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Effect of finerenone on occurrence of vision-threatening complications in patients with non-proliferative diabetic retinopathy: pooled analysis of two studies using routine ophthalmological examinations from clinical trial participants (ReFineDR/DeFineDR)

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/dom.14915

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Word count: 1258

Total number of figures/tables: 2 figures (max 2)

Reference count: 11 (max 12)

Supplementary information: Text + 2 tables (no limit)

Running title: Finerenone for diabetic retinopathy

Key words (min 4, max 6): diabetic retinopathy, type 2 diabetes, randomised trial, phase III study

Background/Context

Diabetic retinopathy (DR) and chronic kidney disease (CKD) are two major forms of microvascular complications in patients with type 1 diabetes and type 2 diabetes (T2D), with shared risk factors (such as poor glycemic control, smoking, hypertension, and dyslipidemia) and clinical manifestations (microvascular lesions).[1] The steroid hormone aldosterone, which binds to mineralocorticoid receptors, promotes vascular pathology in the retina relevant to the development of DR;[2] antagonism of the retinal mineralocorticoid receptor–aldosterone system may delay progression.[3]

Finerenone, a potent and selective, orally administered, nonsteroidal mineralocorticoid receptor antagonist (MRA), slowed progression of CKD and reduced the risk of cardiovascular outcomes vs. placebo in patients with CKD and T2D in the FIDELIO-DKD (NCT02540993; n = 5674) and FIGARO-DKD (NCT02545049; n = 7352) randomized phase 3 trials.[4,5] In total, 2657 (46.8%) patients in FIDELIO-DKD and 2265 (30.8%) in FIGARO-DKD had DR at baseline.[6,7] No further details on DR were collected in these studies. However, data from participants who had routine ophthalmological assessments during the study periods were utilized in ReFineDR (NCT04477707) and DeFineDR (NCT04795726); two identical hypothesis-generating studies to explore the effect of finerenone on progression of DR. Here, we report a pooled analysis of both studies combined.

Methods

Study design

The studies were approved by relevant independent ethics committees and health authorities and were conducted in accordance with the principles of the Declaration of Helsinki, as revised in 2008. Details of the independent ethics committees can be found in the FIDELIO-DKD and FIGARO-DKD protocols.[4,5]

Ophthalmological data from routine examinations were collected retrospectively from patients with a medical history of DR who participated in FIDELIO-DKD or FIGARO-DKD at selected centres (**Supporting Information**). To minimize bias, participant inclusion was masked to treatment assignment in FIDELIO-DKD/FIGARO-DKD. Patient demographic data were derived from the existing FIDELIO-DKD/FIGARO-DKD database.

In both studies, patients ≥18 years of age with T2D and CKD, as defined by international guidelines, treated with optimized renin–angiotensin system (RAS) blockade therapy, were included. Eligible patients had a routine ophthalmological examination between 6 months prior and 1 month post-randomization demonstrating treatment-naïve non-proliferative DR (NPDR) in at least one eye, and at least one subsequent routine ophthalmological examination (**Supporting Information**). Standard grading for NPDR was used per international guidelines.[8] Exclusion criteria were diabetic macular oedema (DME), proliferative DR (PDR) or anterior segment complications; any other retinal disease that could interfere with study objectives (e.g. neovascular age-related macular degeneration or retinal vein occlusion); and prior/planned ocular interventions (retinal laser treatment, intravitreal injection or

vitrectomy). All patients provided signed informed consent to participate in ReFineDR/DeFineDR.

Outcomes

The primary endpoint was progression of NPDR as defined by the occurrence of vision-threatening complications (VTC), a composite endpoint comprising development of anterior segment neovascularization, DME 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 event analyses, including time to VTC after 2 years, and time to required ocular interventions (laser treatment, intravitreal injection or vitrectomy) in at least one eye at any time, were assessed post hoc. Time to VTC was also assessed in subgroups of patients with HbA_{1c} ≤58 mmol/mol (7.5%) and >58 mmol/mol (7.5%).

Statistical analyses

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% CIs for the time-to-event endpoints were computed using Kaplan–Meier estimates.

Results

Of 376 potentially eligible patients, 132 did not meet eligibility criteria; therefore, 244 were included in ReFineDR/DeFineDR. Of these 244 patients, 134 had received at least one dose of finerenone and 110 had received placebo. In total, 216 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, and 3.0% (4/134) and 10.0% (11/110) had severe NPDR, respectively (**Supplementary Table S1**). Fewer patients in the finerenone group had urinary albumin-creatinine ratio (UACR) ≥33.9 mg/mmol (≥300 mg/g) (56.0% [75/134] vs 68.2% [75/110]) and diabetes duration ≥20 years (24.6% [33/134] vs 38.2% [42/110]). Mean baseline HbA_{1c} was similar between the two groups (finerenone: 66.7 mmol/mol [8.25%]; placebo: 65.9 mmol/mol [8.18%]).

By 2 years, 3.7% (5/134) and 6.4% (7/110) of patients in the finerenone and placebo groups had experienced a VTC in at least one eye (difference −0.026 [95% CI −0.082, 0.029]) (**Figure 1**). The number of VTCs increased beyond 2 years, with Kaplan–Meier-estimated cumulative incidence probabilities favoring finerenone increased at 30 months (difference −0.109 [95% CI −0.202, −0.016]) and 36 months (difference −0.118 [95% CI −0.229, −0.007]). Numerical benefits of finerenone were consistent for time to DME or progression to PDR, and in the subgroups of patients with baseline HbA_{1c} ≤58 mmol/mol (7.5%) and >58 mmol/mol (7.5%) (**Supplementary Table S2**), although 95% CIs for the differences at most timepoints included zero. In addition, numerical benefits of finerenone versus placebo for time to VTC and time to required ocular intervention were generally consistent by

baseline severity of NDPR and duration of T2D (Supplementary Tables S3 and S4), although some 95% CIs for the differences included zero.

Fewer patients in the finerenone group vs the placebo group had required ocular interventions (four [3.0%] vs. 17 [15.5%]), with cumulative incidence probabilities favoring finerenone at 24, 30, and 36 months (**Figure 2**).

Conclusions

This was a hypothesis-generating analysis suggesting a potential benefit of finerenone in the delay of progression of NPDR, independent of baseline HbA_{1c}. Potential benefits of finerenone were also observed in the prevention of required ocular interventions.

While the analysis provides a higher level of evidence compared with standard cohort studies, the setup resulted in some limitations; because of a lack of randomization and stratification, an imbalance in some baseline characteristics was observed. In particular, the higher proportion of patients with severe NPDR at baseline in the placebo group compared with the finerenone group may have led to more frequent follow-up in this group, impacting time-to-event analyses. In addition, lower-than-expected recruitment and a lack of data availability impacted data collection. Consequently, the overall number of VTCs was small, limiting power to detect between-group differences. Additionally, most participants were at an early stage of disease at baseline and were on optimized RAS therapy, which may also have limited event rates. Longer term observation may be required to detect significant differences in disease progression in this population. Furthermore, as eye examinations were not predefined as an outcome measure, the studies relied on routine ophthalmological examinations, which may have affected data quality and certainly affected quantity.

Current ocular treatments for DR, such as laser photocoagulation, intravitreal injection of anti-vascular endothelial growth factor agents or corticosteroids and vitreoretinal surgery, are invasive to the eye and generally only applicable upon progression of disease. Management of NPDR is typically limited to control of blood

glucose, or other related factors such as blood pressure and dyslipidemia. To date, the only oral therapies for which a potential effect on progression or incidence of DR has been demonstrated are RAS blockers, including enalapril, losartan, and candesartan.[9,10] Although steroidal MRAs were effective in delaying central serous chorioretinopathy in small clinical studies,[11] and antagonized the mineralocorticoid receptor in preclinical studies,[3] this is the first analysis to assess a non-steroidal MRA for delaying progression of NPDR. Notably, the potential benefits of finerenone vs placebo observed in the current studies were in addition to optimized RAS therapy, which was received by all enrolled patients.

In conclusion, the potential benefit of finerenone observed in this analysis was consistent across outcomes. As this analysis was exploratory and hypothesis-generating in nature, definitive conclusions cannot be drawn. However, these findings suggest that randomized studies with adequate power to detect a potential benefit of finerenone in delaying NPDR progression should be considered, particularly given the lack of alternative options for oral treatment of DR.

Acknowledgements

The authors would like to thank the patients, their families, and all investigators involved in this study. Medical writing support, including assisting authors with the development of the initial draft and incorporation of comments was provided by R. Wright, and editorial support, including referencing, figure preparation, formatting, proofreading, and submission was provided by Ian Norton, PhD, all of Scion, London, supported by Bayer AG according to Good Publication Practice guidelines (Link). These data have been previously presented in part at the American Diabetes Association (ADA) 82nd Scientific Sessions (3–7 June 2022) and the 22nd EURETINA Congress (1–4 September 2022). This work was supported by Bayer AG, who funded the ReFineDR and DeFineDR studies and combined analysis.

Data availability

Availability of the data underlying this publication will be determined later according to Bayer's commitment to the EFPIA/PhRMA "Principles for responsible clinical trial data sharing". This pertains to scope, time point and process of data access.

As such, Bayer commits to sharing, upon request from qualified scientific and medical researchers, patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States (US) and European Union (EU) as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after January 01, 2014.

Interested researchers can use www.clinicalstudydatarequest.com to request access to anonymized patient-level data and supporting documents from clinical

studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the Study sponsors section of the portal.

Data access will be granted to anonymized patient-level data, protocols and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

Conflict of interest statement

PR discloses receiving honorarium from Bayer AG, which was paid to his institution, receiving research support and personal fees from AstraZeneca and Novo Nordisk, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Astellas Pharma Inc., and personal fees given to Steno Diabetes Center Copenhagen from Bayer, Boehringer Ingelheim, Eli Lilly and Company, Gilead, Merck & Co., Inc, Merck Sharp and Dohme, Mundipharma, Sanofi and Vifor Pharma.

SDA discloses grants for investigator-initiated trials (IIT) from Vifor Int and Abbott Vascular, consultancy fees from Cardiac Dimensions, *ad hoc* consultancy fees from Amgen, Respicardia, Brahms and Cordio, fees for trial steering committee work from Vifor and Abbott Vascular, trial steering committee work with Bayer AG, Boehringer Ingelheim, Bioventrix, Janssen, V-Wave and Occlutech, Registry Steering Committee work with Sevier, *ad hoc* advisory board with AstraZeneca, and cancer cachexia focused research company: Chair advisory board & share holder as founder of Actimed.

JGG acts as an advisor and speaker to several pharmaceutical companies (AbbVie, Bayer, Novartis and Roche) and contributes to several clinical studies. The author has no conflicting interests with the findings that are presented in this report.

TO discloses no conflicts of interest in relation to this project.

BP discloses consultancy fees from Bayer, AstraZeneca, KBP Pharmaceuticals, Sarfez, scPharmaceuticals, SQinnovations, G3phrmaceuticlas, Cereno Scientific, Relypsa/Vifor, Ardelyx, Tricida, Sanofi/Lexicon, Phasbio, Boehringer Ingelheim and Brainstrom Medical, issued US patent 9931412 for site specific delivery of Eplerenone to the myocardium, provisional patent US 63/045,784 (pending; histone-acetylation-modulating agents for the treatment and prevention of organ injury), and stock options with KBP Pharmaceuticals, Sarfez, scPharmaceuticals, SQinnovations, G3phrmaceuticlas, Cereno Scientific, Relypsa/Vifor, Ardelyx, Tricida and Brainstrom Medical.

SER discloses research support to Joslin Diabetes Center for clinical trials from Bayer Healthcare and AstraZeneca and clinical research from the US National Institutes of Health (NIH)/National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

LMR discloses consultancy fees from Bayer AG.

DZ discloses fees for advisory boards, scientific presentation and travel support from AstraZeneca and Bayer.

MB, DF and TS are employees of Bayer AG and may hold stock and/or stock options with Bayer AG.

SL is an employee of Bayer Consumer Care AG and may hold stock and/or stock options with Bayer AG.

GB discloses funding for the FIDELITY clinical trial paid directly to University of Chicago Medicine from Bayer AG, consulting fees from Merck, Alnylam and Ionis, involvement with the FLOW trial Steering Committee, with fees paid to University of Chicago from Novo Nordisk, principal investigator of the REFRESH trial, with fees paid to University of Chicago from Quantum Genomics, acting as a steering committee member InREGEN, with fees paid to the University of Chicago.

Contribution statement

PR, JG, SDA, TO, BP, SER, LMR, DZ, MB, DF, SL, TS and GB are responsible for the work described in this article. All authors were involved in at least one of the following: study conception; design of work; or acquisition, analysis and interpretation of data. All authors revised the article critically for important intellectual content and provided final approval of the published version. MB and SL accept full responsibility for the work and/or the conduct of the study and had access to the data.

References

1. Park HC, Lee YK, Cho A, et al. Diabetic retinopathy is a prognostic factor for progression of chronic kidney disease in the patients with type 2 diabetes mellitus. *PLoS One.* 2019;14(7):e0220506.
2. Wilkinson-Berka JL, Suphapimol V, Jerome JR, Deliyanti D, Allingham MJ. Angiotensin II and aldosterone in retinal vasculopathy and inflammation. *Exp Eye Res.* 2019;187:107766.
3. Wilkinson-Berka JL, Tan G, Jaworski K, Harbig J, Miller AG. Identification of a retinal aldosterone system and the protective effects of mineralocorticoid receptor antagonism on retinal vascular pathology. *Circ Res.* 2009;104(1):124-133.
4. Bakris GL, Agarwal R, Anker SD, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med.* 2020;383(23):2219-2229.
5. Pitt B, Filippatos G, Agarwal R, et al. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. *N Engl J Med.* 2021;385:2252-2263.
6. Bakris GL, Agarwal R, Anker SD, et al. Design and baseline characteristics of the finerenone in reducing kidney failure and disease progression in diabetic kidney disease trial. *Am J Nephrol.* 2019;50(5):333-344.
7. Ruilope LM, Agarwal R, Anker SD, et al. Design and baseline characteristics of the finerenone in reducing cardiovascular mortality and morbidity in diabetic kidney disease trial. *Am J Nephrol.* 2019;50(5):345-356.
8. Wong TY, Sun J, Kawasaki R, et al. Guidelines on Diabetic Eye Care: The International Council of Ophthalmology Recommendations for Screening, Follow-up, Referral, and Treatment Based on Resource Settings. *Ophthalmology.* 2018;125(10):1608-1622.

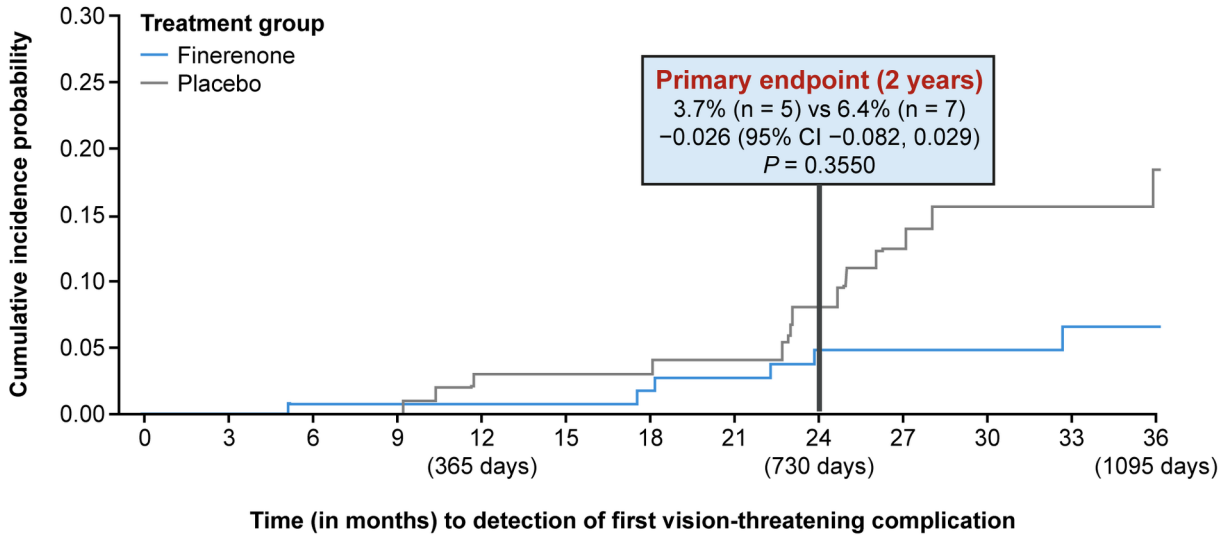
9. Mansour SE, Browning DJ, Wong K, Flynn HW, Jr., Bhavsar AR. The evolving treatment of diabetic retinopathy. *Clin Ophthalmol.* 2020;14:653-678.

10. Wang B, Wang F, Zhang Y, et al. Effects of RAS inhibitors on diabetic retinopathy: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol.* 2015;3(4):263-274.

11. Fusi-Rubiano W, Saedon H, Patel V, Yang YC. Oral medications for central serous chorioretinopathy: a literature review. *Eye (Lond).* 2020;34(5):809-824.

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

FIGURE 2 Cumulative incidence probability of a required ocular intervention



Numbers 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

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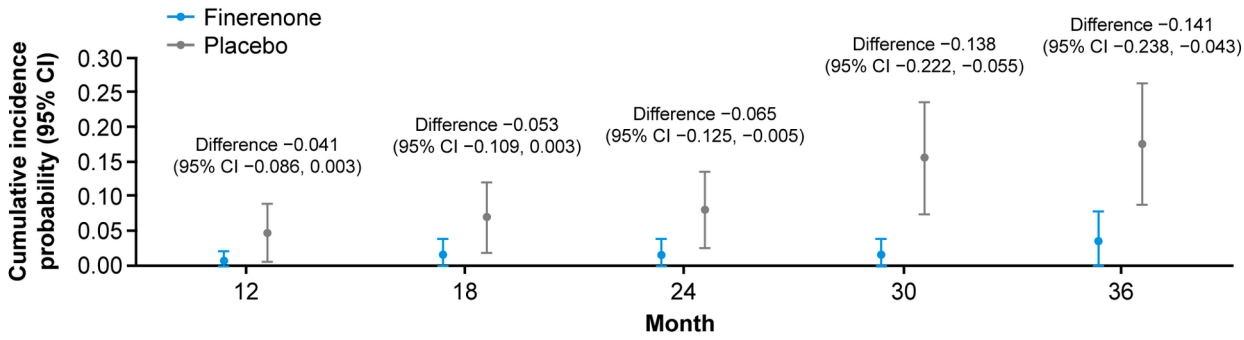

Numbers at risk

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

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