Finerenone dose-exposure-UACR response analyses of FIDELIO-DKD phase 3 and the effect of SGLT2i comedication

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RATIONALE AND OBJECTIVE

- Assess the finerenone dose-exposure-response relationship for urine albumin-to-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR)
- Assess the impact of combined SGLT2i-finerenone use
- Maximize explanatory power by using nonlinear mixed effect models considering individual longitudinal dosing and exposure information and correcting for covariates

KEY FINDINGS

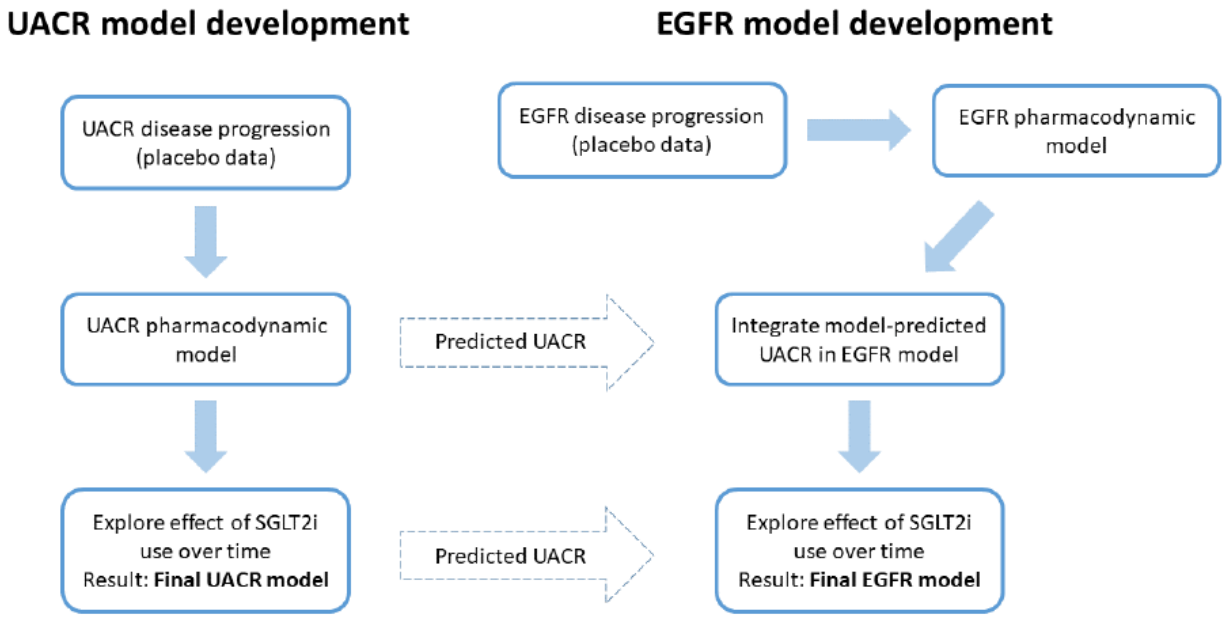
- Models well describe longitudinal UACR & eGFR data in placebo treatment arm (Standard of Care, SoC) and finerenone treatment arm
- In both the finerenone and placebo group sodium-glucose cotransporter 2 inhibitor (SGLT2i) effects on UACR & eGFR were identified
- Effects of finerenone on UACR & eGFR were present regardless of concomitant SGLT2i treatment, i.e. results demonstrate additive effects

Background

- Finerenone is a nonsteroidal, selective mineralocorticoid receptor antagonist (MRA) that demonstrated efficacy in delaying CKD progression and reducing cardiovascular events in patients with CKD and type 2 diabetes (T2D) in FIDELIO-DKD (ClinicalTrials.gov number, NCT02540993), where 5,734 patients were randomized 1:1 to receive finerenone (10 or 20 mg once daily) or placebo, with a median follow-up of 2.6 years.[1]
- Sodium dependent glucose co-transporter 2 inhibitors (SGLT2i) have demonstrated convincing efficacy results for patients with CKD with or without T2D in large outcome trials.[2,3]
- The combination of these therapies holds promise to augment nephroprotection through activation of different pathways.
- Model-based approaches considering individual dosing and exposure and correcting for covariates can aid in characterizing the impact of combined finerenone + SGLT2i versus finerenone alone treatment
- We developed population pharmacokinetic/pharmacodynamics (popPKPD) models (similar to previous models based on ARTS-DN phase 2b data)[4] to assess
  - the finerenone dose-exposure-response relationship for urine albumin-to-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR)
  - the impact of combined SGLT2i-finerenone use on UACR and eGFR

[1]Bakris et al. NEJM 383(23): 2219-2229.
[2]Heerspink et al., NEJM 383(15): 1436-1446.
[3]Perkovic et al., NEJM 380(24): 2295-2306.
[4]Snelder et al., ClinPK 59(3):359-337.

Methods & Purpose



Flow chart describing the PKPD model development strategy of the eGFR and UACR models.

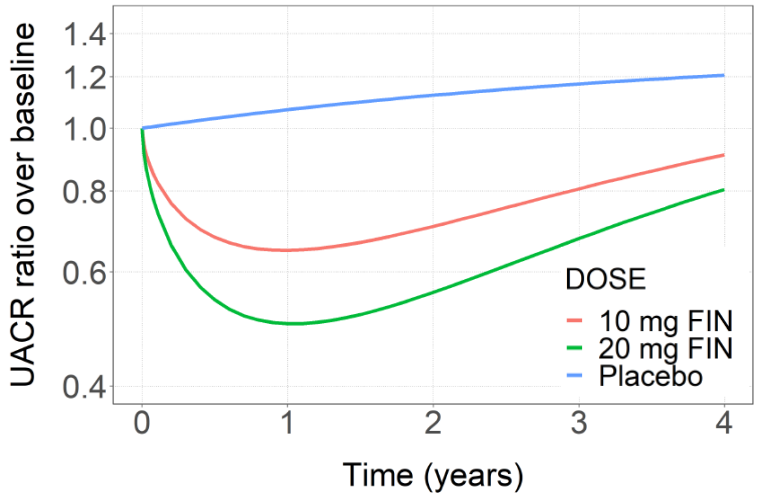
- We analyzed 37,296 UACR and 78,132 eGFR measurements in 5,674 patients included in FIDELIO-DKD (549 patients with any recorded SGLT2i use) using nonlinear mixed-effects population pharmacokinetic-pharmacodynamic (popPKPD) modelling considering individual drug exposure.
- PK parameter posthoc estimates from a separate popPK analysis[1] provided individual exposure information as the starting point for the current analysis.
- Covariates were selected based on forward inclusion and backward deletion and models were selected to best describe the data judged by likelihood ratio tests and Akaike Information Criterion (AIC).

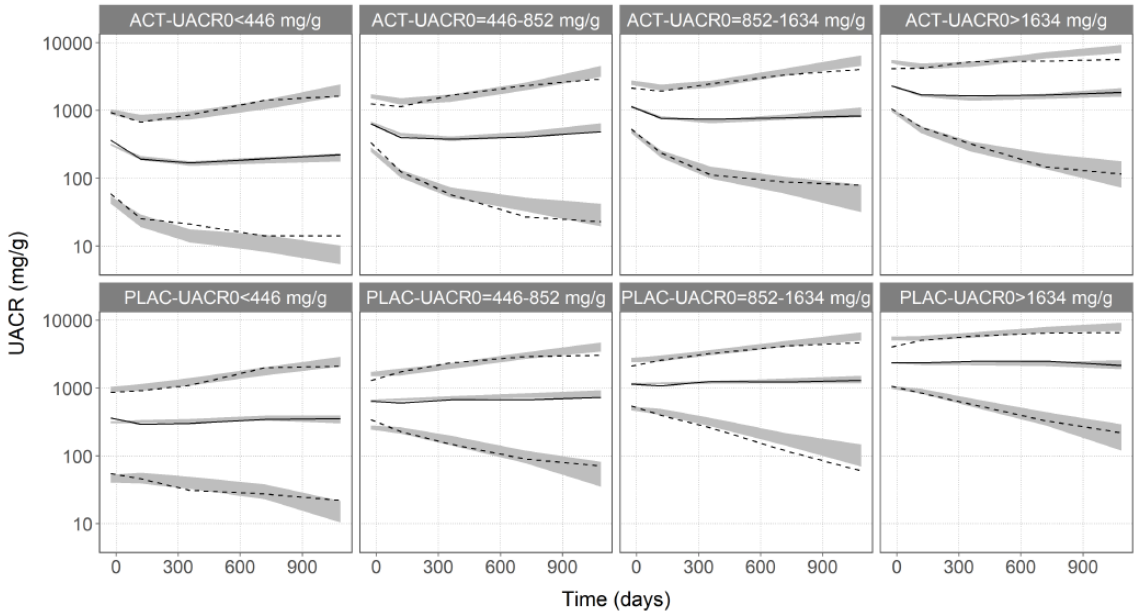
Purpose: The models were used to characterize the trajectory of UACR and eGFR progression over time, the exposure-response relationship of finerenone on UACR and eGFR as well as the effect of SGLT2i.

[1]van den Berg et al. ClinPK accepted: DOI10.1007/s40262-021-01082-2.

Results:
Finerenone dose-exposure-UACR response

- UACR trajectories in both placebo and finerenone treated patients are well characterized by the model including inter-individual variability
- The dose-exposure-response is illustrated in model simulations with typical covariates for finerenone doses of 10 and 20 mg once daily, compared to placebo

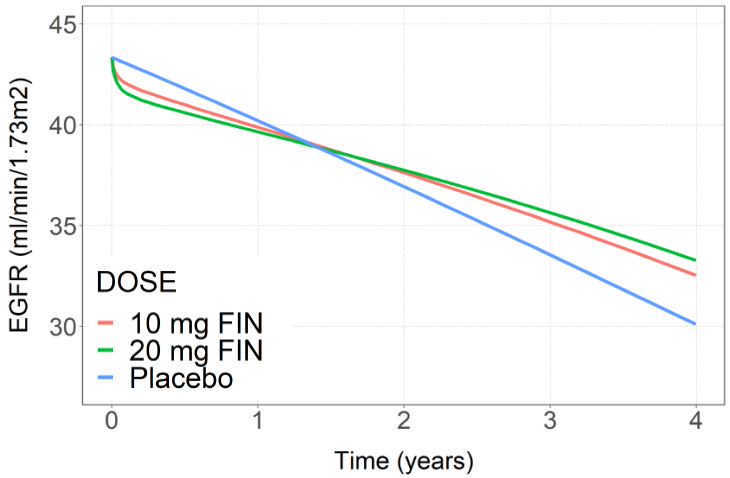


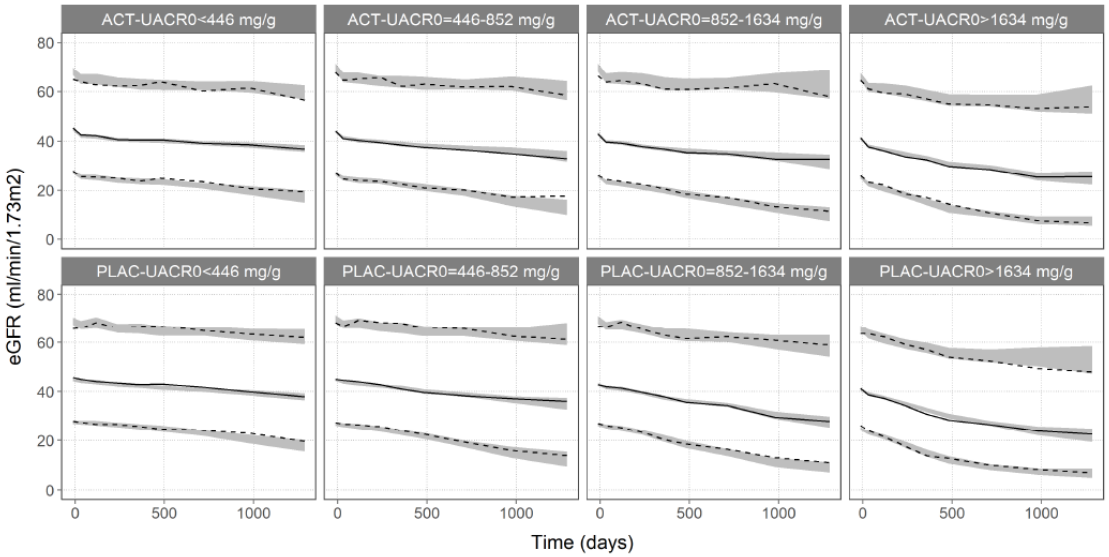


Visual predictive check of absolute UACR over time, stratified by baseline UACR quartiles and treatment arm (ACT=active treatment arm, PLAC=placebo arm).
Solid lines depict the observed median UACR, dashed lines the observed 5th and 95th percentiles, and the grey areas show the intervals of these statistics in the simulations, which include variability (inter-individual and residual error) but not parameter uncertainty.

Results:
Finerenone dose-exposure-eGFR response

- eGFR trajectories in both placebo and finerenone treated patients are well characterized including inter-individual variability
- The dose-exposure-response is illustrated in simulations with typical covariates for finerenone doses of 10 and 20 mg once daily, compared to placebo





Visual predictive check of absolute eGFR over time, stratified by baseline eGFR quartiles and treatment arm (ACT=active treatment arm, PLAC=placebo arm).
Solid lines depict the observed median UACR, dashed lines the observed 5th and 95th percentiles, and the grey areas show the intervals of these statistics in the simulations, which include variability (inter-individual and residual error) but not parameter uncertainty.

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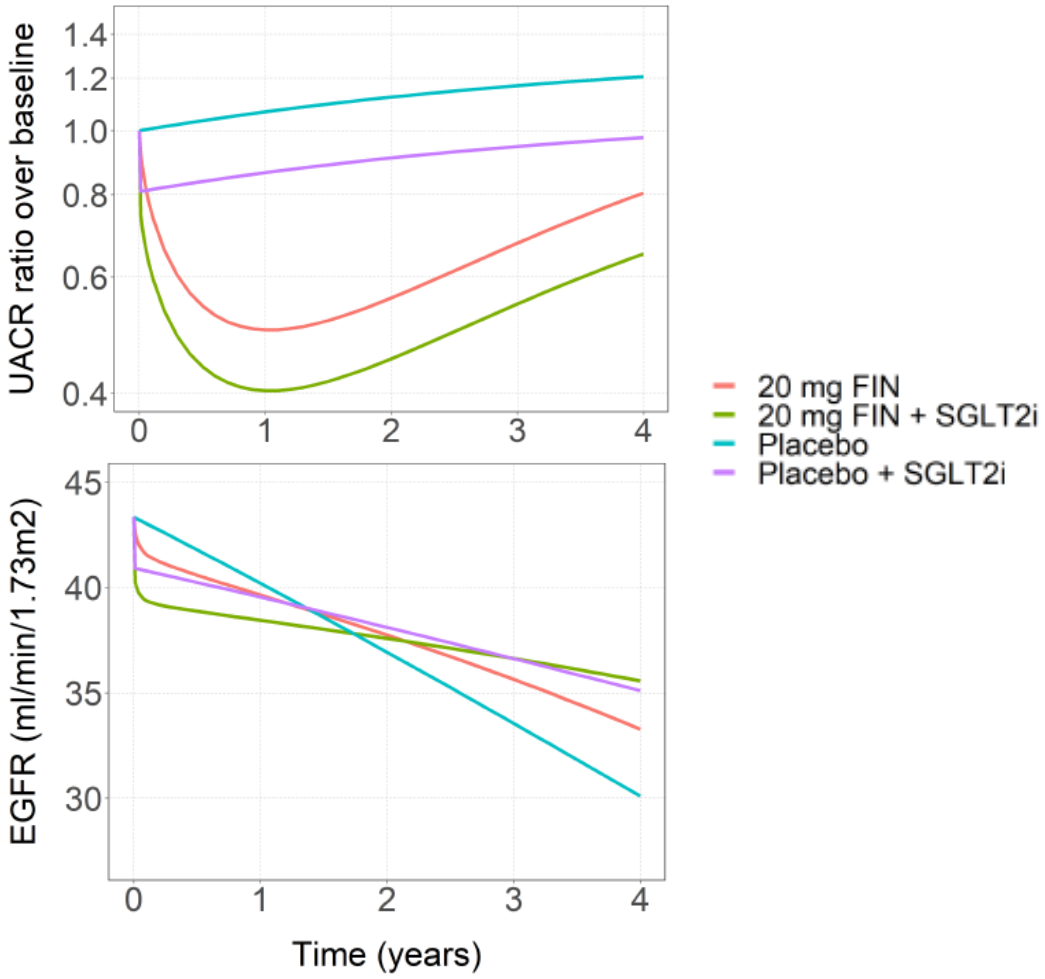
Results:
Independent and additive UACR and eGFR effects of SGLT2i on top of finerenone



- Finerenone but also SGLT2i show highly significant treatment effects in FIDELIO-DKD on UACR as well as on acute and chronic eGFR decline.
- No significant effects of concomitant SGLT2i use on the treatment effect of finerenone was found suggesting independent effects.
- Model simulated UACR and eGFR time-courses based on typical covariates for four treatment regimens (+/- finerenone/SGLT2i) are illustrated in the figures.
  - Estimating the (non-significant) effect of SGLT2i use on finerenone's effect reveals the (high) level of confidence extracted from the data with the model-based analysis:
    - For the UACR reducing effect, the 95% confidence interval of the interaction effect is -5.9% to +22.0% suggesting with 97.5% confidence that finerenone is at least 94.1% as efficacious in reducing UACR in patients currently using SGLT2i compared to patients not currently using SGLT2i
    - For the UACR-mediated effect on chronic eGFR decline, the 95% confidence interval of the interaction effect is -90.5% to +44.2%

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