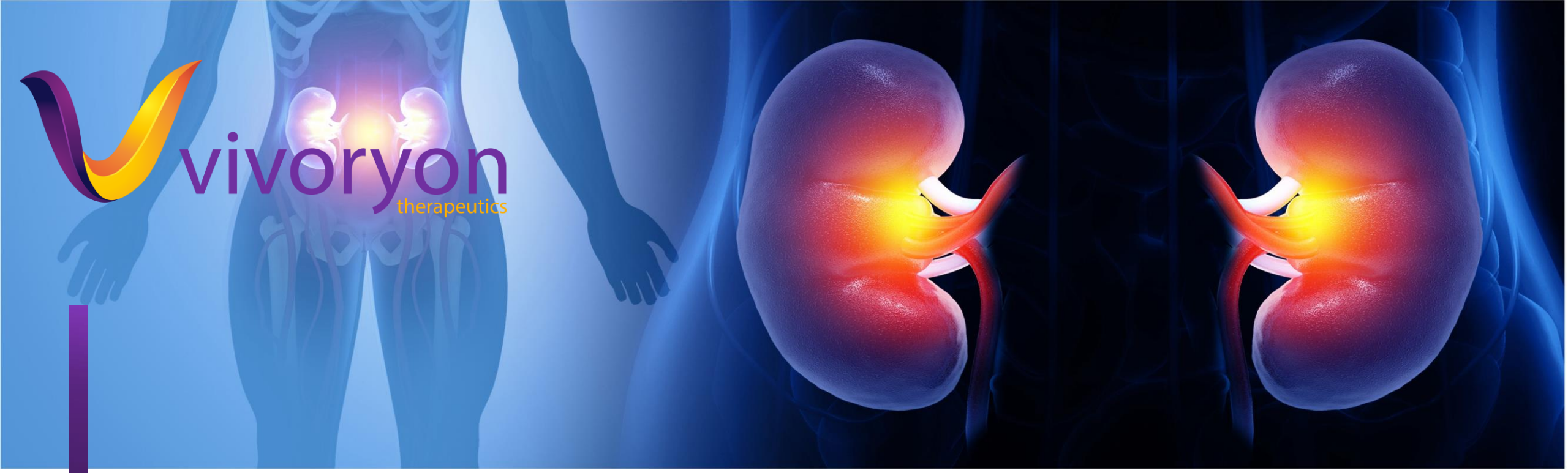

A Novel Path to Addressing the Unmet Need in DKD

Virtual Kidney Disease KOL Event

September 30, 2024

| Vivoryon Therapeutics N.V.

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Forward-looking statements speak only as of the date they are made, and we do not undertake any obligation to update them in light of new information or future developments or to release publicly any revisions to these statements in order to reflect later events or circumstances or to reflect the occurrence of unanticipated events or otherwise, except as required by applicable law.

SPEAKERS

Host	**Frank Weber, MD** CEO Vivoryon Therapeutics
	Tobias Huber, MD Director III. Department of Medicine University Medical Center Hamburg-Eppendorf
	Florian Jehle Pharmaceutical Industry Expert
	Kevin Carroll, PhD CEO KJC Statistics

Frank Weber, MD

CEO
Vivoryon Therapeutics

Vivoryon: Mid-stage clinical biotech company with first-in-class QPCT/L inhibitor targeting high unmet need in kidney disease

Kidney function data in VIVIAD Phase 2 study highlights **varoglutamstat's unique product profile** and has enabled Vivoryon's transformation to a company focused on inflammatory/fibrotic diseases with a **mid-stage asset with potential to change the course of kidney disease**

- **Strong progress in transitioning strategy from a focus on Alzheimer's disease driven by compelling kidney function data**
- **Rigorous scientific research laid foundation for opportunity in inflammatory/fibrotic diseases, including kidney disease**
- **Established deeper understanding of varoglutamstat's MoA and VIVIAD results: QPCTL is an attractive target in kidney disease**
- **Comprehensive body of evidence and large safety dataset underpins plan to advance into Phase 2 in DKD**
- **Pursuing actionable plan to establish presence in kidney disease**

Tobias B. Huber, MD

Chair of the Center of Internal Medicine and Director of the III. Department of Medicine, University Medical Center Hamburg-Eppendorf (UKE)

Kidney Disease

CKD/DKD and orphan diseases need new treatment approaches

Tobias B. Huber | 30. September 2024

Disclosures

Consultancy agreements: Alexion, AstraZeneca, Bayer, Beren Therapeutics, Boehringer-Ingelheim, DaVita, Euroimmun, Fresenius Medical Care, Nipoka, Novartis, Pfizer, Renovate, Retrophin-Travere, Sanofi, Vera Therapeutics, Vifor, Vivoryon Therapeutics

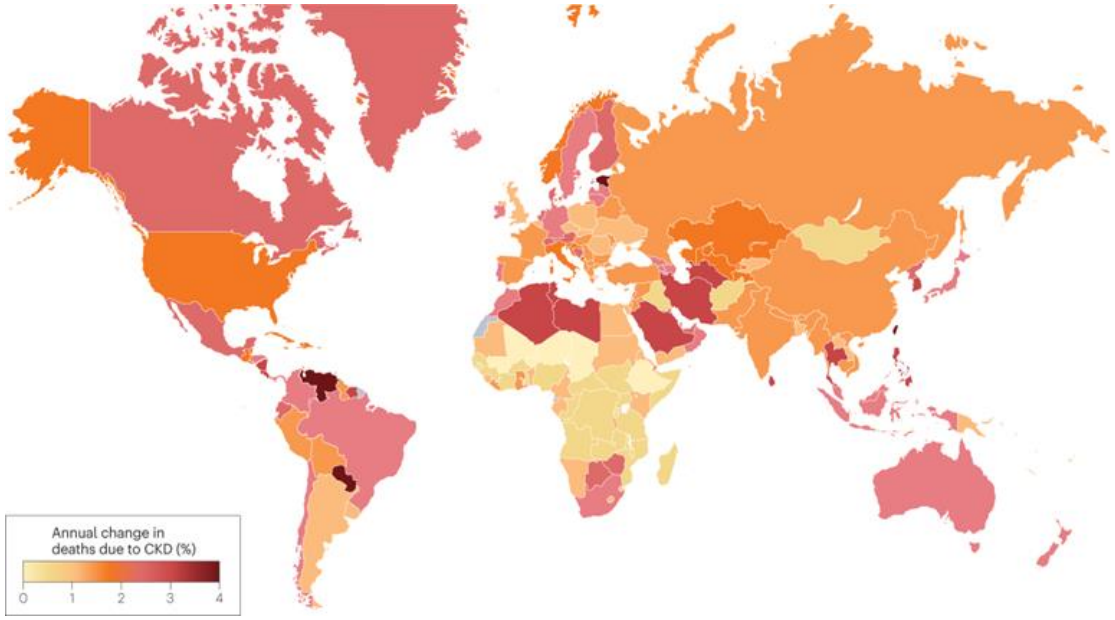
Research funding: Amicus Therapeutics, Fresenius Medical Care, Euroimmun, Vivoryon Therapeutics

Editorial boards: Kidney International, Nature Review Nephrology

Patents: EP23154267.1 “AAV2-vector variant for targeted transfer of genes”
EP23154266.3 “AAV9 capsid variant for targeted gene transfer”
EP23195461. “Novel solution for ex-vivo organ storage during machine perfusion”

President of the International Society of Glomerular Disease

CKD is set to become the 5th cause of years of life lost by 2040



Predicted change in deaths due to CKD from 1990 to 2040
Francis et al., Nat Rev Nephrol (2024)

2016		2040	
1	Ischemic heart disease	1	Ischemic heart disease
2	Stroke	2	Stroke
3	Lower Resp. Infect.	3	Lower Resp. Infect.
4	Diarrhoeal diseases	4	COPD
5	Road injuries	**5**	**Chronic Kidney Disease**
6	Malaria	6	Alzheimer's disease
7	Pre-term birth	7	Diabetes
8	HIV/AIDS	8	Road injuries
9	COPD	9	Lung cancer
10	Neonatal encephalopathy	10	Diarrhoeal diseases
11	Tuberculosis	11	Self-harm
12	Congential defects	12	HIV/AIDS
13	Lung cancer	13	Liver cancer
14	Self-harm	14	Hypertensive heart disease
15	Diabetes	15	Colorectal cancer
16	**Chronic Kidney Disease**	16	Tuberculosis
17	Other neonatal	17	Congential defects
18	Alzheimer's disease	18	Pre-term birth
19	Neonatal sepsis	19	Breast cancer
20	Liver cancer	20	Falls

Predicted change in rank (years of life lost, YLL)
Foreman et al., Lancet (2018)
Based on leading 20 level 3 causes of YLLs globally 2016 and 2040

CKD key characteristics and impact

Key risk factors

- Diabetes
- Hypertension
- Ageing population
- Obesity
- Heart disease

Characteristics

- Kidney damage or glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for 3 months or more, irrespective of cause[1]
- May be “silent” until in crisis stage

Impact

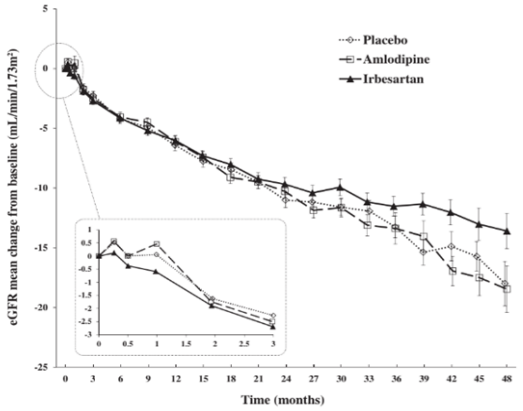
- Premature mortality
- Progression to end stage kidney disease (ESKD) >> need for kidney dialysis and/or kidney transplant
- Disability
- Reduced quality of life
- Psychosocial harm

[1] Levey et al., Kidney International (2005) KDIGO

Current treatments for CKD

Renin-Angiotensin System (RAS) modulators (ACEi, ARBs)

e.g. Irbesartan[1]

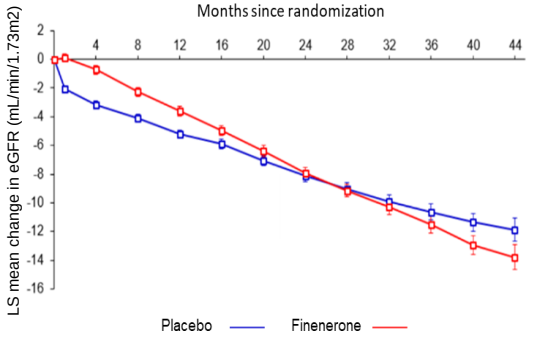


IDNT trial included patients with hypertension, plus T2DM with nephropathy

Hemodynamic

Mineralocorticoid receptor antagonists (non-steroidal)

e.g. Finerenone[2]

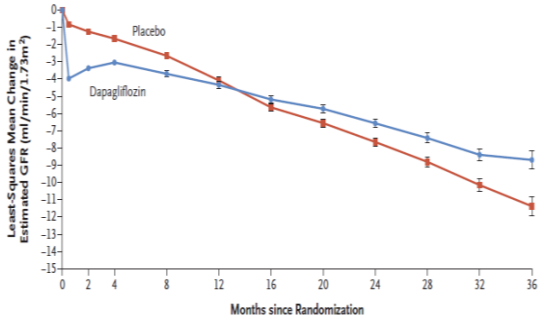


FIDELIO trial included patients with T2DM and CKD treated with an ACEi or ARB^

Renal/metabolic

SGLT2 inhibitors

e.g. Dapagliflozin[3]

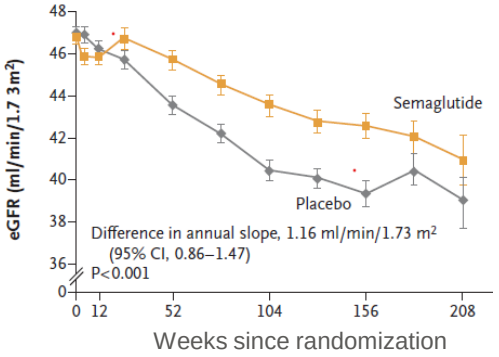


DAPA-CKD trial included CKD patients with or without T2DM receiving an ACEi or ARB^

Metabolic

GLP-1 receptor agonists

e.g. Semaglutide[4]



FLOW trial included T2DM patients with high-risk CKD receiving RAS inhibitors (ACEi/ARBs)^

Metabolic

Additional measures aimed at reduction complications and risk factors including: lipid management, diet & lifestyle modifications, psychosocial support, diabetes education & complications, screening

[1] Evans et al., Nephrol Dial Transplant (2012): eGFR data from post hoc analyses of IDNT trial; mean eGFR at baseline was ~46mL/min/1.73m^2; majority of patients were in CKD stages 2 - 4; [2] Bakris et al, N Engl J Med (2020): CKD defined according to two criteria, i) eGFR 25 to <60 mL/min/1.73m^2 with uACR 30 to <300 and a history of diabetic retinopathy, ii) uACR 300 to 5000 and an eGFR of 25 to <75mL/min/1.73m^2); [3]Heerspink et al. N Engl J Med (2020): eligible patients had an eGFR of 25 to 75 mLmin/1.73m^2 and uACR of 200 to 5000; [4] Perkovic et al., N Engl J Med (2024): eligible patients had an eGFR of 25 to 75 mL/min/1.73m^2 and uACR of 300 to 5000 if eGFR <50mL/min/1.73m^2 or uACR of >100 and <5000 if eGFR was 25 to <50mL/min/1.73m^2; ^patients who were unable to receive RAS inhibitors because of side effects were eligible for inclusion; T2DM: type 2 diabetes mellitus; uACR: urinary albumin-to-creatinine ratio; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker.

Epidemiological insights into rare kidney diseases

Chronic Kidney Disease CKD

2.8M of UK population (> 4%)

Kidney failure

69,000 UK patients (0.1 % of population)

Costs NHS **£660M- £1B/year**

Kidney transplantation (2020)

2349 transplants (**81%** of total organ transplants)

5655 on transplant list

38,895 adults with working transplant/end of 2020

Rare Kidney Diseases (RKD)

<5-10% of patients with CKD;

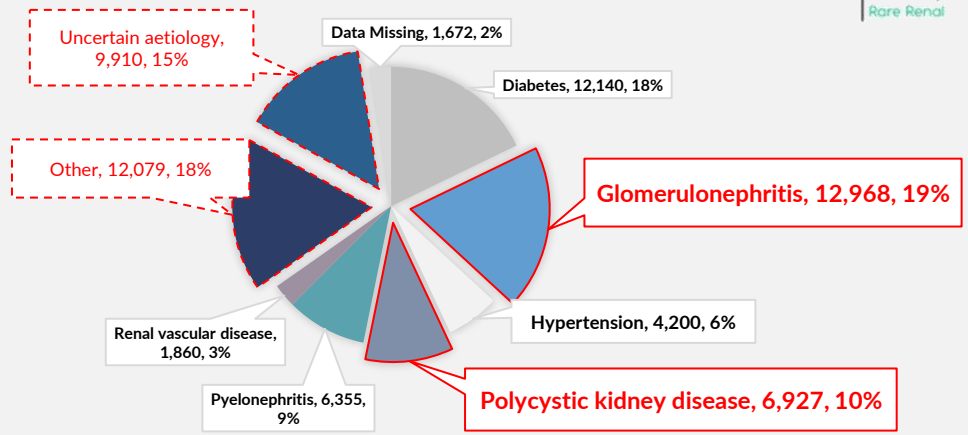
BUT: > 30% of kidney failure

Organ and Tissue Donation and Transplantation Activity Report (2022/23), NHS

UK renal replacement therapy (2019)

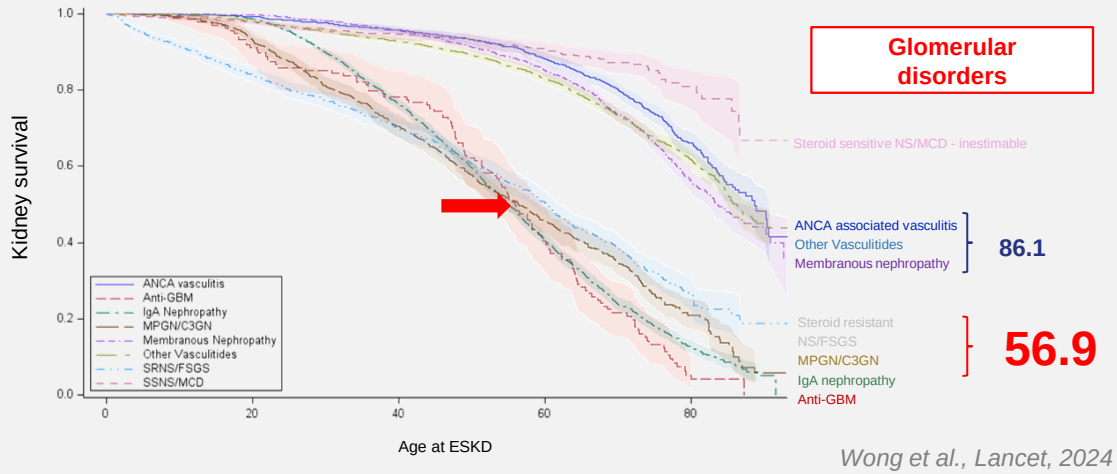
RaDaR

UKKA UK Kidney Association Rare Renal



UK Renal Registry Annual Report (2021)

Age at End Stage Kidney Disease (ESKD)



Wong et al., Lancet, 2024

Novel therapies needed to address CKD epidemiology

Need

Drugs that halt or reverse the decline in kidney function

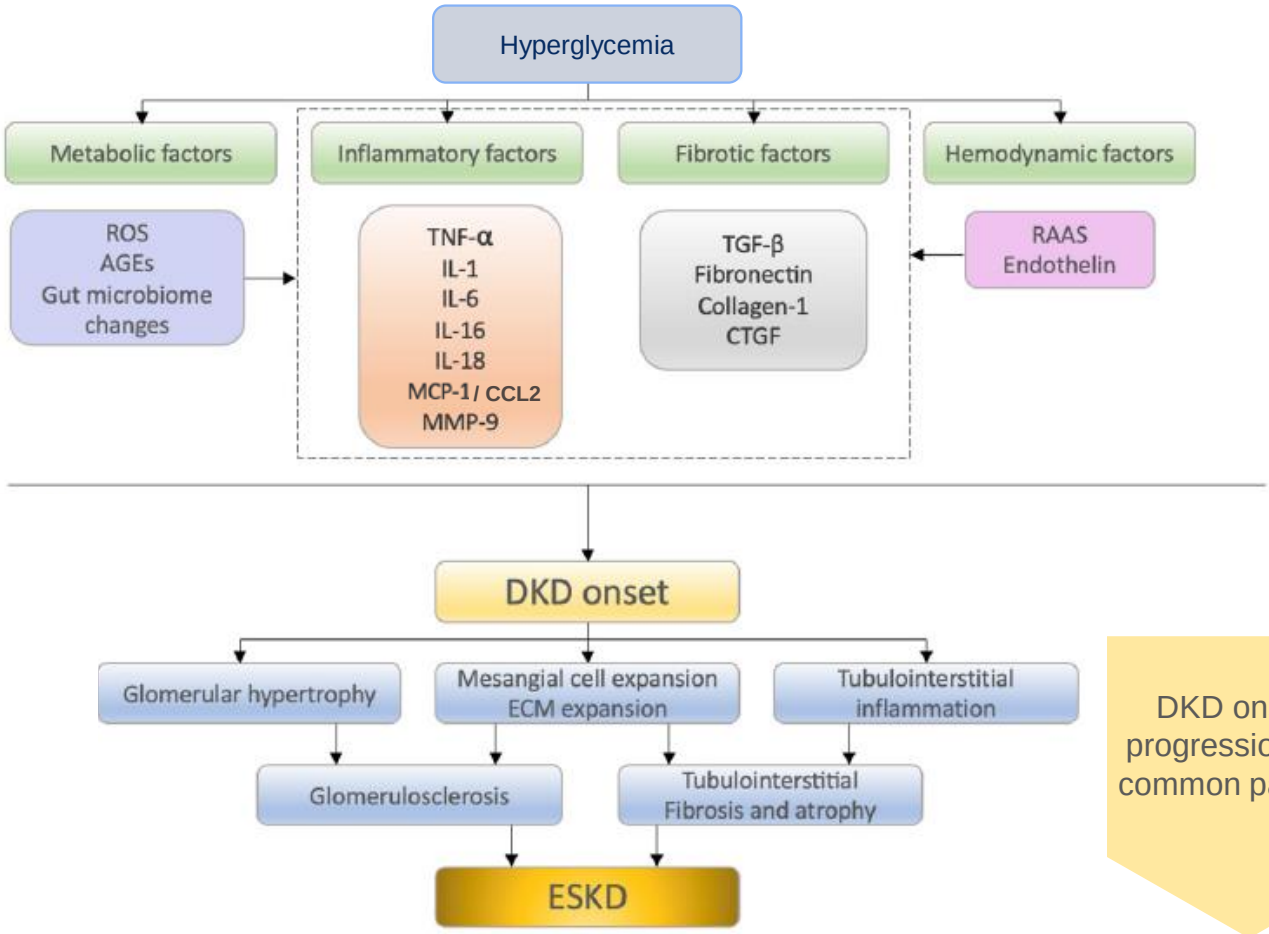
Need

Therapies to reduce kidney failure in people living with rare kidney disorders

Targeting inflammatory pathways could represent an approach to address the unmet needs across both the broader CKD population and rare disease space

Inflammation and fibrosis are key underlying pathways in DKD

- Chronic inflammation plays a key role in the development of diabetic kidney disease (DKD)
- Pathways involve and lead to inflammatory and/or fibrotic tissue transformation

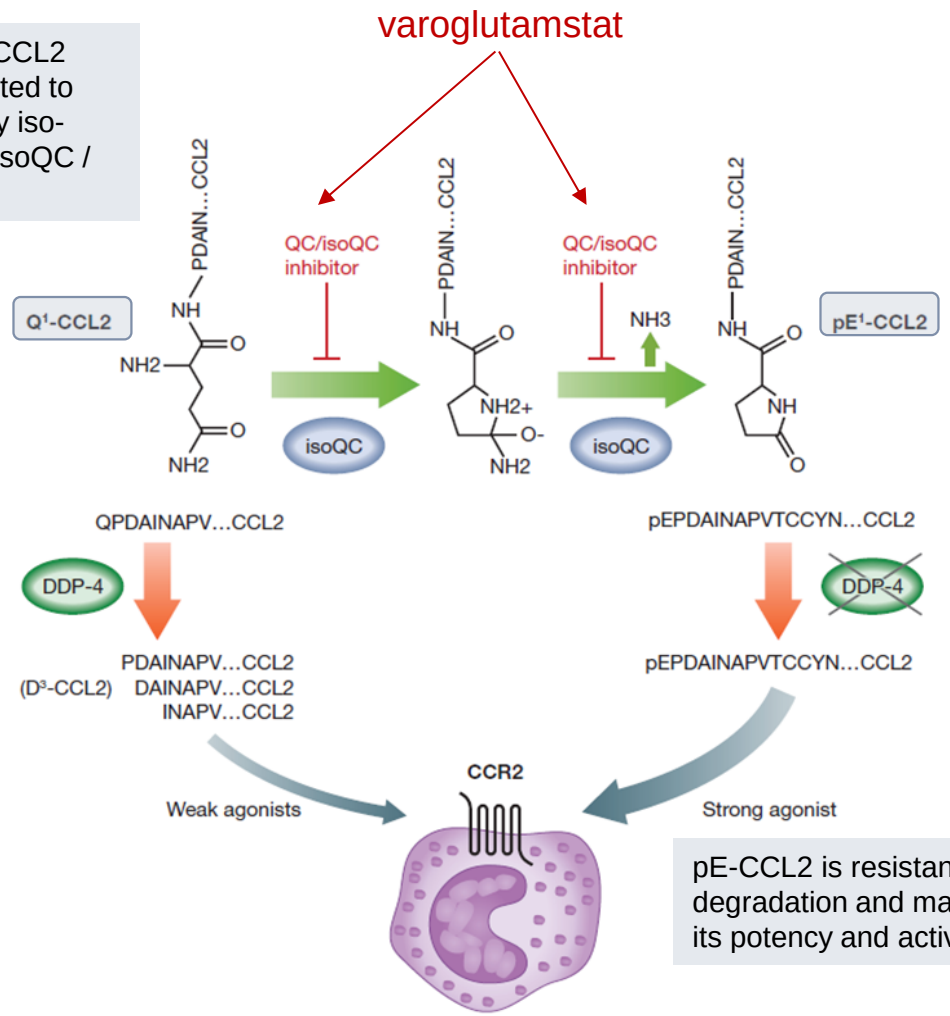


Molecular pathways underlying diabetic kidney disease (DKD)
Adapted from Watanabe et al., Int. J. Mol. Sci (2022)

Varoglutamstat is a specific and selective inhibitor of glutaminyl cyclases (QPCT and QPCTL)

Inhibition of glutaminyl cyclases by varoglutamstat reduces the most active pyro-glutamized versions of selective pro-inflammatory cytokines such as CCL2 and pro-fibrotic markers such as fractalkine (CX3CL1)[1,2,3]

Mature un-cyclized CCL2 (Q^1-CCL2) is converted to cyclized pE-CCL2 by iso-glutaminyl cyclase (isoQC / QPCTL)



Q^1-CCL2 is susceptible to degradation by aminopeptidases, such as DDP-4, which generates products with weaker biological activity

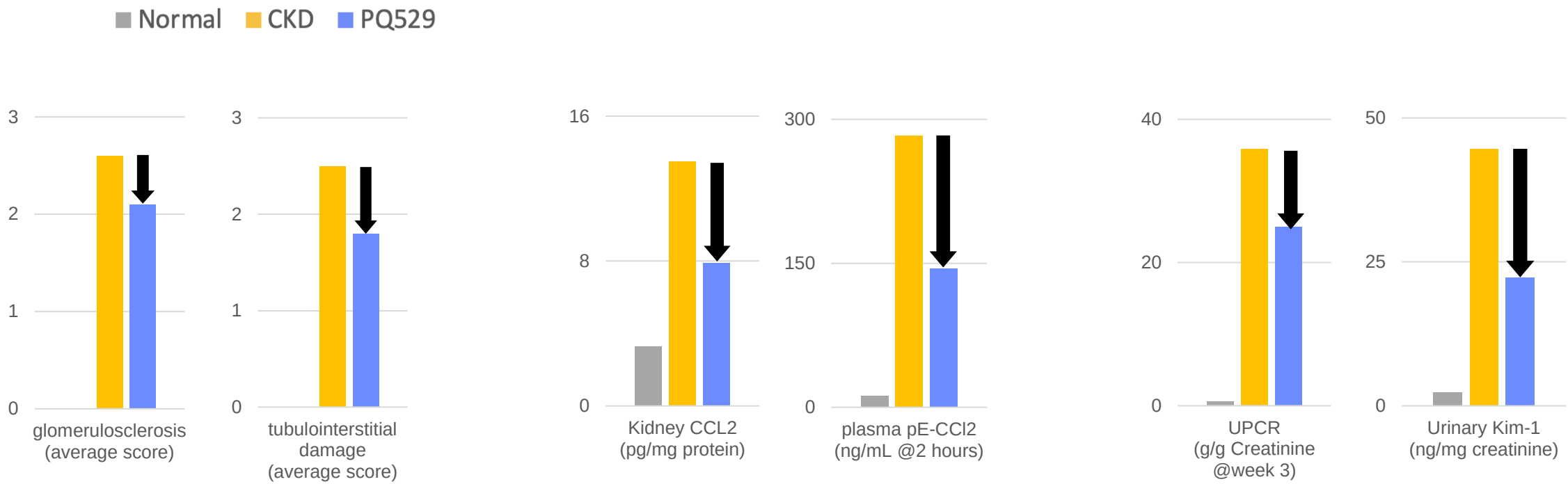
pE-CCL2 is resistant to such degradation and maintains its potency and activity

>> Propagates inflammatory response

[1]Kehlen et.al , Biosci Rep (2017); [2]Cynis et.al., EMBO (2011); [3]Cormican & Griffin, Frontiers in Immunol (2021); Schematic adapted from: Ling & Luster, EMBO Molecular Medicine (2011)

QPCT/L inhibition improves histological and key biomarkers in animal models of kidney disorders

anti-GBM-induced glomerulonephritis in rats
PQ529 - an early compound of Vivoryon's QPCT/L inhibitor portfolio



Histological changes show improvement

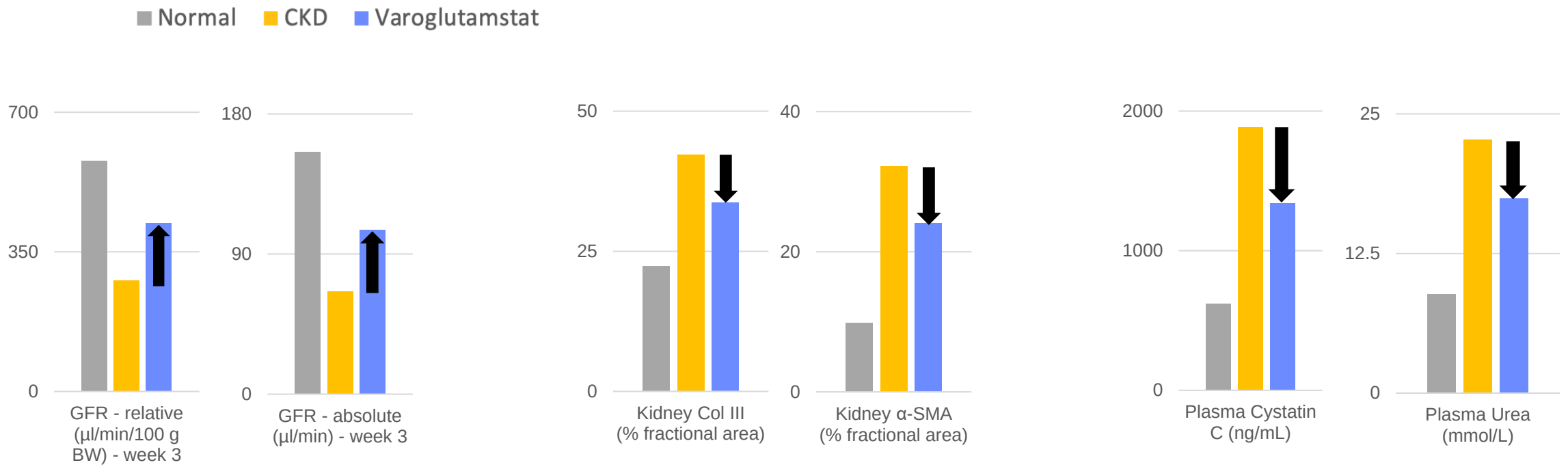
Effects attributed to inflammation

Results in reduced albuminuria and improved urine biomarker

Adapted from: Kanemitsu et al., Naunyn-Schmiedeberg's Arch Pharmacol (2021)

Beneficial effect of QPCT/L inhibition corroborated with varoglutamstat in alternative kidney disease animal model

adenine-induced mouse model of CKD rapidly develops declined kidney function and renal fibrosis
Varoglutamstat - Vivoryon's lead QPCT/L inhibitor



GFR shows improvement

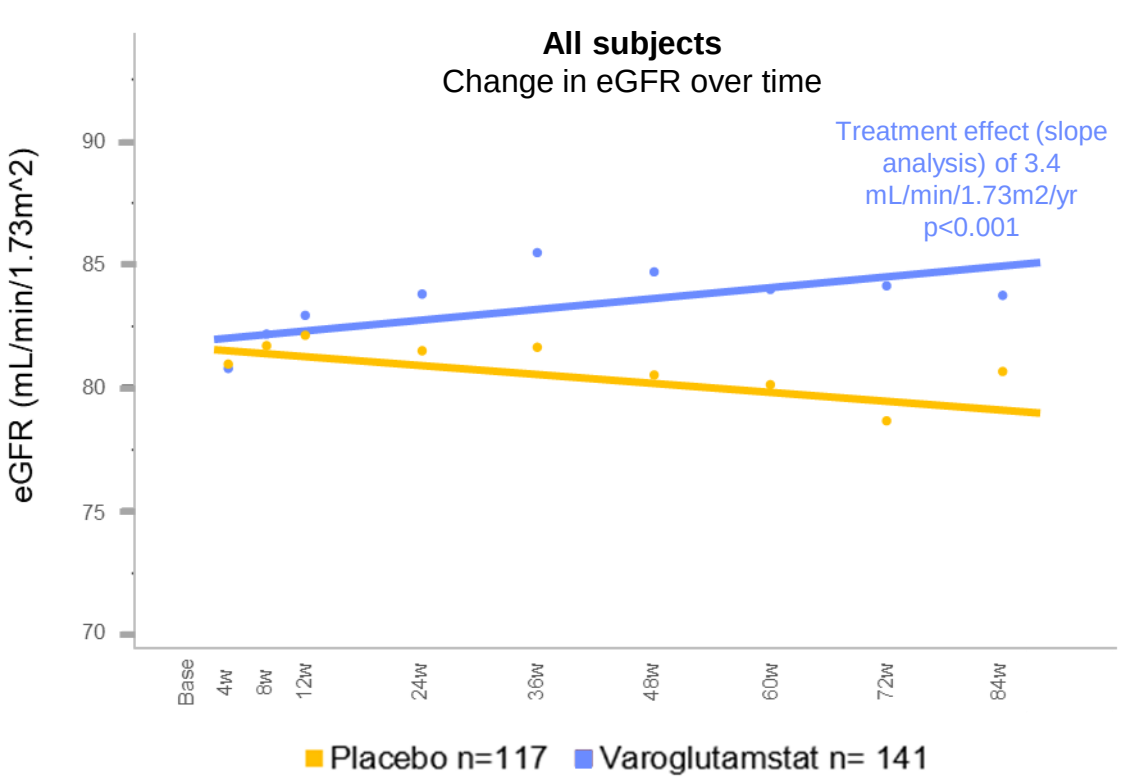
Histological changes show improvement

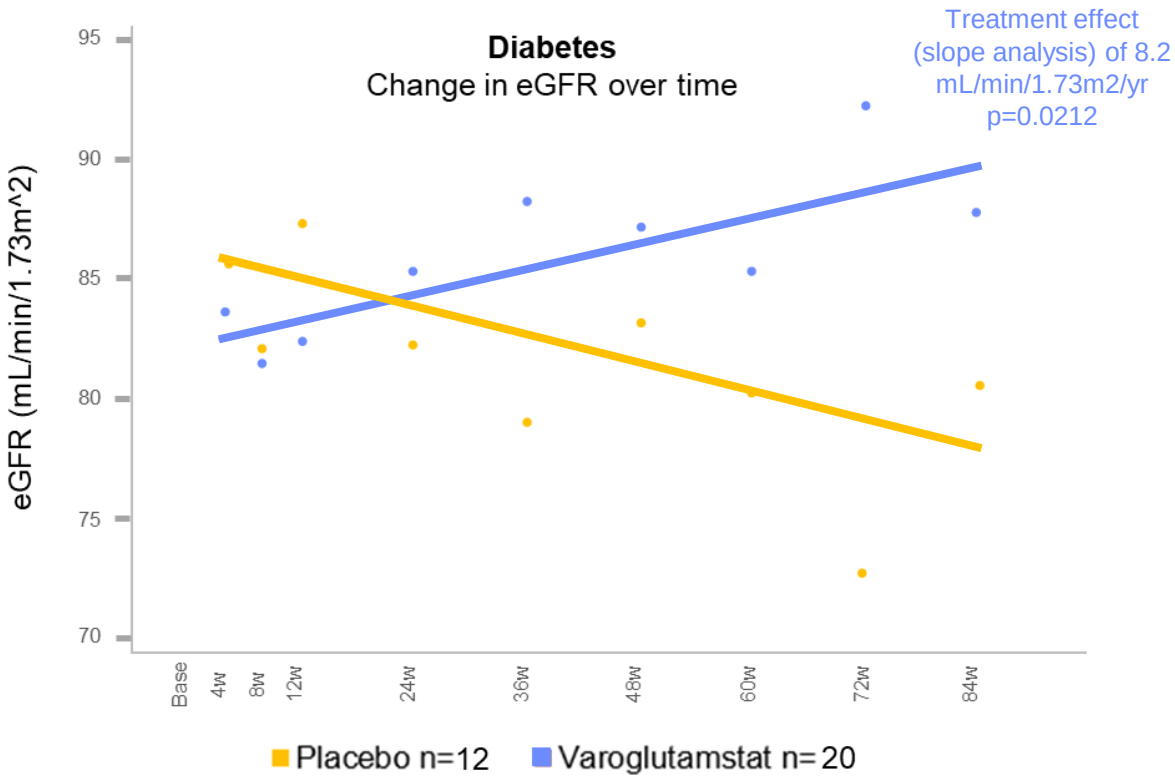
Improved plasma biomarker

Vivoryon Therapeutics N.V., unpublished data

Kidney outcomes - VIVIAD Phase 2b study

Slope analysis of eGFR shows improvement with varoglutamstat in both total population and diabetes subgroup[1] compared to placebo group

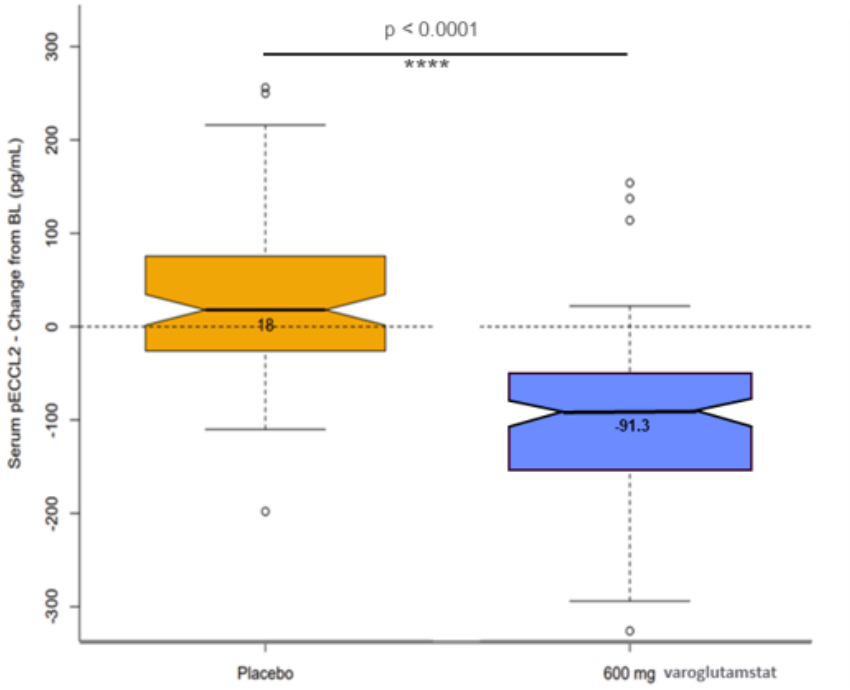




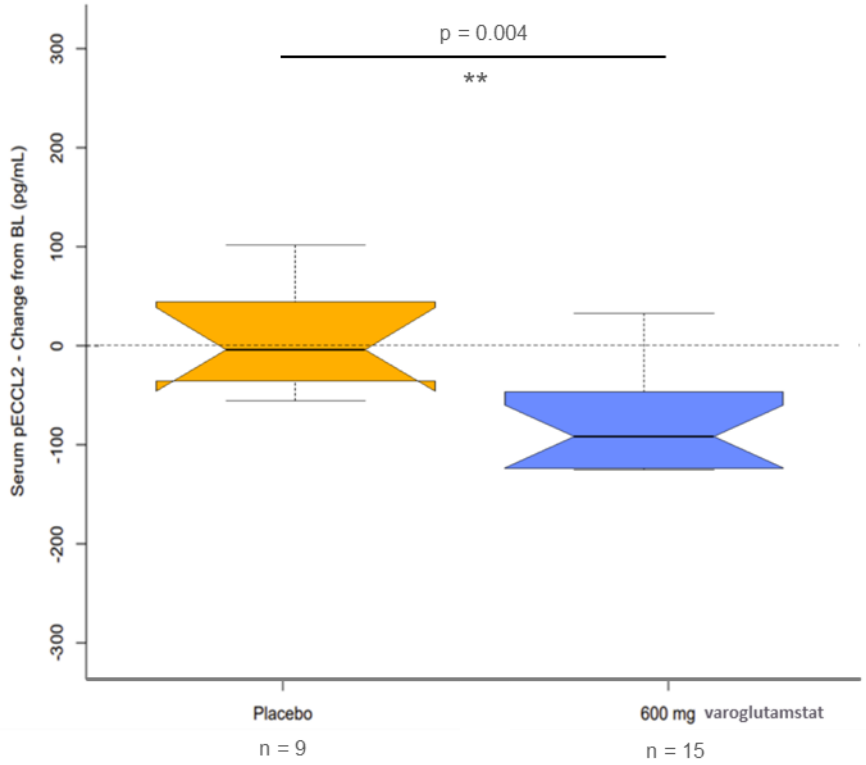
Source: Based on Vivoryon Therapeutics data; R&D Update Presentation, July 18, 2024. Slope analysis: change in eGFR (estimated glomerular filtration rate) over time; eGFR based on creatinine and calculated using modification of diet in renal disease (MDRD) method based on clinical data from the VIVIAD study; creatinine measured at 12-week intervals throughout the study; [1]Diabetes subgroup: patients having at baseline either medical history of diabetes (type 1 or 2) and/or comedication with drugs used in diabetes and/or untreated with a HbA1c > 6.5%

Reduction in inflammatory biomarker in VIVIAD Phase 2b study

Reduction in pE-CCL2 observed in VIVIAD Phase 2b study total population and diabetes subgroup at week 48 confirms MoA and target engagement



Total population



Diabetes subgroup

Source: Based on Vivoryon Therapeutics investor presentations
** p-value < 0.01, **** p-value < 0.0001

What types of novel treatments are needed to treat patients with DKD / CKD?

Portfolio of compounds for the different stages of disease and patient characteristics

Clinical effect sizes that matter - stabilisation of kidney function would be ideal

Long term efficacy resulting in improved outcomes

Well-tolerated in patients with co-morbidities

Initial promising results with varoglutamstat demonstrate it could address unmet clinical and patient needs

R&D program to evaluate targeting QPCTL in orphan diseases including Fabry disease

1

Distribution of glutaminyl cyclase in human- and mouse disease model & renal tissue samples

- Transcriptional and signalling pathway analysis using ERCB biobank[1]

Rationale:

Gain deeper insight into distribution of QPCT/L and related pathways in diseased tissue

2

Cellular effects of varoglutamstat in Fabry disease podocytes

- Proteomics and transcriptomics for QPCT/L
- Pathophysiological investigations including alpha-synuclein, ROS species, lysosomal mass/pH, mitochondrial function, autophagy…

3

Effects of varoglutamstat on Fabry disease organoids

- QPCT/L staining of kidney & heart organoids heart muscle strands (EHT)
- Pathophysiological investigations including alpha-synuclein, EHT analysis, autophagy, proteomics…

Rationale:

Accumulation of alpha-synuclein mediates podocyte injury in Fabry nephropathy[2]

QPCT/L potentially affects alpha synuclein pathology by catalyzing its transformation into aggregation-prone pE-alpha-synuclein[3]

[1]ERCB, European Renal cDNA Bank- Kröner Fresenius Biobank established more than 20 years ago in an interdisciplinary European collaboration of renal research centers to enable systematic gene expression in kidney biopsies. [2]Braun et al., J Clin Invest. (2023); [3]Hartlage-Rübsamen et al., Acta Neuropathol. (2021)

Designing a dedicated study investigating varoglutamstat in stage 3/4 DKD patients

Key characteristics

- Double-blind placebo-controlled study
- Inclusion criteria stage 3/4 DKD patients with albuminuria
- On top of standard of care (SOC) and stratified by existing therapies
- Subgroup of patients may include concomitant NAFLD
- Treatment duration sufficient to establish a sustained benefit on key endpoints of eGFR and albuminuria (UA(p)CR)
- Broad panel of biomarkers to further investigate MoA
- Sufficiently powered to detect meaningful effect size

NAFLD: non-alcoholic fatty liver disease

vivoryon therapeutics

Florian Jehle

Pharmaceutical Industry Expert

CKD Market Perspectives

Florian Jehle

Introduction & Disclosures

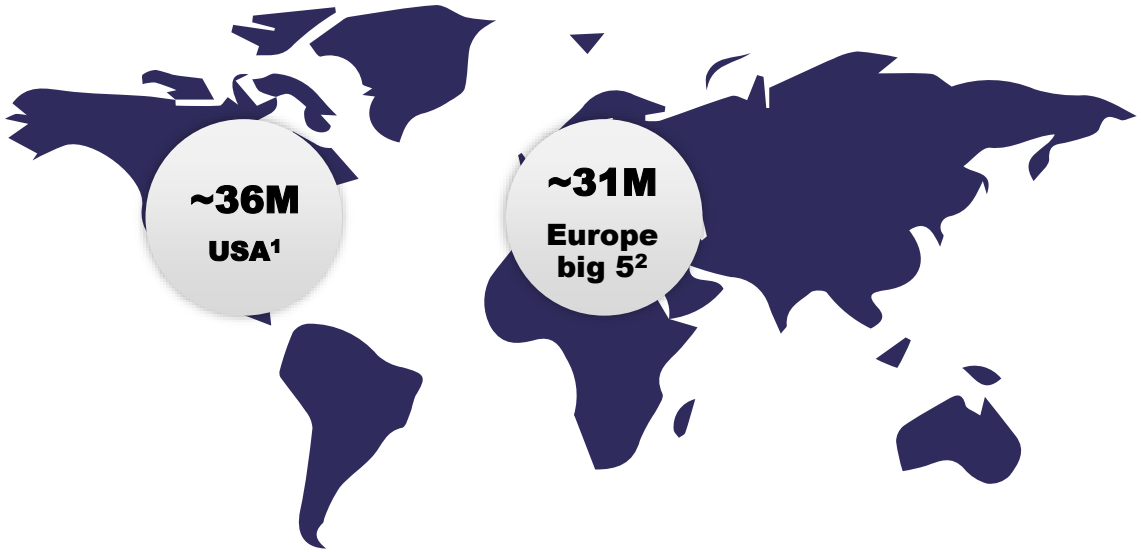
- Vifor-FMC Renal Pharma, Chief Executive Officer
- Vivoryon Therapeutics N.V., Consultant / Industry Expert Advisor role
- 20+ years in pharma and biotech with prior roles at Fresenius Medical Care Ventures; Unicyte AG; Fresenius Medical Care; Catenion Management consultants

The views and opinions expressed here are my personal views and do not necessarily reflect those of Vivoryon Therapeutics N.V., VFMCRP Ltd., or any other party.

Chronic kidney disease (CKD) is a significant global public health problem

- Causes progressive loss of kidney function and may lead to kidney failure or end-stage kidney disease (ESKD)
- In 2021, 68% of people in U.S. receiving kidney replacement therapy (KRT) were on dialysis; 32% transplant[3]
- Many patients do not know they have CKD until the later stages (stage 3+)
- Key risk factors include diabetes and cardiovascular disease

Estimated prevalence of CKD in U.S and Europe



Every 24 hours, ~360 people in the US begin treatment for kidney failure (dialysis or transplant)[1]

In the US, patients aged 40–45 years on hemodialysis have a life expectancy similar to that of individuals aged 75–79 years in the general population (~11 years)[4]

It is estimated that 5.4 million people worldwide will receive KRT in 2030, with most growth in Asia – in 2010 ~2.6 million received KRT[5]

[1]https://www.cdc.gov/kidney-disease/ckd-facts/index.html accessed September 2024; [2]Lancet (2020) GBD Chronic Kidney Disease Collaboration, Global Burden of Disease Study 2017, estimate based on prevalence / count for United Kingdom, Germany, France, Italy, Spain. [3]Stel et al, Nephrology Dialysis Transplantation (2024); prevalence of KRT by modality; "dialysis" includes peritoneal dialysis (PD) and hemodialysis (HD); [4]USRDS, 2023 annual data report, Chapter 6: End Stage Renal Disease; [5]Liyanage et al., Lancet (2015)

Late-stage CKD patients are at greatest risk of kidney failure requiring kidney replacement therapy (KRT; dialysis or transplant)

eGFR Categories	A1: Normal to mildly increased (ACR <30 mg/g)	A2: Moderately increased (ACR 30-299 mg/g)	A3: Severely increased (ACR ≥300 mg/g)	Total
G3b: Moderately to severely decreased (eGFR 30-44 mL/min/1.73m$^{2)}$	1,352,646	713,094	404,118	2,469,858
G4: Severely decreased (eGFR 15-29 mL/min/1.73m$^{2)}$	155,521	186,610	409,412	751,543
G5:Kidney failure (eGFR <15 mL/min/1.73m$^{2)}$	0	34,970	291,233	326,203

KDIGO CKD risk category: High Very high

Prevalence of adult patients with CKD at different disease stages in the US

Source: NIH NIDDK USRDS; data from National Health and Nutrition Examination Survey (NHANES; based on the NHANES 2017 – March 2020 Survey); adults ≥ 20 years of age by eGFR[1] and ACR[2]

In 2021, **808,536** people in the U.S. were receiving KRT (2,436 per million population)

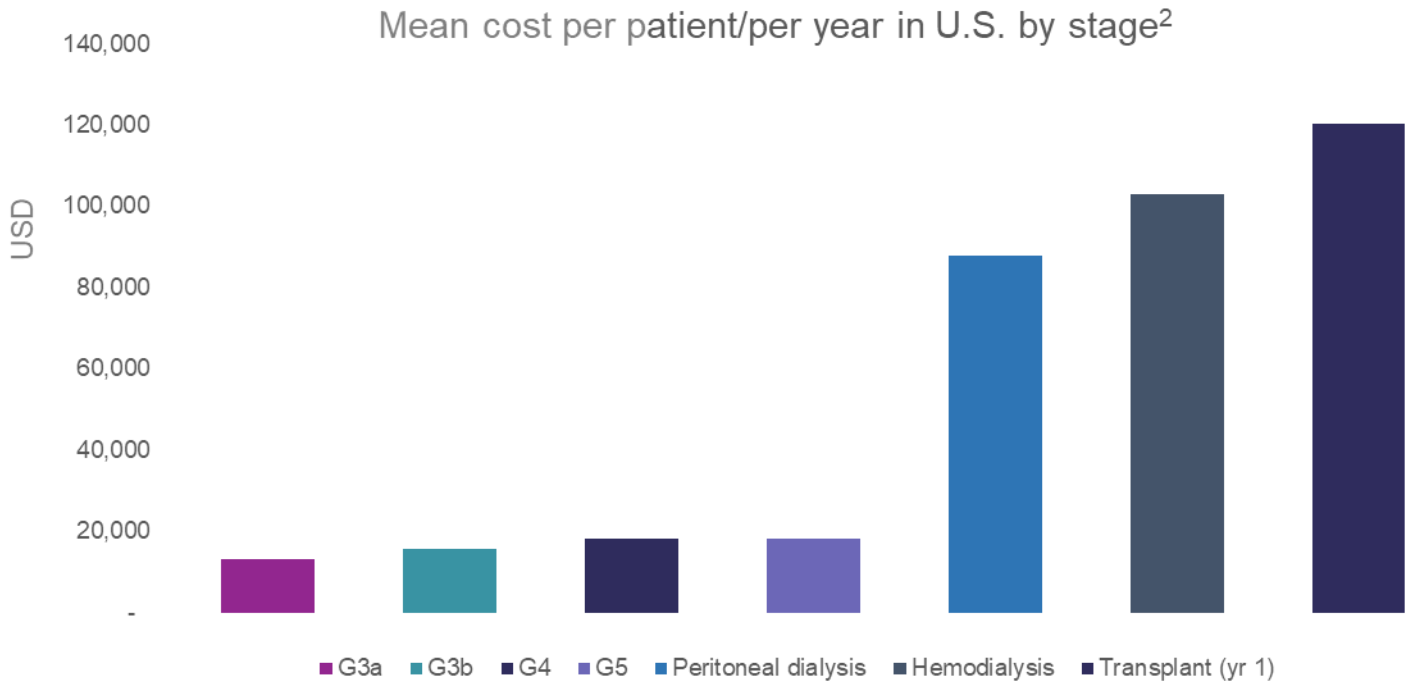
This was double the prevalence in Europe for people receiving KRT (1,187 per million population) in the same study[3]

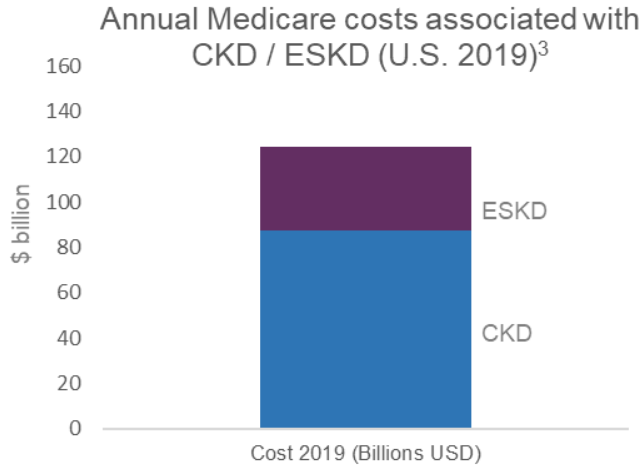
[1]eGFR: estimated glomerular filtration rate. [2]albumin to creatinine ratio [3]Stel et al, Nephrology Dialysis Transplantation (2024)

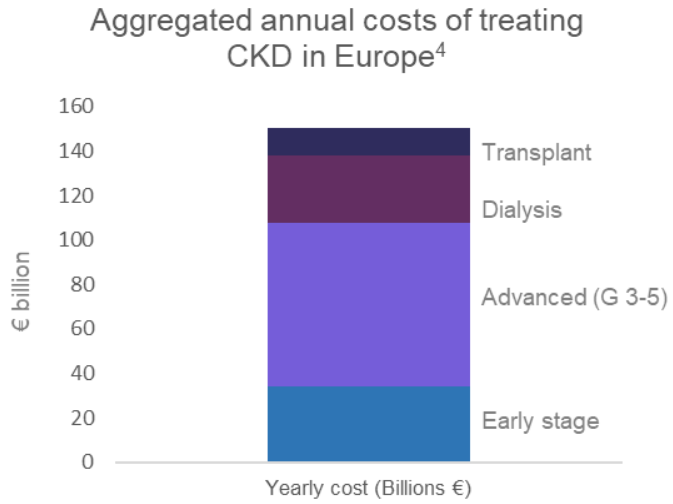
Treatment of CKD poses a major financial burden with costs escalating significantly with later stages of disease

- Most countries use a mix of public and private funding
- Costs increase significantly when people require KRT

  <1% of Medicare beneficiaries in US have kidney failure, but kidney failure expenses were >6% of its spend and exceeding $50 billion[1]



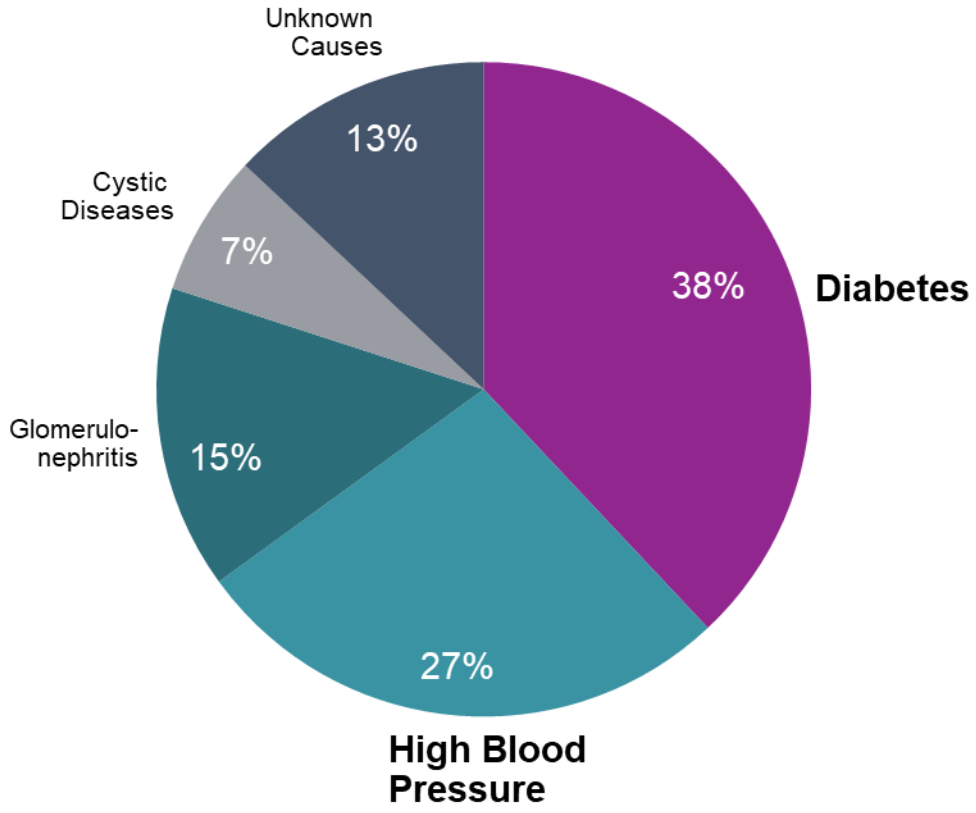




[1]United States Renal Data System. 2022 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States (National Institute of Diabetes and Digestive and Kidney Diseases, 2022). [2]Jha et al., Adv Ther. (2023) Estimated annual per patient CKD management costs by KDIGO GFR stage United States, commercial. [3]U.S. Medicare costs, cdc.gov/kidney disease fast facts; [4]Vanholder et al., Clinical Kidney Journal (2021)

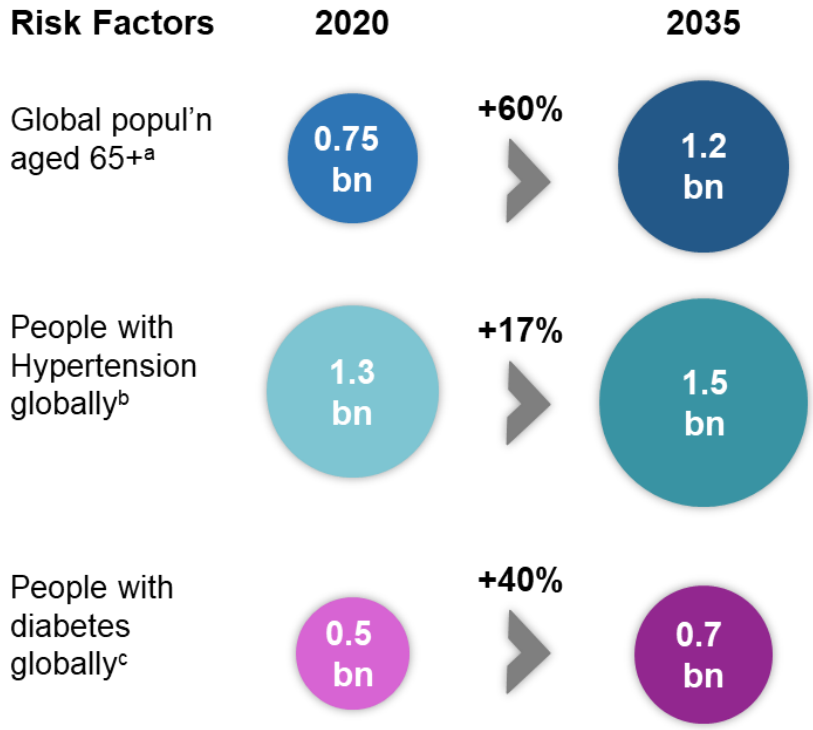
Rate of cardio-metabolic risk factors and age are key dynamics in the CKD market

Diabetes and hypertension are leading causes of end-stage kidney disease[1]



Number of CKD patients and burden of disease expected to increase globally in next decade[2]

Global CKD prevalence:
>10% of general population, or
>800mn CKD patients[3]



[1]US Renal Data System [2]Adapted from Fresenius Medical Care AG, Investor Presentation Q2 2024, page 5, references include [a]United Nations Department of Economic and Social Affairs, Population Division (2022). World Population Prospects 2022: Summary of Results. UN DESA/POP/2022/TR/NO.3. [b]WHO Global Health Observatory (2019), adjusted for population aged >18. [c]IDF Diabetes Atlas 2021 (10th edition); [3]Based on estimates for 2017, Jager et al., Kidney International (2019)

SGLT2s and GLP-1s delay disease progression and affect kidney and CV outcomes but are no cure

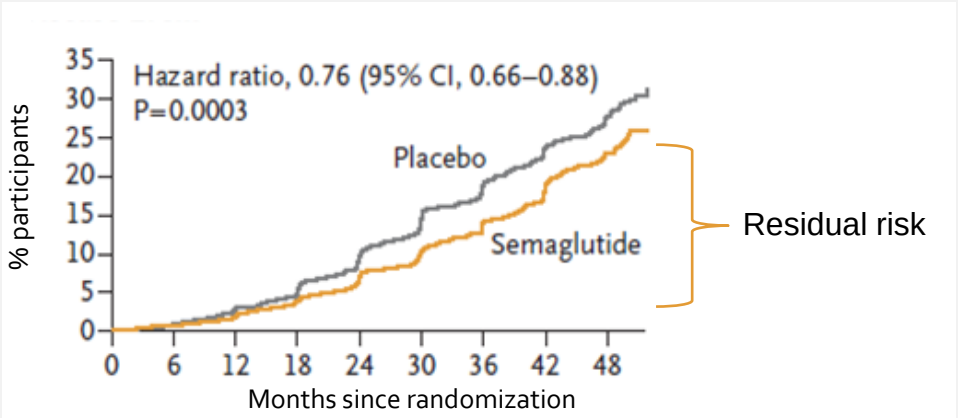
- Improvement of SoC – more treatments available, better implementation of guidelines
- But even with all measures, still a substantial number of patients progress to ESKD and need KRT
- Products stabilising or improving kidney function needed

SGLT2s

Typical changes eGFR following introduction and long-term use of SGLT2 inhibitors in T2 diabetes[1]

GLP-1s

e.g. reduction in major kidney disease events shown in FLOW trial (CKD patients with T2 diabetes)[2]



[1]Bailey et al. Current Diabetes Reports (2022), [2]Perkovic et al., NEJM (2024) FLOW trial

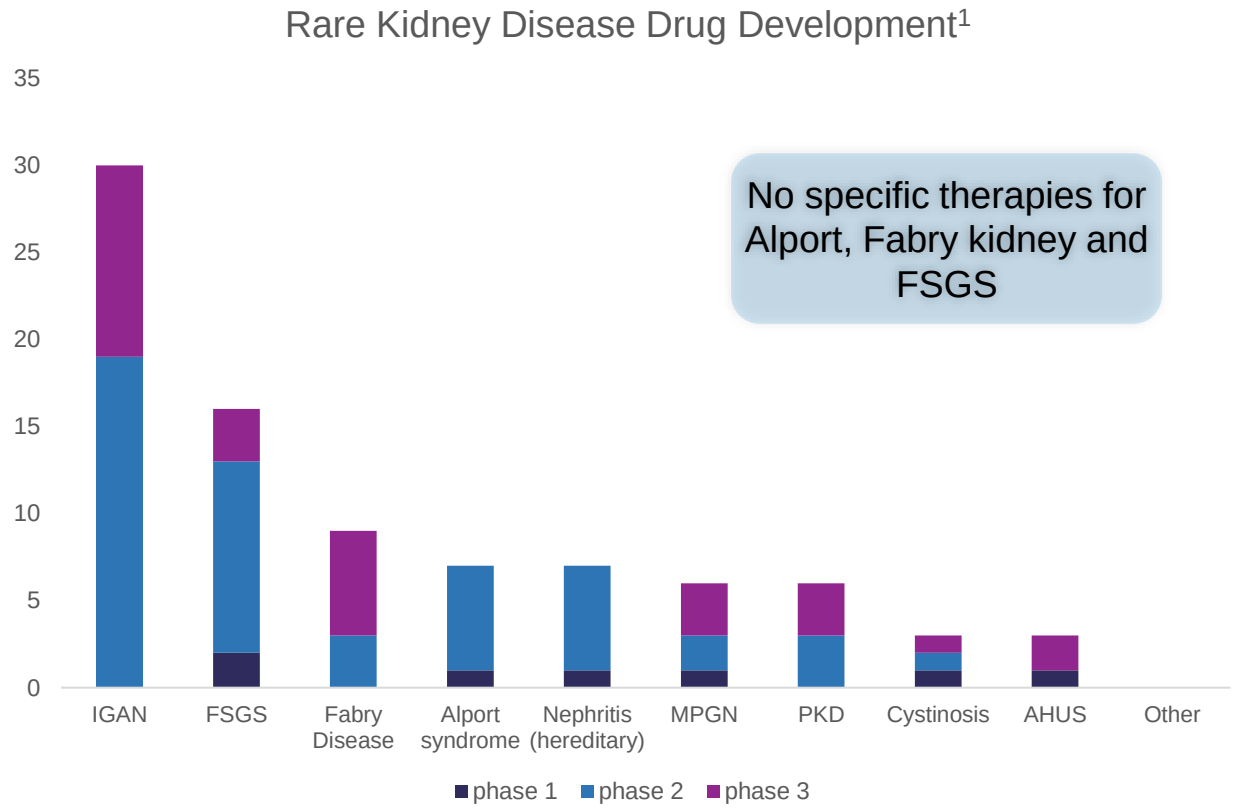
There is a significant medical need for products that stabilize or improve kidney function for both large and rare kidney diseases

CKD / DKD

- Standard of care primarily ACE, ARBi, anti-hypertensives, anti-diabetics
- Still high unmet need to stop disease progression
- Only ProKidney showed stabilization of eGFR in Ph 2, no other potential disease modifying competitor in late clinical development

Rare nephrology diseases

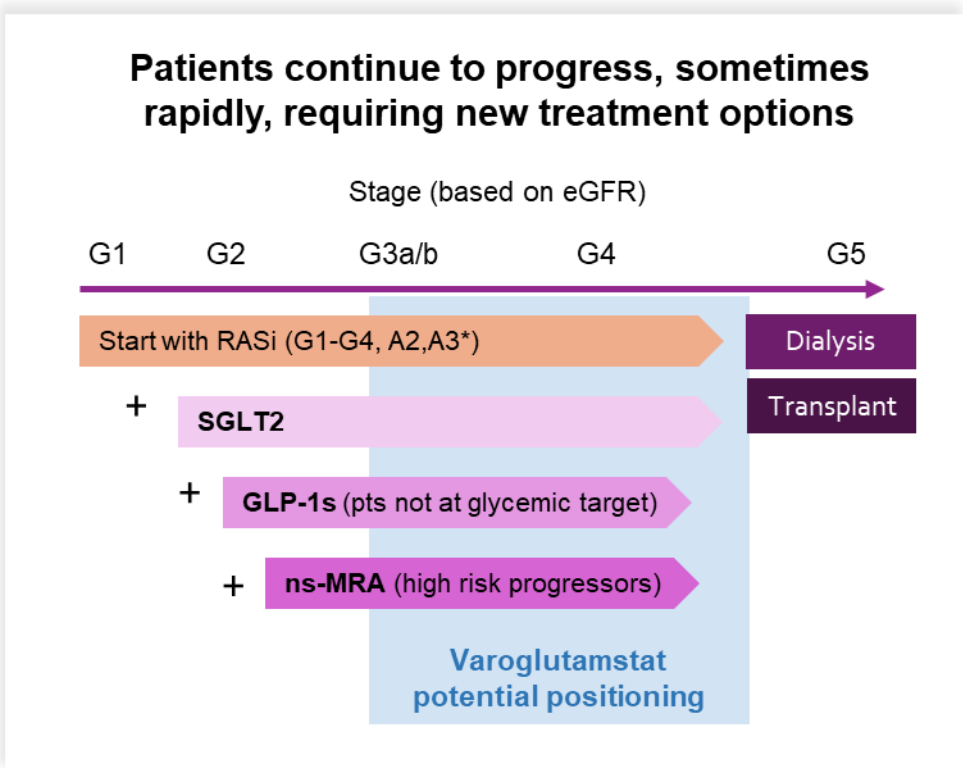
- Development focus on disease modifying therapies
- High reimbursement price levels established
- Concentration of development in only a few areas with unmet needs in other diseases



[1]Provided by Vivoryon based on Adis Insight drug development database September 2024; Abbreviations: IGAN: IgA Nephropathy; FSGS: Focal segmental glomerulosclerosis; MPGN: Membranoproliferative glomerulonephritis; PKD: Polycystic kidney disease; AHUS: Atypical haemolytic uraemic syndrome

Varoglutamstat could be an important addition to the treatment landscape for CKD patients if successful in planned studies

- Limited competition in terms of drugs that could potentially stabilize / improve kidney function
- Novel mechanism of action addressing underlying inflammatory / fibrotic pathways
- Initial clinical studies will assess varoglutamstat on top of existing standard of care
- Oral product easily administered with good combinability potential



Significant market potential for oral varoglutamstat in stage 4 and fast progressing stage 3b CKD / DKD patient population

*A2, A3 refers to albuminuria status. Schematic broadly based on KDIGO guidelines 2024; For illustrative purposes only; not a comprehensive treatment algorithm

Recent transactions highlight increasing interest of big pharma companies in acquiring assets in the kidney disease space

Novartis Acquires Chinook Therapeutics[1]

Deal Value: Up to $3.5 billion

Details: Novartis acquired Chinook Therapeutics, a company specializing in precision medicines for kidney diseases, including two late-stage candidates for IgA nephropathy

Vertex Acquires Alpine Immune Sciences[2]

Deal Value: Approx. $4.9 billion

Details: Vertex acquired Alpine Immune Sciences to enhance its portfolio, particularly with Alpine's lead product, povetacicept, which has shown promising results in early studies in treating IgA nephropathy

Asahi Kasei Acquires Calliditas Therapeutics[3]

Deal Value: Approx. $1.1 billion

Details: Asahi Kasei acquired Calliditas Therapeutics to expand its global healthcare presence, focusing on Calliditas' treatment for IgA nephropathy which is approved in the US, EU and China

[1]Announced June 12, 2023; [2]Announced April 10, 2024; [3]Announced May 28, 2024

Vivoryon is well-positioned with varoglutamstat to address the unmet needs in kidney disease

- Demographics and key risk factors likely to lead to an increase in number of kidney disease patients and growing burden of disease globally
- SGLT2s/GLP1s delay disease progression only, but no cure
- Still a high unmet need for majority of CKD / DKD patients
- Significant market potential for oral varoglutamstat in stage 4 and fast progressing stage 3b CKD / DKD patient population and certain rare diseases e.g Alport and Fabry
- Increasing interest from big pharma in kidney diseases demonstrated by recent deals with high valuations

Kevin Carroll, PhD

CEO
KJC Statistics

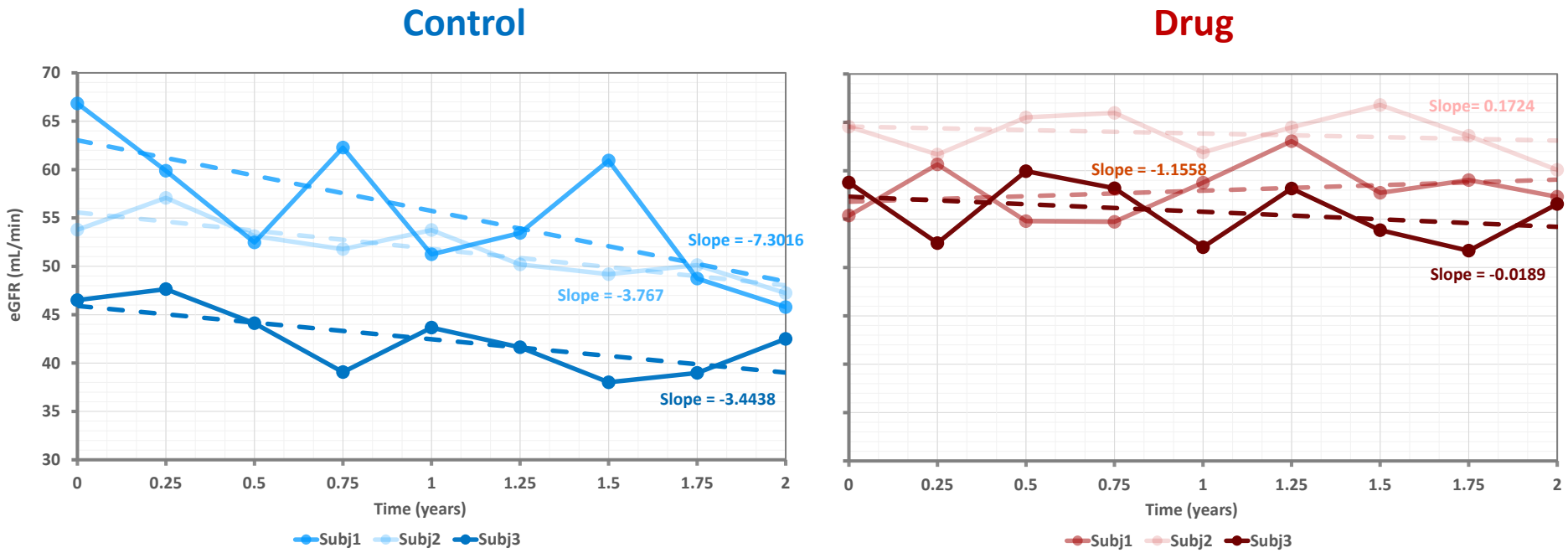
Statistical considerations for clinical development in kidney disease

Kevin Carroll, PhD

Analysis of eGFR in CKD Trials

- Simple CFB via ANCOVA typical analysis in the 80's and 90's
  - Focus on the difference in mean eGFR between arms at some fixed timepoint, e.g. 1 or 2 years
- Shift towards mixed model repeated measures in the 00's
  - Better as includes all datapoints over time, but inference still focusing on the different mean eGFR between arms at a fixed timepoint
- Increasing use of random coefficients analysis in 00's and beyond
  - Does not rely differences at a given timepoint
  - Uses all available data to estimate the overall Annualized Rate of Change (mL/min/yr) [or slope] and compares arms based on this measure
  - Reflects how subjects are managed clinically
- Possible alternatives to eGFR Slope
  - Time Normalized AUC (AUCT)
  - Average eGFR over some time period of interest, e.g. 6-12 months or 12-24 months, [note this is mathematically the same as AUCT]

Random Coefficients (RC) Analysis



	Control Slope (mL/min/yr)	Drug Slope (mL/min/yr)
Subj1	-7.30	0.17
Subj2	-3.77	-1.16
Subj3	-3.44	-0.02
Mean	-4.84	-0.34

RC compared to other approaches[1,2]

- Thorough comparison of approach to the analysis of eGFR data over time
  - RC Single Slope vs RC 2-Slope vs AUCT vs CFB at a single timepoint
- RC slope analysis clearly preferred is underlying rate of decline is approximately linear
- If an acute hemodynamic effect is expected via mechanism, RC 2-Slope examining acute and chronic slopes is preferred
- If eGFR is grossly non-linear then AUCT is preferred
- Simple CFB at a given time point is both least efficient and least satisfactory
- Apparent FDA misconception that if eGFR rate of change over time not fully linear, RC analysis is biased and increases Type I Error
- This is not the case, there is no increase in the risk of false claim of efficacy
- Power may be reduced but the comparison of slopes under the null remains completely valid with Type I Error of 5% maintained

1: DeVries, Carroll & Lewis (2023). A practical guide to the appropriate analysis of eGFR data over time: A simulation study . Pharm Stats
2: Lewis, Carroll, DeVries & Barratt (2023). Conditional power and information fraction calculations at an interim analysis for random coefficient models. Pharm Stats.

Recent FDA Approvals in CKD and Ongoing Phase 3 Trials

- eGFR slope via RC analysis is the primary efficacy endpoint in recent FDA approvals in CKD and many ongoing Phase 3 trials
  - Travere Filspari
  - Novartis [Chinook] Fabhalta
  - Alexion ravulizumab
  - Ostuka Sibeprenlimab
  - Vera Atacicept
  - Allena
- Have either directly supported CKD trial design, analysis & reporting, incl FDA & EMA interactions, or via membership of Executive Trial Steering Committees
- FDA Cardio Renal is, on the whole, an excellent Division with excellent FDA medical leadership driven by good science
- Expect to be challenged regarding (i) the possibility of a short term acute effect on eGFR (ii) the critical importance of complete, ITT follow up for eGFR (iii) the handling and possible influence of missing eGFR data over time

Consistent findings for eGFR with varoglutamstat in VIVIAD

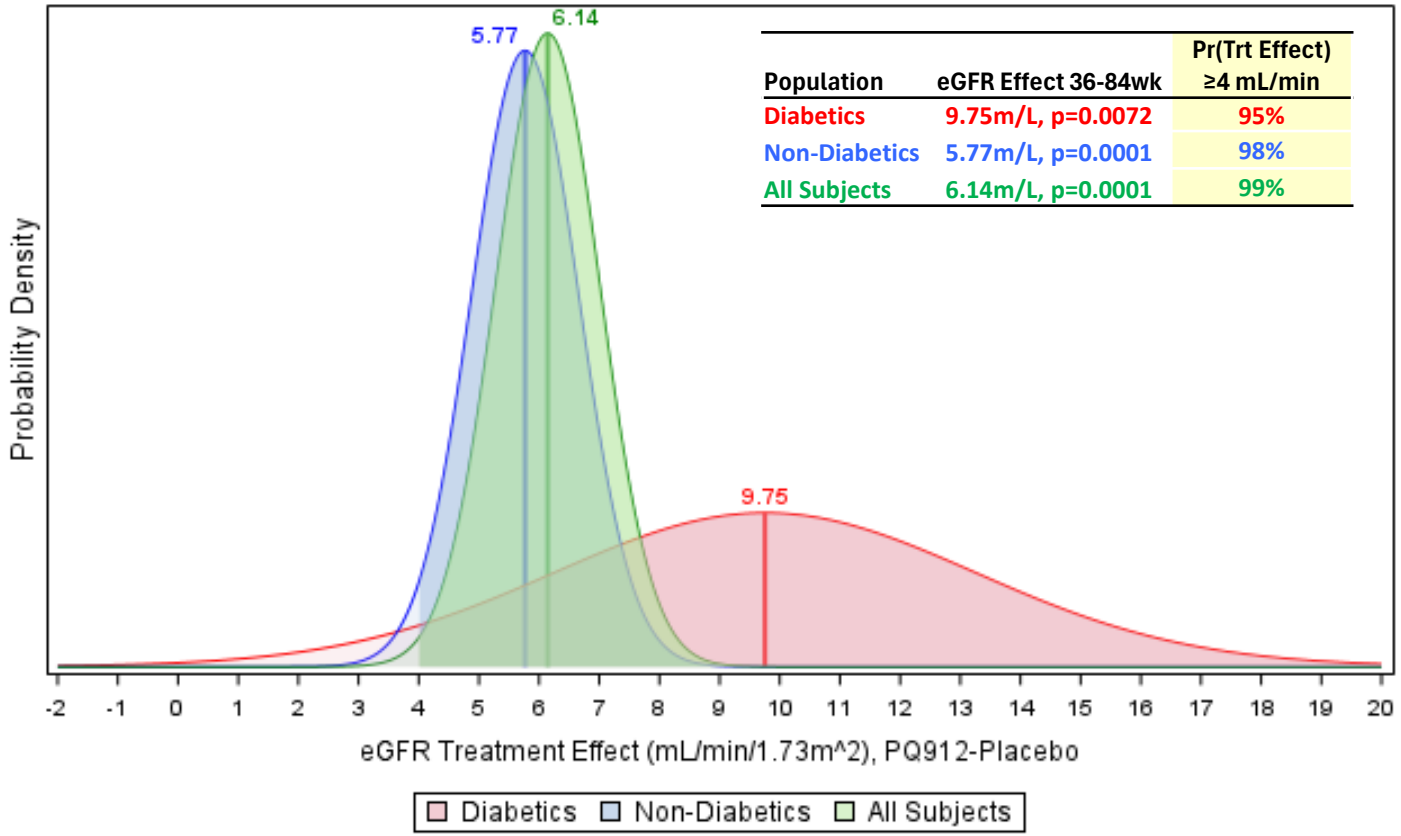
- Very thorough data analysis
  - Overall varoglutamstat vs placebo
  - varoglutamstat by dose vs placebo
  - By risk group for CKD Hypertension (treated with antihypertensives or having a BP > 150/95) or T2DM (being treated with antidiabetics or HbA1c >6.5%)
  - And further modified by existence of concomitant treated cardiac disease and patients having eGFR <=60.
  - Re-analysis of blood for creatinine, recomputation of eGFR and statistical analysis thereof
- As shown, the substantial treatment effect on eGFR slope seen for varoglutamstat vs placebo in the overall pulsation is driven by an even larger effect in patients with T2DM

VIVIAD Study eGFR Analysis

Fig F1. MMRM Analysis eGFR (mL/min/1.73m^2) : MDRD eGFR Equation, All Repeat Creatinine Values Included

Diabetics 9.75 [3.537],p=0.0072, Non Diabetics 5.77 [0.885],p=<.0001, All Subjects 6.14 [0.861],p=<.0001

Prob(Effect >= 4 mL/min): Diabetics 94.62%, Non-Diabetics 97.69%, All Subjects 99.35%



Population	eGFR Effect 36-84wk	Pr(Trt Effect) ≥4 mL/min
Diabetics	9.75m/L, p=0.0072	95%
Non-Diabetics	5.77m/L, p=0.0001	98%
All Subjects	6.14m/L, p=0.0001	99%

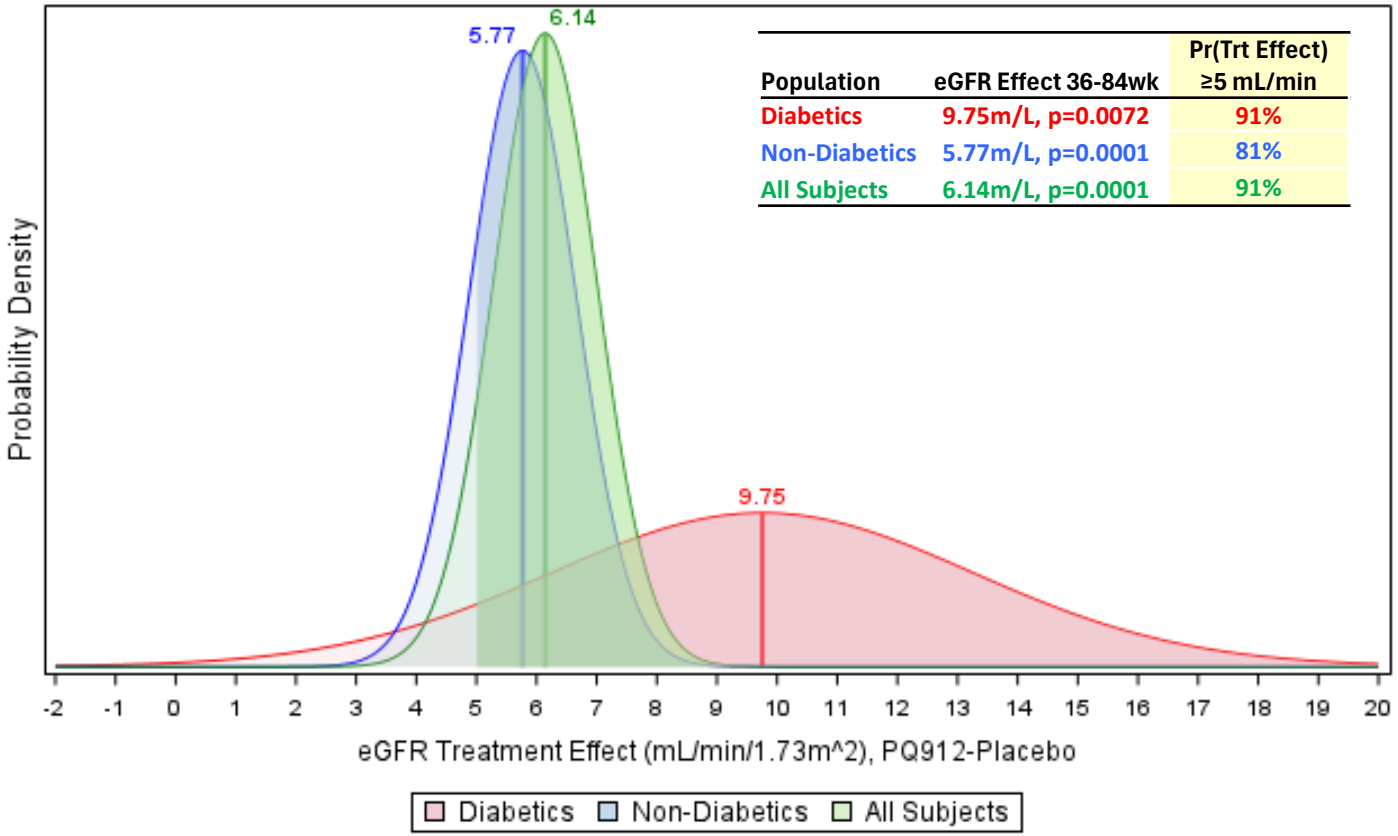
MMRM includes visits 4, 12, 24, 36, 48, 60, 72, 84 and EOT. Baseline is included as a covariate. Week 8 not included due to low N

VIVIAD Study eGFR Analysis

Fig F2. MMRM Analysis eGFR (mL/min/1.73m^2) : MDRD eGFR Equation, All Repeat Creatinine Values Included

Diabetics 9.75 [3.537],p=0.0072, Non Diabetics 5.77 [0.885],p=<.0001, All Subjects 6.14 [0.861],p=<.0001

Prob(Effect >= 5 mL/min): Diabetics 90.87%, Non-Diabetics 80.69%, All Subjects 90.76%



Population	eGFR Effect 36-84wk	Pr(Trt Effect) ≥5 mL/min
Diabetics	9.75m/L, p=0.0072	91%
Non-Diabetics	5.77m/L, p=0.0001	81%
All Subjects	6.14m/L, p=0.0001	91%

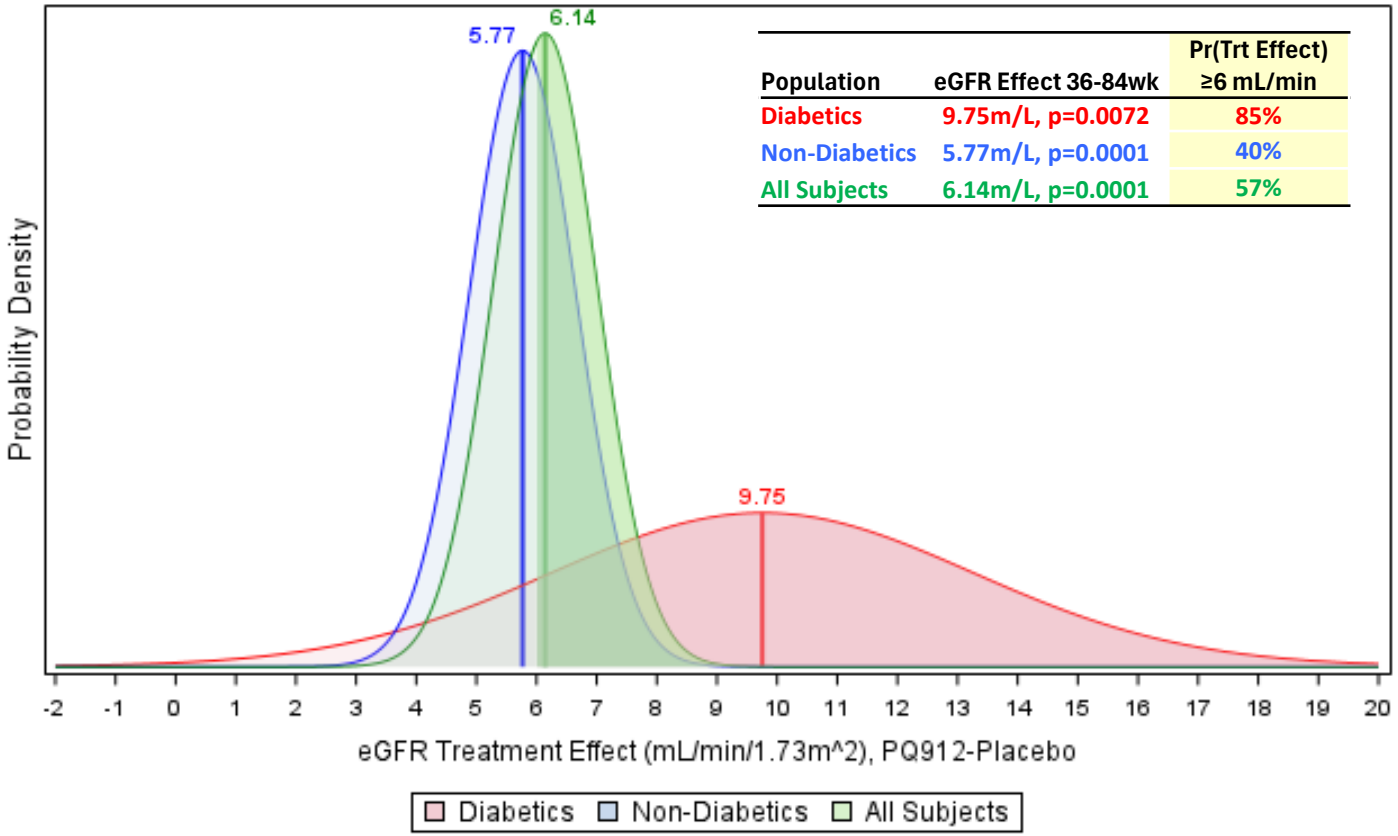
MMRM includes visits 4, 12, 24, 36, 48, 60, 72, 84 and EOT. Baseline is included as a covariate. Week 8 not included due to low N

VIVIAD Study eGFR Analysis

Fig F3. MMRM Analysis eGFR (mL/min/1.73m^2) : MDRD eGFR Equation, All Repeat Creatinine Values Included

Diabetics 9.75 [3.537],p=0.0072, Non Diabetics 5.77 [0.885],p=<.0001, All Subjects 6.14 [0.861],p=<.0001

Prob(Effect >= 6 mL/min): Diabetics 85.41%, Non-Diabetics 39.64%, All Subjects 56.61%



Population	eGFR Effect 36-84wk	Pr(Trt Effect) ≥6 mL/min
Diabetics	9.75m/L, p=0.0072	85%
Non-Diabetics	5.77m/L, p=0.0001	40%
All Subjects	6.14m/L, p=0.0001	57%

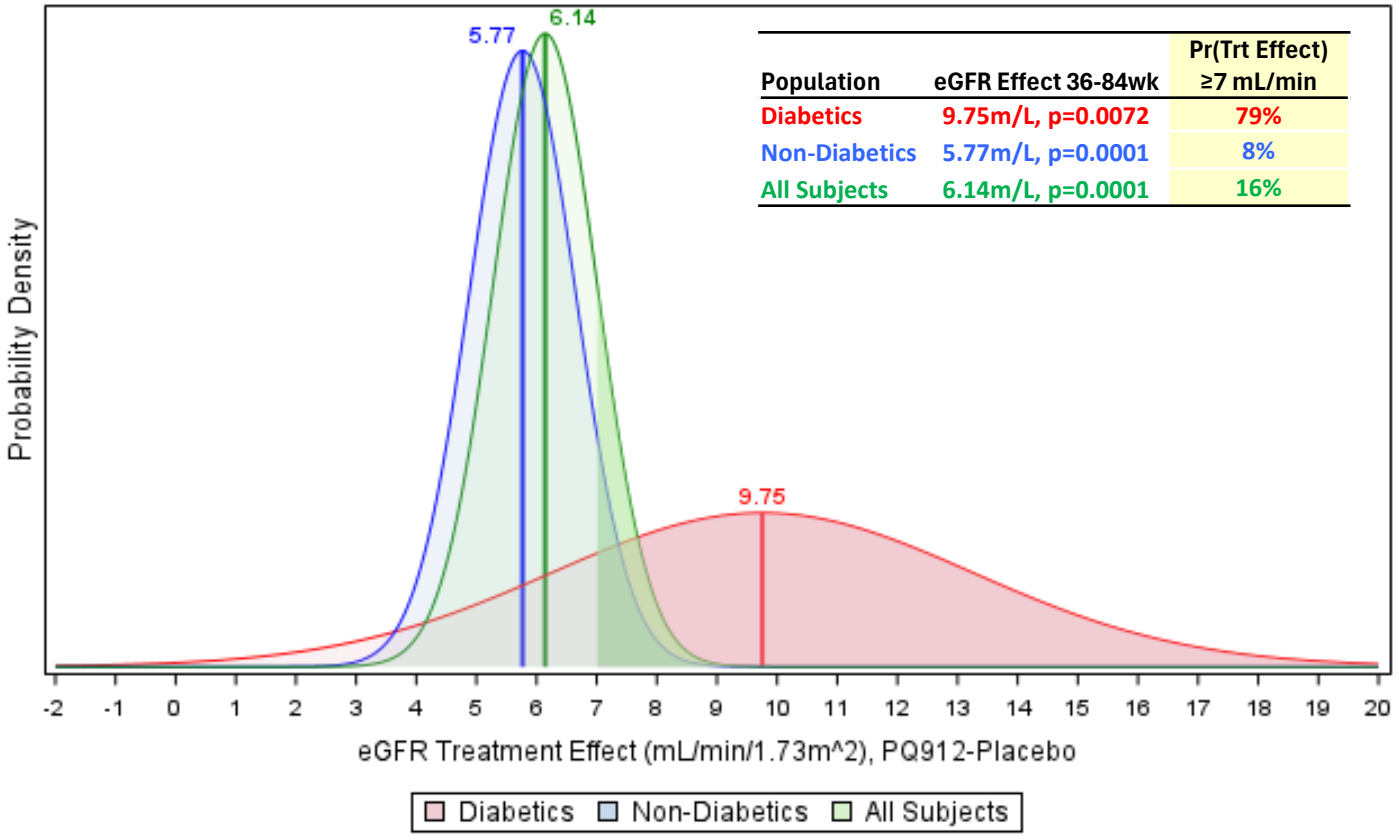
MMRM includes visits 4, 12, 24, 36, 48, 60, 72, 84 and EOT. Baseline is included as a covariate. Week 8 not included due to low N

VIVIAD Study eGFR Analysis

Fig F4. MMRM Analysis eGFR (mL/min/1.73m^2) : MDRD eGFR Equation, All Repeat Creatinine Values Included

Diabetics 9.75 [3.537],p=0.0072, Non Diabetics 5.77 [0.885],p=<.0001, All Subjects 6.14 [0.861],p=<.0001

Prob(Effect >= 7 mL/min): Diabetics 78.08%, Non-Diabetics 8.21 %, All Subjects 16.02%



Population	eGFR Effect 36-84wk	Pr(Trt Effect) ≥7 mL/min
Diabetics	9.75m/L, p=0.0072	79%
Non-Diabetics	5.77m/L, p=0.0001	8%
All Subjects	6.14m/L, p=0.0001	16%

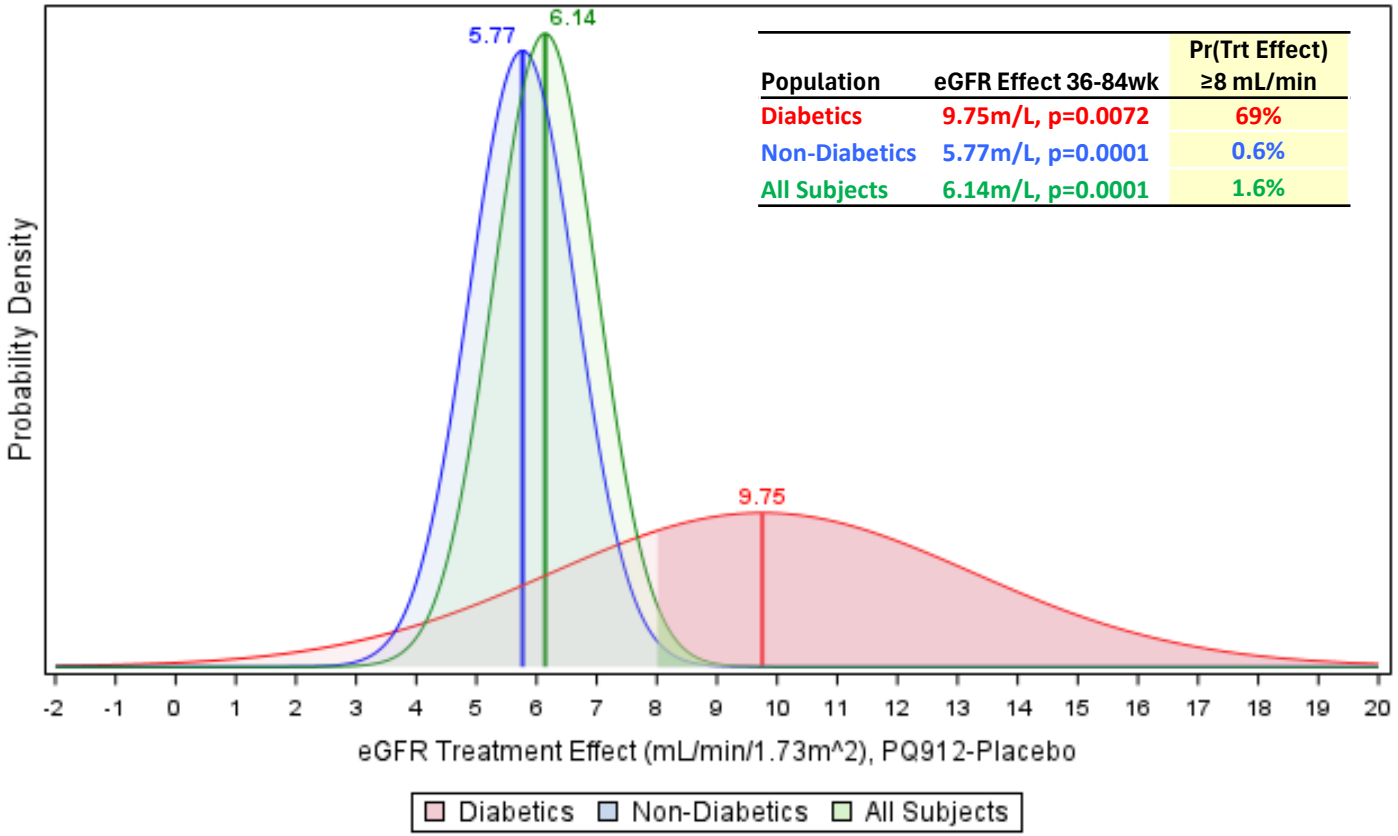
MMRM includes visits 4, 12, 24, 36, 48, 60, 72, 84 and EOT. Baseline is included as a covariate. Week 8 not included due to low N

VIVIAD Study eGFR Analysis

Fig F5. MMRM Analysis eGFR (mL/min/1.73m^2) : MDRD eGFR Equation, All Repeat Creatinine Values Included

Diabetics 9.75 [3.537],p=0.0072, Non Diabetics 5.77 [0.885],p=<.0001, All Subjects 6.14 [0.861],p=<.0001

Prob(Effect >= 8 mL/min): Diabetics 68.93%, Non-Diabetics 0.59 %, All Subjects 1.57 %



Population	eGFR Effect 36-84wk	Pr(Trt Effect) ≥8 mL/min
Diabetics	9.75m/L, p=0.0072	69%
Non-Diabetics	5.77m/L, p=0.0001	0.6%
All Subjects	6.14m/L, p=0.0001	1.6%

MMRM includes visits 4, 12, 24, 36, 48, 60, 72, 84 and EOT. Baseline is included as a covariate. Week 8 not included due to low N

Prospective Phase 2 PoC Design in Diabetic Subjects

- VIVIAD results in N=11 vs 19 diabetic subjects only (w/o hypertension), eGFR equation=MDRD equation, weighted mean eGFR (mL/min/m^2) over 36w-84w :
  - Varoglutamstat Lsmean (SE) (mL/min) 94.97 (2.040)
  - Pcbo Lsmean (SE) (mL/min) 86.54 (2.756)
  - Treatment Effect (mL/min) 9.75 (3.537) 95% CI (2.72, 16.79), p=0.0072
- Residual SD=125.66 (mL/min), auto correlation = 0.4538

- PoC recruitment non-linear over 48 weeks (η=1)[1]
- Follow-up = 48 weeks
- Primary Endpoint = average eGFR over weeks 20 to 48
- 4 weekly assessment of eGFR
- Interim cut after last subject reaches 24 weeks follow-up
  - Information Fraction = 62-63%

1: Carroll(2009). Back to Basics: Explaining sample size in outcome trials, are statisticians doing a thorough job?. Pharm Stats.

Phase 2 PoC Design in Diabetic Subjects

Overall Study Design				Interim 24 weeks after last subject randomized			
Hyp Effect (mL/min/m²)	SD (mL/min/m²)	Total N	Critical value (mL/min/m²)	≤ Observed Effect (mL/min/m²)	SD (mL/min/m²)	Fraction of Information	Conditional power
3.50	6.2857	80	2.3153	1.256	7.9624	62.5%	5%
3.50	6.2857	80	2.3153	1.490	7.9624	62.5%	10%
4.00	6.2857	62	2.6461	1.449	7.9624	63.3%	5%
4.00	6.2857	62	2.6461	1.714	7.9624	63.3%	10%
4.50	6.2857	48	2.9768	1.604	7.9624	62.0%	5%
4.50	6.2857	48	2.9768	1.908	7.9624	62.0%	10%

1 sided α error, Power=80%
Endpoint = average eGFR over weeks 20 to 48

- Hence, if N=62 Subjects, interim takes place 24 weeks after last subject randomized
- If observed effect on eGFR is ≤ 1.714 mL/min/m² then PoS is ≤10% and, hence, the trial can be stopped for futility

Beyond Futility

- As study is a Phase 2 PoC, the Sponsor could decide to have full sight of, and release, the interim results
- Downside is the potential for unintentional bias in the conduct of the study post the interim
- Also while there is no alpha penalty for a futility analysis, examining the interim data for efficacy would incur and alpha penalty
- And FDA and EMA would also recommend against full unblinding of the Sponsor
- To minimize such bias would require there to be no changes made whatsoever to the trial and its conduct post interim
- Further, would need to commit to examining the data arising pre and post interim separately to (hopefully) show no material difference in eGFR treatment effect estimate

1: Carroll(2009). Back to Basics: Explaining sample size in outcome trials, are statisticians doing a thorough job?. Pharm Stats.

Abbreviations

ANCOVA - analysis of covariance
AUC - area under the curve
AUCT - time normalized AUC (area under the curve)
CFB - Change from baseline
CKD - chronic kidney disease
eGFR - estimated glomerular filtration rate
EMA European Medicines Agency
FDA - Food and Drug Administration
ITT - Intention-to-Treat
Lsmean - Least-Squares Mean
MDRD - Modification of Diet in Renal Disease
MMRM - mixed model for repeated measures
Pcbo - placebo
PoC - proof of concept
PoS - probability of success
Pr / Prob - Probability
SD - standard deviation
SE - standard error
Trt - treatment
T2DM - Type 2 diabetes mellitus
RC - Random Coefficients
wk - week
w/o - without
yr - year

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Q&A

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