WCN25-AB-662

Efficacy and safety of finerenone in patients with nephrectomy: A FIDELITY subanalysis

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Background

- Nephrectomy may be performed in patients with localized kidney tumors, in cases of severe kidney stones and pyelonephritis, and for living kidney donation[1–4]
- Chronic kidney disease (CKD) may develop or worsen in patients who have undergone nephrectomy[5,6]; this at-risk population may, therefore, benefit from therapies that reduce CKD progression
- Finerenone, a nonsteroidal mineralocorticoid receptor antagonist, significantly reduced the risk of cardiovascular and kidney outcomes in patients with CKD and type 2 diabetes (T2D) in FIDELITY, a prespecified pooled analysis of the phase III FIDELIO-DKD (NCT02540993) and FIGARO-DKD (NCT02545049) trials[7]
  - Finerenone also reduced albuminuria as measured by the urine albumin-to-creatinine ratio (UACR) in the FIDELITY population
- This post hoc analysis examined the efficacy and safety of finerenone in patients with CKD and T2D from FIDELITY who had undergone nephrectomy, using UACR as a surrogate for CKD progression

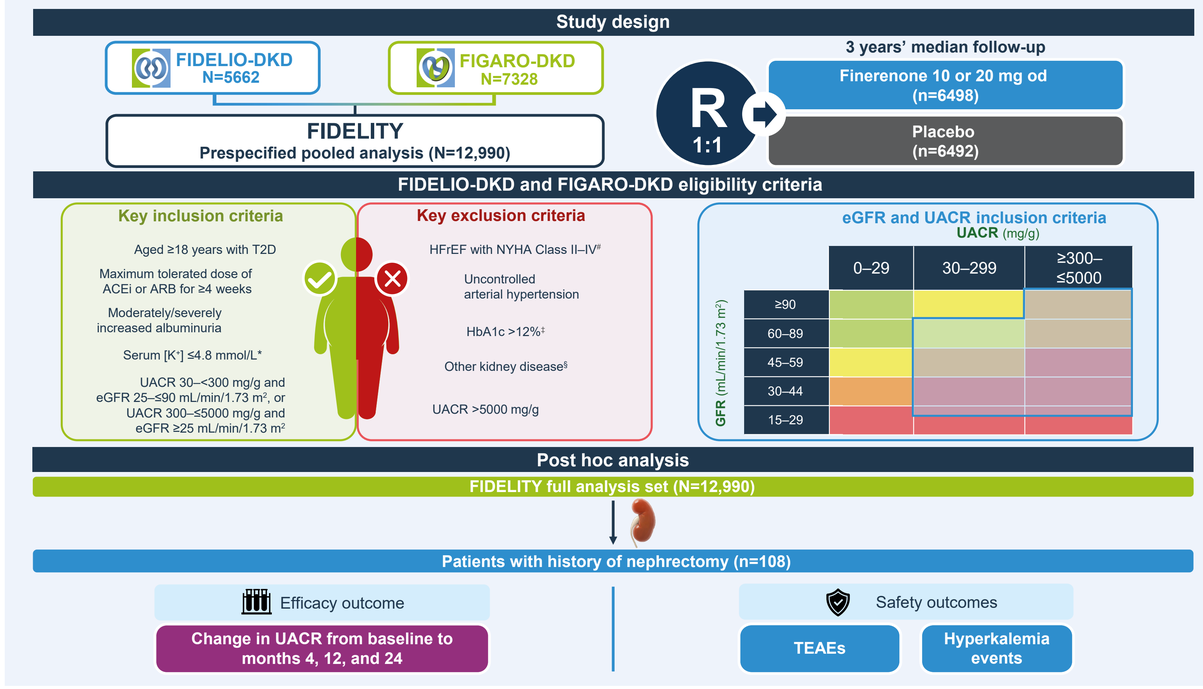
Study design and methods

- Patients in FIDELITY were randomized 1:1 to finerenone (10 mg or 20 mg) or placebo treatment and were on maximum tolerated renin–angiotensin system inhibition
- Key eligibility criteria and efficacy and safety outcomes are described in **Figure 1**
  - For efficacy, change in UACR was assessed as a surrogate marker of kidney disease progression
  - The safety outcomes included investigator-reported treatment-emergent adverse events (TEAEs) and hyperkalemia events, as well as adverse events leading to treatment discontinuation and hospitalization
- Nephrectomy was identified in patients' medical histories based on the Medical Dictionary for Regulatory Activities Preferred Term
  - Location (right vs left), type (partial vs radical, with radical nephrectomy assumed if type was not available in the patient's history), and procedure date were recorded
  - Patients were grouped based on history of nephrectomy (yes vs no)

Statistical analysis

- Baseline characteristics and efficacy outcomes were reported for the full analysis set (all randomized participants without critical Good Clinical Practice violations)
- Safety analyses were performed on the safety analysis set (all randomized participants without critical Good Clinical Practice violations who took ≥1 dose of study drug)
- Treatment efficacy was analyzed for each subgroup using a mixed model with factors of treatment group, region, estimated glomerular filtration rate (eGFR) category at screening, type of albuminuria at screening, history of cardiovascular disease, study, time, treatment by time, baseline value nested within eGFR category at screening, and baseline value by time as covariates
- An analysis of covariance was also performed with factors of treatment group, region, eGFR category at screening, type of albuminuria at screening, history of cardiovascular disease, study, log-transformed baseline value nested within type of albuminuria, and the interaction between study and treatment

Figure 1. Study design, key eligibility criteria, and outcomes



*At run-in or screening visit; #run-in only; ‡at the run-in or screening visit; §known significant nondiabetic kidney disease, including clinically relevant renal artery stenosis
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HbA1c, glycated hemoglobin; HFrEF, heart failure with reduced ejection fraction; [K+], potassium concentration; NYHA, New York Heart Association; od, once daily; R, randomization; T2D, type 2 diabetes; TEAE, treatment-emergent adverse event; UACR, urine albumin-to-creatinine ratio

Results

Baseline characteristics

- Of 12,990 patients included in FIDELITY, 108 patients (0.8%) had a history of nephrectomy at baseline
  - 101 (94.0%) had radical nephrectomy
  - 55 (50.9%) received finerenone
  - The median time from nephrectomy to randomization was ~15 years
- More patients with nephrectomy than without were White (91.7% vs 68.1%, respectively) and fewer patients with nephrectomy than without were Asian (5.6% vs 22.2%, respectively)
- At baseline, the mean eGFR was lower in patients with nephrectomy (47.7 ± 17.1 mL/min/1.73 m²) than in those without (57.7 ± 21.7 mL/min/1.73 m²) (**Table 1**)
- Other baseline characteristics were generally well balanced between the two groups (**Table 1**)

Table 1. Baseline demographics and clinical characteristics according to nephrectomy in medical history (full analysis set)

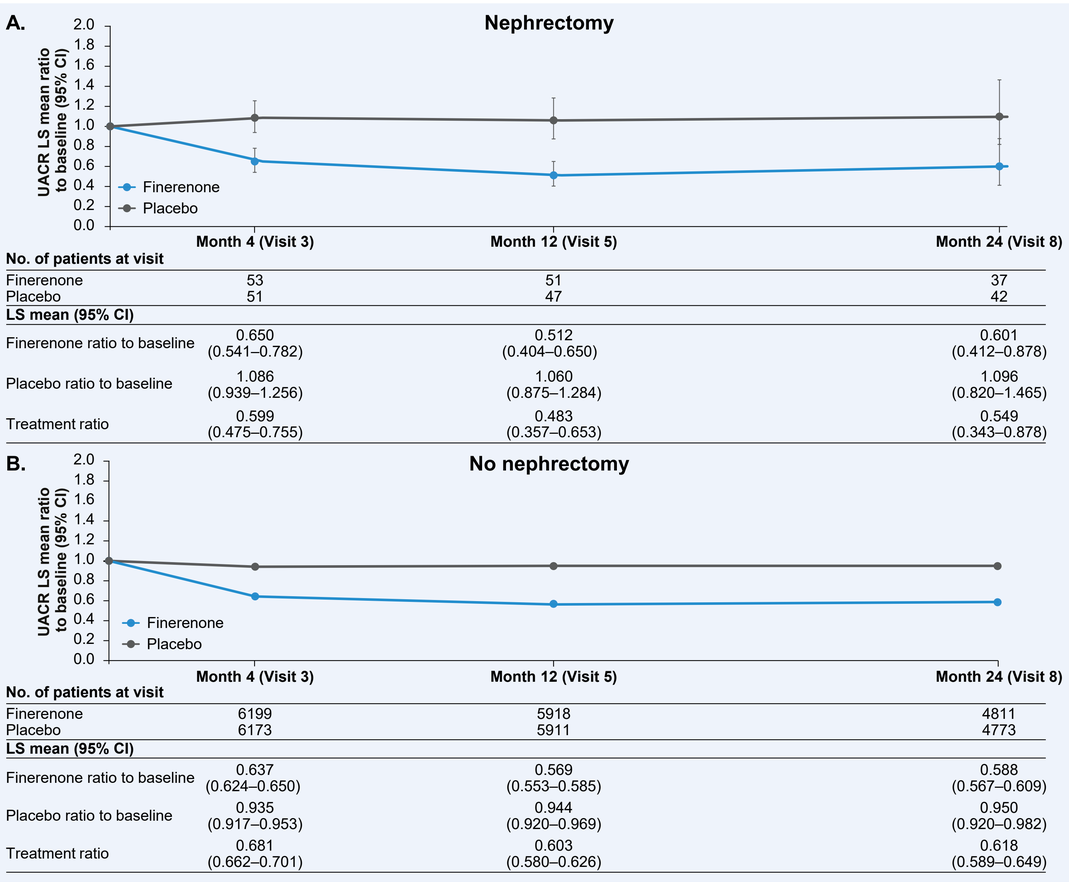
Characteristic	Nephrectomy (n=108)	No nephrectomy (n=12,882)
Age, years, mean ± SD	65.9 ± 9.0	64.8 ± 9.5
Sex, male, n (%)	66 (61.1)	8992 (69.8)
Race, n (%)		
White	99 (91.7)	8770 (68.1)
Black/African American	2 (1.9)	518 (4.0)
Asian	6 (5.6)	2854 (22.2)
eGFR,* mL/min/1.73 m², mean ± SD	47.7 ± 17.1	57.7 ± 21.7
UACR, mg/g, median (IQR)	538.9 (209.6–1115.3)	514.7 (197.9–1149.1)

*Calculation of eGFR was done based on the CKD-EPI formula
CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; IQR, interquartile range; SD, standard deviation; UACR, urine albumin-to-creatinine ratio

Efficacy outcome

- Among patients with a history of nephrectomy, those receiving finerenone had a greater reduction in UACR from baseline vs placebo at 4 months (least-squares [LS] mean ratios to baseline 0.65 vs 1.09; LS mean treatment ratio 0.60; 95% confidence interval 0.48–0.76; $p<0.0001$) (**Figure 2**)
  - A slight increase in UACR was seen in the placebo group (**Figure 2A**)
  - These effects were maintained through year 2 (**Figure 2A**)
- A similar trend in UACR reduction with finerenone vs placebo was observed in patients without a history of nephrectomy (**Figure 2B**)

Figure 2. Change in UACR from baseline



No. of patients at visit			
Finerenone	53	51	37
Placebo	51	47	42
LS mean (95% CI)			
Finerenone ratio to baseline	0.650 (0.541–0.782)	0.512 (0.404–0.650)	0.601 (0.412–0.878)
Placebo ratio to baseline	1.086 (0.939–1.256)	1.060 (0.875–1.284)	1.096 (0.820–1.465)
Treatment ratio	0.599 (0.475–0.755)	0.483 (0.357–0.653)	0.549 (0.343–0.878)

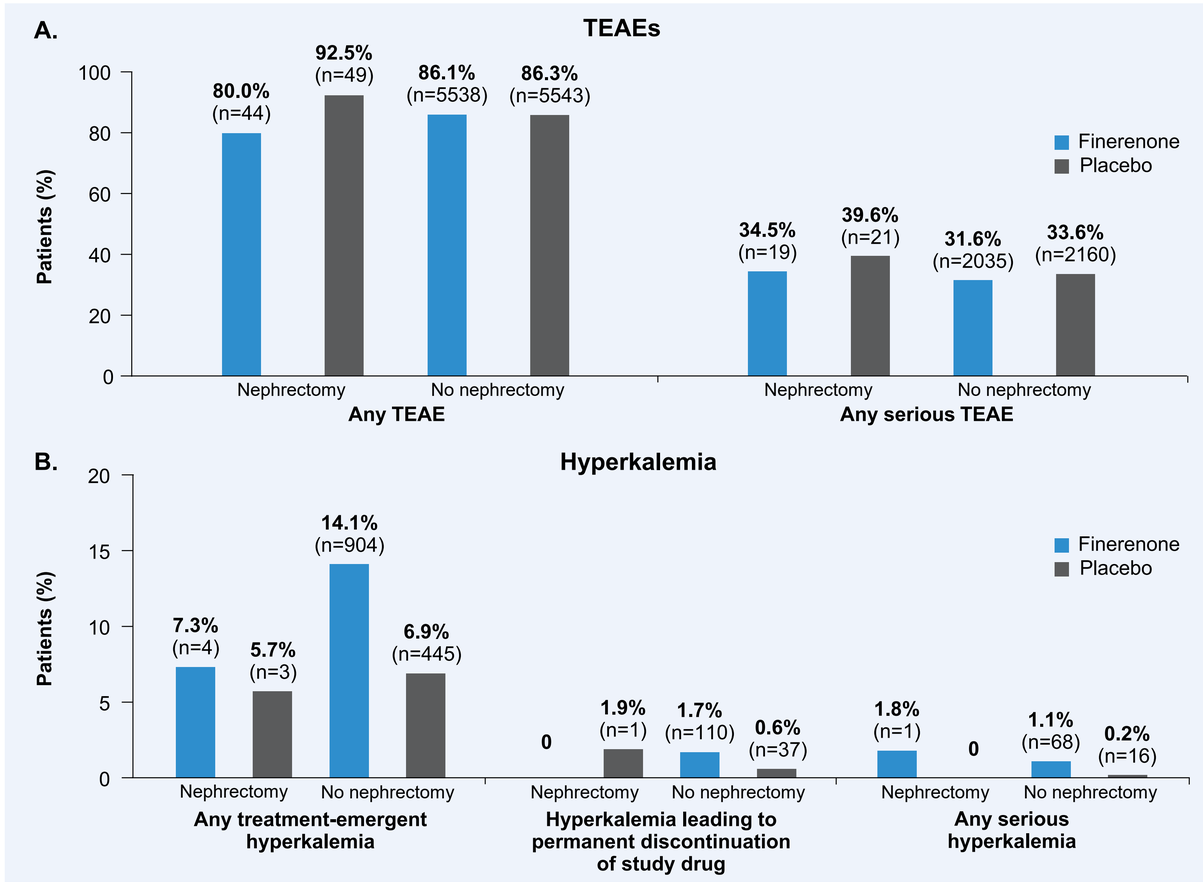
No. of patients at visit			
Finerenone	6199	5918	4811
Placebo	6173	5911	4773
LS mean (95% CI)			
Finerenone ratio to baseline	0.637 (0.624–0.650)	0.569 (0.553–0.585)	0.588 (0.567–0.609)
Placebo ratio to baseline	0.935 (0.917–0.953)	0.944 (0.920–0.969)	0.950 (0.920–0.982)
Treatment ratio	0.681 (0.662–0.701)	0.603 (0.580–0.626)	0.618 (0.589–0.649)

LS mean and 95% CI results from a mixed model with factors including treatment group, region, eGFR category at screening, type of albuminuria at screening, history of cardiovascular disease, study, time, treatment*time, baseline value nested within eGFR category at screening, and baseline value*time as covariate. Separate unstructured covariance patterns were estimated for each treatment group
CI, confidence interval; eGFR, estimated glomerular filtration rate; LS, least-squares; UACR, urine albumin-to-creatinine ratio

Safety outcomes

- Overall, safety outcomes were similar between the finerenone and placebo groups for patients with and without nephrectomy (**Figure 3A**)
  - In patients with a history of nephrectomy, the incidence of any TEAE was lower in those treated with finerenone (80.0%; n=44) compared with placebo (92.5%; n=49) (**Figure 3A**)
- Among patients with a history of nephrectomy, treatment-emergent hyperkalemia was more common in patients treated with finerenone (7.3%; n=4) compared with placebo (5.7%; n=3) (**Figure 3B**)
  - Respective values in patients without nephrectomy were 14.1% (n=904) and 6.9% (n=445) (**Figure 3B**)
  - There were few serious hyperkalemia events (**Figure 3B**)

Figure 3. Incidence of TEAEs and hyperkalemia



TEAE, treatment-emergent adverse event

Conclusions

- Finerenone treatment reduced albuminuria compared with placebo in patients with and without nephrectomy
- Safety outcomes in patients with nephrectomy were consistent with the known safety profile of finerenone
- These results suggest that finerenone may safely delay CKD progression and associated morbidity in patients with CKD and T2D, irrespective of nephrectomy status

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Disclosures: JMM has nothing to disclose. **MW** reports that he is a scientific advisor for AstraZeneca, Novo Nordisk, Mineralys, CSL Vifor, Boehringer Ingelheim, and Bayer. **SDA** has received research support from Abbott Vascular and Vifor Pharma, and personal fees from Abbott Vascular, Bayer, Boehringer Ingelheim, BRAHMS, Cardiac Dimensions, Impulse Dynamics, Novartis, Servier, and Vifor Pharma. **GF** reports lecture fees and/or that he is a committee member of trials and registries sponsored by Amgen, Bayer, Boehringer Ingelheim, Medtronic, Novartis, Servier, and Vifor Pharma. He is a senior consulting editor for *JACC Heart Failure* and has received research support from the European Union. **PR** reports personal fees from Bayer during the conduct of this study. He has received research support and personal fees from AstraZeneca, Bayer, and Novo Nordisk, and personal fees from Astellas Pharma, Abbott, Boehringer Ingelheim, Eli Lilly, Gilead, Mundipharma, Novartis, Sanofi, and Vifor Pharma; all fees are given to Steno Diabetes Center Copenhagen. **STF** was a full-time employee of Bayer at the time of the analysis. **CA, MB, AHB,** and **KR** are full-time employees of Bayer AG. **AF** is an inventor on pending or issued patents (US10.183.038, US10.052.345) aimed at diagnosing or treating proteinuric kidney diseases and therefore stands to gain royalties from their future commercialization. She is Chief Scientific Officer of L&F Health LLC, holds equity interests in L&F Research, and is the inventor of assets developed by ZyVersa Therapeutics. ZyVersa has licensed worldwide rights to develop and commercialize hydroxypropyl-β-cyclodextrin for the treatment of kidney disease from L&F Research. AF is also the inventor of assets developed by River 3 Renal Corporation and holds equity in River 3 Renal Corporation. She has received research support from Pfizer and from Aurinia.

Acknowledgements: The FIDELIO-DKD and FIGARO-DKD studies and prespecified pooled FIDELITY analysis were funded by Bayer AG. Medical writing assistance was provided by Alyanna Publico, MD (HCG), with funding from Bayer AG.

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Abstract WCN25-AB-662 presented at the World Congress of Nephrology 2025 (WCN'25); 6–9 February 2025; New Delhi, India