



# Innovation to Improve Kidney Health Outcomes

## Lead Program: Varoglutamstat in Diabetic Kidney Disease

July 2025

Vivoryon Therapeutics N.V.

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# Vivoryon: Poised to improve kidney health with varoglutamstat's novel mechanism of action and breakthrough clinical results



Strong scientific base; novel MoA (QPCT/L inhibition); pE-CCL2 data confirms target engagement



Two independent Phase 2 studies<sup>1</sup>; compelling long-term kidney function improvement



Extensive safety data package for varoglutamstat with convenient dose escalation scheme



Focused development plan for significant commercial opportunity in DKD and beyond



Additional potential orphan indications e.g. Alport syndrome / Fabry disease



Composition of matter protection in US until 2044+<sup>2</sup>; expansions to ROW due end 2025



Cash runway into January 2026; actively pursuing funding and BD opportunities



# Inhibiting QPCTL has potential to halt the progressive course of kidney disease through unique approach to tackle inflammation and fibrosis

## Huge unmet medical need



Current treatments do not stabilize / improve kidney function leaving significant risk of ESRD (dialysis, transplant) or cardiovascular event

## Inflammation a key underlying driver



Inflammation and fibrosis have long been known as key drivers of disease yet attempts to develop effective therapeutics selectively targeting key pathways have had limited success

## Targeting QPCTL to unlock inflammatory approach



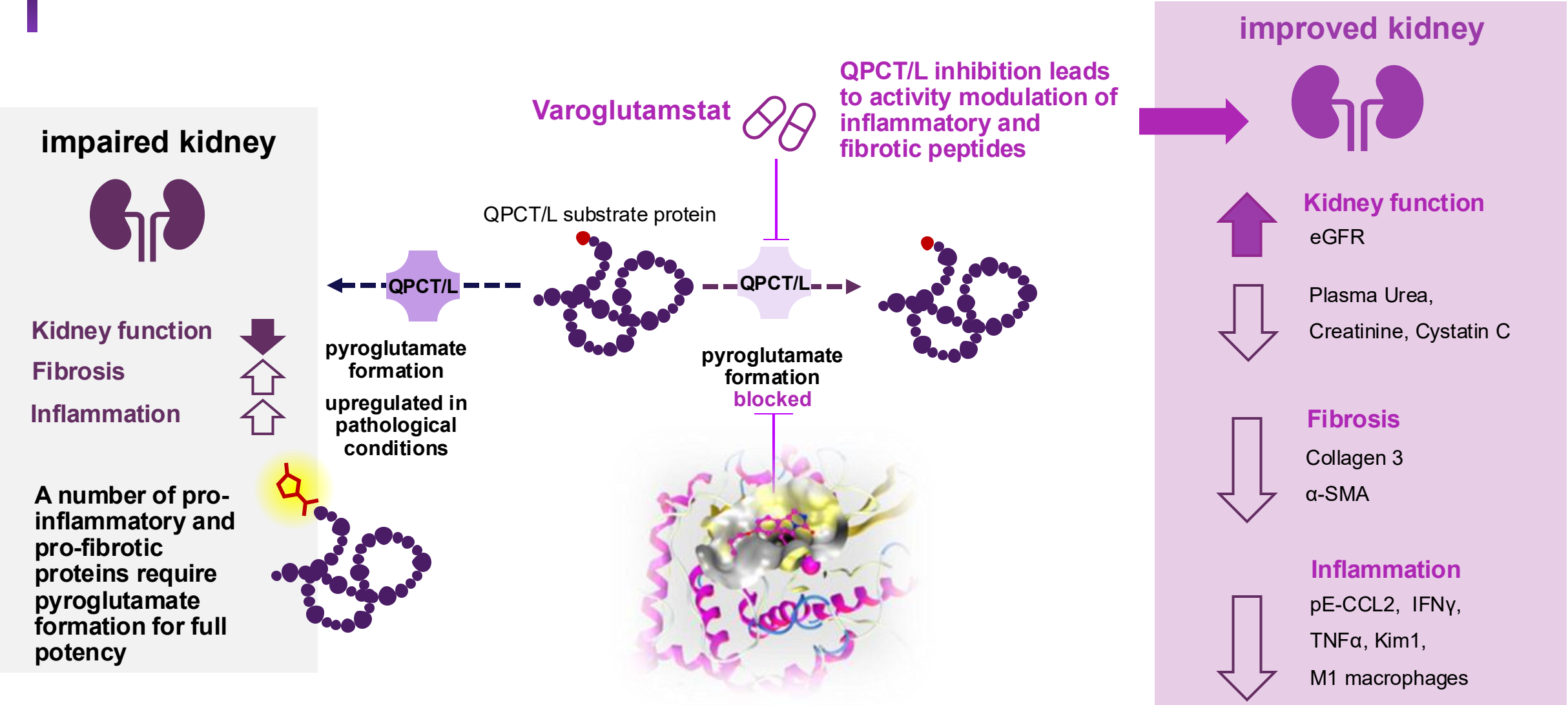
Vivoryon has identified QPCTL, an enzyme that creates pro-inflammatory pE-versions of key inflammatory proteins, as a promising target with potential to stabilize disease

## Varoglutamstat

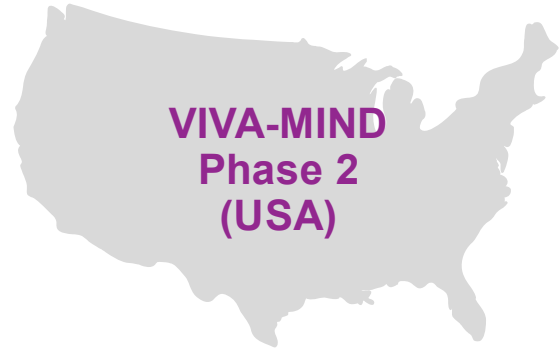
- Oral, selective QPCTL inhibitor
- Significantly improved kidney function<sup>1</sup> in two independent Phase 2 studies<sup>2</sup>
- Unprecedentedly large and sustainable effect size over two years



# Groundbreaking discovery: Inhibition of QPCT/L reduces kidney inflammation and fibrosis, and improves pathophysiology and kidney function



Vivoryon has evaluated varoglutamstat’s effect on kidney function in two independent randomized double-blind placebo-controlled Phase 2 studies



Similarities and differences between VIVIAD & VIVA-MIND

Parameter	VIVIAD (Europe)	VIVA-MIND (U.S.)
Patient selection	Mild AD, mean age 68 yrs	Mild AD, mean age 72 yrs
No. of patients treated	n=259	n=109
Varoglutamstat dose	300 and 600 mg BID	600 mg BID
Dose escalation period	Slow: 600 mg start week 13	Fast: 600 mg start week 9
Treatment duration	76 wks (mean) / 96 wks (max.)	46 wks (mean) / 72 wks (max.)
eGFR <sup>1</sup> sampling	Every 12 weeks plus week 4	Every 12 weeks plus weeks 4, 8, 16
No. of patients with diabetes	n=32 (12.4%)	n=16 (14.7%)

*Kidney function, measured using eGFR, was a pre-specified safety / exploratory endpoint*





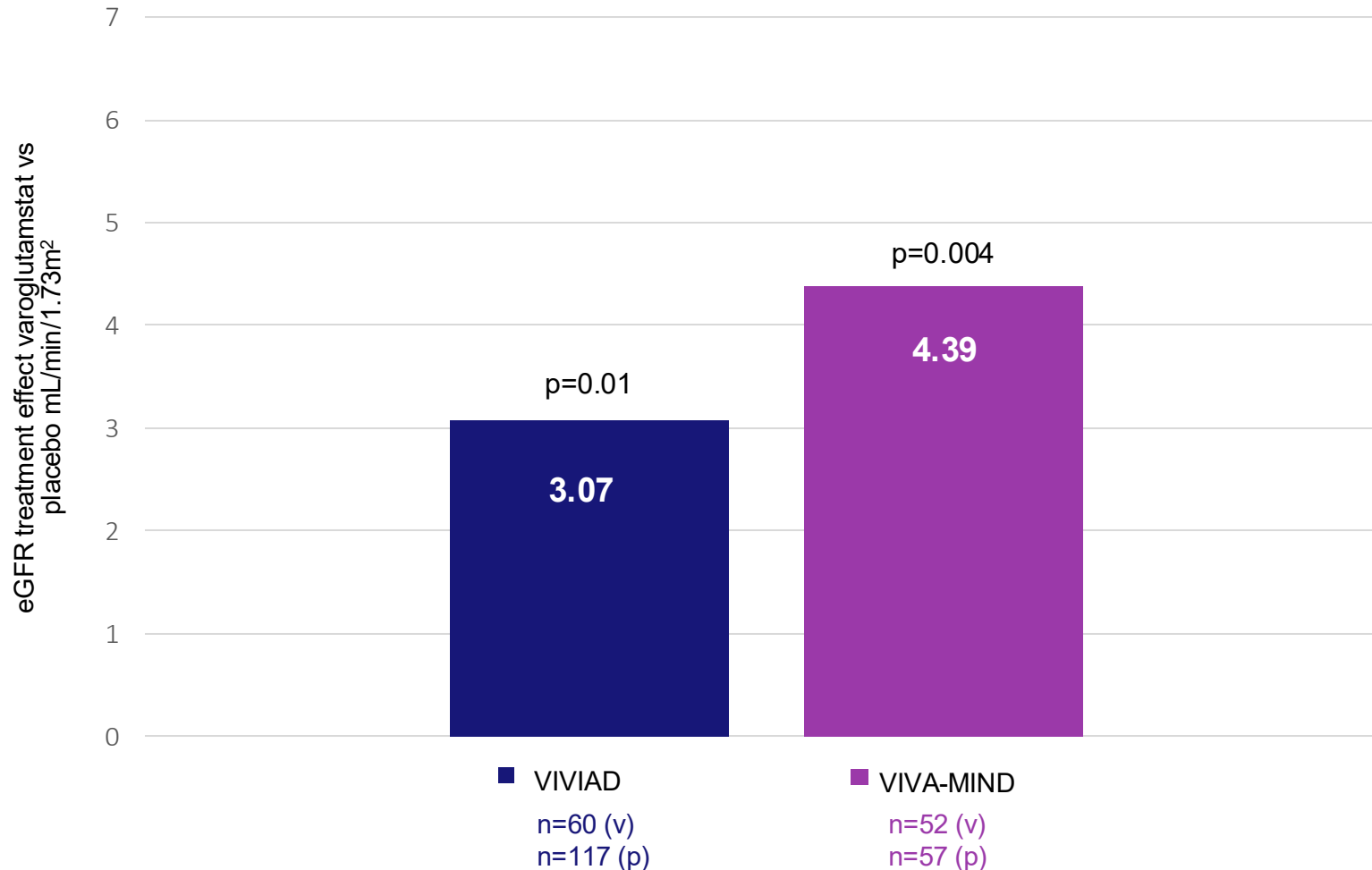
# VIVIAD and VIVA-MIND both show a statistically significant and clinically meaningful improvement in eGFR over baseline

eGFR results (MDRD); all patients randomized to 600 mg BID varoglutamstat (v) and placebo (p)

## eGFR treatment effect:

Difference between varoglutamstat and placebo (LSmean change from baseline)

Total population, 600 mg BID patients only, all visits



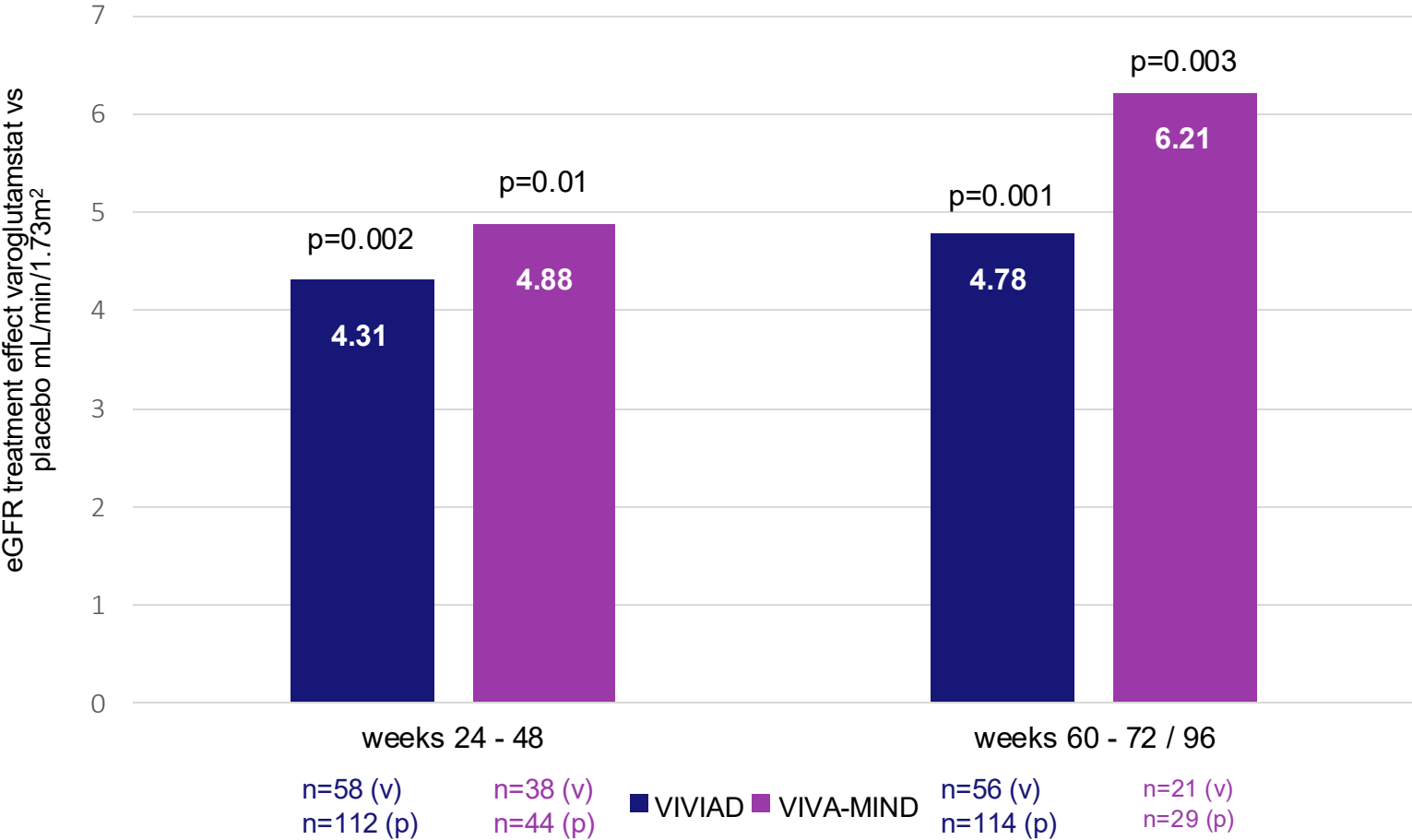
eGFR: estimated glomerular filtration rate, based on creatinine and calculated using the modification of diet in renal disease (MDRD) method. eGFR data were analysed over time using MMRM (mixed model for repeated measures) modelling including fixed effect terms for treatment, visit window and treatment-by-visit interaction using data from patients randomized to 600 mg and all visits on treatment, for VIVIAD (4 – 96 weeks) and VIVA-MIND (4 – 72 weeks)

# Consistent improvement in kidney function and effect size across distinct treatment periods in both studies

Sensitivity analysis; all patients randomized to 600 mg BID varoglutamstat (v) and placebo (p)

**eGFR treatment effect:**

Difference between varoglutamstat and placebo (LSmean change from baseline)



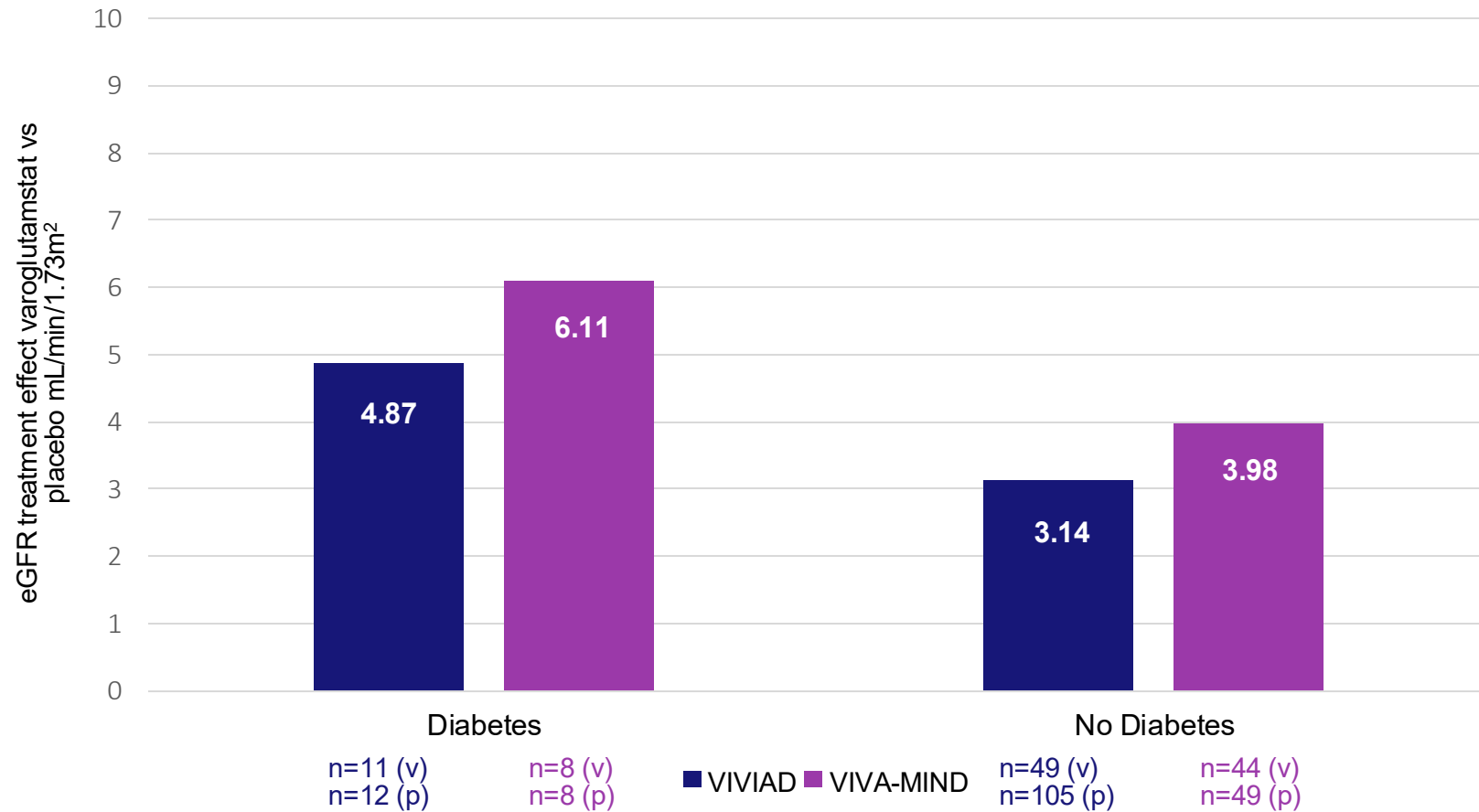


Results are nearly identical between studies when comparing treatment effect in patients with or without diabetes, with consistently higher effect in diabetes

Subgroup analysis; with and without diabetes; 600 mg BID varoglutamstat (v) and placebo (p)

**eGFR treatment effect:**

Difference between varoglutamstat and placebo (LSmean change from baseline)



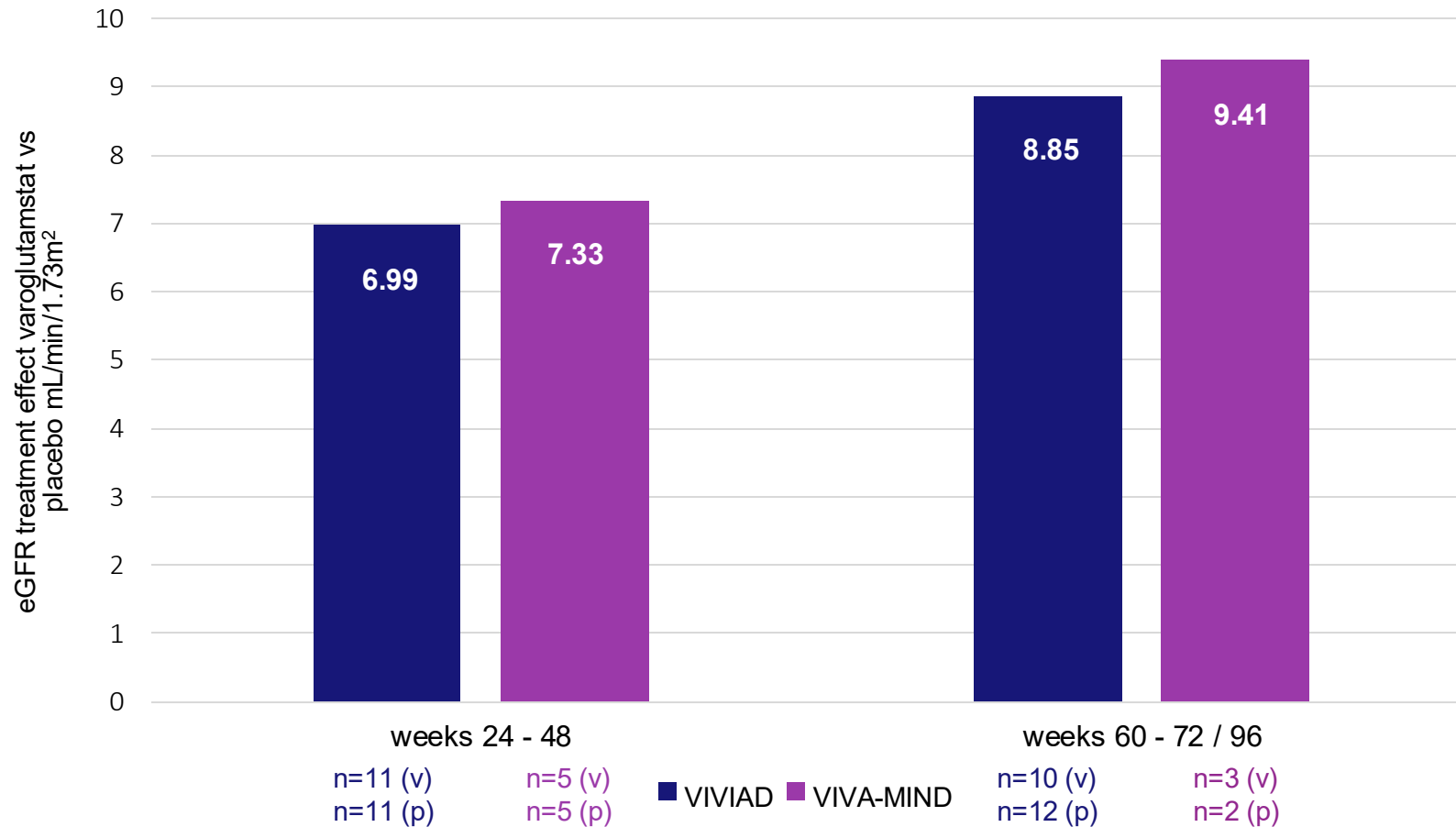
eGFR: estimated glomerular filtration rate, based on creatinine and calculated using the modification of diet in renal disease (MDRD) method. eGFR data were analysed over time using MMRM (mixed model for repeated measures) modelling including fixed effect terms for treatment, visit window and treatment-by-visit interaction using data from patients randomized to 600 mg and all visits on treatment, for VIVIAD (4 – 96 weeks) and VIVA-MIND (4 - 72 weeks). Diabetes patients identified as defined on slide 9; LSmean: least squares mean

# Consistent and very strong efficacy signal and large treatment effect observed in both studies in patients with diabetes at different timepoints

Subgroup analysis; patients with diabetes; 600 mg BID varoglutamstat (v) and placebo (p)

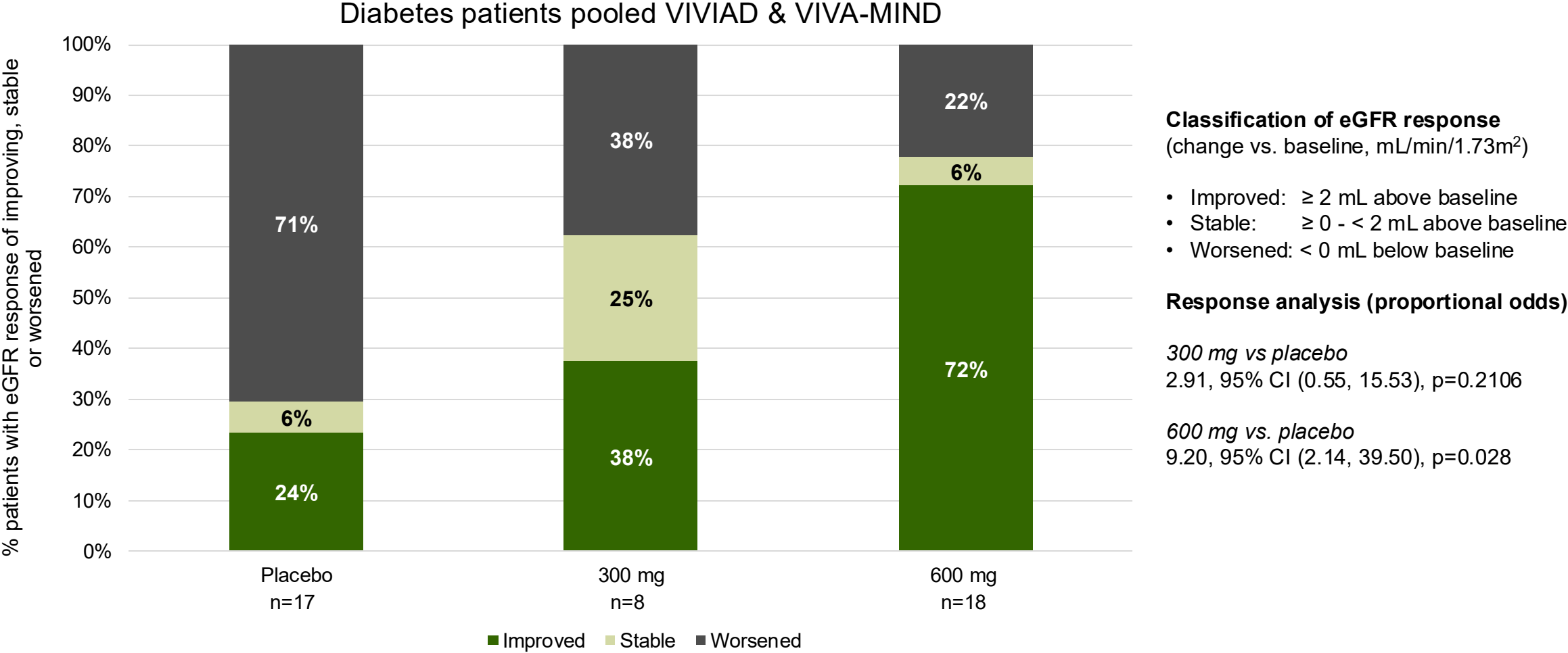
## eGFR treatment effect:

Difference between varoglutamstat and placebo (LSmean change from baseline)

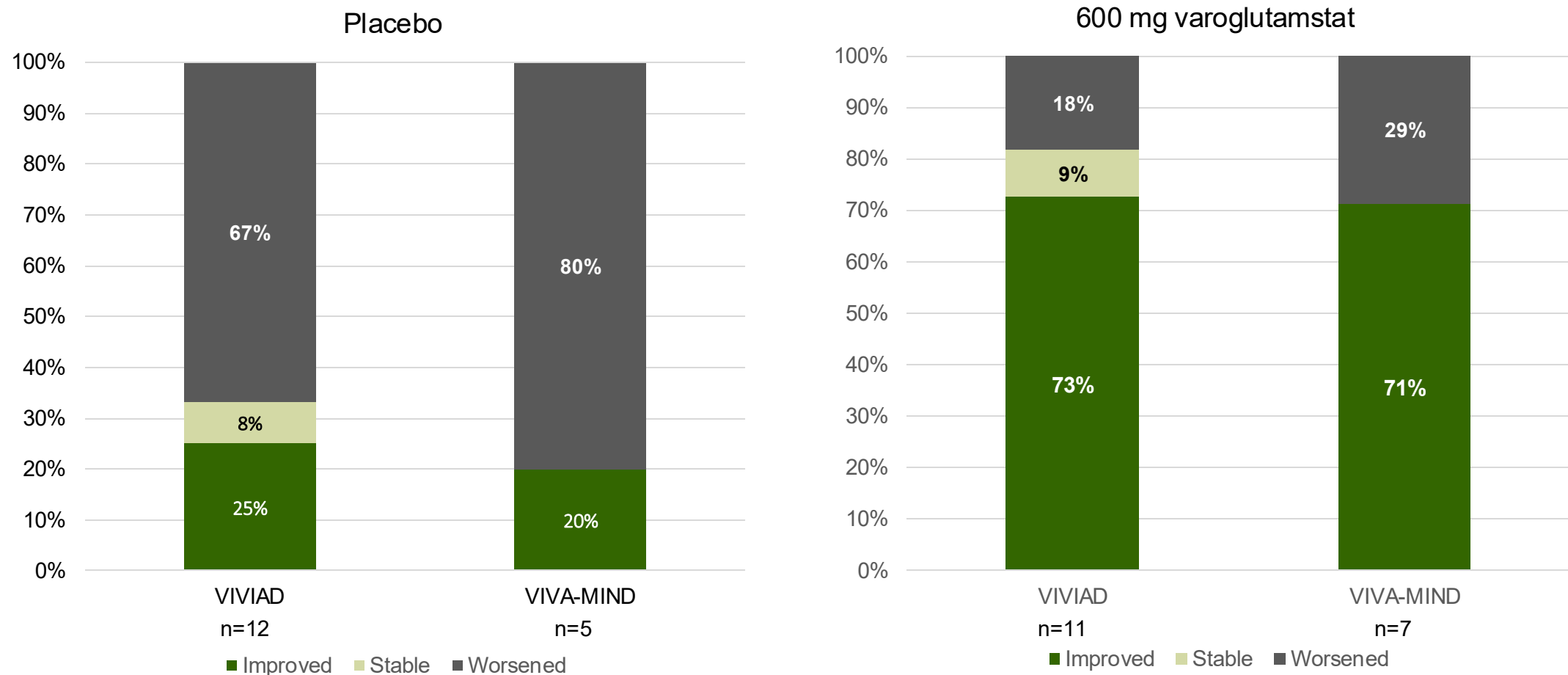


eGFR: estimated glomerular filtration rate, based on creatinine and calculated using the modification of diet in renal disease (MDRD) method. eGFR data were analysed over time using MMRM (mixed model for repeated measures) modelling including fixed effect terms for treatment, visit window and treatment-by-visit interaction using data from patients randomized to 600 mg and all visits on treatment, for VIVIAD (4 – 96 weeks) and VIVA-MIND (4 - 72 weeks). Diabetes patients identified as defined on slide 9; LSmean: least squares mean

# Responder analysis: kidney function predominantly improved or stabilized in varoglutamstat treated patients compared to a decline in the placebo group



# Sensitivity analysis: side by side comparison of responder analysis in diabetes patients shows high consistency between studies in diabetes patients

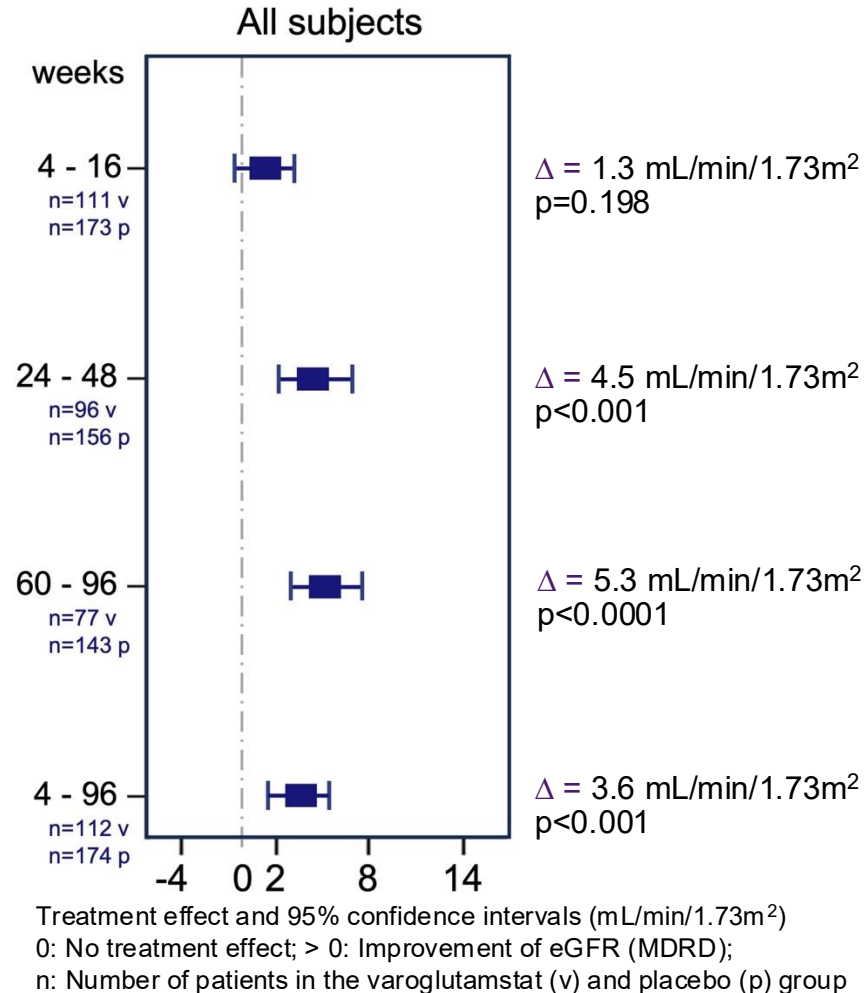


**Classification of eGFR response** (change mean eGFR (week 12-EOT) vs. baseline, mL/min/1.73m<sup>2</sup>):  
Improved:  $\geq 2$  mL above baseline, Stable:  $\geq 0$  -  $< 2$  mL above baseline, Worsened:  $< 0$  mL below baseline



# VIVIAD and VIVA-MIND: Meta-analysis shows strong effect on eGFR

Difference of change from baseline between  
varoglutamstat (v) and placebo (p) of eGFR (MDRD)

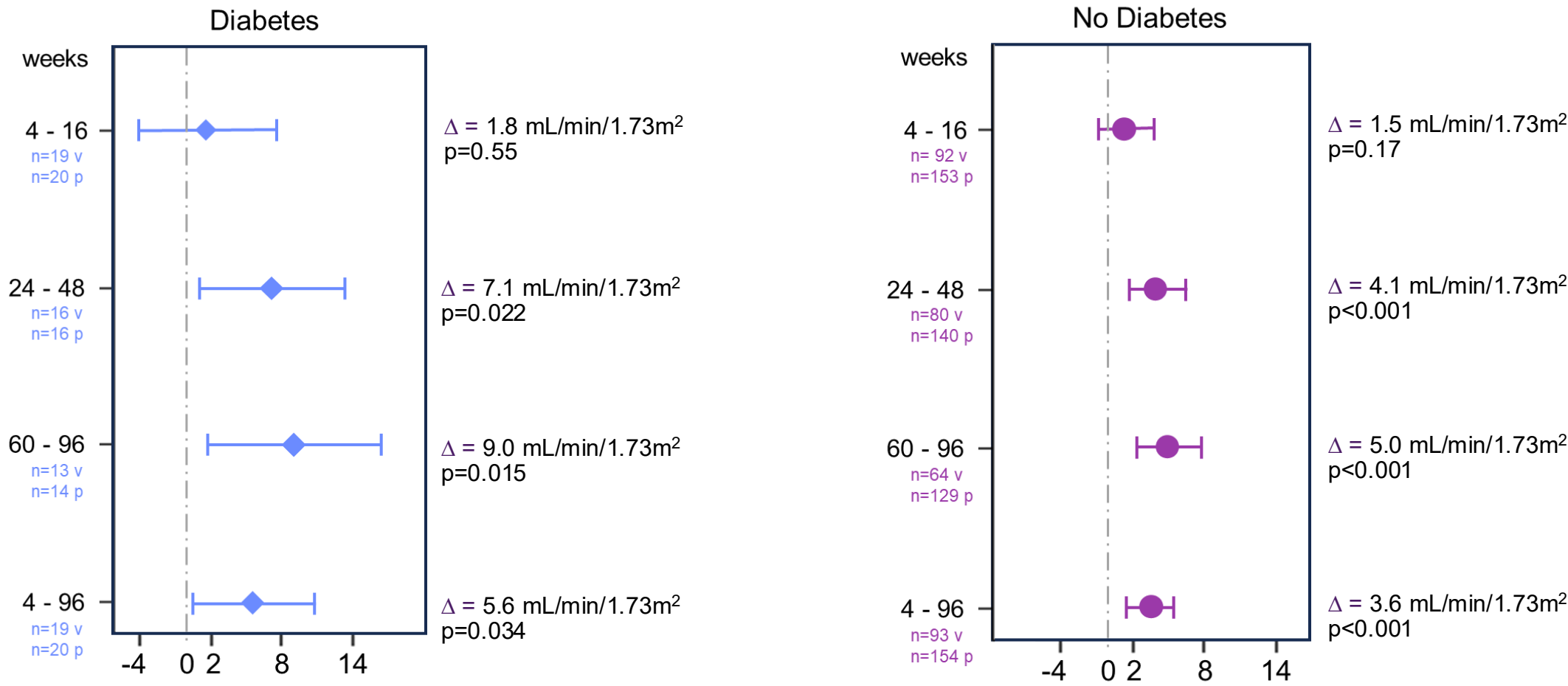


- ◆ Meta-analysis includes all patients on placebo and all patients randomized to 600 mg varoglutamstat BID of both studies (patients randomized to 300 mg BID in VIVIAD not included)
- ◆ Improvement of eGFR – kidney function is demonstrated in the total population
- ◆ Difference of change from baseline between varoglutamstat and placebo becomes significant at week 24
- ◆ Treatment effect is maintained for 2 years



# VIVIAD and VIVA-MIND: Meta-analysis shows a larger effect size in diabetes versus non-diabetes patients

Difference of change from baseline between varoglutamstat (v) and placebo (p) of eGFR (MDRD)



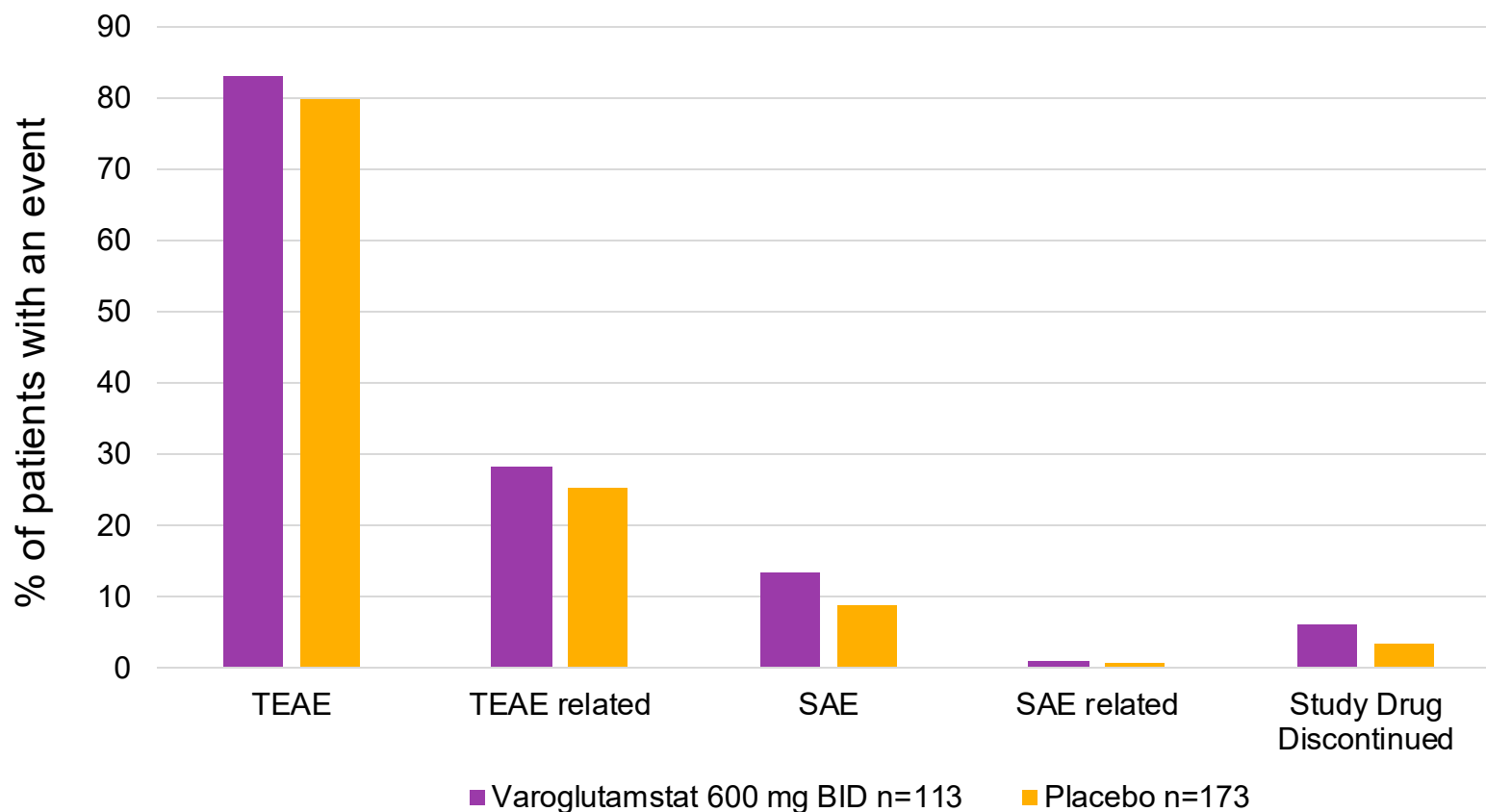
Treatment effect and 95% confidence intervals (mL/min/1.73m²)  
0: No treatment effect; > 0: Improvement of eGFR (MDRD);  
n: Number of patients in the varoglutamstat (v) and placebo (p) group



# Safety: pooled analysis of VIVIAD and VIVA-MIND

## 600 mg varoglutamstat is well tolerated

All patients randomized to 600 mg varoglutamstat BID and placebo



### Extensive safety package (# / duration)

#### Pharmacology / Phase 1

- ◆ Phase 1 study: large trial with 205 subjects
- ◆ Human ADME / mass balance study completed

#### Phase 2 double-blind, placebo-controlled

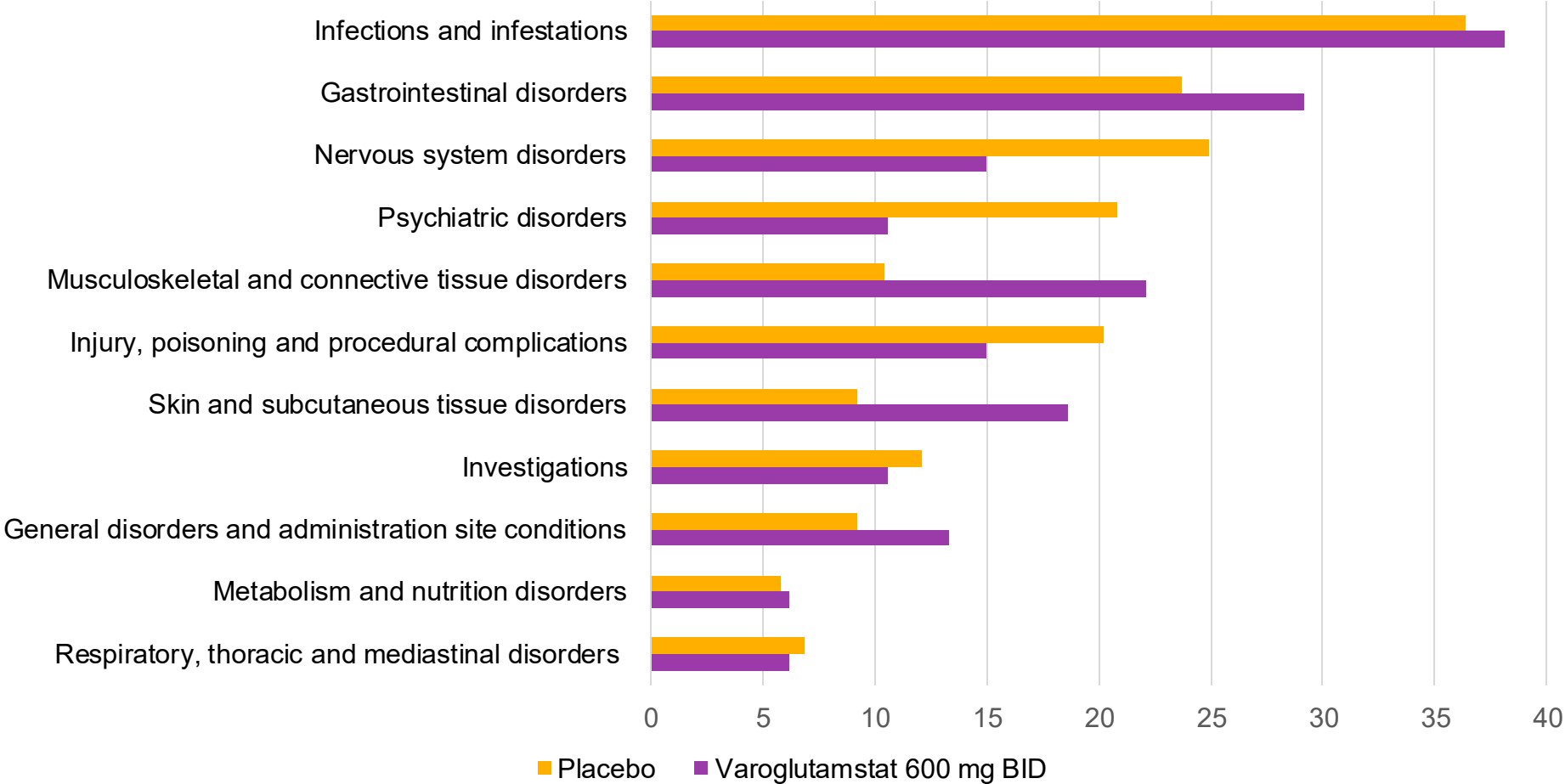
- ◆ Phase 2a study: 120 patients, 12 weeks
- ◆ VIVIAD Phase 2b study: 259 patients, avg. treatment duration ~80 weeks
- ◆ VIVA-MIND Phase 2 study: 109 patients treated, avg. treatment duration ~46 weeks



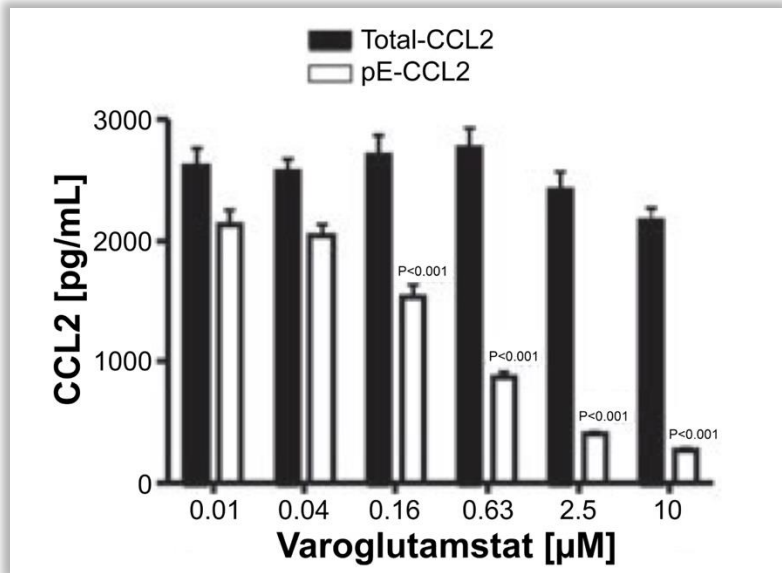


# Pooled safety analysis VIVIAD and VIVA-MIND: TEAE by system organ class

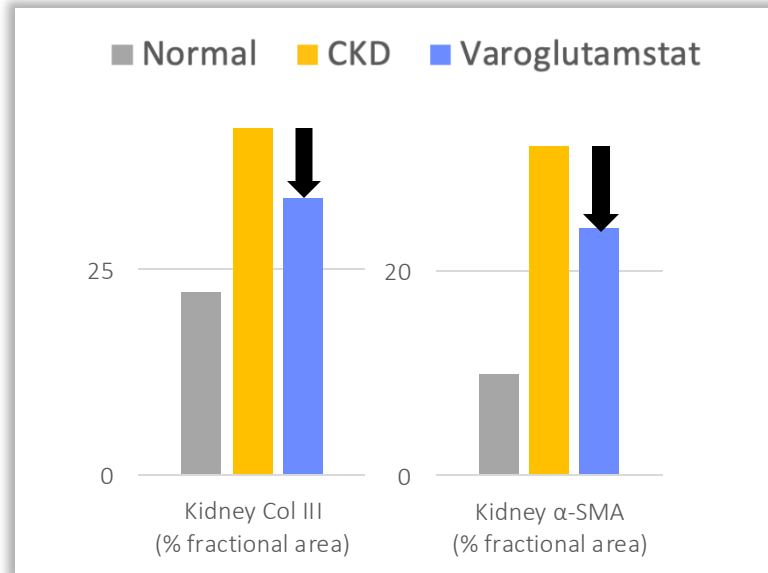
All patients randomized to 600 mg varoglutamstat BID and placebo  
All events independent of relationship assessment



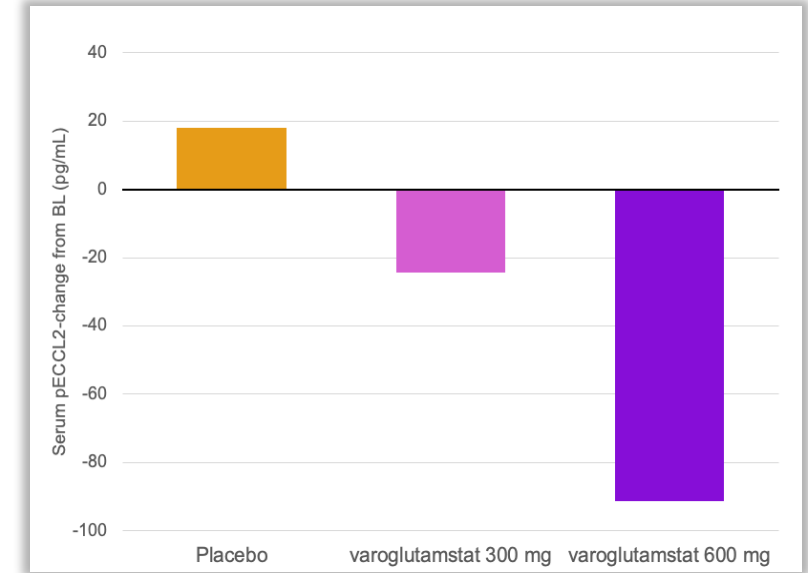
# Robust evidence demonstrating inhibition of intracellular QPCTL decreases activity of pro-inflammatory cytokines and kidney fibrosis



**Decrease of pE-CCL2 levels by QPCTL inhibitor application.** LPS-stimulation of RAW264.7 cells. Analysis of varoglutamstat effect on total-CCL2 and pE-CCL2.



**Histological changes show improvement of kidney Col-III and α-SMA.** Adenine-induced mouse model of CKD.



**Median reduction in pE-CCL2 levels compared to baseline with varoglutamstat.** VIVIAD, total population, at week 48.



# Varoglutamstat: Potential to become a convenient new oral therapy to transform the treatment of kidney disease

## Medical Need

Therapies that can stabilize or improve kidney function for majority of patients

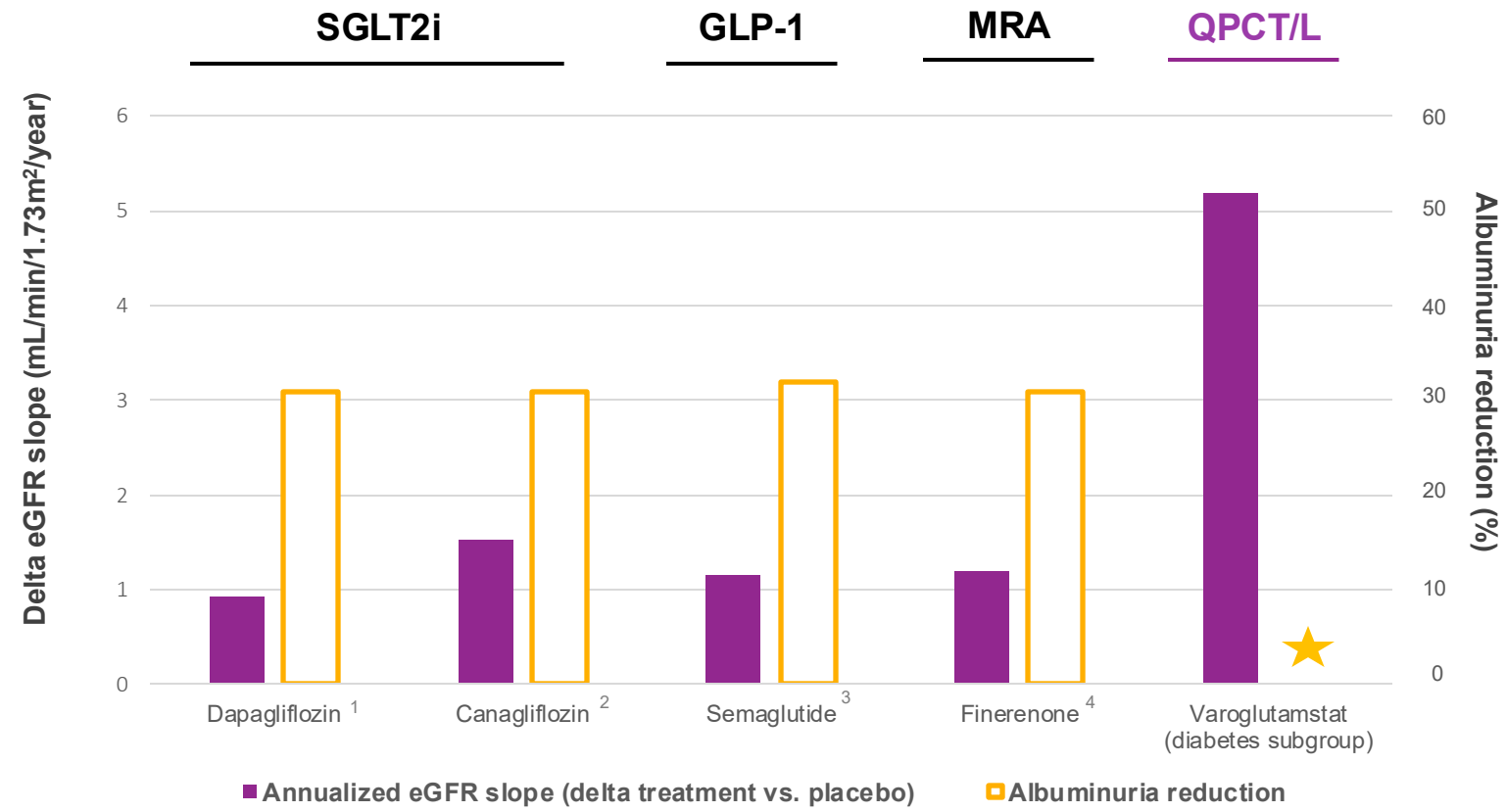
## Opportunity

Varoglutamstat is a first-in-class **single agent** oral compound that has been shown to **stabilize and partially recover** kidney function

- ◆ Clear development path to market
- ◆ Future program based on robust available data
  - ✓ Statistically significant and clinically meaningful improvement in eGFR
  - ✓ Effects observed in two independent Phase 2 studies
  - ✓ Substantially larger effect size in participants with diabetes
  - ✓ Excellent safety profile consistent across two years of study duration
  - ✓ Highly synergistic effect on top of current DKD SoC
  - ✓ Planned Phase 2b in DKD stage 3b/4 to evaluate effect in target population<sup>1</sup>



# Effect size substantially higher than observed with current standard of care (SGLT2i / GLP-1)

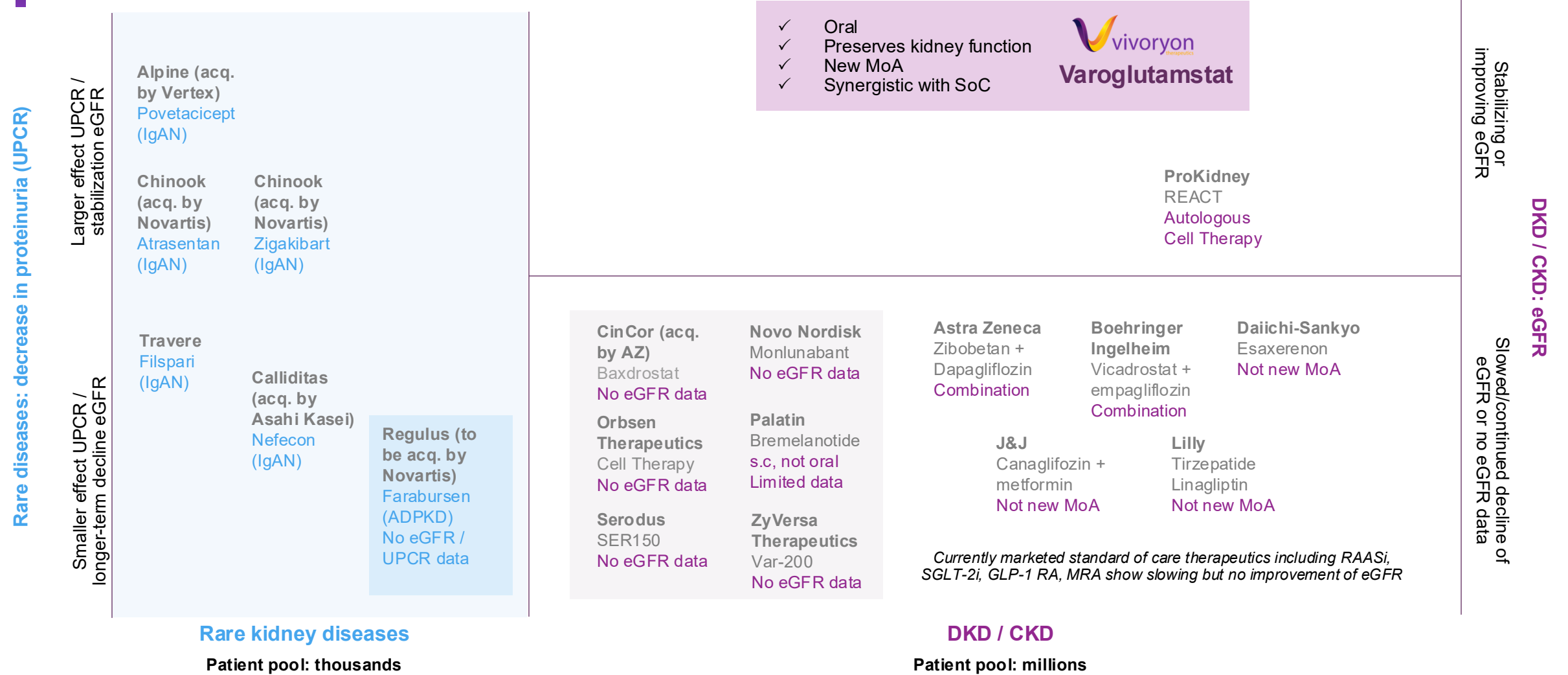


★ Conducted qualitative assessment, no increase in albuminuria observed; analysis of albuminuria planned for next Phase 2b study



Note: data comparisons are for illustrative purposes and not from head-head-studies or comparable patient populations, timelines or methods; Data for varoglutamstat is from pooled slope analysis for VIVIAD / VIVA-MIND Phase 2 study, diabetes subgroup; SGLT2 – sodium glucose cotransporter-2 inhibitor class; GLP-1 Glucagon-like peptide class; MRA: mineralocorticoid receptor antagonist; QPCT/L – varoglutamstat inhibits the glutaminy cyclases QPCT and QPCTL; eGFR: estimated glomerular filtration rate; <sup>1</sup> Heerspink et al. N Engl J Med, 2020; <sup>2</sup> Perkovic et al., N Engl J Med, 2019; <sup>3</sup> Perkovic et al., N Engl J Med, 2024; <sup>4</sup> Bakris et al., N Engl J Med, 2020

Varoglutamstat’s ability to stabilize and partially recover kidney function sets it apart in the kidney space and supports its potential to transform disease outcomes

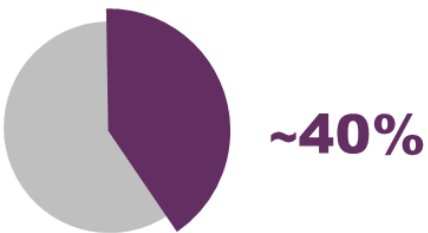
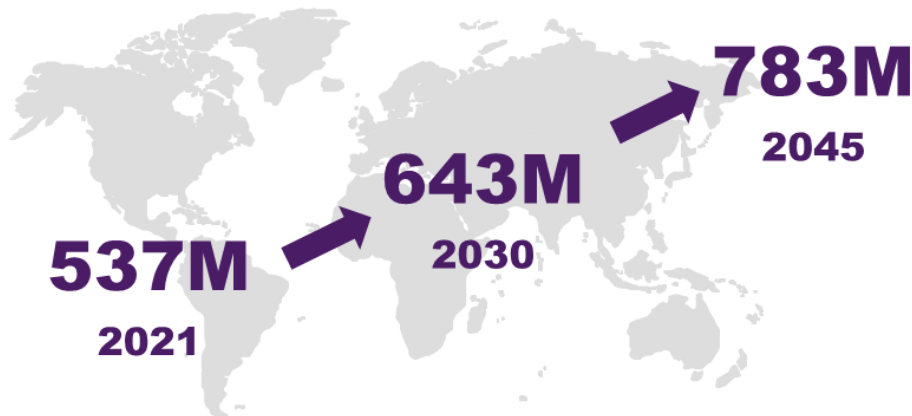


eGFR: estimated glomerular filtration rate; The above graphic includes select development / marketed drug candidates in the rare and CKD/DKD space and is for representation purposes only; data comparisons are for illustrative purposes and not from head-head-studies or comparable patient populations, timelines or methods; IgAN: IgA Nephropathy; ADPKD: autosomal dominant polycystic kidney disease; acq: acquisition / to be acquired by.

# Initial target market represents an attractive patient opportunity with potential label expansion to earlier stages of DKD / CKD

## Diabetes is a significant and growing global challenge

(adults aged 20-79 years with diabetes, worldwide)<sup>1</sup>

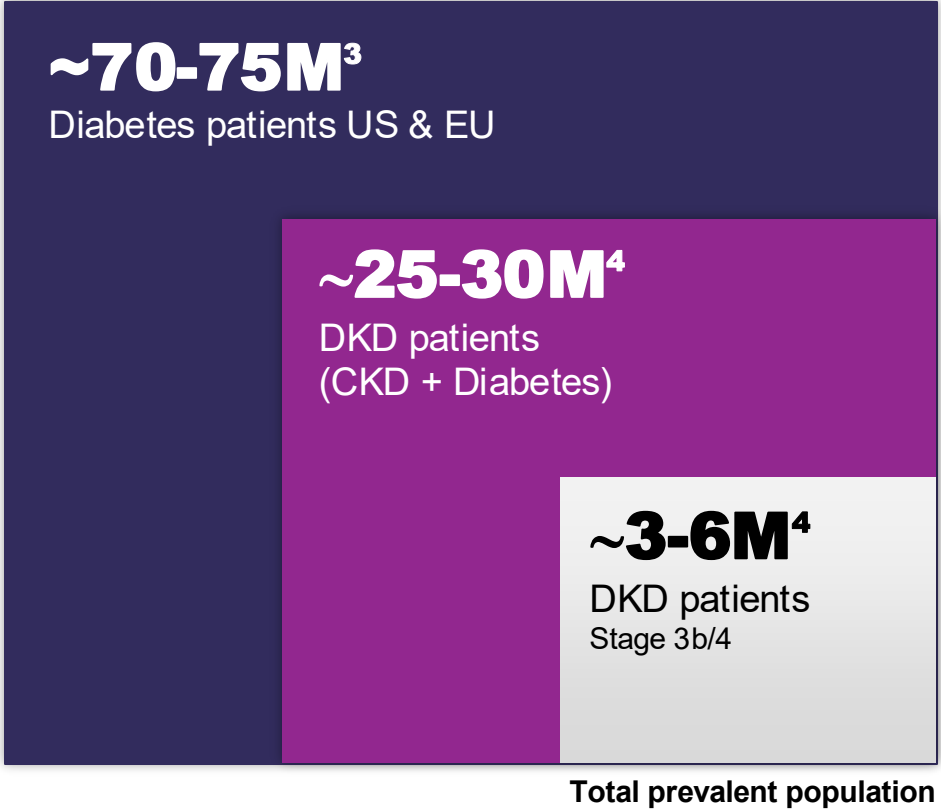


of people with diabetes may develop diabetic kidney disease (DKD)<sup>2</sup>



**1 in 10**

people with diabetes may end up with end-stage kidney disease<sup>2</sup>



<sup>1</sup>International Diabetes Federation (IDF) Atlas 2021; <sup>2</sup>Qazi et al., EMJ Nephrol, 2022; <sup>3</sup>CDC National Diabetes Statistics Report 2024; Eurostat 2017; CDC Chronic Kidney Disease in the United States, 2023; Brück et al., J Am Soc Nephrol, 2015; Sundström et al., The Lancet, Regional Health Europe, 2022; <sup>4</sup>Prevalent population assumptions based on internal analyses using a combination of public sources and management estimates, including Wu et al., BMJ Open Diabetes Research and Care, 2016; Feng et al., Kidney Med, 2022, CDC Kidney Disease Surveillance System (NHANES); This information may prove to be inaccurate because this information cannot always be verified with complete certainty due to the limits on the availability and reliability of raw data, the voluntary nature of the data gathering process and other limitations and uncertainties.

# New Study: Efficient study design to confirm the treatment effect in patients with advanced DKD<sup>1</sup>

## Primary Goal

- ◆ Aiming to confirm the efficacy of varoglutamstat 600mg BID on eGFR in people with advanced diabetic kidney disease in an efficient and timely manner

## Key Metrics and Considerations

- ◆ Double-blind randomized placebo-controlled multi-center study
- ◆ Patients with T2DM with stage 3b/4 CKD on top of SoC incl. SGLT2-i
- ◆ Adequately powered for meaningful data readout
- ◆ No. of patients: ~100 – 150
- ◆ Topline data ~24 months; design could include interim analysis at ~15 months to give earlier proof-of-concept<sup>2</sup>
- ◆ Typical trial cost approx. €12 -18m - dependent on patient number



<sup>1</sup> Draft trial considerations as part of scenario planning; study start and final trial design subject to additional financing / partnership; <sup>2</sup> timelines refer to from study start.  
BID: twice daily; T2DM: type 2 diabetes mellitus; CKD: Chronic Kidney Disease; SoC: standard of care; SGLT2-i: sodium-glucose cotransporter-2 inhibitor



# Pipeline focused on kidney disorders and inflammatory/fibrotic diseases

	Program	Approach	Discovery	Preclinical	Phase 1	Phase 2	Phase 3	Status
Inflammatory/fibrosis incl. kidney	DKD (Varoglutamstat/PQ912)	SMI QPCT/L	POC in VIVIAD & VIVA-MIND results					Preparing for Phase 2b DKD study
	Kidney orphan diseases (Varoglutamstat/PQ912)	SMI QPCT/L			Pre-IND			Pre-clinical orphan disease models
	Kidney disorders, fibrotic/inflammatory (VY2149)	SMI QPCT/L			Pre-IND			
	Fibrotic indications (NCE)	SMI Meprin			Research program			
Alzheimer's disease	Varoglutamstat (PQ912)	SMI QPCT/L						AD program: discontinued after negative topline data March 2024 (VIVIAD) & December 2024 (VIVA-MIND)
	Varoglutamstat (SIM0408, PQ912)	SMI QPCT/L	CTA approval in China					Partnered with Sincere in Greater China; under evaluation
	PBD-C06	mAb N3pE amyloid			Pre-IND			Partnered with Sincere in Greater China; under evaluation



DKD: diabetic kidney disease; SMI: small molecule inhibitor; IND: investigational new drug;  
NCE: novel chemical entity; CTA: Clinical Trial Application; mAb: monoclonal antibody

# QPCTL inhibitors have a large market potential: Development opportunities across a range of diseases driven by underlying inflammation / fibrosis

## DKD / CKD / earlier stages

Replication of a sustained improvement of kidney function in two independent Phase 2 studies<sup>1</sup>

Initial focus on stage 3b/4 DKD given high unmet need and large effect in diabetes subgroup

Opportunity to expand market potential by moving into earlier and later stage DKD / CKD

## Rare kidney diseases

e.g. Alport / Fabry disease

Novel mode of action, effect on inflammatory markers and observed effect on kidney function holds promise for QPCTL inhibitors in certain rare diseases

## Disorders progressing through inflammation & fibrosis

e.g. NAFLD

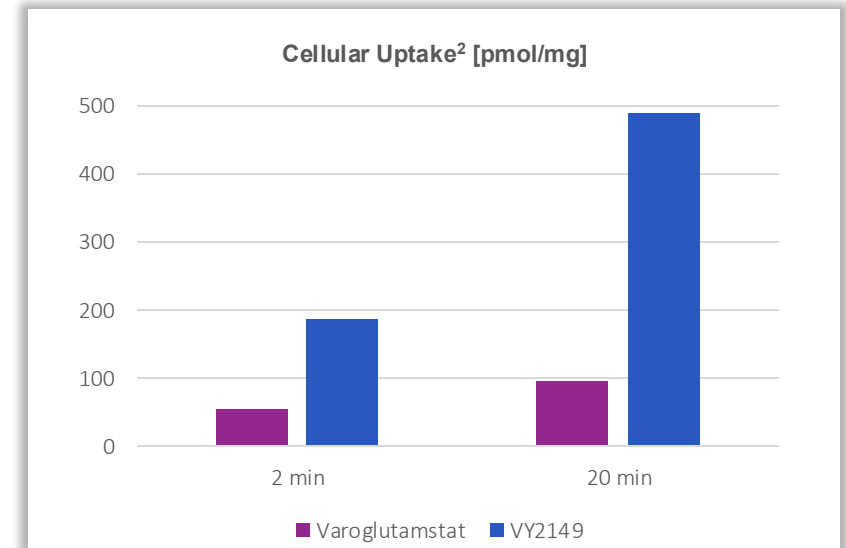
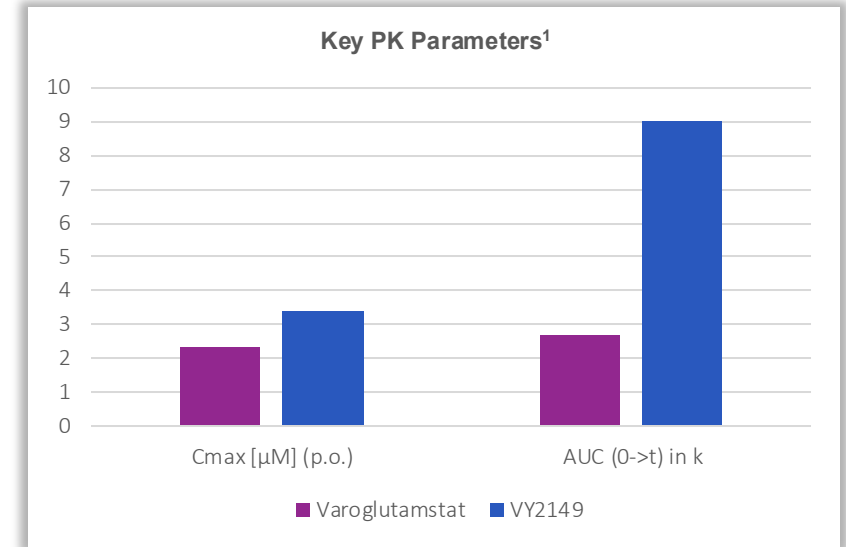
NAFLD is the most prevalent form of liver disease which may advance to metabolic dysfunction-associated steatohepatitis ("MASH") and cirrhosis

*In vivo* proof of concept in NAFLD mice<sup>2</sup>



# New development compound VY2149 shows improved cellular uptake, PK profile and superior outcomes in kidney animal studies

- ◆ Higher intracellular QPCTL inhibition translates to better activity, lower doses and the opportunity for once daily dosing
- ◆ Pre-clinical stage follow-on candidate VY2149, has shown improved molecular properties including
  - ◆ Improved peak concentration (C<sub>max</sub>) of VY2149 compared to varoglutamstat at comparable bioavailability upon oral dosing
  - ◆ Markedly increased overall drug exposure (AUC)
  - ◆ Significantly higher passive uptake into cells
- ◆ Assessment of once daily dosing for VY2149 in an animal model has shown strong effects on eGFR, creatinine, cystatin C levels and  $\alpha$ -SMA levels and collagens

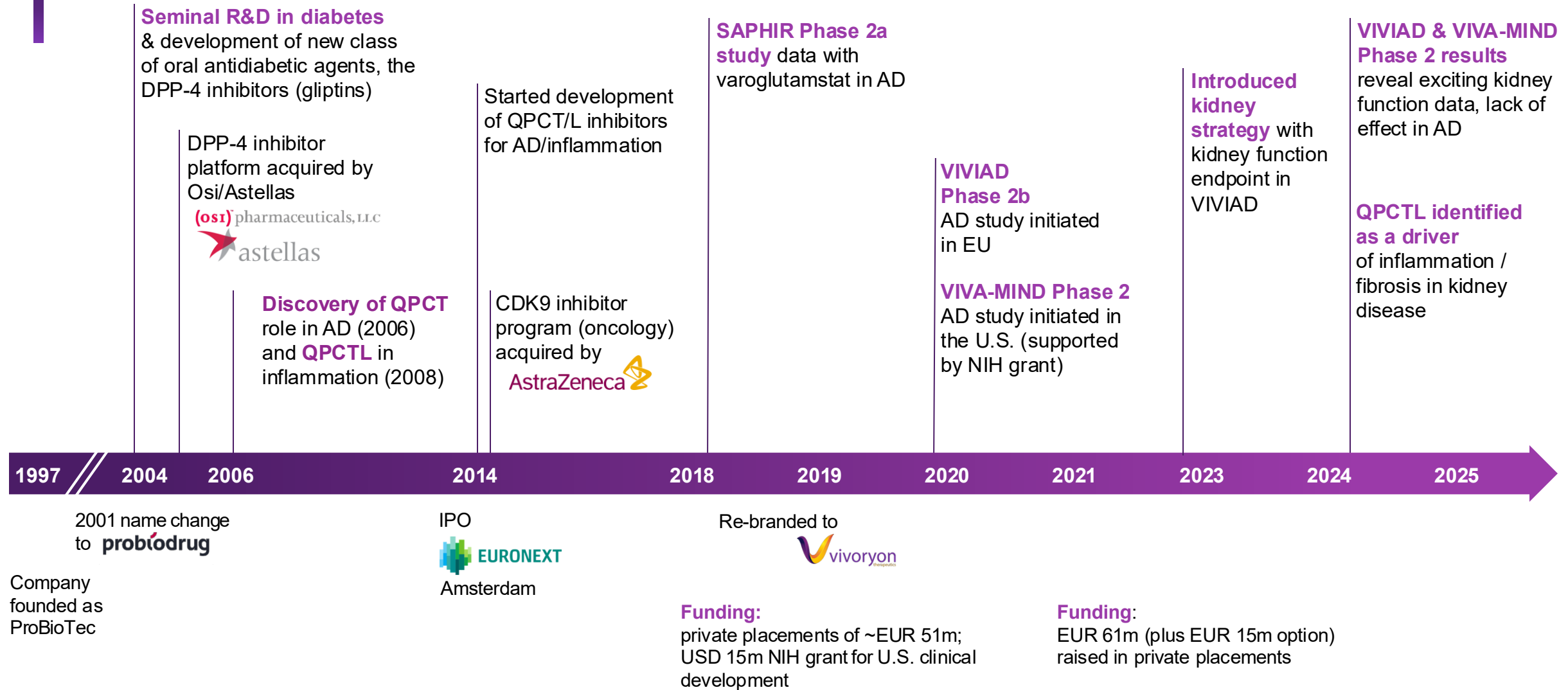


<sup>1</sup> Single low dose (10mg/kg); p.o.= oral; PK = pharmacokinetics; AUC = Area under the curve; C<sub>max</sub> = peak concentration

<sup>2</sup> Passive uptake into HEK293 cells incubated for 2 vs. 20 min with 1 μM compound in medium (37°C); reported as pmol/mg protein of a reference protein.



# Vivoryon: A history of groundbreaking discoveries and developments



# A trusted company: Senior management team with a strong track record

## Management

**Frank Weber, MD**  
*Chief Executive Officer*



**Anne Doering, CFA**  
*Chief Financial Officer*



**Michael Schaeffer, PhD**  
*Chief Business Officer*



**Julia Neugebauer, PhD**  
*Chief Operating Officer*



## Non-executive Directors

**Erich Platzer, MD, PhD**  
*Chairman of the Board*

**Charlotte Lohmann**

**Claudia Riedl, PhD**  
*Chair Audit Committee*

**Samir Shah, MD**

## Decades of collective experience in biopharma industry, e.g.:

**First** approved drug in pulmonary fibrosis

**Successful** development of biomarker driven oncology & diabetes programs

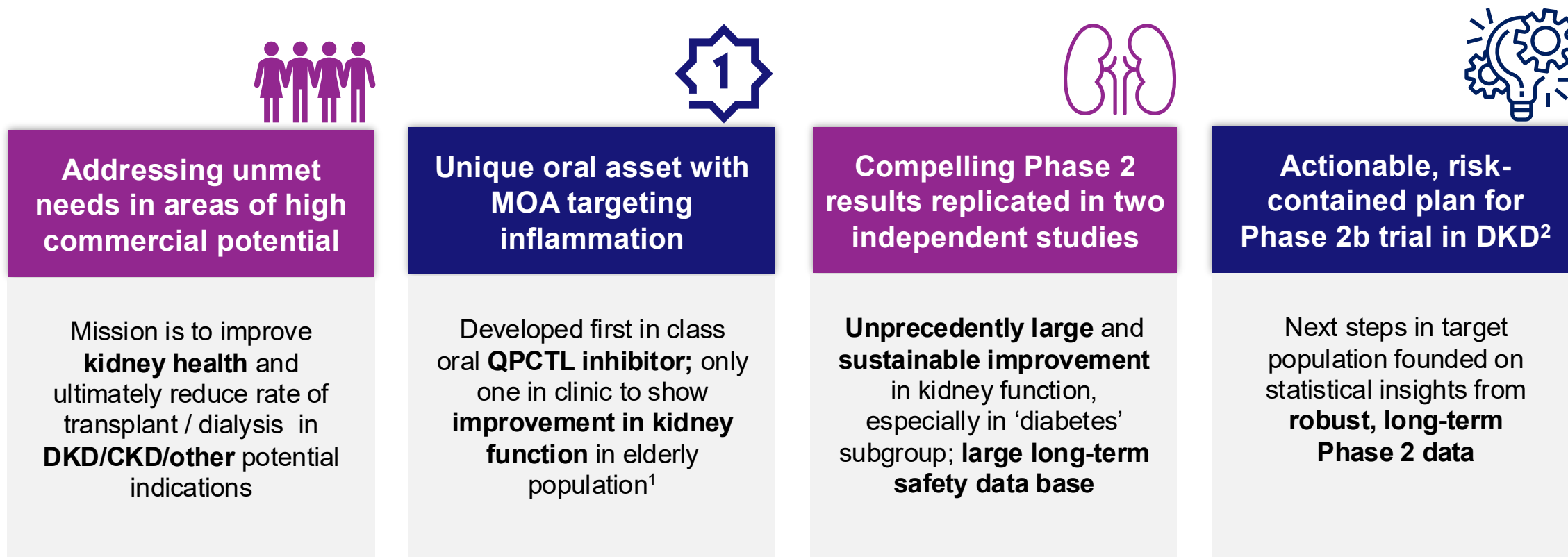
M&A and business development **expertise** from transactions with large biopharma

**Know-how** in life science research & development, biophysical and structure-based drug discovery

Strong financial, capital markets and legal **experience**



# Vivoryon: Poised to improve kidney health with varoglutamstat's novel mechanism of action and breakthrough clinical trial results



*Extensive intellectual property portfolio<sup>3</sup>; pipeline of additional early-stage QPCTL inhibitors; experienced management team with track record in inflammation and business development*



<sup>1</sup> VIVIAD and VIVA-MIND Phase 2 studies in early Alzheimer's disease (AD) included prospectively defined measures of kidney function as safety and other exploratory endpoints, the primary and secondary endpoints in early AD were not met; <sup>2</sup> Subject to funding / partnership; <sup>3</sup> Composition of matter patent protection expected to 2044+ with additional potential for Hatch-Waxman extension of up to 5 years



## **Vivoryon Therapeutics N.V.**

Halle (Saale)  
Weinbergweg 22  
06120 Halle (Saale), Germany

Munich  
Franz-Josef-Delonge-Str. 5  
81249 München, Germany

IR@vivoryon.com  
+49 (0)345 555 99 00

[www.vivoryon.com](http://www.vivoryon.com)