Efficacy and safety of finerenone in patients with CKD and T2D by baseline insulin treatment

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RATIONALE AND OBJECTIVE

- In FIDELIO-DKD (NCT02540993), finerenone reduced the incidence of cardiorenal events in patients with CKD and T2D without affecting HbA1c[1]
- This **subgroup analysis** reports outcomes by insulin (and insulin analogs) use at baseline

FIDELIO-DKD
FInerenone in reducing kiDnEy faiLure and dIsease prOgression in DKD

KEY FINDINGS

- Finerenone reduced the relative risk of a primary composite kidney outcome by 18% and a key secondary composite CV outcome by 14% versus placebo[1]
  - Results were consistent regardless of insulin use at baseline (*p*-interaction 0.56 and 0.33, respectively)
- Adverse events were similar between finerenone and placebo, independent of insulin use

CKD, chronic kidney disease; CV, cardiovascular; HbA1c, glycated hemoglobin; T2D, type 2 diabetes

1. Bakris GL, *et al*. *N Engl J Med* 2020;383:2219–2229

DISCLOSURES
Professor Rossing has received the following:

Consultancy and/or speaking fees (paid to his institution) from Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Gilead, Eli Lilly, Merck, MSD, Mundipharma, Novo Nordisk, and Sanofi Aventis

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RA reports personal fees and non-financial support from Bayer Healthcare Pharmaceuticals Inc., during the conduct of the study; he also reports personal fees and non-financial support from Akebia Therapeutics, Janssen, Relypsa, Vifor Pharma, Boehringer Ingelheim, Sanofi, Eli Lilly, AstraZeneca, and Fresenius; he has received personal fees from Ironwood Pharmaceuticals, Merck & Co., Lexicon, and Reata, and non-financial support from Otsuka America Pharmaceutical, Opko Pharmaceuticals, and E. R. Squibb & Sons; he is a member of data safety monitoring committees for Amgen, AstraZeneca, and Celgene; a member of steering committees of randomized trials for Akebia Therapeutics, Bayer, Janssen, and Relypsa; a member of adjudication committees for AbbVie, Bayer, Boehringer Ingelheim, and Janssen; he has served as Associate Editor of the *American Journal of Nephrology* and *Nephrology Dialysis and Transplantation* and has been an author for UpToDate; and he has received research grants from the U.S. Veterans Administration and the National Institutes of Health; **SDA** has received research support from Abbott Vascular and Vifor International, and personal fees from Abbott Vascular, Boehringer Ingelheim, Bayer, BRAHMS, Novartis, Servier, Vifor International, Impulse Dynamics, and Cardiac Dimensions; **GF** reports lectures fees and/or that he is a committee member of trials and registries sponsored by Bayer, Novartis, Vifor, Medtronic, Servier, Amgen, and Boehringer Ingelheim. He is a Senior Consulting Editor for *JACC Heart Failure,* and he has received research support from the European Union; **BP** reports consultant fees for Bayer, AstraZeneca, Sanofi/Lexicon, scPharmaceuticals, SQ Innovation, G3 Pharmaceuticals, Sarfez, Phasebio, Vifor/Relypsa, Cereno Scientific, Ardelyx, KBP Biosciences, Boehringer Ingelheim, Brainstorm Medical, and Tricida; he has stock options for Ardelyx, KBP Biosciences, SQ Innovation, Sarfez, scPharmaceuticals, Cereno Scientific, G3 Pharmaceuticals, Vifor/Relypsa, Brainstorm Medical, and Tricida; he also holds a patent for site-specific delivery of eplerenone to the myocardium (US patent #9931412) and a provisional patent for histone-acetylation-modulating agents for the treatment and prevention of organ injury (provisional patent US 63/045,784); **LMR** has no disclosures; **RJM** has received research grants from Novo Nordisk, Servier, Medtronic, The Rebecca Cooper Medical Research Foundation, St Vincent's Research Foundation, The Juvenile Diabetes Research Foundation, Grey Innovations, The Diabetes Australia Research Trust/Program, and The National Health and Medical Research Council of Australia; he has received honoraria for lectures from Eli Lilly, Novo Nordisk, Sanofi Aventis, AstraZeneca, Merck Sharp & Dohme, Novartis, and Boehringer Ingelheim and is on advisory boards for Novo Nordisk, Boehringer Ingelheim–Eli Lilly Diabetes Alliance, AstraZeneca, and Merck Sharp & Dohme; travel support has been supplied by Novo Nordisk, Sanofi, Boehringer Ingelheim, and AstraZeneca; he has been a principal investigator for industry-sponsored clinical trials run by Novo Nordisk, Sanofi, Bayer, Janssen-Cilag, and AbbVie; **JW** has received research support from Eli Lilly, Novo Nordisk, Sanofi, Boehringer Ingelheim, AstraZeneca, and Merck Sharp & Dohme; he has also received honoraria for lectures from Eli Lilly, Novo Nordisk, AstraZeneca, and Merck Sharp & Dohme; **AJ** and **LRo** are full-time employees of Bayer AG, Division Pharmaceuticals, Germany; **CS** is a full-time employee of Bayer PLC, United Kingdom; **GLB** reports research funding, paid to the University of Chicago Medicine from Bayer, during the conduct of the study; he also reports research funding, paid to the University of Chicago Medicine from Novo Nordisk and Vascular Dynamics; he acted as a consultant and received personal fees from for Merck, Relypsa, and Alnylam; he is an Editor of the *American Journal of Nephrology*, *Nephrology*, and *Hypertension*, and Section Editor of UpToDate; and he is an Associate Editor of *Diabetes Care* and *Hypertension Research*.

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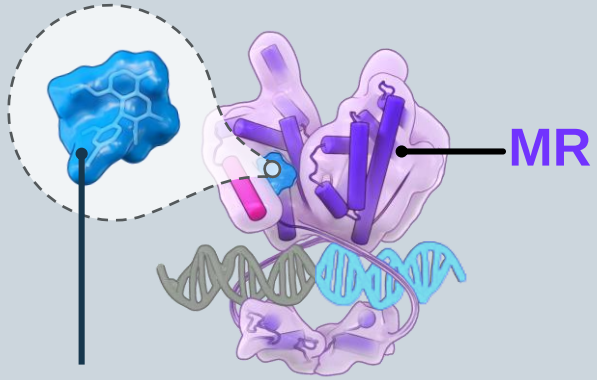
The FIDELIO-DKD trial demonstrated kidney and CV benefits with finerenone in patients with CKD and T2D[1]

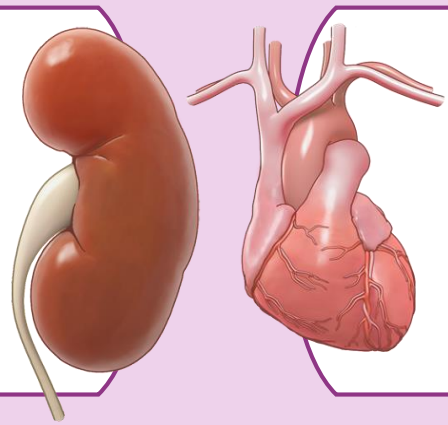
Finerenone is a **novel, nonsteroidal, selective MRA** that **inhibits inflammation and fibrosis**[2]



In FIDELIO-DKD,
finerenone significantly reduced the risk of:[1]

CKD progression by **18%**

NNT = 29*



CV morbidity and **mortality** by **14%**

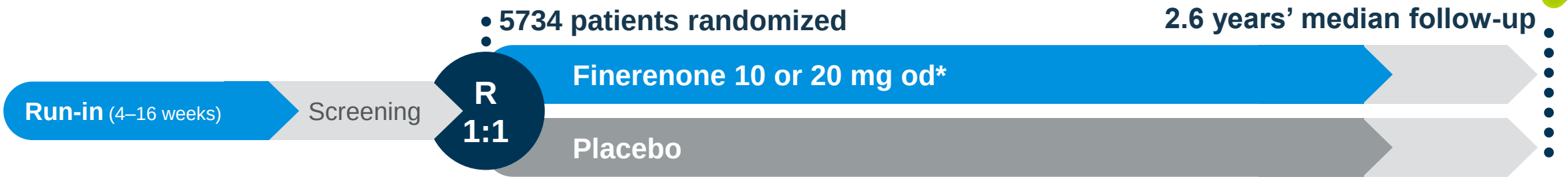
NNT = 42*

This analysis examines outcomes in FIDELIO-DKD by insulin use at baseline and during the trial, because many patients with CKD and T2D are treated with insulin in clinical practice

*NNT to prevent one event based on absolute risk reductions at 36 months
MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist; NNT, number needed to treat

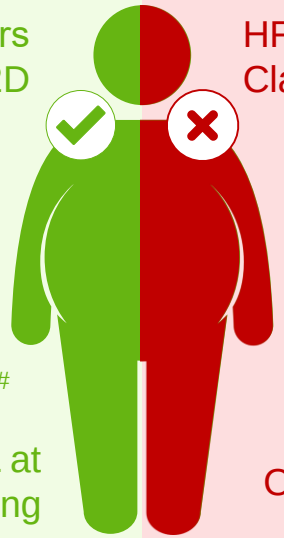
1. Bakris GL, *et al. N Engl J Med* 2020;383;2219–2229; 2. Agarwal R, *et al. Eur Heart J* 2021;42:152–161

A subgroup analysis from FIDELIO-DKD to evaluate the impact of baseline insulin use in adults with CKD and T2D[1]



Key inclusion criteria

- Aged ≥18 years with T2D
- On max. tolerated dose of ACEi or ARB for ≥4 weeks
- eGFR ≥25 to <75 mL/min/1.73 m^2
- UACR ≥30 to ≤5000 mg/g[#]
- Serum [K^+] ≤4.8 mmol/L at run-in and screening



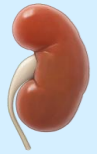
Key exclusion criteria

- HFrEF with NYHA Class II–IV
- Uncontrolled arterial hypertension[‡]
- HbA1c >12%
- Other kidney disease[§]

Key endpoints

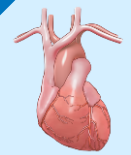
1. Kidney composite

Time to kidney failure, sustained ≥40% decrease in eGFR from baseline, or renal death



2. CV composite

Time to CV death, nonfatal MI, nonfatal stroke, or HHF



Aim of this subgroup analysis

To evaluate the impact of baseline insulin use (including insulin analogs) on composite kidney and CV outcomes and safety in patients treated with finerenone or placebo

*10 mg if screening eGFR <60 mL/min/1.73 m^2; 20 mg if ≥60 mL/min/1.73 m^2, up-titration encouraged from month 1 if serum potassium ≤4.8 mmol/L and eGFR stable; a decrease in the dose from 20 to 10 mg od was allowed any time after the initiation of finerenone or placebo; [#]patients with moderately elevated albuminuria (UACR 30–300 mg/g) were required to also have diabetic retinopathy; [‡]mean sitting SBP ≥170 mmHg or mean sitting DBP ≥110 mmHg at the run-in visit or mean sitting SBP ≥160 mmHg or mean sitting DBP ≥100 mmHg at the screening visit; [§]known significant nondiabetic kidney disease, including clinically relevant renal artery stenosis

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; [K^+], potassium concentration; MI, myocardial infarction; NYHA, New York Heart Association; od, once daily; R, randomization; RASi, renin–angiotensin system inhibitor; SBP, systolic blood pressure; UACR, urine albumin-to-creatinine ratio

1. Bakris GL, *et al*. *N Engl J Med* 2020;383:2219–2229

Patients using insulin at baseline had longer duration of diabetes, more CVD, and higher BMI, HbA1c, and UACR

Patient characteristics*	No insulin (n=2037)	Insulin (n=3637)
Age, years	66.4±9	65.1±9
Sex, male	1469 (72)	2514 (69)
SBP, mmHg	137.2±14.4	138.5±14.3
BMI, kg/m^2	30.1±6	31.7±6
Duration of diabetes, yrs	13.0±8	18.6±9
HbA1c, %	7.0±1	8.0±1
eGFR, mL/min/1.73 m^2	45.1±12.5	43.9±12.6
UACR, mg/g, median (IQR)	785 (443–1482)	819 (448–1715)
History of CVD	836 (41)	1769 (49)

At baseline, 3637 (64.1%) patients were using insulin

After the study start, insulin was initiated as a new medication in 469 (8.3%) patients

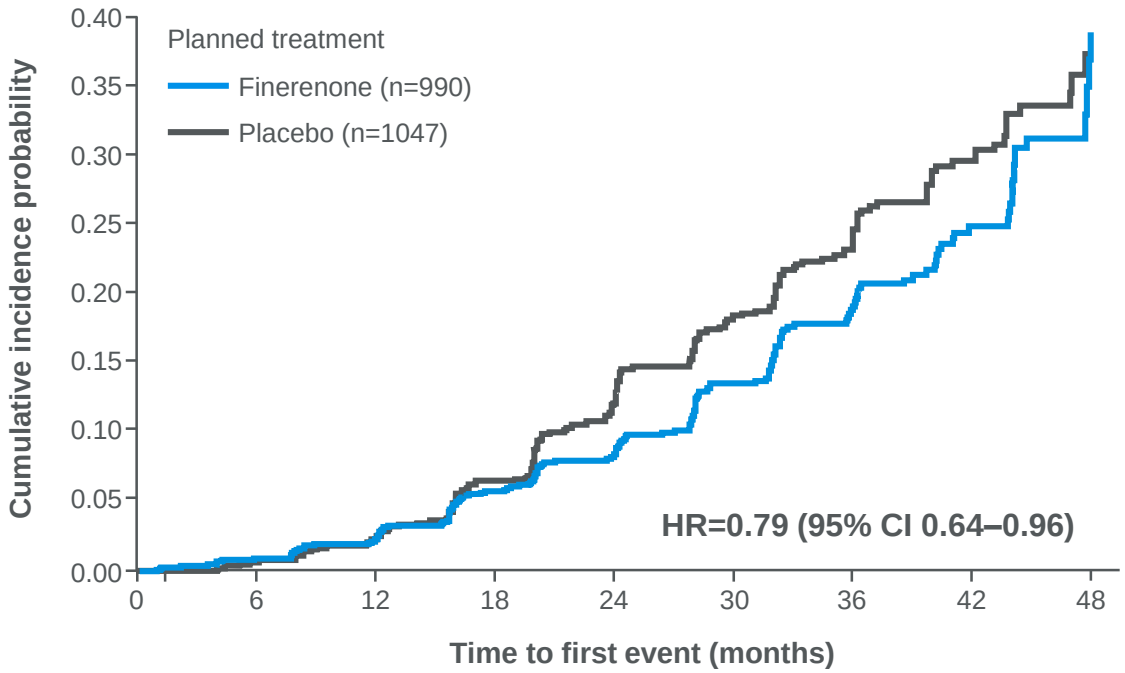
Medication use, n (%)	No insulin (n=2037)	Insulin (n=3637)
ACE inhibitor	664 (33)	1278 (35)
ARB	1367 (67)	2358 (65)
Beta blockers	989 (49)	1979 (54)
Diuretics	1055 (52)	2159 (59)
Statins	1458 (72)	2757 (76)
Antidiabetic therapies	1887 (93)	3637 (100)
Metformin	1146 (56)	1344 (37)
Sulfonylureas	909 (45)	418 (11)
DPP-4 inhibitors	782 (38)	740 (20)
GLP-1RAs	111 (5)	283 (8)
SGLT-2 inhibitors	86 (4)	173 (5)
α-glucosidase inhibitors	137 (7)	187 (5)

*Values are n (%) or mean ±SD unless otherwise stated

ACE, angiotensin-converting enzyme; BMI, body mass index; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; IQR, interquartile range; SD, standard deviation; SGLT-2, sodium-glucose co-transporter-2

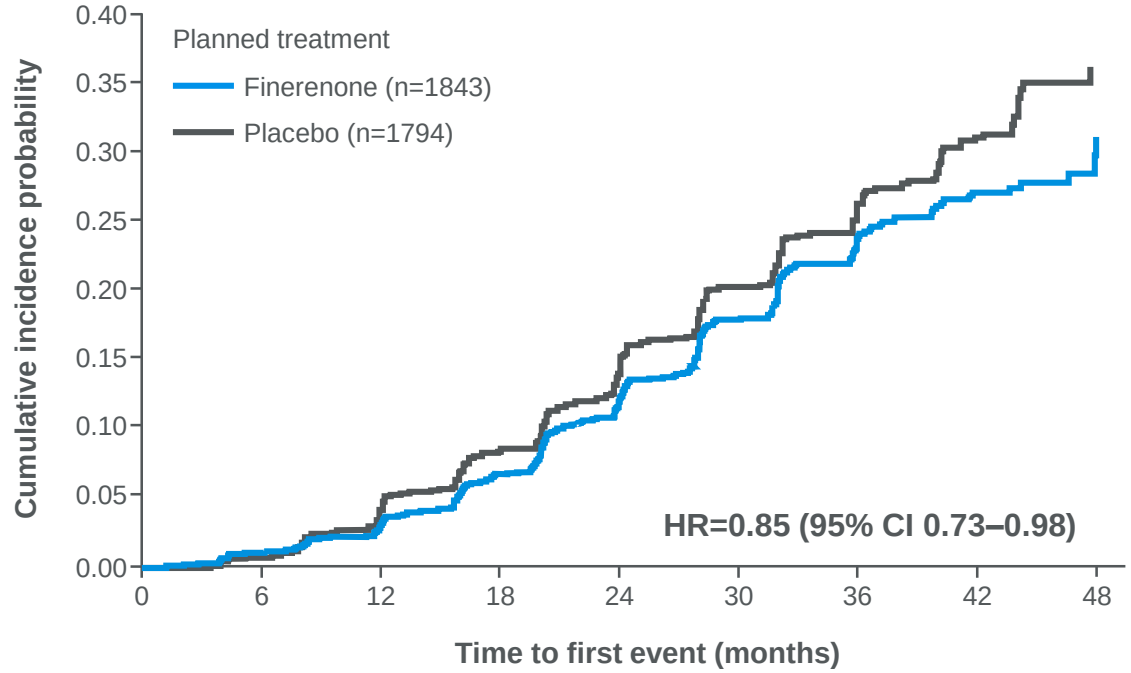
The effects of finerenone on the primary composite kidney outcome were consistent irrespective of baseline insulin use

No insulin



No. at risk									
Finerenone	990	948	923	857	681	493	304	168	29
Placebo	1047	1004	962	895	668	484	317	179	32

Insulin



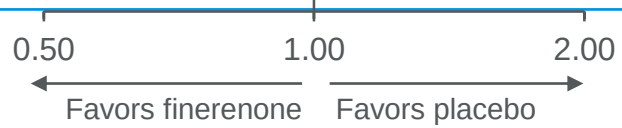
No. at risk									
Finerenone	1843	1757	1684	1540	1127	781	483	273	54
Placebo	1794	1720	1624	1484	1090	764	475	274	50

***p*-value for interaction = 0.56**

Full analysis set
CI, confidence interval; HR, hazard ratio

Cardiorenal benefits of finerenone were consistent independent of insulin use at baseline

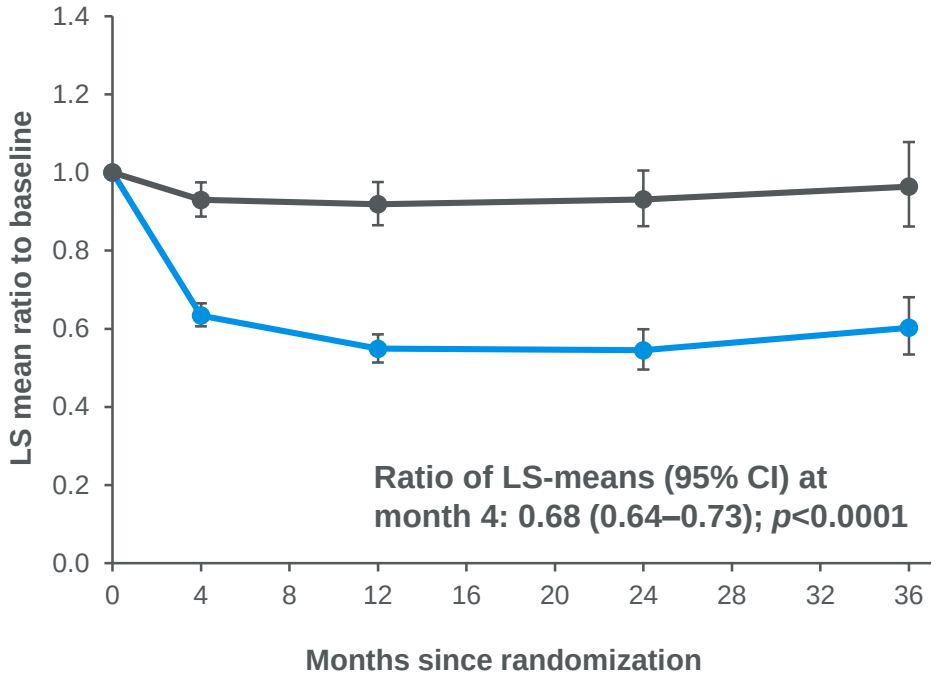
Outcome	Finerenone n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	*p*-interaction
Primary composite kidney outcome*				
Overall FIDELIO-DKD population[1]	**504/2833 (17.8)**	**600/2841 (21.1)**	**0.82 (0.73–0.93)**	
No insulin	172/990 (17.4)	218/1047 (20.8)	0.79 (0.64–0.96)	0.56
Insulin	332/1843 (18.0)	382/1794 (21.3)	0.85 (0.73–0.98)	
Secondary composite kidney outcome#				
Overall FIDELIO-DKD population[1]	**252/2833 (8.9)**	**326/2841 (11.5)**	**0.76 (0.65–0.90)**	
No insulin	86/990 (8.7)	119/1047 (11.4)	0.75 (0.57–1.00)	0.93
Insulin	166/1843 (9.0)	207/1794 (11.5)	0.77 (0.62–0.94)	
Key secondary composite CV outcome‡				
Overall FIDELIO-DKD population[1]	**367/2833 (13.0)**	**420/2841 (14.8)**	**0.86 (0.75–0.99)**	
No insulin	112/990 (11.3)	121/1047 (11.6)	0.95 (0.74–1.23)	0.33
Insulin	255/1843 (13.8)	299/1794 (16.7)	0.82 (0.69–0.97)	



Full analysis set
*Kidney failure, sustained ≥40% decrease in eGFR from baseline, or renal death;
#kidney failure, sustained ≥57% decrease in eGFR from baseline, or renal death;
‡a composite of time to first onset of death from CV causes, nonfatal MI, nonfatal stroke, or HHF

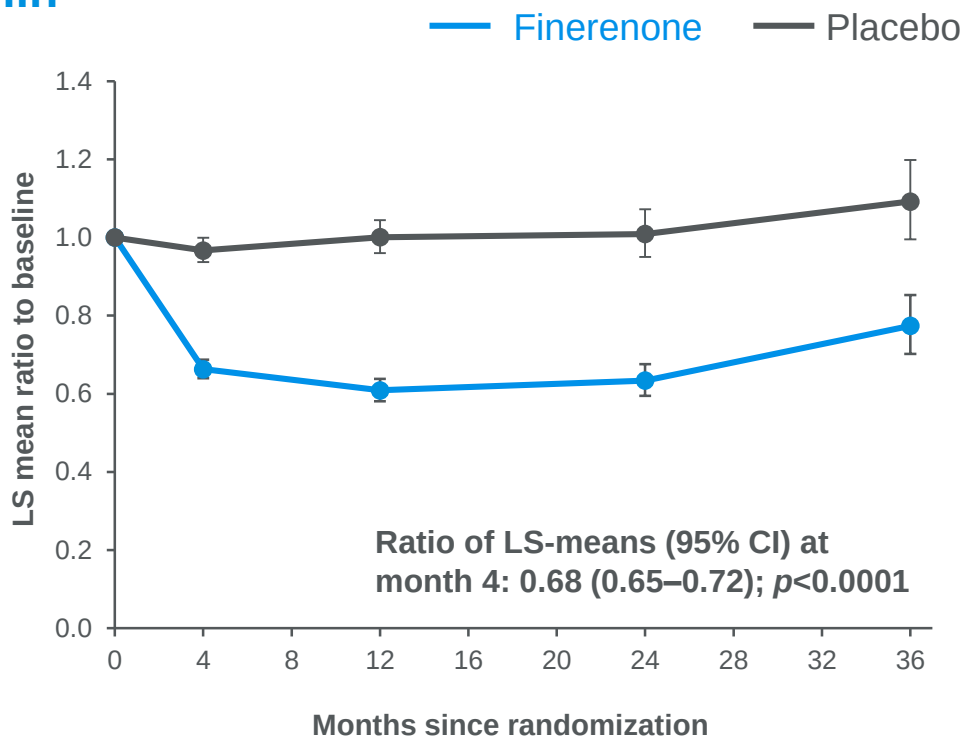
The change in UACR from baseline to month 4 was consistent irrespective of insulin use at baseline

No insulin



No. of patients				
Finerenone	955	917	680	323
Placebo	1003	958	704	335

Insulin



No. of patients				
Finerenone	1770	1665	1161	533
Placebo	1723	1640	1121	499

Full analysis set. Mixed model including covariates: treatment group, stratification factors (region, eGFR category, and type of albuminuria at screening), time, treatment over time, log-transformed baseline value nested within type of albuminuria at screening, and log-transformed baseline value over time
LS, least squares

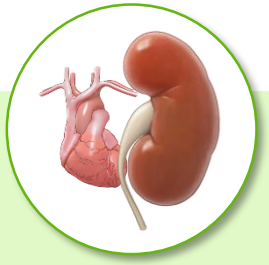
The safety profile of finerenone was consistent regardless of insulin use at baseline

n (%)	No insulin		Insulin	
	Finerenone (n=989)	Placebo (n=1041)	Finerenone (n=1838)	Placebo (n=1790)
Any AE	854 (86.3)	903 (86.7)	1614 (87.8)	1575 (88.0)
AE related to study drug	205 (20.7)	148 (14.2)	441 (24.0)	301 (16.8)
AE leading to permanent discontinuation	76 (7.7)	69 (6.6)	131 (7.1)	99 (5.5)
Any serious AE	282 (28.5)	318 (30.5)	620 (33.7)	653 (36.5)
Serious AE related to study drug	12 (1.2)	11 (1.1)	36 (2.0)	23 (1.3)
Serious AE leading to permanent discontinuation	26 (2.6)	33 (3.2)	49 (2.7)	45 (2.5)
Most common AEs by organ class (>8% of patients)				
Hyperkalemia	133 (13.4)	67 (6.4)	313 (17.0)	154 (8.6)
Peripheral edema	47 (4.8)	87 (8.4)	139 (7.6)	217 (12.1)
Nasopharyngitis	106 (10.7)	119 (11.4)	135 (7.3)	131 (7.3)
Hypertension	67 (6.8)	97 (9.3)	145 (7.9)	176 (9.8)
Hypoglycemia	30 (3.0)	29 (2.8)	121 (6.6)	165 (9.2)

Safety analysis set

AE, adverse event; TEAE, treatment-emergent adverse event

Conclusions



Consistent kidney and CV benefits of finerenone versus placebo, irrespective of insulin use

Overall, AEs were similar with finerenone and placebo, independent of insulin use

Hyperkalemia was increased with finerenone, but its clinical impact was minimal

LIMITATIONS Secondary subgroup analysis – patients not recruited according to baseline insulin use

This subgroup analysis suggests finerenone may be an important advance in treatment for patients with CKD and T2D, independent of insulin use