Date of study report	09-Mar-2022
Study title	A clinical trial collecting Data from routine ophthalmological examinations of patients who were randomized to either finerenone or placebo in the two Bayer sponsored Phase 3 clinical trials FIDELIO-DKD and FIGARO-DKD to investigate the effect of Finerenone on delaying the progression of Diabetic Retinopathy [DeFineDR]
Sponsor	Bayer
Sponsor's study ID	21618
NCT number	NCT04795726
EudraCT number	2020-003865-20
Study Phase	N/A
Indication	Diabetic retinopathy (DR)
Study objectives	Primary objective: • This study aimed to investigate the effect of orally administered finerenone on the progression of diabetic retinopathy compared to placebo at year 2 Secondary objectives: • Progression of NPDR up to the end of Year 1 • Progression of NPDR to PDR up to the end of Year 1, and up to the end of Year 2 • Development of DME up to the end of Year 1 and up to the end of Year 2 • Development of ASN up to the end of Year 1 and up to the end of Year 2 • Change in severity of DR at Year 1 (Year 2)
Test drug	Finerenone (Kerendia, BAY 94-8862)
Active ingredient(s)	Finerenone micronized
Dose	10 mg and 20 mg
Route of administration	Oral
Duration of treatment	Treatment during the respective Phase 3 clinical trials FIGARODKD and FIDELIO-DKD
Reference drug	Placebo
Dose	N/A
Route of administration	Oral
Duration of treatment	Treatment during the respective Phase 3 clinical trials FIGARODKD and FIDELIO-DKD

Main inclusion criteria	Participants from the Phase 3 trials FIDELIO-DKD study 16244 and FIGARO-DKD study 17530 (referred to as FIDELIO-DKD and FIGARO-DKD) with a diagnosis of DR at baseline. Documented NPDR in at least one eye, as documented by ophthalmological records within 6 months prior to baseline in FIDELIO-DKD or FIGARO-DKD, and up to one month after baseline in FIDELIO-DKD or FIGARO-DKD. An ophthalmological assessment available 6 month before or maximum 1 month after the baseline examination in FIDELIODKD or FIGARO-DKD, and at least one additional assessment afterwards.
Study design	Multi-center, placebo-controlled study conducted at 11 selected centers in 2 countries (Bulgaria and United Kingdom) who already participated in the double-blind Phase 3 trials FIDELIO-DKD and FIGARO-DKD. In these studies participants were randomized 1:1 to either receive finerenone or placebo. The study was conducted to support data collection of observational ReFineDR study 21311.
Methodology	Data from routine ophthalmological examinations of participants with documented DR at baseline in the Phase 3 clinical trials FIDELIO-DKD and FIGARO-DKD were collected and analyzed together with FIDELIO-DKD and FIGARO-DKD data from the same participants. The ophthalmological examinations should have occurred in the time period from 6 months prior to randomization in FIDELIO-DKD or FIGARO-DKD until the end of participation in these trials. Blinding was maintained to ensure data integrity.
Statistical methods	All analyses for this study were exploratory. No adjustment for multiplicity was done for testing of the different hypotheses. 95% confidence intervals were provided where applicable. Tests used a nominal significance level of 5%.
Early termination	No
Substantial protocol changes	No substantial changes to the protocol were made.
Study period	Study Start Date: 10-Mar-2021 Study End Date: 30-Jun-2021
Study center(s)	11 clinical sites in 2 countries: Bulgaria (7), United Kingdom (4)
Number of subjects	Planned: 90 Analyzed: 57

Criteria for evaluation	
Efficacy	Primary variable: • Progression of NPDR defined by the occurrence of vision threatening events i.e. PDR, DME and ASN up to the end of Year 2 after planned start of treatment Secondary variables: • Progression of NPDR up to the end of Year 1 • Progression of NPDR to PDR up to the end of Year 1, and up to the end of Year 2 • Development of DME up to the end of Year 1 and up to the end of Year 2 • Development of ASN up to the end of Year 1 and up to the end of Year 2 • Change in severity of DR at Year 1 (Year 2)
Safety	No additional safety data were collected in this study (DeFineDR); Instead, safety data from the selected subset of participants from FIDELIO-DKD / FIGARO-DKD were assessed in a retrospective manner.
Clinical pharmacology	N/A

Subject disposition and baseline

A total of 74 participants (38 finerenone, 36 placebo) were screened (signed informed consent) from the studies FIDELIO-DKD (29 participants) and the FIGARO-DKD (45 participants). 70 of them (36 finerenone, 34 placebo) had available ophthalmological assessments (including screening failures). 57 participants (29 finerenone, 28 placebo) were included in the FAS. A total of 51 participants (26 finerenone, 25 placebo) completed the end of treatment in their respective Phase 3 trial, FIDELIO-DKD or FIGARO-DKD, and were valid for the PP analysis.

Due to the low overall number of participants, data must be interpreted carefully. Overall, more male than female participants were included (54.4% vs. 45.6%). The mean age of the study population was 60.67 years (SD 8.65 years; age range: 38 to 82 years). Slight imbalances between the finerenone and placebo arms were observed regarding sex and weight. Overall, more participants were included from the FIGARO-DKD than from the FIDELIO-DKD (66.7% vs. 33.3%).

Some differences were observed between the treatment arms regarding the following baseline characteristics.

In the placebo arm more participants (39.3%) were recruited from the FIDELIO-DKD study compared to the finerenone arm (27.6%).

The mean baseline UACR (mg/g) was higher in the placebo arm [546.77 mg/g (SD 3.34 mg/g)] than in the finerenone arm [326.57 mg/g (SD 3.68 mg/g)]. Less participants in the finerenone arm had very high albuminuria (⩾300 mg/g) than in the placebo arm (55.2% vs. 64.3%).

The timepoint of baseline DR assessment was “within 3 to 6 months before baseline examination in FIDELIO-DKD or FIGARO-DKD” in less participants in the finerenone arm than in the placebo arm (27.6% vs. 50.0%). More participants in the finerenone arm had their baseline DR assessment “within less than 3 months until baseline examination in FIDELIO-DKD or FIGARO-DKD” than in the placebo arm (48.3% vs. 35.7%).

More participants in the placebo arm had a longer duration of diabetes (⩾20 years) than in the finerenone arm (25.0% vs. 10.3%).

More participants in the placebo arm had a baseline Hb1Ac >7.5% compared to the finerenone arm (82.1% vs. 62.1%).

The mean baseline systolic blood pressure (mmHg) was higher in the placebo arm than in the finerenone arm [140.21 mmHg (SD 9.12 mmHg) vs. 132.57 mmHg (SD 11.13 mmHg)]. More participants in the placebo arm had a blood pressure ranging from 130 to 160 mmHg compared to the finerenone arm (85.7% vs. 69.0%).

Differences between the treatment arms were observed for the following medication at baseline: beta-blocker (37.9% on finerenone vs. 67.9% on placebo), biguanides (65.5% on finerenone vs. 42.9% on placebo) and sulfonamides (20.7% on finerenone vs. 10.7% on placebo).

Efficacy

Primary variable:
This study (DeFineDR) aimed to investigate the effect of orally administered finerenone on progression of DR compared to placebo. The composite primary efficacy variable was the progression of NPDR (i.e., development of PDR, DME or ASN) up to the end of Year 2.

In the FAS, 0/29 participants in the finerenone arm and 1/28 participants (3.6%) in the placebo arm showed progression of NPDR up to the end of Year 2 (p=0.3085).

The cumulative incidence probability in the FAS after 2 years (24 months) was 0.0 on finerenone and 0.050 on placebo with a treatment difference of -0.050 (95% CI: -0.146; 0.046).

Secondary variables:

1 (3.6%) participant in the placebo arm had experienced an event of progression: progression of NPDR to PDR up to the end of Year 2. The treatment difference was -0.036 with a 95%-CI of (-0.104; 0.033) (p=0.3085).

Change in severity of DR was found for 1 participant (3.6%) at Year 1. This was improvement of DR severity from mild/moderate NPDR to no DR. In the remaining 11 participants (37.9%) in the finerenone arm and 7 participants (25.0%) in the placebo arm, no change in DR severity was observed.

At Year 2, progression of DR compared to baseline was found in no participants in the finerenone arm and in 1 participant (3.6%) in the placebo arm (mild/moderate NPDR progressed to PDR). No improvement of DR was found in either treatment arms.

Safety

In this study no additional safety data were collected. Incidence tables were provided for participants included into this study (DeFineDR). Detailed safety data can be found in the respective CSR of the Phase 3 clinical trials (FIGARO-DKD and FIDELIO-DKD).

Overall, the proportion of participants with TEAEs was 65.5% in the finerenone arm and 67.9% in the placebo arm.

The proportion of participants with serious TEAEs was 24.1% in the finerenone arm and 21.4% in the placebo arm.

The safety profile of finerenone observed in participants of this study is in line with what has been observed in the Phase 3 clinical trials (FIGARO-DKD and FIDELIO-DKD).

Overall conclusions

No conclusions can be drawn from this study alone due to the low number of participants with primary efficacy events (only 1 participant in the placebo arm had an event of NPDR progression up to the end of Year 2). The safety profile of finerenone observed in participants of this study is in line with what has been observed in the Phase 3 clinical trials (FIGARODKD and FIDELIO-DKD). A combined analysis of both data from the ReFineDR and DeFineDR study is reflected in the report of the ReFineDR study.

Publication(s) based on the study

None at the time of report creation