

# Nieuwe therapieën voor de behandeling van nierziekten

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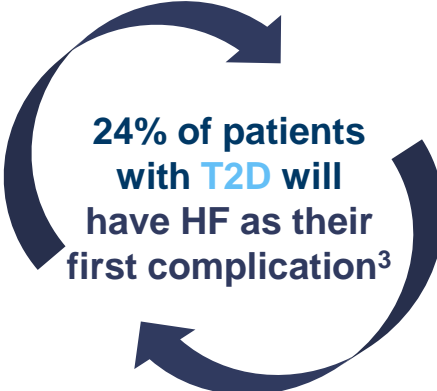

# CKD, heart failure, and T2D are interrelated, leading to a vicious circle of cardiac, renal, and metabolic risk



### Diabetes



2017 global prevalence<sup>1</sup>  
~476M



### CKD




2017 global prevalence<sup>1</sup>  
~698M



### Heart failure



2017 global prevalence<sup>1</sup>  
~64M



CKD, chronic kidney disease; HF, heart failure; T2D, type 2 diabetes  
1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. *Lancet* 2018;392:1789–1858; 2. Parving HH, et al. *Kidney Int* 2006;69:2057–2063;  
3. Birkeland KI, et al. *Diabetes Obes Metab* 2020;22:1607–1618; 4. Ronco C, et al. *J Am Coll Cardiol* 2008;52:1527–1539

# 2022 KDIGO treatment algorithm for patients with type 2 diabetes and CKD

 Lifestyle therapy


Physical activity  
Nutrition  
Weight loss

 **First-line therapy**  
eGFR  $\geq 20$  mL/min/1.73m<sup>2</sup>

**Metformin**  
eGFR <45: reduce dose  
eGFR <30 or dialysis: D/C



**SGLT2i**  
eGFR <20: do not initiate  
Dialysis: D/C

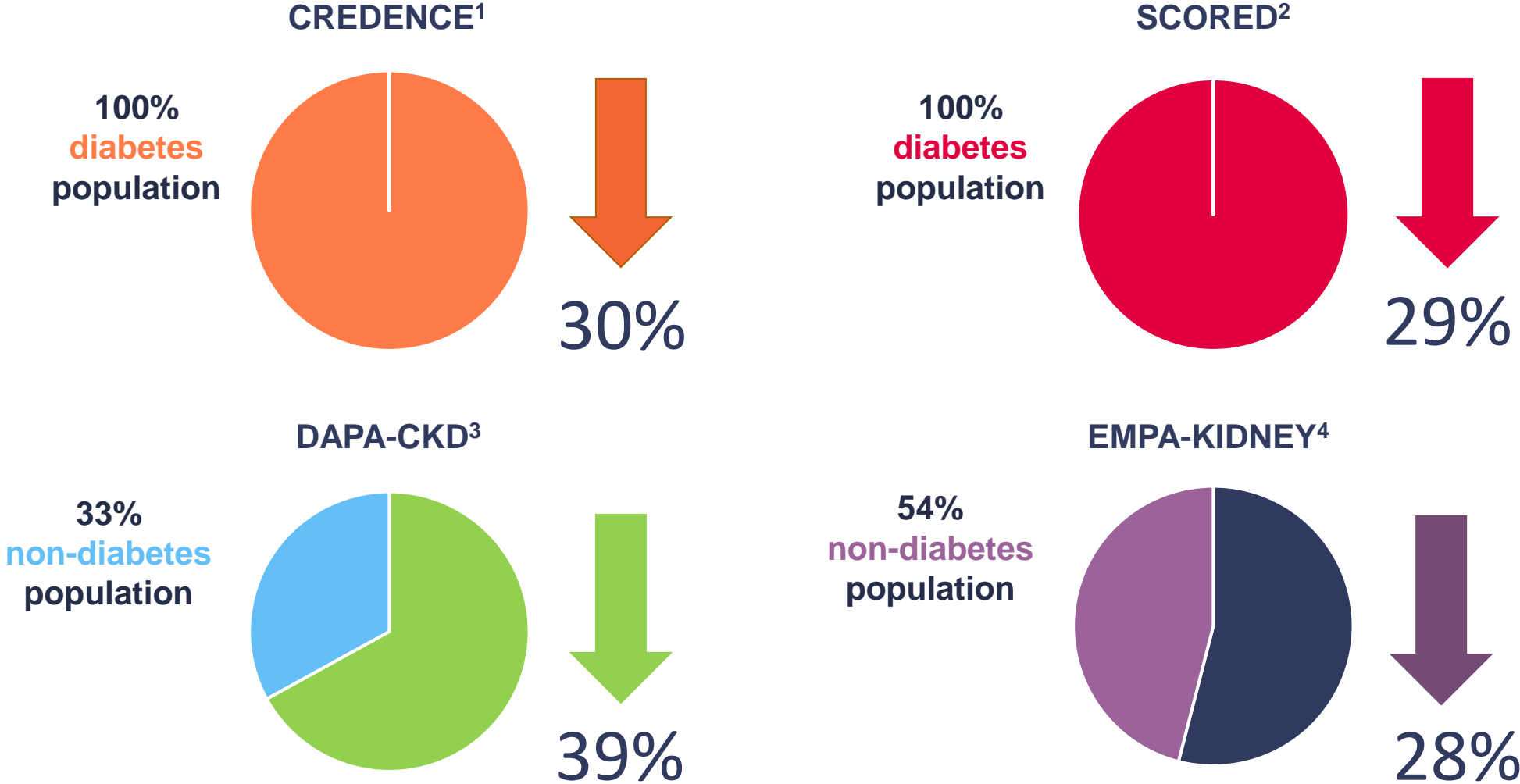
 Additional drug therapy as needed for glycemic control

**GLP-1 RA**  
(preferred)

- |        |         |
|--------|---------|
| DPP-4i | Insulin |
| SU     | TZD     |
| AGi    |         |

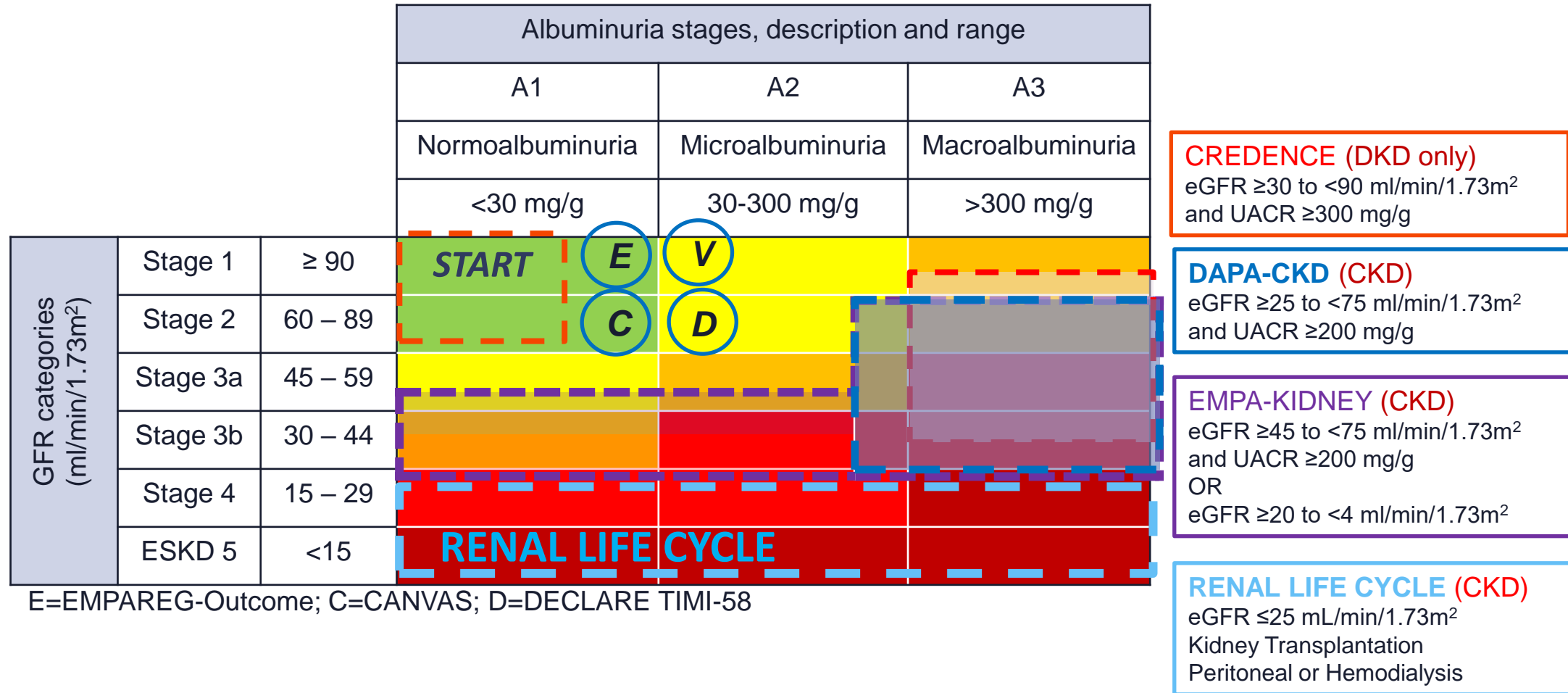
- Guided by patient preferences, comorbidities, eGFR and cost
- Includes patients with eGFR <30 mL/min/1.73m<sup>2</sup> or treated with dialysis

# SGLT2 inhibitor trials have recruited patients with CKD with and without diabetes



CKD, chronic kidney disease  
1. Perkovic V, et al. *N Engl J Med* 2019;380:2295–306; 2. Bhatt DL, et al. *N Engl J Med* 2021;384:129–139;  
3. Heerspink HJL, et al. *N Engl J Med* 2020;383:1436–1446; 4. EMPA-KIDNEY Collaborative Group. *N Engl J Med* Nov 4. doi: 10.1056/NEJMoa2204233

# Kidney outcome trials with SGLT2 inhibitors address the spectrum of CKD



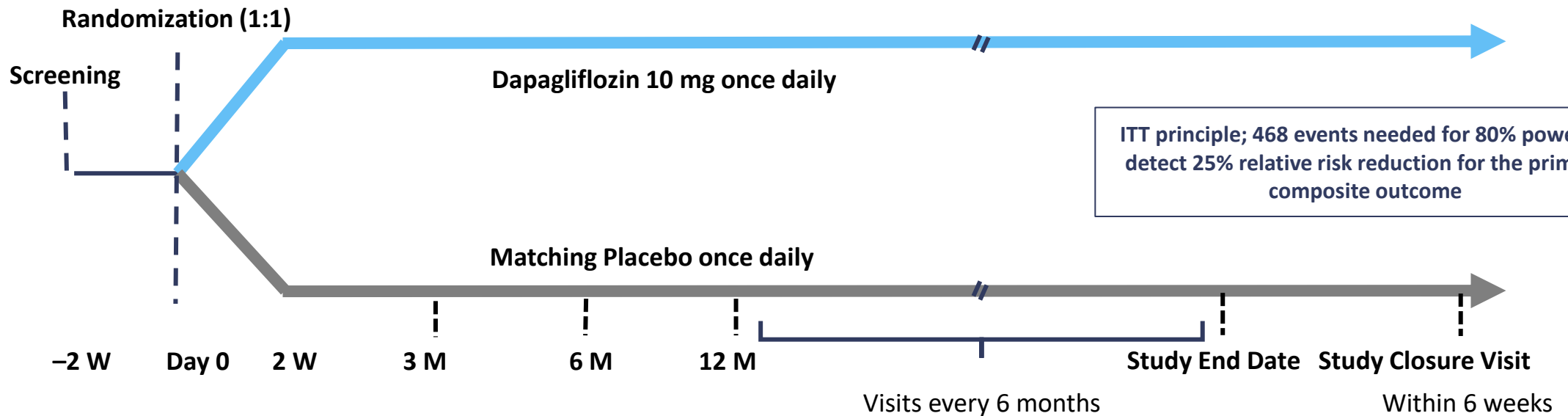
# RENAL LIFE CYCLE Trial

## Key inclusion criteria:

- $\geq 18$  years of age
- Three main patient groups:
  - $eGFR \leq 25$  mL/min/1.73m<sup>2</sup>
  - Kidney Transplantation and  $eGFR \leq 45$  mL/min/1.73m<sup>2</sup>
  - Peritoneal or hemodialysis (residual diuresis  $> 500$  mL/24hr)

## Key exclusion criteria:

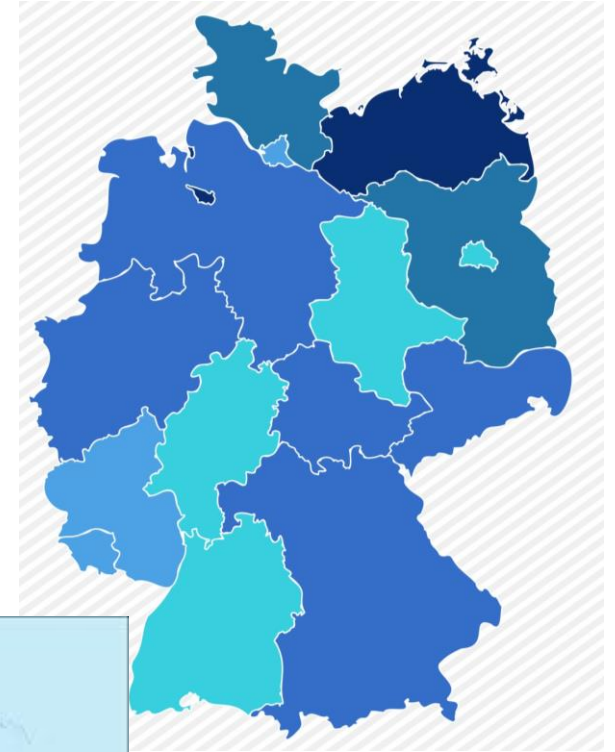
- Type 1 diabetes
- Life expectancy  $< 6$  months
- Concurrent treatment with SGLT2 inhibitor
- Scheduled start dialysis or kidney transplantation  $< 6$  months
- Known severe hepatic impairment



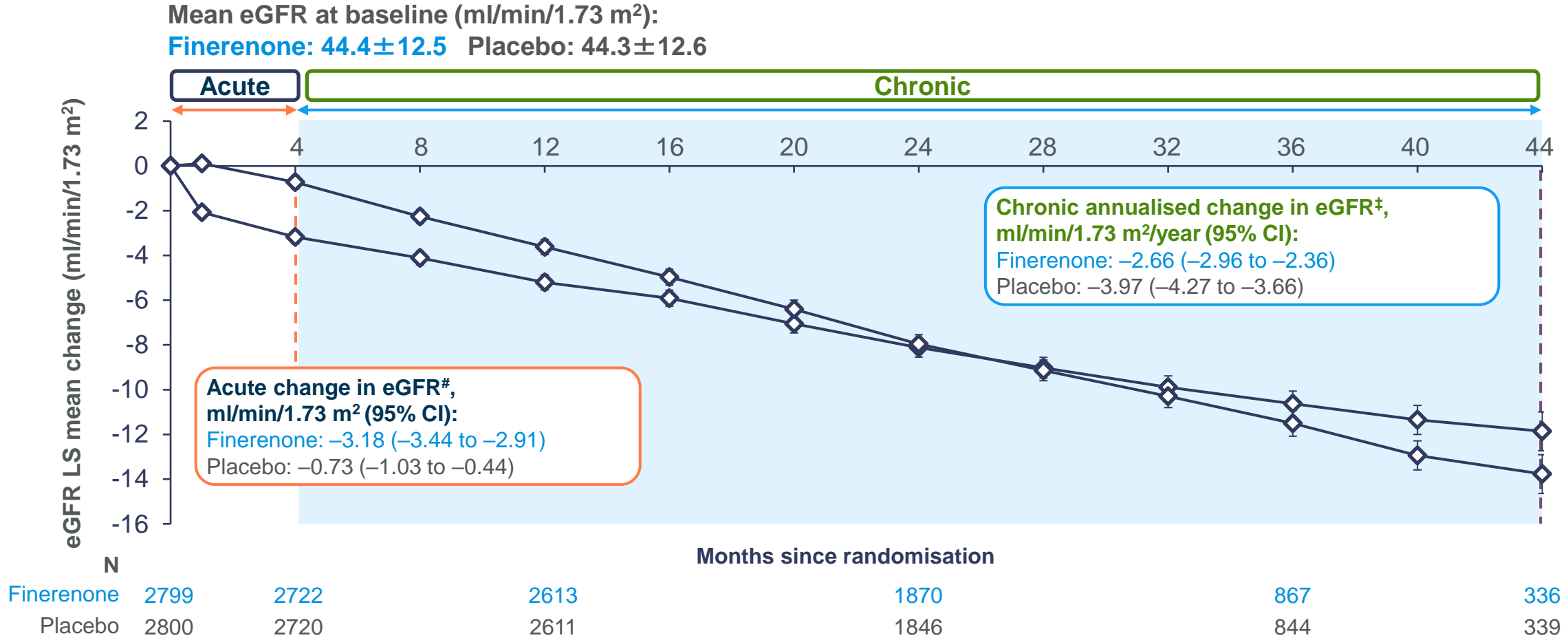
- Primary outcome: All cause mortality; heart failure hospitalization; dialysis or kidney transplantation (in pre-dialysis stratum)
- Outcome analysis based on Cox proportional hazard model stratified by subgroup and type 2 diabetes status

# Renal Life Cycle: A joint Dutch-German-Australian effort

- An investigator initiated Randomized Placebo-Controlled Trial (Coordination Center Groningen)
- 90 Peripheral and Academic hospitals in the Netherlands, Germany and Australia
- First patient enrolled in October 2022



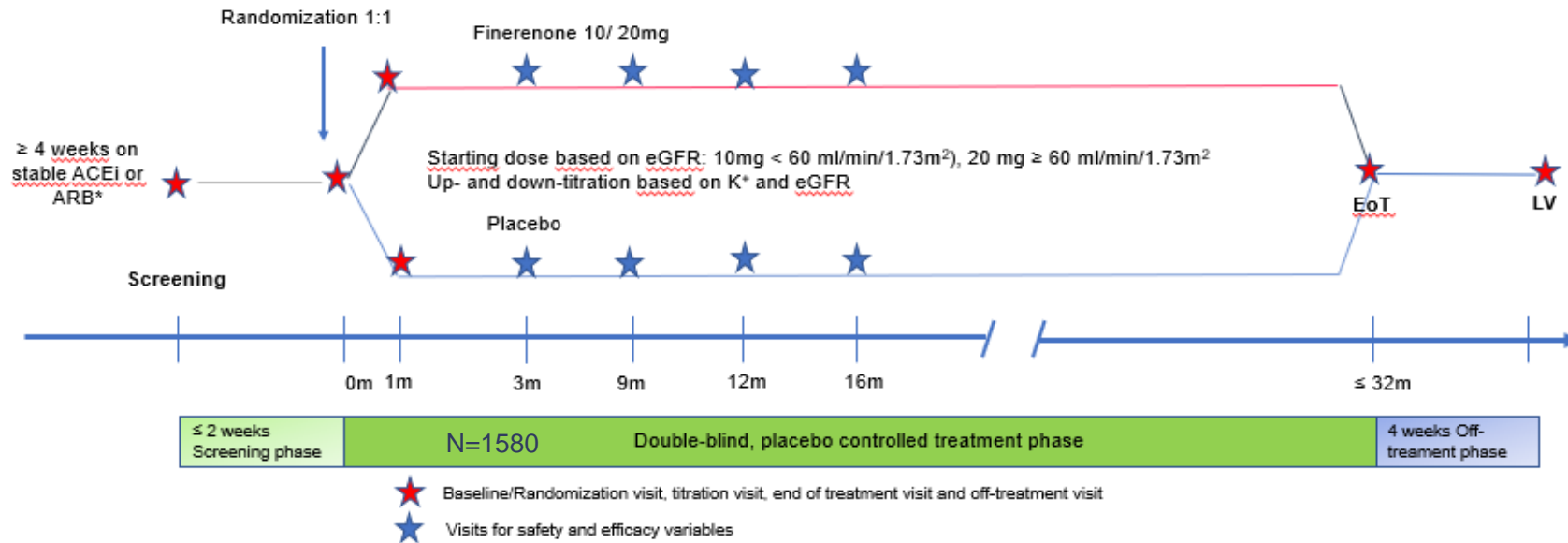
# FIDELIO-DKD: The MRA finerenone reduces the rate of eGFR decline over time in Type 2 Diabetes and CKD



\*Mixed model analysis of eGFR over time. Full analysis set; <sup>#</sup>LS mean change in eGFR slope from baseline to month 4; <sup>‡</sup>LS mean change in eGFR slope from month 4 to the permanent discontinuation or end-of-study visit  
 CI, confidence interval; eGFR, estimated glomerular filtration rate; LS, least-squares  
 Bakris GL, et al. N Engl J Med 2020;383:2219-2229



# FIND-CKD: finerenone in Non-Diabetic CKD



## Innovative ph3 design

- eGFR slope is a valid endpoint from a clinical and increasingly from regulatory perspective
- Full decentralized clinical trial approach (pilot for Bayer)

## Study Endpoints

### Primary Endpoint

- **Total eGFR slope difference**

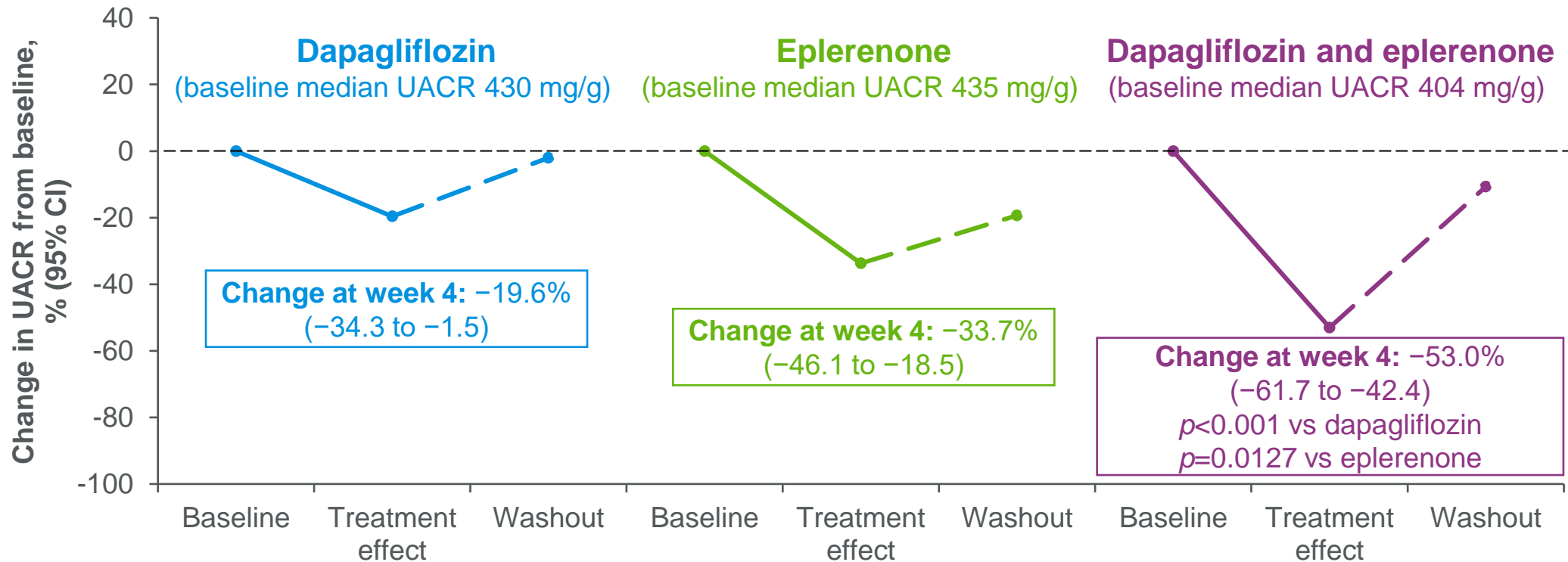
Supportive evidence

- Chronic eGFR slope
- eGFR change from baseline to 1 month off-treatment
- ≥ 30% UACR reduction at month 6

### Secondary Endpoints

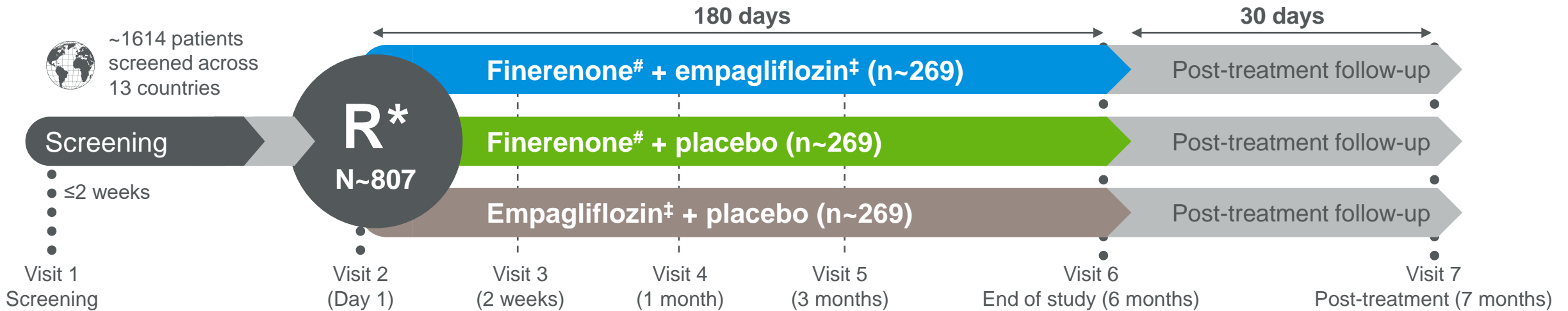
- Time to the composite of confirmed eGFR decline of ≥57%, kidney failure, HHF and CV death
- Time to the composite of confirmed eGFR decline of ≥57%, kidney failure
- Time to HHF or CV death

# ROTATE-3: additive kidney benefit of SGLT2i and MRA



Significant fewer hyperkalemia with combination treatment (4.3%) vs. eplerenone (17.4%) vs dapagliflozin (0%)

# CONFIDENCE is a phase II, randomised, double-blind, multicentre, prospective trial



## Primary endpoints

Relative change in UACR from baseline to 180 days for:

Finerenone + empagliflozin combination vs empagliflozin

OR

Finerenone + empagliflozin combination vs finerenone

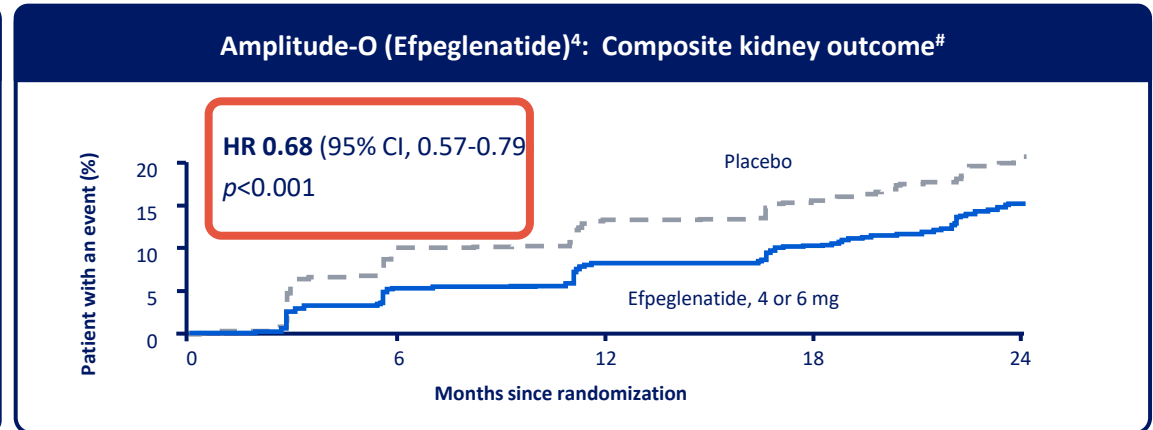
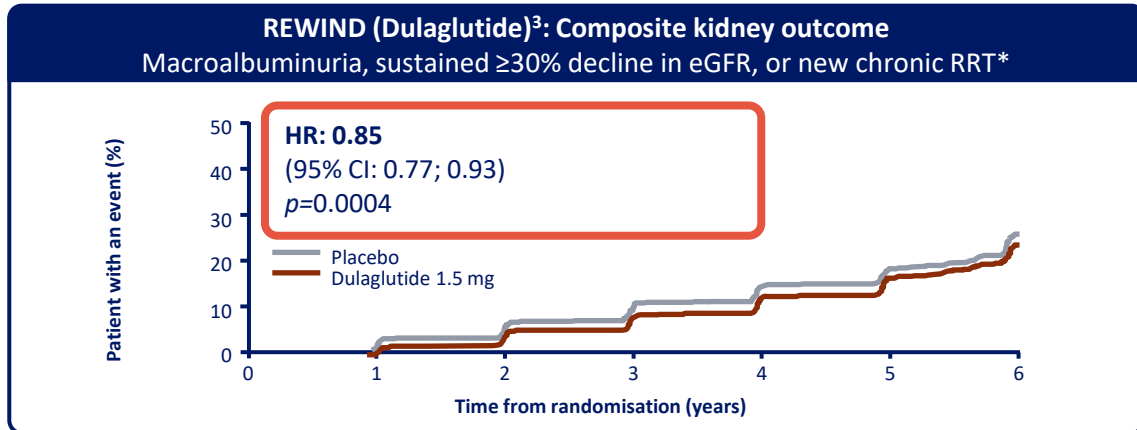
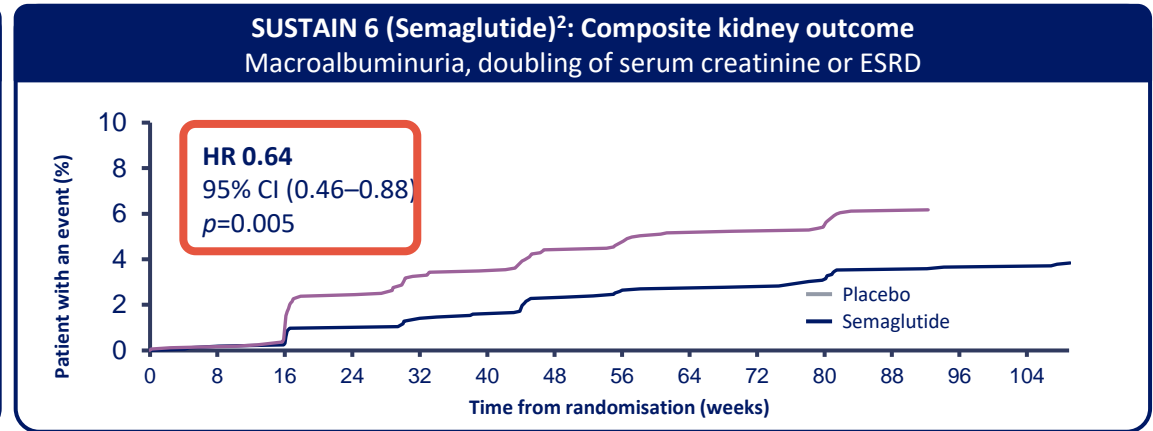
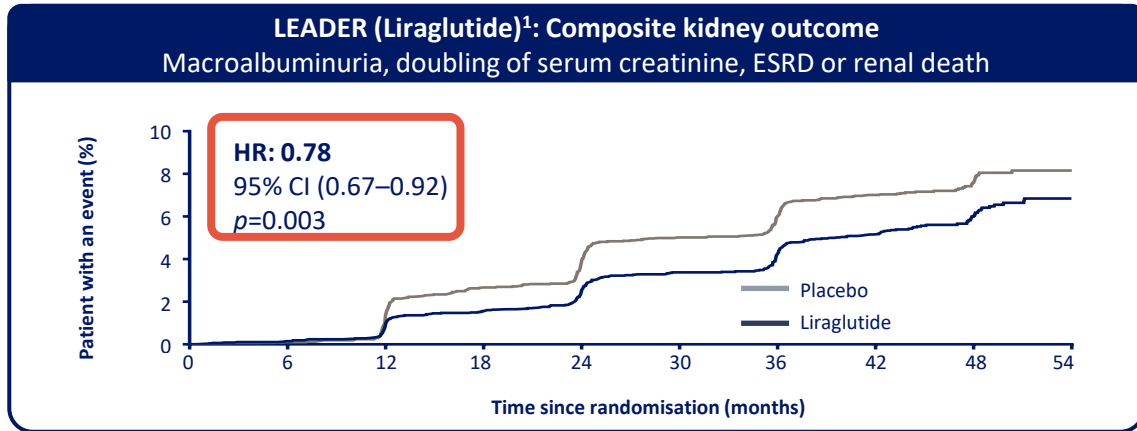
## Key safety endpoints

- Change in eGFR from baseline to 30 days
- Change in eGFR from 30 days to 180 and 210 days
- eGFR decline >30% from baseline to 30 days
- Incidences (n, %) of: AKI, hyperkalaemia, severe hypoglycaemia, symptomatic hypotension, and genital mycotic events
- Monitoring of AEs, ECG, laboratory and vital signs

\*Randomised patients stratified by eGFR (<60 and ≥60 ml/min/1.73 m<sup>2</sup>) and UACR (≤850 mg/g and >850 mg/g); #10 to 20 mg od based on serum [K<sup>+</sup>] and eGFR. Up-titration to target dose of 20 mg od allowed from visit 4 onwards. Down-titration allowed at any time during the study for safety reasons; ‡10 mg od  
AKI, acute kidney injury; ECG, electrocardiogram; [K<sup>+</sup>], potassium concentration  
Bayer. <https://www.clinicaltrials.gov/ct2/show/NCT05254002> [accessed 23 Aug 2022]

# Renal outcomes from CVOTs

## REWIND, LEADER, SUSTAIN 6 and AMPLITUDE-O



\*RRT is defined as either dialysis or renal transplantation; #Composite renal outcome defined by one or more of new macroalbuminuria (ACR > 300 mg/g) and  $\geq 30\%$  rise from baseline decrease in eGFR by  $\geq 40\%$  from baseline for  $\geq 30$  days, Kidney replacement therapy for  $\geq 90$  days, eGFR < 15 ml/min/1.73 m<sup>2</sup> for  $\geq 30$  days

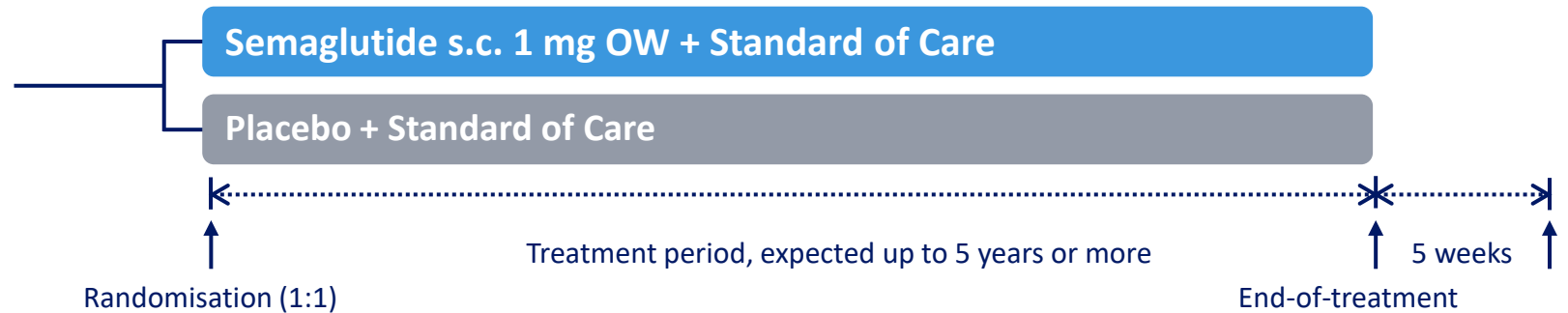
CI, confidence interval; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease

1. Mann JFE et al. N Engl J Med 2017; 377(9):839–848; 2. Marso SP et al. N Engl J Med 2016; 375:1834–1844; 3. Gerstein HC et al. Lancet 2019; 394(10193):131–138; 4. Gerstein HC et al. N Engl J Med. 2021; 385:896–907

# FLOW: study design

## 3508 patients

- T2D, HbA<sub>1c</sub> ≤10%
- eGFR ≤75 to ≥50\* and UACR >300 to <5000 mg/g *OR* eGFR <50 to ≥25\* and UACR >100 to <5000 mg/g
- RAAS blocker

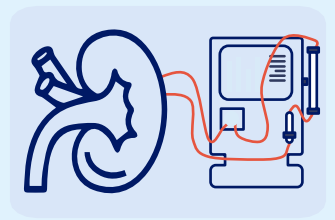


## Time to first occurrence of a composite endpoint consisting of:

Onset of persistent\* **≥50% eGFR reduction** (CKD-EPI) compared with baseline



Onset of persistent\* eGFR <15mL/min /1.73 m<sup>2</sup> or **Renal replacement therapy\*\***

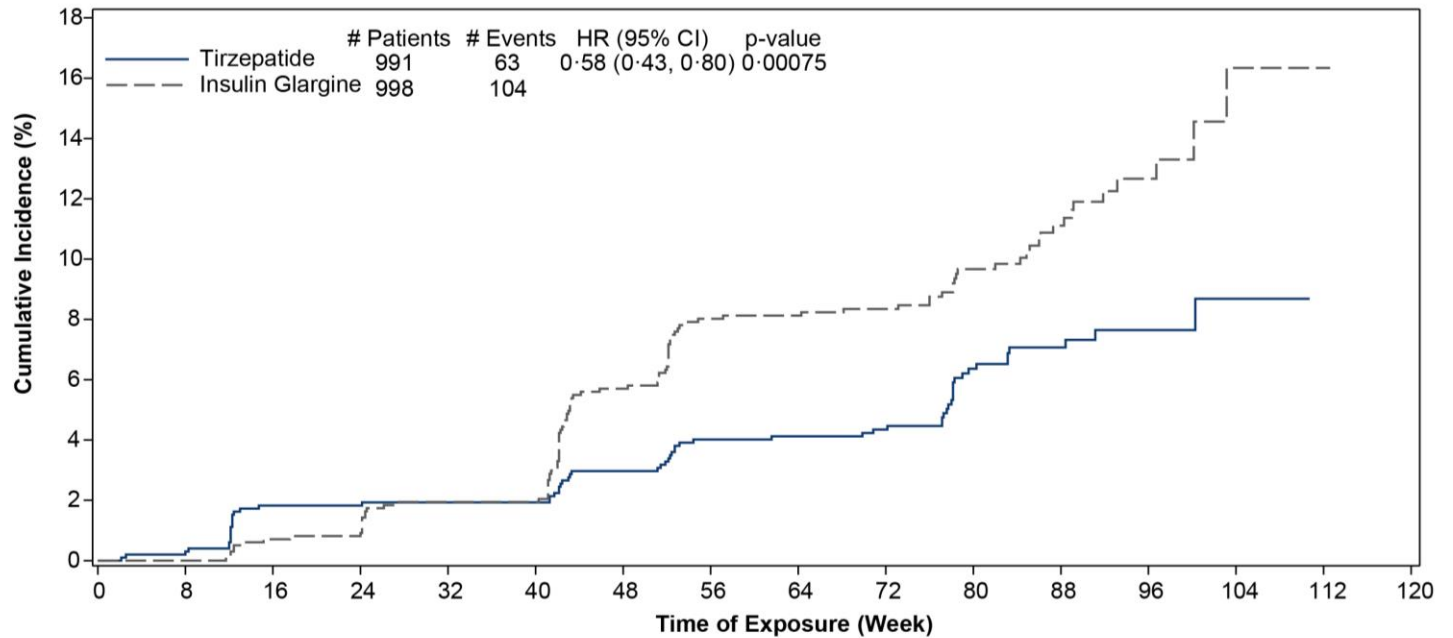


**Cardiovascular or renal death**



# Tirzepatide reduces the risk of the composite kidney endpoint (macroalbuminuria, 40% eGFR decline, ESKD, renal death)

Incidence composite kidney endpoint



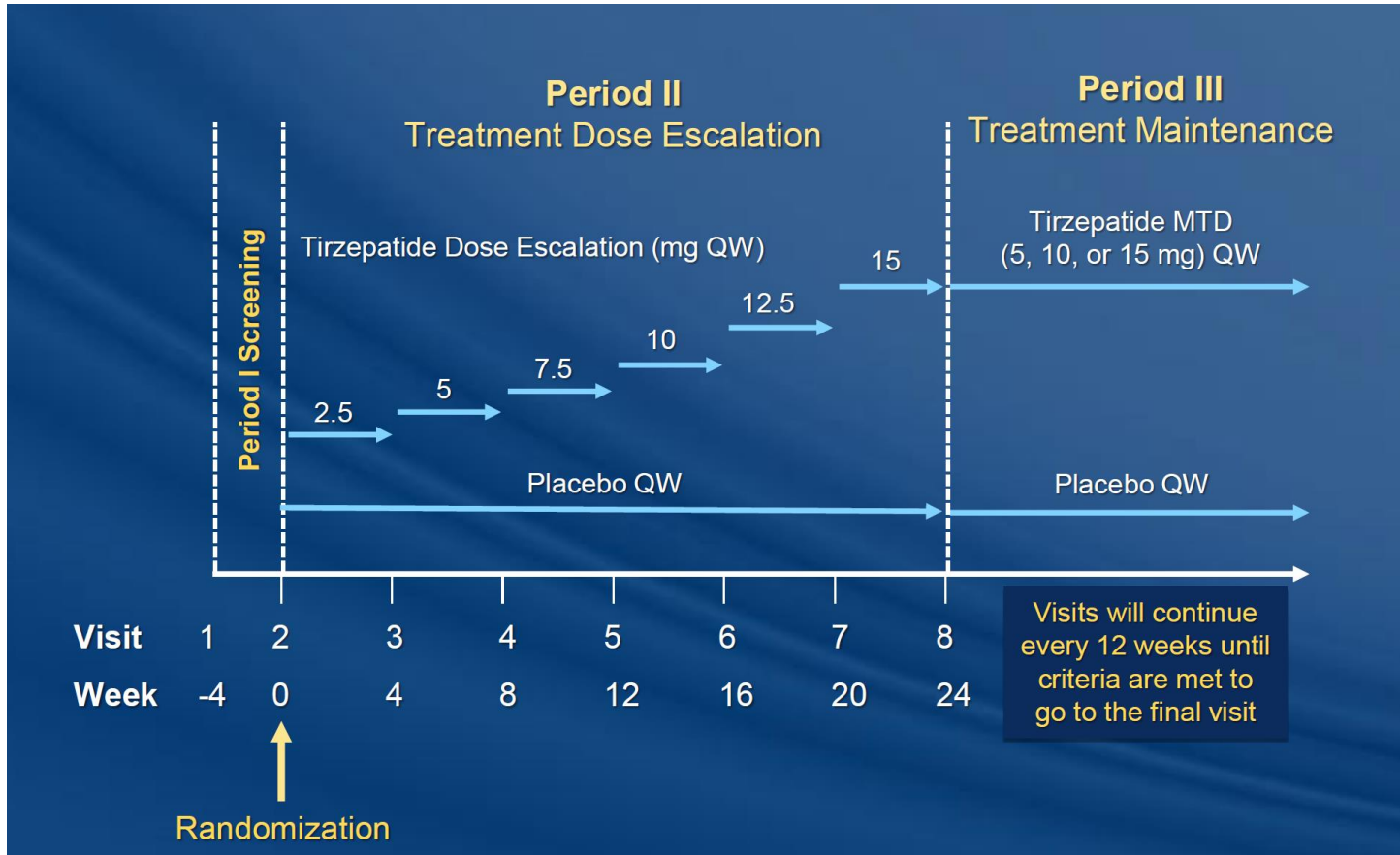
Cumulative number of events: Numbers at risk  
 Tirzepatide 0:991 3:985 18:962 18:952 19:947 19:944 29:930 39:912 40:902 42:815 56:609 60:391 62:180 63:41 63:0 63:0  
 Insulin Glargine 0:998 0:988 7:973 9:966 19:946 19:940 55:901 77:867 78:849 80:755 89:555 96:369 101:164 104:35 104:1 104:0

Component	Treatment	N (%)	HR (95%CI)
eGFR decline ≥40% from baseline	TZP	38 (3.8%)	0.87 (0.56,1.33)
	iGLAR	45 (4.5%)	
Renal death	TZP	0	-
	iGLAR	0	
Progression to ESKD	TZP	0	-
	iGLAR	5 (0.5%)	
New onset macroalbuminuria <sup>a</sup>	TZP	25 (2.5%)	0.41 (0.26,0.66)*
	iGLAR	61 (6.1%)	

Cumulative incidence of time to renal composite endpoint 1. HR, CI, and p-value are derived from a Cox proportional-hazards model with treatment (tirzepatide vs. insulin glargine) as a fixed effect. Heerspink et.al. Lancet Diabetes & Endocrinology

HR estimate with CI is not calculated when either the TZP or iGLAR arm has no event. <sup>a</sup>UACR ≥30 mg/g. \*P<.05 versus iGLAR.

# SURMOUNT-MMO



## Endpoint:

### Primary

- Time to CV composite

### Secondary

- Time to new-onset diabetes
- Renal endpoint (Win-ratio)

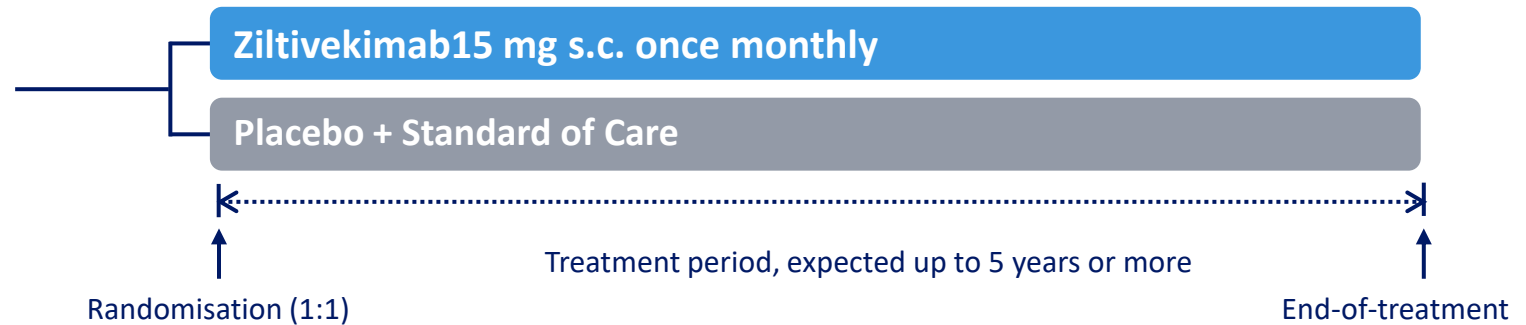
## Population:

- Obese individuals with CV disease or CV risk factors
- Pre-specified number of patients with established CKD

# ZEUS trial: Ziltivekimab in chronic kidney disease

## 6200 patients

- T2D, HbA<sub>1c</sub> ≤10%
- eGFR 15 -60
- hsCRP > 2mg/L
- Evidence of CV disease



## Time to first occurrence of a composite endpoint consisting of:

**Primary:** Cardiovascular (CV) death, non-fatal Myocardial Infarction (MI) and non-fatal stroke. [Time Frame: From randomisation (month 0) to end-of-study (up to 48 months)]

**Secondary:** eGFR decline



# Current and new treatment strategies for patients with CKD

ACEi  
and  
ARBs

SGLT2i

MRA

Incretins  
GLP-1 /  
  
GLP-1-  
GIP

Anti-  
inflammation  
IL-6  
inhibition