Finerenone Dose-Exposure-Response for the Primary Kidney Outcome in FIDELIO-DKD Phase III: Population Pharmacokinetic and Time-to-Event Analysis

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Introduction

Finerenone reduces the risk of kidney failure in patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) [1]. Phase III study FIDELIO-DKD investigated the efficacy and safety of finerenone compared to placebo on top of standard-of-care in patients with CKD and T2D [2]. Patients received either finerenone (starting dose depended on eGFR at screening) or placebo p.o. once daily and could be up- or down-titrated according to changes in serum potassium and eGFR and at the discretion of the investigator [2,3]. The primary endpoint of FIDELIO-DKD was a composite of (1) time to the first occurrence of kidney failure, (2) a sustained decrease of eGFR ≥ 40% from baseline over at least 4 weeks, or (3) renal death.

Objectives

- Characterize the PK of finerenone in patients from FIDELIO-DKD, including identification of covariate effects.
- Provide posthoc estimates for exposure-response analyses.
- Characterize the relationship between finerenone exposure and the time to reach the primary kidney endpoint, including investigation of selected prognostic factors (PFs).

Data & Methods

- Data from pivotal phase 3 trial FIDELIO-DKD included in analysis:
  - 5,674 subjects, randomised (1/1) to placebo or finerenone (10 mg/20 mg)
  - 5057 finerenone plasma concentrations (from 2284 subjects)
  - 1104 primary composite kidney events (504 / 2833 patients (17.8%) in the finerenone group and in 600 / 2841 patients (21.1%) in the placebo group) [4].
- Non-linear mixed-effects modelling (NONMEM 7.4.3)
- PopPK model development
  - Existing model used as starting point [5]
  - Stepwise covariate modelling
  - Simulations done to support labelling: (1) assess the magnitude and uncertainty of a single covariate effect and (2) to compare the finerenone exposure at steady-state in subgroups of interest taking combined individual covariate effects into account.
- Kidney TTE model development
  - Placebo model (CPH screening / lumping of PF, hazard shape + PF (full model + BWD)
  - Implement exposure-response (model-predicted individual PK drives effect on hazard)
  - Investigate potential effect of long-term sodium glucose cotransporter 2 inhibitor (SGLT2i) use on the effect of Finerenone.

Results

PopPK model

- A two-compartmental population PK model with volumes set equal and absorption through a series of transit compartments and first-order elimination adequately captured the finerenone concentration–time data in FIDELIO-DKD [6].
- Single covariate effects (Fig. 1) were generally contained within the equivalence range of 80–125% around typical $C_{max,md}$ and $AUC_{\tau,md}$.
- Simulations in subgroups of interest were also generally contained within the 80–125% range when comparing the median $C_{max.md}$ and $AUC_{\tau.md}$ values (see Fig. 2 for CKD subgroups).

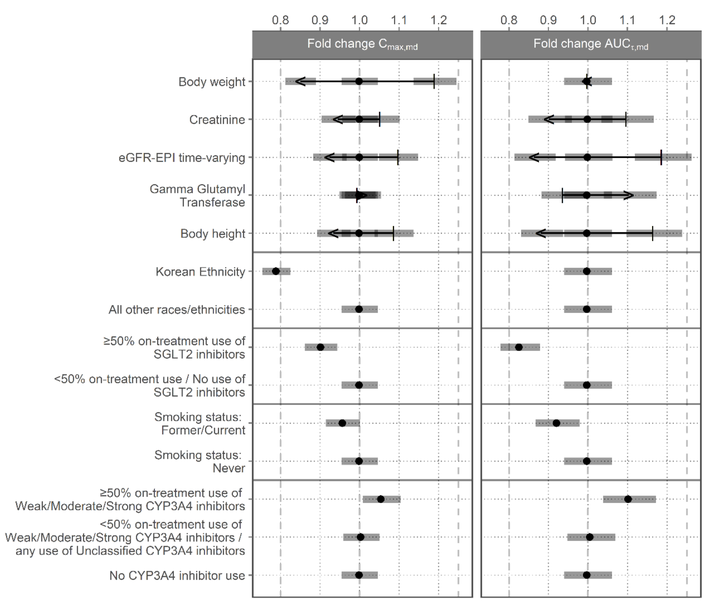

Figure 1. Forest plots illustrating the influence of the identified covariate effects on $C_{max,md}$ and $AUC_{\tau,md}$ relative to the median covariate value (continuous) or reference subgroup (categorical). Black dots: reference or the fold change relative to the reference. Whiskers shaped as an arrow to indicate the direction of the effect: PK parameter values at the 5^{th}–95^{th} percentiles of the covariate distribution. Gray bars: uncertainty shown as 5^{th} – 95^{th} percentiles of the simulated 5th percentile, median, and 95th percentile. Vertical dashed lines indicate unity and general acceptance range for equivalence of 0.8–1.25.

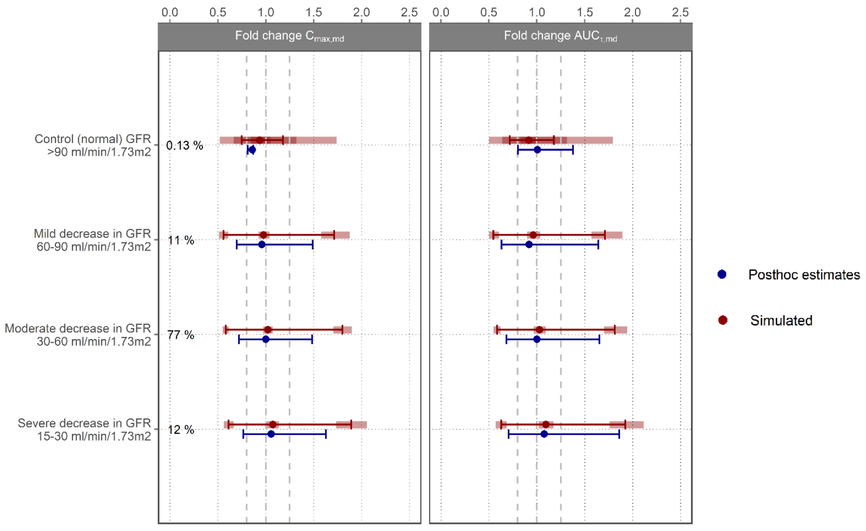

Figure 2. Forest plots comparing the $C_{max,md}$ and $AUC_{\tau,md}$ between eGFR groups relative to the overall population. The % indicates the percentage of subjects within each group when compared to the total population of subjects in analyzed data. Red dots and whiskers: median and 5^{th} – 95^{th} percentiles of the $C_{max,md}$ and $AUC_{\tau,md}$ ratio using a subject with median $C_{max,md}$ and $AUC_{\tau,md}$ as reference. The red areas indicate the uncertainty (5^{th} – 95^{th} percentiles of the simulated 5th percentile, median, and 95^{th} percentile). Blue dots and whiskers represent the median and 5^{th} – 95^{th} percentiles of the $C_{max,md}$ and $AUC_{\tau,md}$ ratio using a subject with median $C_{max,md}$ and $AUC_{\tau,md}$ as reference, based on the posthoc estimates. Vertical dashed lines indicate unity and the 0.8 – 1.25 lines.

Kidney TTE model

- A Weibull hazard model with model predicted finerenone plasma concentration driving the exposure-response (E_{max} model) adequately captured the kidney composite TTE data (Fig. 3).
- Half-maximal effect concentration and the maximal hazard decrease were estimated at 0.166 µg/L and -36.1%, respectively.
- PFs (treatment-independent) included a low eGFR and a high urine albumin-creatinine ratio increasing the risk, while concomitant sodium-glucose transport protein 2 inhibitor (SGLT2i) use decreased the risk.

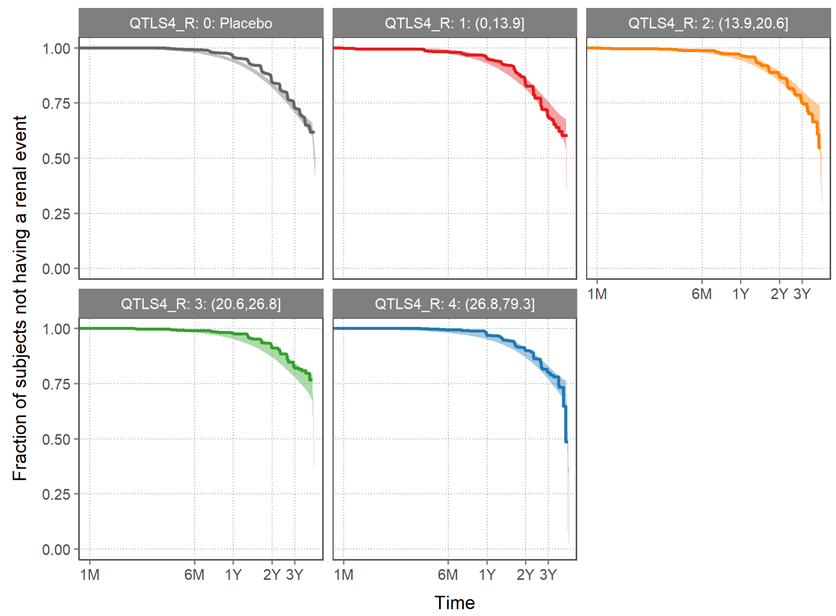

Figure 3. VPC of the kidney time-to-event model. Next to the fit of the placebo data (gray), the finerenone-treated subjects were divided into four exposure quartiles based on average concentration until (censored) event. The QTLS4_R numbers at the top indicate the exposure ranges in µg/L. Thick lines indicate the observed KM curves, where, owing to the visit-related nature of the event, the left corner of each step should be used to evaluate the goodness of fit relative to the ribbon, which indicates the 95% Prediction Interval.

Analyses indicate independent and additive effects of finerenone and SGLT2is on the primary kidney endpoint.

- SGLT2i use reduced the risk of a kidney event independent of finerenone treatment by 50.7% (95% confidence interval 29.8–71.6).
- No significant effect of SGLT2i use on the effect of finerenone was found.
- Results strengthened by recently published results on exposure-response analyses for the biomarkers/surrogates UACR and eGFR [7]:

Typical Subject Simulation Results	Finerenone 10 mg OD	Finerenone 20 mg OD	SGLT2i	Finerenone 20 mg OD + SGLT2i
Change in chronic eGFR slope vs placebo (%)	-27.3	-36.9	-56.1	-71.5

Conclusion

- Either covariate effects or multivariate forward-simulations in subgroups of interest were contained within the equivalence range of 80–125% around typical exposure indicating that these were not clinically relevant in FIDELIO-DKD.
- Finerenone effects on kidney outcomes approached saturation towards 20 mg once daily.
- SGLT2i use provided additive benefits [6].

[1] Agarwal R, et al. Nephrol Dial Transplant. 2020.
[2] Bakris GL, et al. Am J Nephrol. 2019;50(5):333–44.
[3] Goulooze B, et al. Clin Pharmacokinet. 2022;61(3):451-462.
[4] Bakris GL, et al. N Engl J Med 2020;383:2219-29.
[5] Snelder N, et al. Clin Pharmacokinet. 2020;59(3):359–70.
[6] Van den Berg P, et al. Clin Pharmacokinet. 2022;61(3):439-450.
[7] Goulooze SC, et al. Clin Pharmacokinet. 2022; https://doi.org/10.1007/s40262-022-01124-3