Poster 407-P

Efficacy of finerenone in patients with abnormal markers of liver steatosis and fibrosis: A FIDELITY subgroup analysis

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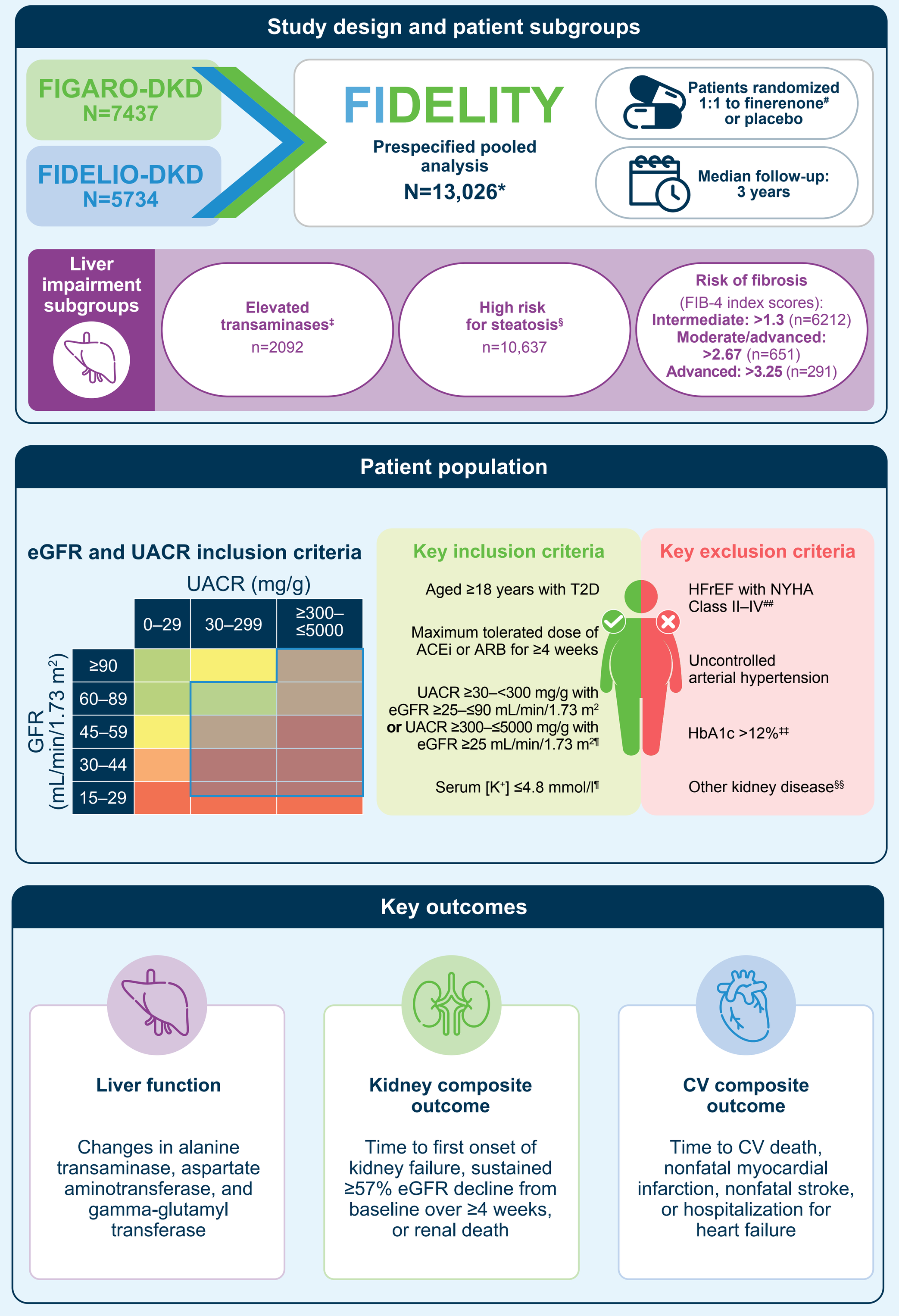
1. Introduction

- Nonalcoholic fatty liver disease (NAFLD) occurs in over 50% of patients with type 2 diabetes (T2D), with a higher prevalence among patients with comorbid chronic kidney disease (CKD) versus those without[1,2]
  - NAFLD is associated with an increased risk of CKD progression and, potentially, with an increased risk of cardiovascular (CV) disease[3–8]
- Finerenone, a selective, nonsteroidal mineralocorticoid receptor antagonist, has shown CV and kidney benefits versus placebo in patients with CKD and T2D[9]
- This exploratory analysis aimed to assess the association between liver pathology and the effect of finerenone on liver function, and CV and kidney composite outcomes in patients with CKD and T2D

2. Methods

- The analysis included patients from FIDELITY, a prespecified pooled dataset combining individual patient-level data from the phase III, multicenter, randomized, double-blind trials FIDELIO-DKD (NCT02540993) and FIGARO-DKD (NCT02545049)[9]
- Study design, key outcomes, and eligibility criteria for FIDELITY are shown in **Figure 1**
- Patients were split into subgroups according to liver pathology status (**Figure 1**): high risk for steatosis (hepatic steatosis index [HSI] >36); elevated transaminases (alanine transaminase [ALT] >33 [males] and >25 IU/L [females]); and Fibrosis-4 [FIB-4] Index scores >3.25, >2.67, and >1.30. Liver function was assessed by changes in ALT, aspartate aminotransferase, and gamma-glutamyl transferase
- HSI was calculated as HSI = 8 × ALT/AST (U/L) + body mass index (+ 2 if T2D present, + 2 if female). FIB-4 scores were analyzed using the safety analysis set and calculated as FIB-4 = age (years) × AST (U/L)/(platelet count [PLT; 10^9/L] × ALT1/2 [U/L])
- The full analysis set (consisting of all randomized subjects without any critical Good Clinical Practice violations) was used for exploratory subgroup efficacy analyses, and the safety analysis set (consisting of all randomized subjects without any critical Good Clinical Practice violations, who had taken at least 1 dose of study drug) was used for post hoc laboratory and safety analyses. All results were summarized descriptively
- Time-to-event treatment effects were analyzed using stratified Cox proportional hazards regression models within each of the liver pathology status subgroups
- All analyses are stratified by region, UACR category at screening, eGFR category at screening, study (FIDELIO-DKD or FIGARO-DKD), and CV disease history

Figure 1. Study design, patient population, and key outcomes



*Prospective exclusion of 145 patients; #10 or 20 mg od; ‡alanine transaminase >25 IU/L if female and >33 IU/L if male; §HSI >36; ¶in FIDELIO-DKD, the presence of diabetic retinopathy was a requirement for patients with UACR ≥30–<300 mg/g and eGFR 25–≤60 mL/min/1.73 m²; **at run-in or screening visit; ##run-in only; ‡‡ at the run-in or screening visit; §§known nondiabetic kidney disease, including clinically relevant renal artery stenosis

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CV, cardiovascular; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis-4; GFR, glomerular filtration rate; HbA1c, glycated hemoglobin; HFrEF, heart failure with reduced ejection fraction; HSI, hepatic steatosis index; [K⁺], potassium concentration; NYHA, New York Heart Association; od, once daily; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio

3. Results

Baseline characteristics

- Baseline characteristics for the FIDELITY patient population have previously been published[9]
  - These were generally balanced within the analyzed liver impairment subgroups (**Table 1**)

Table 1. Key patient baseline characteristics by liver impairment subgroup (FAS)

	Patients with elevated transaminases (ALT >25* if female and >33* if male)		Patients with steatosis (HSI >36*)		Patients with intermediate liver fibrosis (FIB-4 score >1.3*)		Patients with moderate/advanced liver fibrosis (FIB-4 score >2.67*)		Patients with advanced liver fibrosis (FIB-4 score >3.25*)	
Baseline characteristic	Finerenone n=1067	Placebo n=1025	Finerenone n=5340	Placebo n=5297	Finerenone n=3130	Placebo n=3082	Finerenone n=331	Placebo n=320	Finerenone n=152	Placebo n=139
Age, years, mean ± SD	61.9 ± 9.8	61.7 ± 10.1	64.3 ± 9.3	64.3 ± 9.6	68.6 ± 7.8	69.0 ± 7.8	70.6 ± 7.8	71.80 ± 8.0	70.9 ± 7.1	72.4 ± 8.0
Sex, n (%)										
Female	423 (39.6)	372 (36.3)	1763 (33.0)	1654 (31.2)	830 (26.5)	718 (23.3)	86 (26.0)	77 (24.1)	41 (27.0)	36 (25.9)
Male	644 (60.4)	653 (63.7)	3577 (67.0)	3643 (68.8)	2300 (73.5)	2364 (76.7)	245 (74.0)	243 (75.9)	111 (73.0)	103 (74.1)
SBP, mmHg, mean ± SD	136.0 ± 14.2	135.8 ± 14.1	137.0 ± 13.8	137.1 ± 14.0	137.2 ± 14.2	137.1 ± 14.4	137.3 ± 14.6	136.7 ± 15.6	136.2 ± 15.6	138.8 ± 15.8
DBP, mmHg, mean ± SD	77.7 ± 9.5	77.6 ± 9.3	76.8 ± 9.4	77.0 ± 9.4	75.2 ± 9.8	74.8 ± 9.7	73.3 ± 10.3	73.7 ± 10.3	73.0 ± 10.8	73.9 ± 10.4
HbA1c, %, mean ± SD	7.9 ± 1.4	7.9 ± 1.4	7.8 ± 1.4	7.8 ± 1.4	7.5 ± 1.3	7.4 ± 1.2	7.3 ± 1.3	7.3 ± 1.2	7.3 ± 1.2	7.3 ± 1.3
Duration of diabetes, years, mean ± SD	14.1 ± 8.3	13.4 ± 8.0	15.3 ± 8.7	15.1 ± 8.5	16.4 ± 9.2	16.4 ± 9.1	17.0 ± 9.9	16.3 ± 9.4	16.8 ± 9.5	17.1 ± 9.4
eGFR, mL/min/1.73 m², mean ± SD	63.9 ± 22.8	64.4 ± 22.5	58.5 ± 22.0	58.4 ± 22.1	53.6 ± 19.2	53.2 ± 18.9	50.2 ± 18.5	49.7 ± 17.5	49.7 ± 18.9	52.8 ± 19.3
UACR, mg/g, median (IQR)	481.4 (175.0–1006.3)	468.2 (190.9–1017.0)	510.3 (195.3–1101.7)	511.8 (204.7–1152.4)	457.0 (153.1–1036.3)	443.2 (152.9–1039.6)	345.4 (101.1–851.9)	410.1 (151.0–1052.7)	266.4 (103.3–798.3)	479.7 (144.4–1062.0)
History of CVD, n (%)										
Yes	426 (39.9)	394 (38.4)	2429 (45.5)	2450 (46.3)	1591 (50.8)	1580 (51.3)	182 (55.0)	171 (53.4)	85 (55.9)	73 (52.5)
No	641 (60.1)	631 (61.6)	2911 (54.5)	2847 (53.7)	1539 (49.2)	1502 (48.7)	149 (45.0)	149 (46.6)	67 (44.1)	66 (47.5)
History of hyperlipidemia, n (%)	493 (46.2)	478 (46.6)	2330 (43.6)	2351 (44.4)	1397 (44.6)	1387 (45.0)	153 (46.2)	138 (43.1)	70 (46.1)	59 (42.4)

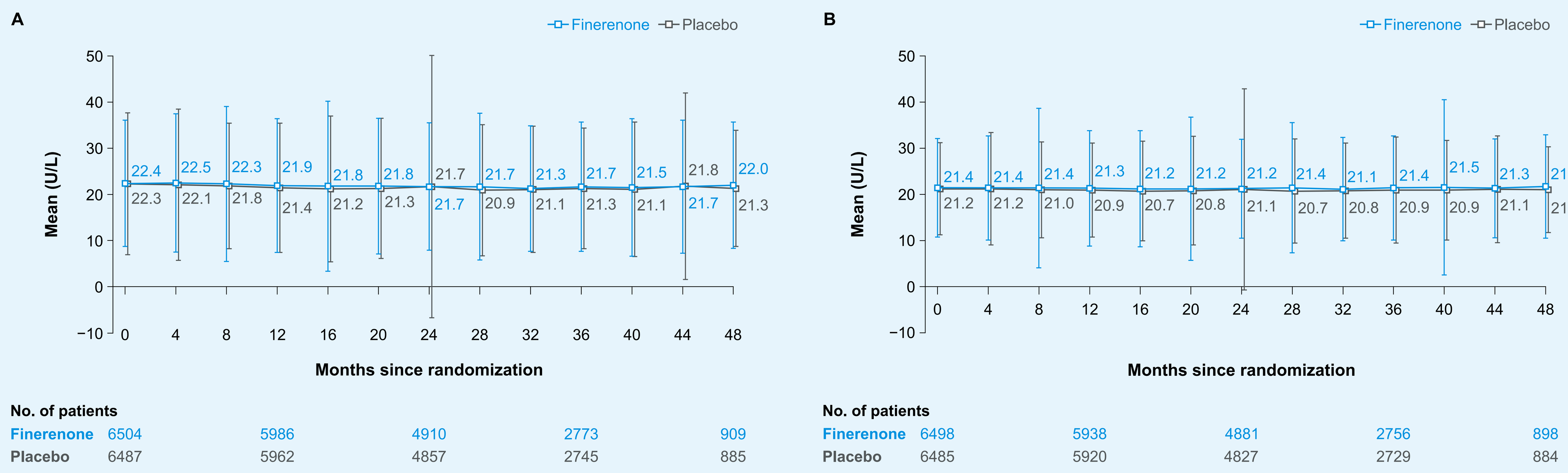
*At baseline

ALT, alanine transaminase; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FAS, full analysis set; FIB-4, fibrosis-4; HbA1c, glycated hemoglobin; HSI, hepatic steatosis index; IQR, interquartile range; SBP, systolic blood pressure; SD, standard deviation; UACR, urine albumin-to-creatinine ratio

Effect of finerenone on liver function

- Liver transaminase levels remained consistent between treatment groups throughout the study (**Figure 2**)

Figure 2. ALT, AST, and GGT over time in FIDELITY patients with liver impairment (SAS)



Mean levels of (A) serum or plasma ALT, (B) serum AST, and (C) serum or plasma GGT over time in the overall population with altered liver function

ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; SAS, safety analysis set

Effect of finerenone on kidney outcomes

- As shown in **Figure 3**, finerenone reduced the risk of the composite kidney outcome compared with placebo in the following liver impairment subgroups:
  - Elevated transaminases (hazard ratio [HR]=0.75; 95% confidence interval [CI] 0.50–1.13; $P_{interaction}$=0.71)
  - High risk of steatosis (HR=0.75; 95% CI 0.64–0.88; $P_{interaction}$=0.45)
  - Intermediate risk of fibrosis (HR=0.75; 95% CI 0.60–0.93; $P_{interaction}$=0.85)

Figure 3. Kidney outcomes in patients with altered liver function (FAS)

Subgroup	Finerenone n/N (n/100 PY)	Placebo n/N (n/100 PY)	Hazard ratio (95% CI)	P value for interaction
Overall	360/6519 (1.96)	465/6507 (2.55)	0.77 (0.67–0.88)	
Patients with steatosis (HSI >36)				
No	94/1136 (3.01)	107/1179 (3.32)	0.86 (0.65–1.14)	0.45
Yes	264/5340 (1.75)	356/5297 (2.38)	0.75 (0.64–0.88)	
Patients with elevated transaminases				
No	314/5436 (2.08)	40/5463 (2.67)	0.78 (0.67–0.90)	0.71
Yes	45/1067 (1.40)	58/1025 (1.93)	0.75 (0.50–1.13)	
Patients with liver fibrosis (FIB-4)				
Advanced (>3.25)				
No	352/6313 (1.98)	455/6331 (2.56)	0.77 (0.67–0.89)	0.68
Yes	5/152 (1.23)	9/139 (2.51)	0.78 (0.22–2.78)	
Moderate/Advanced (>2.67)				
No	333/6134 (1.93)	444/6150 (2.57)	0.74 (0.64–0.86)	0.04
Yes	24/331 (2.63)	20/320 (2.31)	1.55 (0.80–3.00)	
Intermediate (>1.3)				
No	205/3335 (2.19)	272/3388 (2.86)	0.78 (0.65–0.94)	0.85
Yes	152/3130 (1.72)	192/3082 (2.22)	0.75 (0.60–0.93)	

0.20 1.00 5.00
Favors finerenone | Favors placebo

Composite kidney outcome in patients with liver pathology: patients with steatosis (HSI >36 at baseline), with elevated transaminases (ALT at baseline >33 if male and >25 if female), and across FIB-4 score categories: advanced (FIB-4 score >3.25 at baseline); moderate/advanced (FIB-4 score >2.67 at baseline); and intermediate (FIB-4 score >1.30 at baseline). HSI was calculated as 8 × ALT/AST + BMI (+2 if T2D yes, +2 if female yes); FIB-4 score was calculated as age (years) × AST (U/L)/(PLT [10^9/L] × ALT1/2 [U/L]); composite kidney outcome was defined as time to first onset of kidney failure, sustained ≥57% eGFR decline from baseline over ≥4 weeks, or renal death

ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set; FIB-4, fibrosis-4; HSI, hepatic steatosis index; PLT, platelet count; PY, patient-years; T2D, type 2 diabetes

Effect of finerenone on CV outcomes

- As shown in **Figure 4**, finerenone reduced the risk of the composite CV outcome compared with placebo in all analyzed liver impairment subgroups. Stronger reductions were observed at higher FIB-4 scores.

Figure 4. CV outcomes in patients with altered liver function (FAS)

Subgroup	Finerenone n/N (n/100 PY)	Placebo n/N (n/100 PY)	Hazard ratio (95% CI)	P value for interaction
Overall	825/6519 (4.34)	939/6507 (5.01)	0.86 (0.78–0.95)	
Patients with steatosis (HSI >36)				
No	146/1136 (4.5)	161/1179 (4.74)	0.89 (0.71–1.12)	0.63
Yes	671/5340 (4.29)	772/5297 (5.06)	0.85 (0.77–0.95)	
Patients with elevated transaminases				
No	716/5436 (4.58)	822/5463 (5.27)	0.87 (0.79–0.96)	0.67
Yes	104/1067 (3.10)	112/1025 (3.61)	0.81 (0.62–1.07)	
Patients with liver fibrosis (FIB-4)				
Advanced (>3.25)				
No	792/6313 (4.30)	899/6331 (4.92)	0.87 (0.79–0.96)	0.03
Yes	20/152 (4.54)	33/139 (9.06)	0.48 (0.25–0.90)	
Moderate/Advanced (>2.67)				
No	764/6134 (4.27)	866/6150 (4.87)	0.87 (0.79–0.96)	0.13
Yes	48/331 (4.94)	66/320 (7.42)	0.61 (0.41–0.92)	
Intermediate (>1.3)				
No	407/3335 (4.19)	426/3388 (4.33)	0.98 (0.85–1.12)	0.01
Yes	405/3130 (4.42)	506/3082 (5.75)	0.76 (0.67–0.87)	

0.20 1.00 5.00
Favors finerenone | Favors placebo

Composite CV outcome in patients with liver pathology: patients with steatosis (HSI >36 at baseline), with elevated transaminases (ALT at baseline >33 if male and >25 if female), and across FIB-4 score categories: advanced (FIB-4 score >3.25 at baseline); moderate/advanced (FIB-4 score >2.67 at baseline); and intermediate (FIB-4 score >1.30 at baseline). HSI was calculated as 8 × ALT/AST + BMI (+2 if T2D yes, +2 if female yes); FIB-4 was calculated as age (years) × AST (U/L)/(PLT [10^9/L] × ALT1/2 [U/L]); composite CV outcome was defined as CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure

ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; CV, cardiovascular; FAS, full analysis set; FIB-4, fibrosis-4; HSI, hepatic steatosis index; PLT, platelet count; PY, patient-years; T2D, type 2 diabetes

Safety

- No relevant differences were observed between liver impairment subgroups for adverse events related to treatment with finerenone or placebo
- Incidence of hyperkalemia was low and consistent between treatment arms within each liver impairment subgroup

4. Conclusions

- Overall, finerenone had neutral effects on liver parameters in patients with CKD and T2D
- Finerenone demonstrated robust and consistent kidney benefits in patients with altered liver function
- The CV benefits of finerenone were most pronounced in patients with higher FIB-4 scores, who were also at high risk of developing CV complications

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