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Effect of Finerenone on Vision-threatening Complications in Patients with Diabetic Retinopathy

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Introduction

- Diabetic retinopathy and chronic kidney disease (CKD) are two forms of microvascular complications in patients with type 1 and type 2 diabetes (T2D), with shared risk factors and manifestations.[1]
- Diabetic retinopathy can already be present in newly diagnosed T2D and is a prognostic factor for progression of CKD.[1,2]
- Mineralocorticoid receptor overactivation is involved in the pathogenesis of CKD.[3]
- Antagonism of the retinal mineralocorticoid receptor–aldosterone system may delay progression of diabetic retinopathy through the modulation of inflammatory mediators.[4]
- Finerenone, a potent and selective, orally administered, non-steroidal mineralocorticoid receptor antagonist (MRA), slowed progression of CKD and reduced the risk of cardiovascular outcomes versus placebo in patients with CKD and T2D in the FIDELIO-DKD (NCT02540993, N=5674) and FIGARO-DKD (NCT02545049, N=7352) randomized phase III trials.[5,6]
  - Incidence of hyperkalemia was higher with finerenone versus placebo; however, the incidence of discontinuation due to this adverse event was low (FIDELIO-DKD 2.3%, FIGARO-DKD 1.2%).[5,6]
- As no ophthalmological assessments were performed in FIGARO-DKD/FIDELIO-DKD, data from participants who had routine ophthalmological assessments during the study periods were used in ReFineDR (NCT04477707), an observational study to explore the effect of finerenone on the progression of diabetic retinopathy.
  - Data from participants in Bulgaria/UK were used in a second study (DeFineDR, NCT04795726) with identical design to ReFineDR, submitted as interventional per regulatory agency request.

Objectives

- To evaluate, using pooled data from the ReFineDR and DeFineDR studies:
  - The effects of finerenone versus placebo on the primary endpoint of progression of non-proliferative diabetic retinopathy (NPDR).
  - The effects of finerenone versus placebo on time to vision-threatening complications (VTCs), the individual primary endpoint components, and required ocular interventions.
  - The effects of finerenone versus placebo on time to VTCs in subgroups of patients with glycated hemoglobin (HbA1c) ≤7.5% (58 mmol/mol) and >7.5% (58 mmol/mol).

Methods

Study Design

- Ophthalmological data were collected retrospectively, in an observational manner, from patients with a medical history of diabetic retinopathy who participated in FIDELIO-DKD or FIGARO-DKD.
- Inclusion criteria for FIDELIO-DKD and FIGARO-DKD have been previously reported.[5–8] In brief, patients were ≥18 years of age, with CKD and T2D, and were treated with optimized renin–angiotensin system (RAS) blockade therapy.
- Eligible patients for ReFineDR and DeFineDR had an ophthalmological examination performed in routine clinical practice demonstrating treatment-naïve NPDR in at least one eye between 6 months prior and 1 month post-randomization in FIDELIO-DKD/FIGARO-DKD.
- Eligible patients also had at least one subsequent routine ophthalmological examination.
- Standard grading for NPDR was used per international guidelines.[8]
- Exclusion criteria were diabetic macular edema, proliferative diabetic retinopathy (PDR), or anterior segment complications; any other retinal disease that could interfere with the study objectives.
- The primary endpoint was progression of NPDR as defined by occurrence of VTCs, a composite endpoint comprising development of anterior segment neovascularization, diabetic macular edema, or progression to PDR, in at least one eye up to 2 years after treatment initiation (day of randomization in FIDELIO-DKD/FIGARO-DKD).
- Time to VTC, the individual primary endpoint components, and required ocular interventions (laser treatment, intravitreal injection, and vitrectomy) in at least one eye up to 36 months after randomization, were assessed post hoc.
- Time to VTC was also assessed in subgroups of patients with HbA1c ≤7.5% (58 mmol/mol) and >7.5% (58 mmol/mol).

Statistical Analyses

- All analyses were performed for both studies combined in the full analysis set (all enrolled participants), with no adjustment for multiplicity, using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).
- The primary endpoint was assessed using a two-sided z-test for the difference of two proportions (unpooled variances) using normal approximation.
- Cumulative incidence probabilities with 95% confidence intervals (CIs) for the time-to-event endpoints were computed using Kaplan–Meier estimates.
- Baseline demographics are expressed as number and percentage or mean and standard deviation (SD).

Results

Patients

- 244 patients were included in ReFineDR/DeFineDR, of whom 134 had received finerenone and 110 had received placebo.
- In total, 216 of these patients (finerenone: n=123, placebo: n=93) completed the treatment course in FIDELIO-DKD and FIGARO-DKD.
- At baseline, 68.7% (92/134) and 71.8% (79/110) of patients in the finerenone and placebo groups had mild/moderate NPDR, 3.0% (4/134) and 10.0% (11/110) had severe NPDR, and 27.6% (37/134) and 15.5% (17/110) had NPDR of unknown severity, respectively.
- Fewer patients in the finerenone group had urinary albumin-to-creatinine ratio (UACR) ≥300 mg/g (33.9 mg/mmol) (56.0% [75/134] versus 68.2% [75/110]) and diabetes duration ≥20 years (24.6% [33/134] versus 38.2% [42/110]) (**Table 1**).
- Mean baseline HbA1c was similar between the two groups (finerenone: 8.25% [66.7 mmol/mol]; placebo: 8.18% [65.9 mmol/mol]).

Vision-threatening Complications and Ocular Interventions

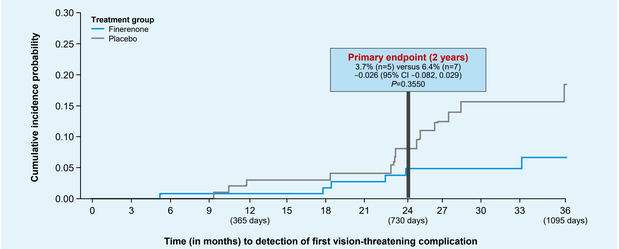
- By 2 years, 3.7% (5/134) and 6.4% (7/110) of patients in the finerenone and placebo groups, respectively, had experienced a VTC in at least one eye (difference −0.026, 95% CI −0.082 to 0.029) (**Figure 1**).
  - The number of VTCs increased beyond 2 years, with Kaplan–Meier estimated cumulative incidence probabilities favoring finerenone at 30 months (difference −0.109, 95% CI −0.202 to −0.016) and 36 months (difference −0.118, 95% CI −0.229 to −0.007).
  - Numerical benefits of finerenone were consistent for time to diabetic macular edema or progression to PDR and in the subgroups of patients with baseline HbA1c ≤7.5% (58 mmol/mol) and >7.5% (58 mmol/mol), although 95% CIs at most timepoints crossed one.
- Fewer patients in the finerenone group versus the placebo group had required ocular interventions (four [3%] versus 17 [15.5%]), with cumulative incidence probabilities favoring finerenone at 24, 30, and 36 months (**Figure 2**).

Table 1. Baseline characteristics

Characteristic	Finerenone n=134	Placebo n=110
Phase III clinical trial		
FIGARO-DKD	87 (64.9)	64 (58.2)
FIDELIO-DKD	47 (35.1)	46 (41.8)
Age, years		
Mean (SD)	62.8 (8.5)	63.7 (8.4)
Sex		
Male	70 (52.2)	79 (71.8)
Female	64 (47.8)	31 (28.2)
Duration of diabetes		
<5 years	11 (8.2)	6 (5.5)
5 to <10 years	17 (12.7)	13 (11.8)
10 to <15 years	31 (23.1)	16 (14.5)
15 to <20 years	42 (31.3)	33 (30.0)
≥20 years	33 (24.6)	42 (38.2)
HbA1c		
≤7.5% (58 mmol/mol)	39 (29.1)	39 (35.5)
>7.5% (58 mmol/mol)	94 (70.1)	71 (64.5)
Missing	1 (0.7)	0
Mean (SD)	8.25 (1.41) %† 66.7 (15.4) mmol/mol†	8.18 (1.34) % 65.9 (14.6) mmol/mol
UACR		
Mean (SD)	319.2 (3.5) mg/g 36.1 (0.4) mg/mmol	489.4 (3.5) mg/g 55.3 (0.4) mg/mmol
<30 mg/g (3.39 mg/mmol)	3 (2.2)	1 (0.9)
30 to <300 mg/g (3.39 to <33.9 mg/mmol)	56 (41.8)	34 (30.9)
≥300 mg/g (33.9 mg/mmol)	75 (56.0)	75 (68.2)

N (%) unless otherwise stated. †N=133.
HbA1c, glycated hemoglobin; SD, standard deviation; UACR, urinary albumin-to-creatinine ratio.

Figure 1. Time to vision-threatening complication (Kaplan–Meier analysis)

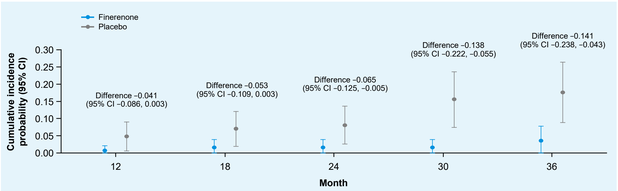


Numbers of subjects at risk

Finerenone	134	133	129	125	120	115	103	98	87	76	61	51	43
Placebo	110	108	104	100	94	91	88	80	66	59	46	39	28

CI, confidence interval.

Figure 2. Cumulative incidence probability of a required ocular intervention



Numbers at risk

Finerenone	120	103	90	63	44
Placebo	92	84	66	47	30

CI, confidence interval.

Conclusion

- Although the effect of finerenone on reduction of incidence of VTCs, including diabetic macular edema, PDR, and anterior segment neovascularization, was not significant at 2 years, benefits of finerenone were consistent across endpoints, including the requirement for ocular interventions to treat diabetic retinopathy, such as laser treatment, intravitreal injection, and vitrectomy.
  - Notably, the potential benefits of finerenone versus placebo observed in the current studies were in addition to optimized RAS therapy, which was received by all enrolled patients.
- The effects of finerenone in patients with NPDR seem to be independent of blood glucose control.
- Larger randomized studies to further assess the benefits of finerenone in patients with diabetic retinopathy are justified.

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