IMPACT OF FINERENONE ON CARDIAC BIOMARKERS IN PATIENTS WITH T2D AND CKD -

A PRESPECIFIED FIDELITY BIOMARKER SUBSTUDY

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DISCLOSURES

Mario Berger, **Katja Rohwedder, Frank Kramer, Karen Paraschin, Laura Goea**, **Peter Kolkhof**, and **Adam Skubala** are employees of Bayer AG, Germany.

Andrea Scalise is an employee of Bayer Hispania SL.

Sebastian Voss is an employee of CHRESTOS Concept GmbH & Co. KG, Germany, a contract partner of Bayer.

Faiez Zannad has received personal fees from Boehringer Ingelheim during the conduct of the study; has received personal fees from Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boston Scientific, Cardior, Cellprothera, Cereno Pharmaceutical, CVRx, Fresenius, Janssen, Merck, Novartis, and Vifor; and is the co-founder of CVCT and Cardiorenal, outside of the submitted work.

Peter Rossing has received grants from AstraZeneca, Bayer, and Novo Nordisk A/S, as well as consulting fees from Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Gilead, Merck, Mundipharma, Novo Nordisk A/S, and Sanofi. All fees to Steno Diabetes Center Copenhagen.

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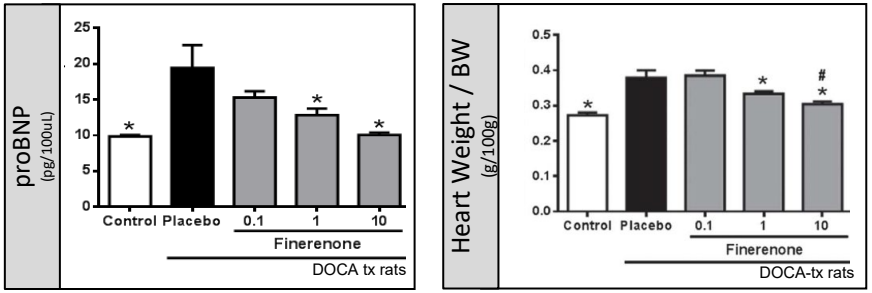
RATIONALE

Confirming preclinical findings that finerenone protects heart (and kidney)[1] by measuring biomarkers of cardiac stress and injury in human plasma samples from two phase III studies (FIDELITY analysis)



Adapted from Kolkhof *et al.* 2014[1]

Finerenone reduces **proBNP** plasma levels and cardiac hypertrophy (HW/BW) in a chronic rat model of hyperaldosteronism-induced end-organ damage

p<0.05 versus placebo; DOCA, deoxycorticosterone acetate; proBNP, fragment of N-terminal BNP peptide (27-62).

1. Adapted from Kolkhof P, *et al. J Cardiovasc Pharmacol* 2014;64:69–78

FIDELITY IS A LARGE, POOLED PRESPECIFIED DATA ANALYSIS[1] OF FIDELIO-DKD[2] AND FIGARO-DKD[3]

48 countries

13,171 patients randomized

3 years median follow-up

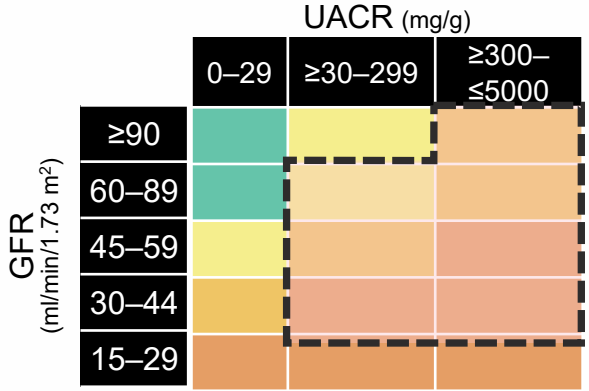
R

Finerenone 10 or 20 mg od*

Placebo

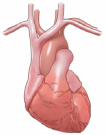
Key eligibility criteria

- T2D
- CKD
- On single RASi
- Serum [K^+] ≤4.8 mmol/l
- Symptomatic HFrEF (NYHA class II–IV)



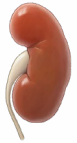
CV composite

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



57% eGFR kidney composite

Time to kidney failure,# sustained ≥57% decrease in eGFR from baseline, or kidney-related death

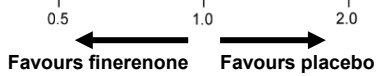


*Up-titration of study drug was encouraged from visit 2 provided potassium value was 4.8 mmol/l or less and eGFR was stable; down-titration was allowed any time after treatment initiation for safety reasons; #kidney failure defined as initiation of chronic dialysis for ≥90 days or kidney transplantation or sustained eGFR <15 mL/min/1.73 m^2; CKD, chronic kidney disease; CV, cardiovascular; GFR, glomerular filtration rate; GFR, 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; T2D, type 2 diabetes; UACR, urin albumin-to-creatinine ratio

1. Agarwal R, *et al., Eur Heart J* 2022;43:474–484; 2. Bakris G, *et al., N Eng J Med* 2020;383:2219–2229; 3. Pitt B, *et al., N Eng J Med* 2021;385:2252–2263

KEY LEARNINGS FROM FIDELITY

Outcome	Finerenone (n = 6519)		Placebo (n = 6507)		Hazard ratio (95% CI)	*P*-value[a]
	Number of patients with event (%)	Number of patients with event per 100 patient-years	Number of patients with event (%)	Number of patients with event per 100 patient-years		
Composite cardiovascular outcome[b]	825 (12.7)	4.34	939 (14.4)	5.01	0.86 (0.78–0.95)	0.0018
Death from cardiovascular causes	322 (4.9)	1.61	364 (5.6)	1.84	0.88 (0.76–1.02)	0.092
Non-fatal myocardial infarction	173 (2.7)	0.88	189 (2.9)	0.97	0.91 (0.74–1.12)	0.36
Non-fatal stroke	198 (3.0)	1.01	198 (3.0)	1.02	0.99 (0.82–1.21)	0.95
Hospitalization for heart failure	256 (3.9)	1.31	325 (5.0)	1.68	0.78 (0.66–0.92)	0.0030
eGFR 57% composite kidney outcome[c]	360 (5.5)	1.96	465 (7.1)	2.55	0.77 (0.67–0.88)	0.0002
Kidney failure	254 (3.9)	1.38	297 (4.6)	1.62	0.84 (0.71–0.99)	0.039
End-stage kidney disease[d]	151 (2.3)	0.76	188 (2.9)	0.96	0.80 (0.64–0.99)	0.040[e]
Sustained decrease in eGFR to <15 mL/min/1.73 m^2	195 (3.0)	1.06	237 (3.6)	1.29	0.81 (0.67–0.98)	0.026[e]
Sustained ≥57% decrease in eGFR from baseline	257 (3.9)	1.40	361 (5.5)	4.03	0.70 (0.60–0.83)	< 0.0001
Renal death	2 (<0.1)	0.01	4 (<0.1)	0.02	0.53 (0.10–2.91)	0.46[e]



Finerenone reduced the risk of CV morbidity and mortality by 14% (NNT=46)

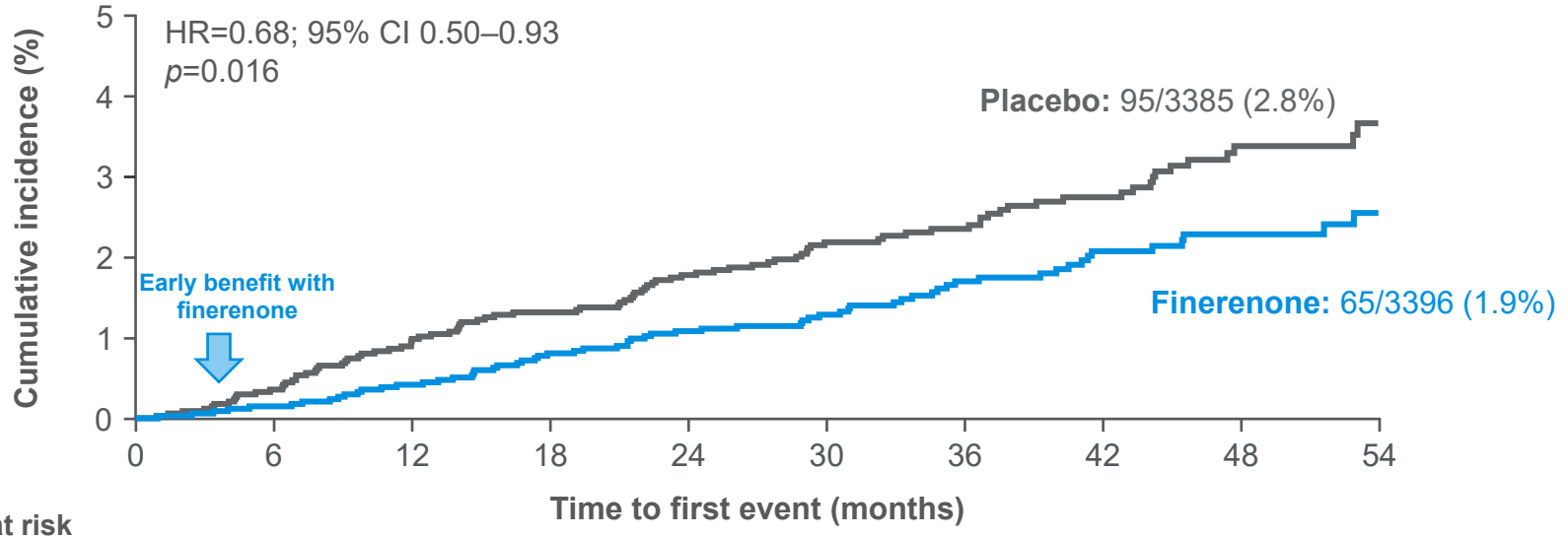
The CV benefit of finerenone was primarily driven by 22% reduction in HHF

Finerenone reduced the risk of CKD progression by 23% (NNT=60)

Table Adapted from: Agarwal *et al.*, *Eur Heart J*, 2022; 43:474–484

[a]Analyses for *P*-values not prespecified; [b]the composite of time to first onset of CV death, non-fatal MI, non-fatal stroke, or HHF; [c]**the composite of time to first onset kidney failure,** sustained ≥57% decrease in eGFR from baseline, or kidney-related death; [d]kidney failure defined as initiation of chronic dialysis for ≥90 days or kidney transplantation or sustained eGFR <15 mL/min/1.73 m^2; [e]Statistical test where *P*-values provided are exploratory in nature; therefore, no adjustment for multiplicity was performed; NNT, number needed to treat; PY, patient-years

FINERENONE SIGNIFICANTLY REDUCED THE RISK OF NEW-ONSET HF BY 32% IN PATIENTS WITHOUT A HISTORY OF HF AT BASELINE



No. at risk										
Finerenone	3396	3367	3323	3274	3195	2710	2168	1705	1091	608
Placebo	3385	3351	3294	3236	3154	2694	2131	1674	1091	606

FIGARO-DKD

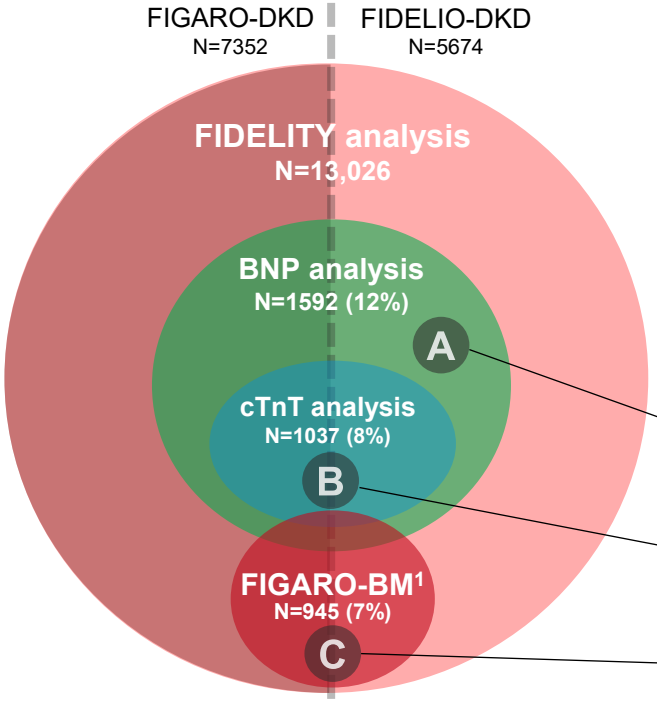
CI, confidence interval; HF, heart failure; HR, hazard ratio; RAS, renin–angiotensin system
modified from Filippatos G. *Circulation Vol 145 Issue 6, 2022:437-447*

FINERENONE HAS A 1A RECOMMENDATION TO PREVENT HF IN PATIENTS WITH CKD AND T2D

Recommendations	Class*	Level#
In patients with T2DM and CKD,† SGLT2 inhibitors (dapagliflozin or empagliflozin) are recommended to reduce the risk of HF hospitalization or CV death.	I	A
In patients with T2DM and CKD,† finerenone is recommended to reduce the risk of HF hospitalization.	I	A

*Class of recommendation; #level of evidence; †CKD was defined as follows: an eGFR 25–75 mL/min/1.73 m^2 and a UACR ≥200–5000 mg/g in DAPA-CKD; an eGFR 20–45 mL/min/ 1.73 m^2 or an eGFR 45–90 mL/min/1.73 m^2 with a UACR ≥200 mg/g in EMPA-KIDNEY; an eGFR 25–60 mL/min/1.73 m^2, a UACR 30–300 mg/g, and diabetic retinopathy, or an eGFR 25–75 mL/min/1.73 m^2 and a UACR 300–5000 mg/g, in FIDELIO-DKD;10 and an eGFR 25–90 mL/min/1.73 m^2 and a UACR 30 to <300 mg/g, or an eGFR >60 mL/min/1.73 m2 and a UACR 300–5000 mg/g, in FIGARO-DKD
McDonagh TA, *et al.*, *Eur Heart J* 2023;44:3627–3639

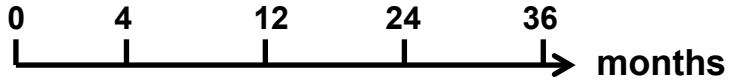
COMPOSITION OF COHORTS AND BIOANALYTICS IN BIOMARKER STUDY



Up to 24 participating countries#

e.g. Israel, Denmark, Canada, Spain, Germany, Argentina, Sweden, Australia, Belgium, Finland, UK, Brazil #

Sampling



Assays used

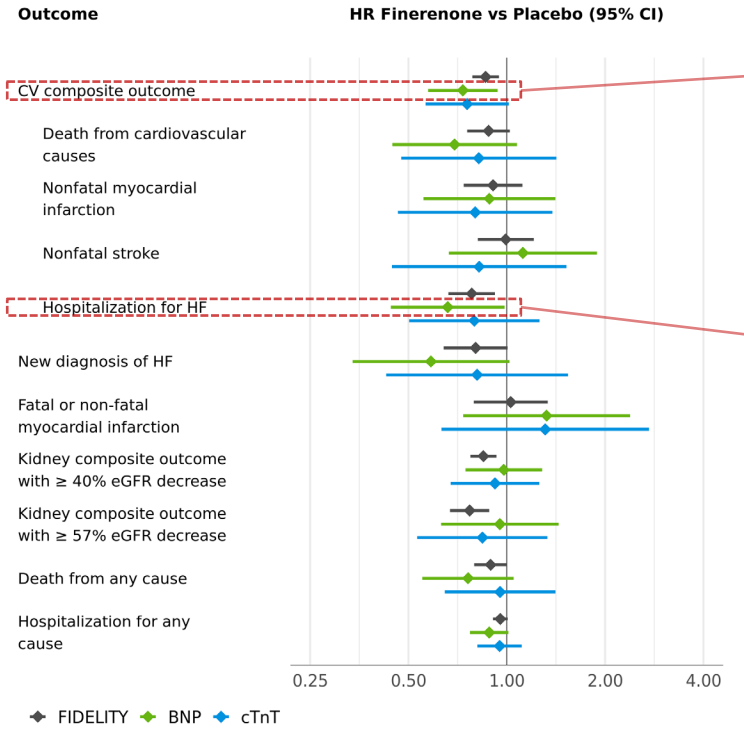
NT-proBNP in plasma
Siemens Immulite 2000

High-sensitivity cTnT in serum
Roche Cobas e-601

Olink Explore 3072® (in plasma)

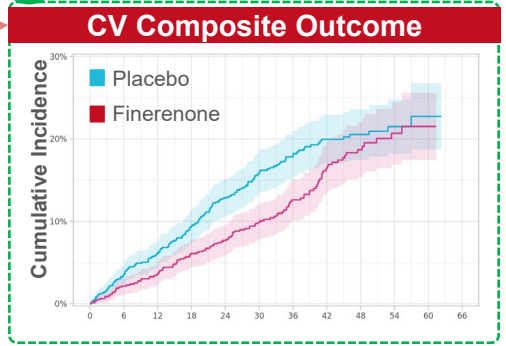
BNP/cTnT analysis: patient set in which NT-proBNP or cTnT (high sensitivity cardiac troponin T) was measured;
#top countries countributing ≥3.2% patients to BNP analysis
1 Berger M, *et al. JASN* 2023;34:16 (Supplement [Kidney Week 2023])

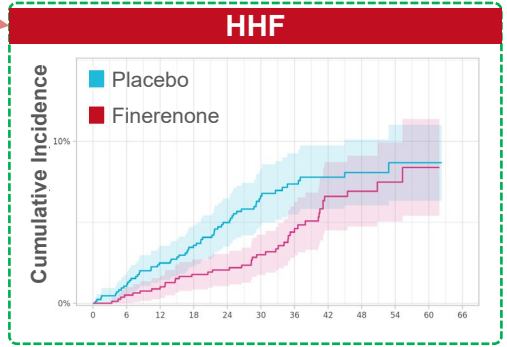
BIOMARKER SUBPOPULATIONS ARE REPRESENTATIVE OF FIDELITY COHORT



Number of events (%)		
	Placebo	Finerenone
0.86 (0.78; 0.95)	939 (14.4%)	825 (12.7%)
0.73 (0.57; 0.94)	155 (18.2%)	118 (14.9%)
0.76 (0.56; 1.01)	106 (19.2%)	85 (16.3%)
0.88 (0.76; 1.02)	364 (5.6%)	322 (4.9%)
0.69 (0.45; 1.07)	51 (6.0%)	34 (4.3%)
0.82 (0.48; 1.42)	29 (5.3%)	24 (4.6%)
0.91 (0.74; 1.12)	189 (2.9%)	173 (2.7%)
0.88 (0.56; 1.41)	40 (4.7%)	35 (4.4%)
0.80 (0.46; 1.38)	31 (5.6%)	24 (4.6%)
0.99 (0.82; 1.21)	198 (3.0%)	198 (3.0%)
1.12 (0.66; 1.89)	28 (3.3%)	31 (3.9%)
0.82 (0.45; 1.52)	23 (4.2%)	20 (3.8%)
0.78 (0.66; 0.92)	325 (5.0%)	256 (3.9%)
0.66 (0.44; 0.98)	60 (7.0%)	41 (5.2%)
0.80 (0.50; 1.26)	42 (7.6%)	34 (6.5%)
0.80 (0.64; 1.01)	169 (2.8%)	138 (2.3%)
0.59 (0.34; 1.02)	33 (4.2%)	21 (2.8%)
0.81 (0.43; 1.54)	21 (4.1%)	18 (3.7%)
1.03 (0.79; 1.33)	111 (3.0%)	116 (3.1%)
1.32 (0.74; 2.39)	20 (4.2%)	27 (6.1%)
1.31 (0.63; 2.73)	13 (4.6%)	17 (6.4%)
0.85 (0.77; 0.93)	995 (15.3%)	854 (13.1%)
0.98 (0.75; 1.28)	117 (13.7%)	106 (13.4%)
0.92 (0.67; 1.26)	89 (16.1%)	79 (15.2%)
0.77 (0.67; 0.88)	465 (7.1%)	360 (5.5%)
0.95 (0.63; 1.44)	54 (6.3%)	43 (5.4%)
0.84 (0.53; 1.33)	44 (8.0%)	34 (6.5%)
0.89 (0.79; 1.00)	614 (9.4%)	552 (8.5%)
0.76 (0.55; 1.05)	90 (10.6%)	66 (8.3%)
0.95 (0.65; 1.41)	54 (9.8%)	50 (9.6%)
0.96 (0.91; 1.01)	2926 (45.0%)	2836 (43.5%)
0.88 (0.77; 1.01)	471 (55.2%)	412 (52.0%)
0.95 (0.81; 1.11)	347 (62.9%)	324 (62.2%)

A Biomarker subcohort (BNP)



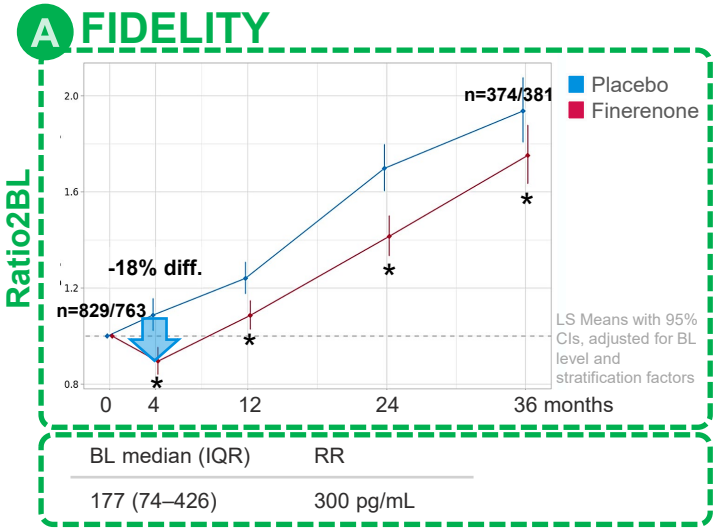


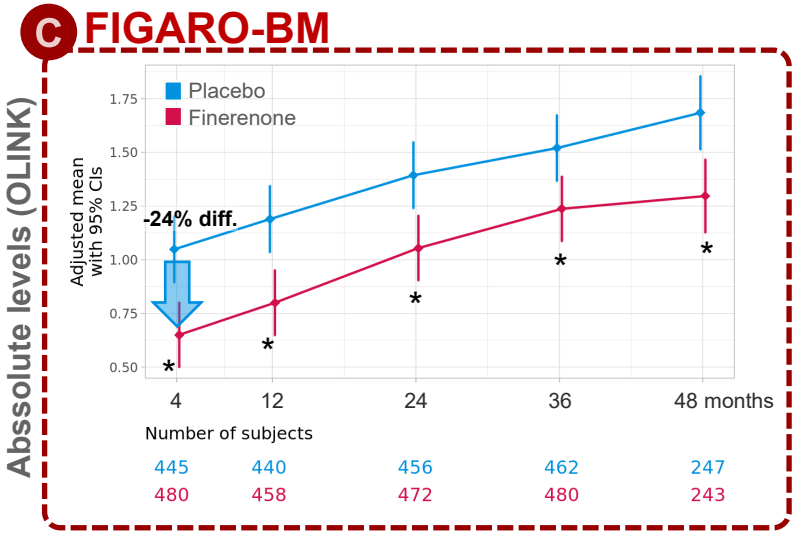
BASELINE CHARACTERISTICS

Characteristic	FIDELITY	BNP population		cTnT population	
	Total (N=13026)	Finerenone (N=793)	Placebo (N=853)	Finerenone (N=521)	Placebo (N=552)
Age [years], mean ± SD	64.8 ± 9.5	66.4 ± 8.5	66.8 ± 8.8	66.8 ± 8.1	67.3 ± 8.5
Male sex, n (%)	9088 (69.8%)	609 (76.8%)	670 (78.5%)	416 (79.8%)	439 (79.5%)
White race/ethnicity	8869 (68.1)	733 (92.4)	789 (92.5)	495 (95.0)	520 (94.2)
BMI [kg/m^2], mean ± SD	31.3 ± 6.0	32.1 ± 5.6	32.1 ± 5.7	32.3 ± 5.4	32.1 ± 5.7
History of CV disease, n (%)	5935 (45.6%)	386 (48.7%)	409 (47.9%)	243 (46.6%)	255 (46.2%)
SBP [mmHg], mean ± SD	136.7 ± 14.2	138.3 ± 15.1	138.2 ± 15.1	137.8 ± 14.6	137.2 ± 15.0
eGFR [mL/min/1.73m^2], mean ± SD	57.6 ± 21.7	55.9 ± 20.8	55.4 ± 20.5	53.8 ± 18.9	53.3 ± 18.9
UACR [mg/g]*	515 (198 - 1147)	407 (135 - 975)	440 (134 - 1015)	379 (116 - 925)	347 (106 - 894)
Serum potassium [mmol/L]*	4.3 (4.1 - 4.6)	4.3 (4.1 - 4.6)	4.3 (4.1 - 4.6)	4.3 (4.0 - 4.6)	4.3 (4.1 - 4.6)
Serum sodium [mmol/L]*	139 (137 - 141)	138 (137 - 140)	138 (137 - 140)	138 (137 - 140)	138 (137 - 140)
hsCRP [mg/L]*	2.21 (0.95 - 5.13)	2.36 (1.00 - 5.28)	2.32 (1.08 - 5.20)	2.38 (1.00 - 5.15)	2.32 (1.07 - 5.20)
HbA1C [%]*	7.5 (6.7 - 8.5)	7.5 (6.7 - 8.4)	7.5 (6.8 - 8.4)	7.5 (6.7 - 8.4)	7.5 (6.8 - 8.3)
NT-proBNP [pg/mL]*	-	177 (78 - 422)	177 (72 - 431)	177 (74 - 421)	177 (70 - 429)
(hs) cTnT [pg/mL]*	-	-	-	17.7 (6.5 - 25.0)	19.0 (6.5 - 28.2)

* Median and IQR; Abbreviations: hsCRP, high sensitivity C-reactive protein; hs cTnT, high sensitivity cardiac troponin T, HbA1c, glycated hemoglobin; IQR, interquartile range; SBP, systolic blood pressure; SD, standard deviation

NT-PROBNP LEVELS IMPROVE UPON FINERENONE TREATMENT (1/2)

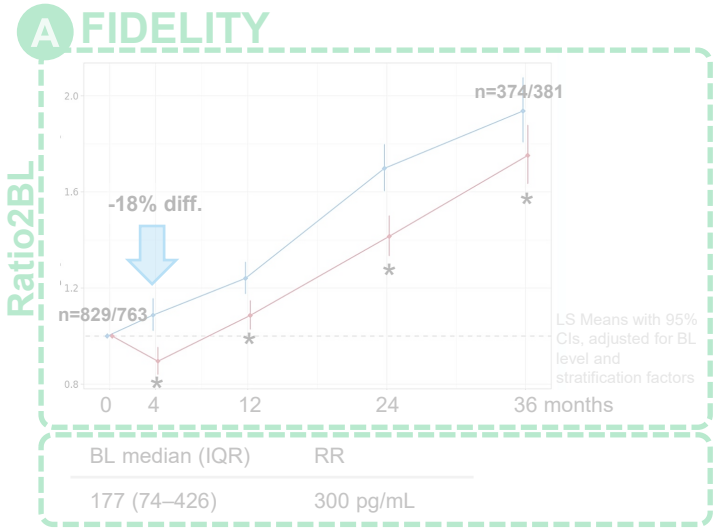


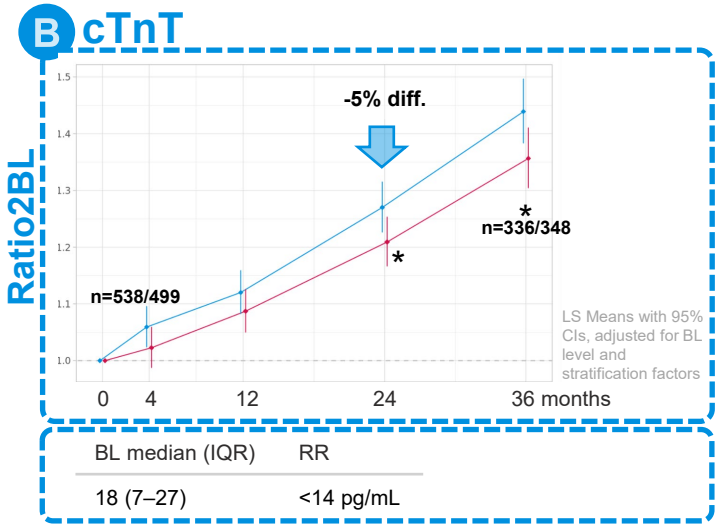


In the FIDELITY subcohort (**A**), levels of **NT-proBNP were reduced by ~18% early and persistently** in the finerenone arm (vs placebo). In FIGARO-BM (**C**), these findings were confirmed!

Unpublished data
*$p \leq 0.05$, RR = reference range; BL= 0 months (baseline)

CTNT LEVELS IMPROVE UPON FINERENONE TREATMENT (2/2)



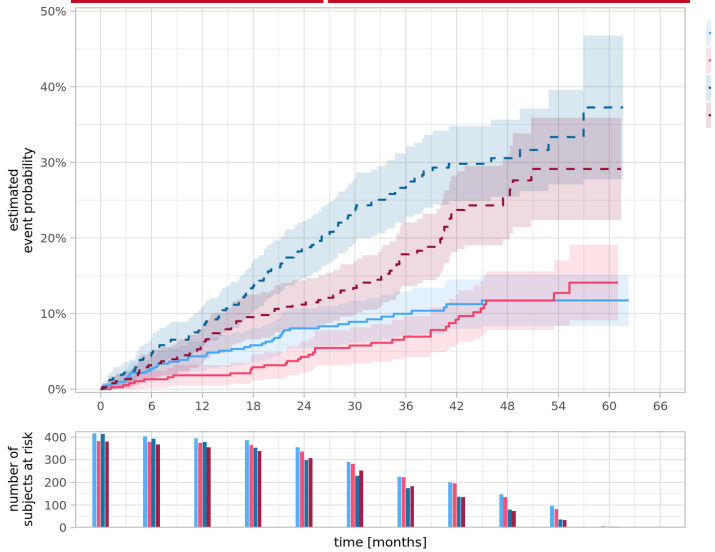


- Significant **reduction in both cardiac markers** of cardiac stress and injury upon finerenone treatment (vs placebo)
- Biomarker findings are **consistent with overall heart and kidney benefits** in phase III studies

Unpublished data
*$p \leq 0.05$

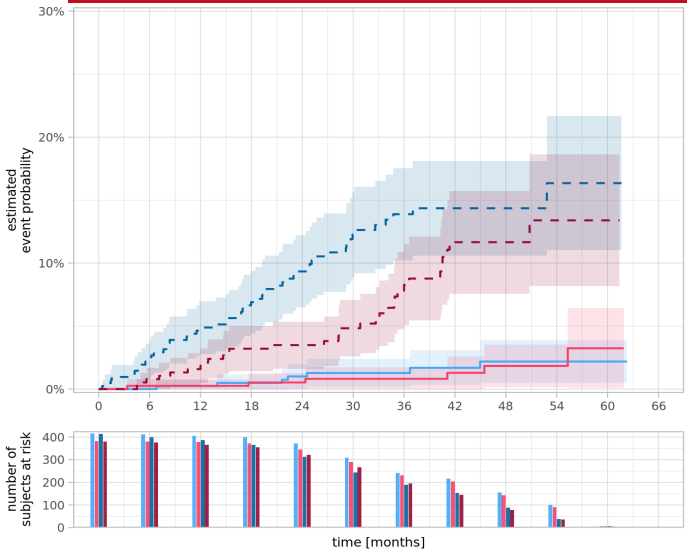
NT-PROBNP AT BASELINE IS PROGNOSTIC FOR CV COMPOSITE AND HOSPITALIZATION FOR HF

CV Composite Outcome

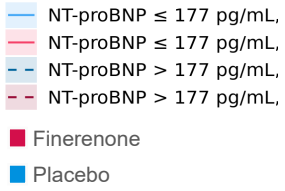


Cox analysis:
33% risk increase when doubling **NT-proBNP** (p<0.001)

HHF

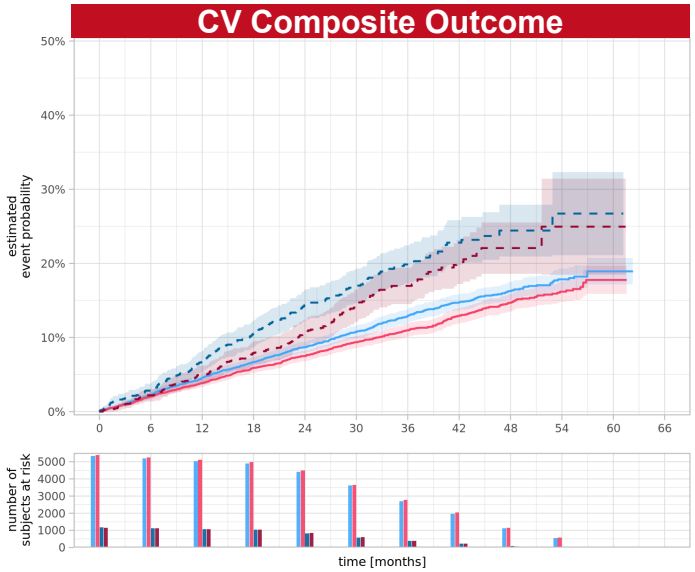


Cox analysis:
68% risk increase when doubling **NT-proBNP** (p<0.001)

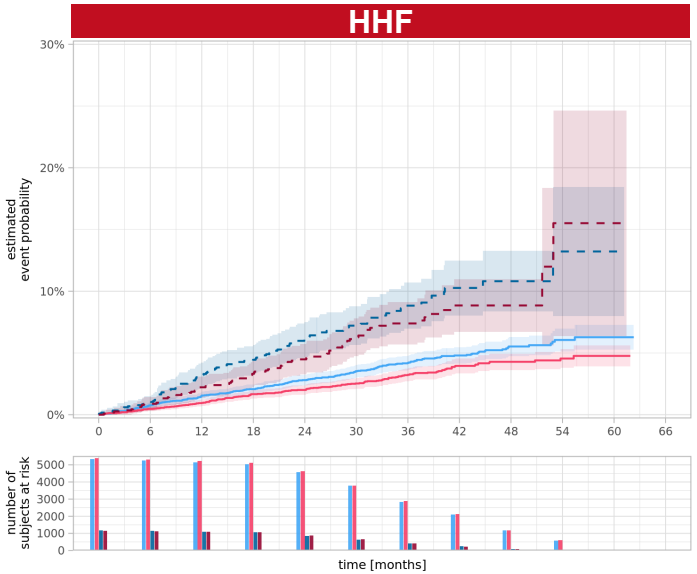


Unpublished data

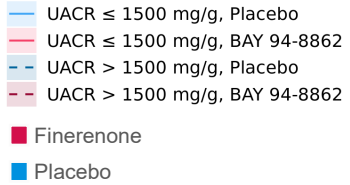
BASELINE UACR IS PROGNOSTIC FOR CV COMPOSITE AND HOSPITALIZATION FOR HF



Cox analysis:
19% risk increase when doubling **UACR** (p<0.001)



Cox analysis:
33% risk increase when doubling **UACR** (p<0.001)



TAKE-HOME MESSAGES

- Finerenone led to **an early and persisting reduction in NT-proBNP** plasma levels compared with placebo, on top of maximum tolerated labeled doses of RASi
- Likewise, finerenone **improved (high-sensitivity) cTnT** serum levels significantly after ≥24 months of treatment
- Our biomarker findings are in line with outcome data from phase III studies showing a **22% risk reduction for HHF (FIDELITY)**[1] and a **32% risk reduction of new-onset HF** in patients without a history of HF at baseline (FIGARO-DKD)[2]
- Altogether, our findings are suggestive of **reduced adverse cardiac remodeling**
- These data further substantiate the **1A recommendation** to use finerenone to prevent HF in patient with CKD and T2D[3]
- Finerenone is currently tested in HF patients, as part of the **MOONRAKER program, which includes more than 15,000 patients** across clinical settings and ejection fractions.

SoC, standard of care

1. Agarwal R, *et al., Eur Heart J* 2022;43:474–484; 2. Pitt B, *et al., N Eng J Med* 2021;385:2252–2263; 3. McDonagh TA, *et al., Eur Heart J* 2023;44:3627–3639

THANK YOU