Rationale and Design of a Phase 3 Registration Trial Investigating Finerenone in Participants with Chronic Kidney Disease and Type 1 Diabetes Using a UACR Endpoint (FINE-ONE)

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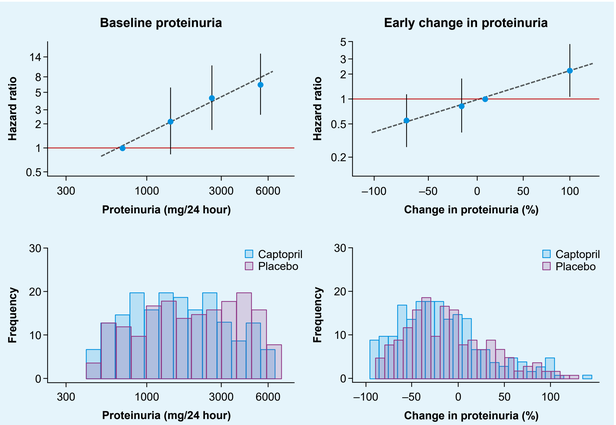
Introduction

- Chronic kidney disease (CKD) is a complication of diabetes and affects up to 40% of people with type 1 diabetes (T1D).[1-3]
- People with T1D and CKD are at higher risk of experiencing kidney failure and cardiovascular disease and have a shorter life expectancy than people with T1D without CKD.[4]
- The benefit-to-risk profile of finerenone has been well described in two large clinical studies enrolling over 13,000 people with type 2 diabetes (T2D) and CKD randomized to finerenone or placebo on top of optimized renin–angiotensin system therapy (FIDELIO-DKD [NCT02540993] and FIGARO-DKD [NCT02545049] studies).[5–7]
- Finerenone was associated with a consistent reduction in the urine albumin/creatinine ratio (UACR) as well as a decreased risk of adverse kidney and cardiovascular outcomes in the pooled FIDELITY analysis.[8]
- Based on (1) the efficacy of finerenone on kidney outcomes in people with T2D and CKD;[5,6,8] (2) analysis from a landmark trial of captopril demonstrating that in people with T1D and CKD, an early reduction in albuminuria with captopril was associated with a reduction in the risk of adverse kidney outcomes[9] (**Figure 1**); and (3) earlier studies demonstrating that spironolactone reduces UACR in people with T1D and CKD,[10,11] it is postulated that finerenone will also reduce UACR, and thereby slow CKD progression in people with T1D and CKD.
- The FINE-ONE study aims to assess the efficacy and safety of finerenone, in addition to standard of care (SOC) consisting of angiotensin-converting enzyme inhibitor- or angiotensin receptor blocker-treatment, compared with placebo in people with T1D and CKD.

Figure 1. CSG-Captopril trial: in patients with T1D, proteinuria predicts kidney failure, and early reduction in proteinuria is associated with kidney protection

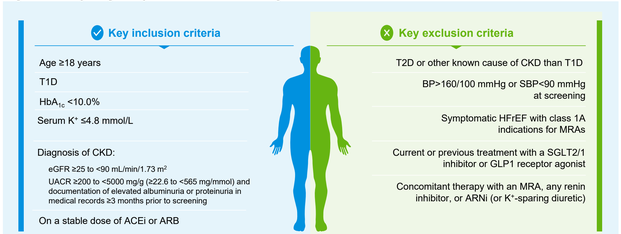


Analyses adjusted for age, sex, race, systolic blood pressure, estimated glomerular filtration rate, and albuminuria. CSG, Collaborative Study Group; T1D, type 1 diabetes.
Figure adapted from Heerspink et al. under the terms of the Creative Commons CC-BY 4.0 license.[12]

Rationale and design

- FINE-ONE (NCT05901831) is a randomized, prospective, double-blind, global multicenter, phase 3 study in people with T1D and CKD.[12]
  - It is anticipated that approximately 440 individuals will be screened to reach the required total of 220 randomized participants.
- The key inclusion and exclusion criteria are detailed in **Figure 2**.

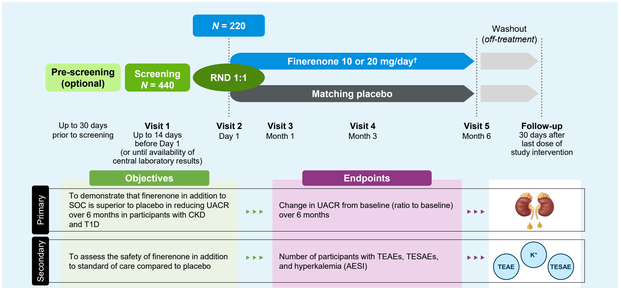
Figure 2. Key eligibility criteria at screening



ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor neprilysin inhibitor; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GLP1, glucagon-like peptide-1; HbA_{1c}, glycated hemoglobin; HFrEF, heart failure with reduced ejection fraction; K^+, potassium; MRA, mineralocorticoid receptor antagonist; SBP, systolic blood pressure; SGLT2/1, sodium–glucose cotransporter 2 or 1; T1D, type 1 diabetes; T2D, type 2 diabetes; UACR, urine albumin/creatinine ratio.
Details on eligibility criteria are published in Heerspink et al.[12]

- Participants will be randomized 1:1 to finerenone or matching placebo (**Figure 3**).
- Visits following randomization will occur at months 1, 3 and 6 (the planned end of the study treatment). A follow-up/end-of-study visit will be scheduled at month 7 (30 days after discontinuation of study treatment to assess off-drug effects; **Figure 3**).

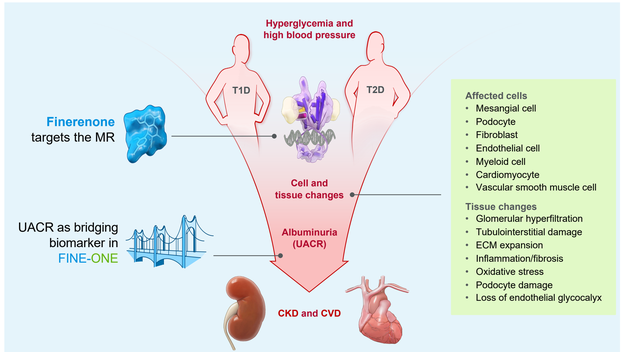
Figure 3. Study design



†Starting dose of finerenone: 10 mg once daily if eGFR is ≥25 mL/min/1.73 m² and <60 mL/min/1.73 m² or 20 mg once daily if eGFR is ≥60 mL/min/1.73 m² at screening visit.
AESI, adverse event of special interest; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; K+, potassium; RND, randomization; SOC, standard of care; T1D, type 1 diabetes; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event; UACR, urine albumin/creatinine ratio.
Figure adapted from Heerspink et al. under the terms of the Creative Commons CC-BY 4.0 license.[12]

- Additional safety visits will take place 4 weeks (±7 days) after each uptitration or after restart of study drug following treatment interruption for >7 days. Blood and urine samples will be collected at study visits for assessment of UACR, estimated glomerular filtration rate, and potassium.[14]
- The primary objective of the study is to demonstrate that the addition of finerenone to SOC is superior in reducing UACR over 6 months compared with placebo.
- UACR is used as a bridging biomarker, since the treatment effect of finerenone on UACR was associated with its efficacy on kidney outcomes in the FIDELIO-DKD and FIGARO-DKD trials.
- Based on regulatory authority feedback, UACR can be used as a bridging biomarker to translate the obtained evidence of finerenone from people with T2D and CKD to those with T1D and CKD[13] as it meets the necessary requirements:
  1. A small target population with no or few proven effective interventions.
  2. The role of albuminuria in the pathophysiology of CKD is largely similar in T1D and T2D (**Figure 4**).
  3. Meta-regression of clinical trials demonstrates that treatment effects on albuminuria are strongly associated with treatment effects on kidney failure.
  4. The reduction in albuminuria in the FIDELIO-DKD and FIGARO-DKD trials explained 87% of the effect of finerenone in reducing the risk of the composite kidney outcome (**Figure 5**).
  5. The intervention used should not have unintended or new side effects in the population to be studied; the safety profile of finerenone is not anticipated to be meaningfully different between T1D and T2D

Figure 4. Albuminuria has a similar role in the pathophysiology of CKD in T1D and T2D

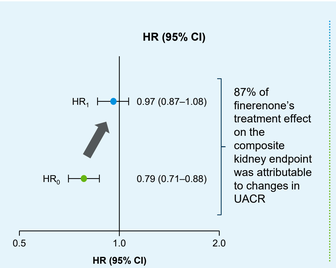


CKD, chronic kidney disease; CVD, cardiovascular disease; ECM, extracellular matrix; MR, mineralocorticoid receptor; T1D, type 1 diabetes; T2D, type 2 diabetes; UACR, urine albumin/creatinine ratio.

References

1. Cressman M, et al. *Diabetes*. 2018;67:544-P.
2. Mora-Fernández C, et al. *J Physiol*. 2014;592:3997-4012.
3. Costacou T, et al. *Diabetes Care*. 2018;41:426-433.
4. Jansson Sigfrids F, et al. *Lancet Diabetes Endocrinol*. 2022;10:489-498.
5. Bakris GL, et al. *N Engl J Med*. 2020;383:2219-2229.
6. Pitt B, et al. *N Engl J Med*. 2021;385:2252-2263.
7. Agarwal R, et al. *J Am Soc Nephrol*. 2022;33:225-237.
8. Agarwal R, et al. *Eur Heart J*. 2022;43:474-484.
9. Lewis EJ, et al. *N Engl J Med*. 1993;329:1456-1462.
10. Schjoedt KJ, et al. *Kidney Int*. 2005;68:2829-2836.
11. Nielsen SE, et al. *Diabet Med*. 2012;29:e184-e190.
12. Heerspink HJL, et al. *Diabet Res Clin Pract*. 2023: doi: 10.1016/j.diabres.2023.110908.
13. Fleming TR, et al. *Ther Innov Regul Sci*. 2023;57: 109-120.

Figure 5. UACR reduction associated with finerenone's treatment effect on the composite kidney endpoint in a restricted† FIDELIO-DKD and FIGARO-DKD pooled population



Proportion of treatment effect on 40% kidney composite outcome (onset of kidney failure, a sustained decrease in eGFR ≥40% over at least 4 weeks, or renal death) explained in the restricted† FIDELIO-DKD and FIGARO-DKD population

Variable	HR_1-adjusted analysis (95% CI)	HR_0-adjusted analysis (95% CI)	Proportion explained (%)
Time-varying log(UACR)	0.97 (0.87-1.08)	0.79 (0.71-0.88)	87.0

†Restricted to patients with a UACR ≥200 mg/g (22.6 mg/mmol) and eGFR ≥25 and <90 mL/min/1.73 m². CI, confidence interval; eGFR estimated glomerular filtration rate; HR, hazard ratio; UACR, urine albumin/creatinine ratio.
Figure adapted from Heerspink et al. under the terms of the Creative Commons CC-BY 4.0 license.[12]

- The analysis of UACR will be performed on the log-transformed UACR values, followed by a back-transformation to the original scale.
- The log-transformed ratio of UACR at baseline up to month 6 (visit 5) will be analyzed by a mixed model for repeated measures with the following factors: treatment group, visit, treatment-by-visit interaction, log-transformed baseline value as a covariate, and log-transformed baseline value-by-visit interaction to characterize the patients' baseline-specific response over time.

Conclusions

- The FINE-ONE phase 3 study will evaluate the efficacy and safety of finerenone in CKD associated with T1D. Finerenone could become a new registered treatment for slowing kidney disease progression in CKD associated with T1D.
- FINE-ONE, with its use of UACR as a bridging biomarker, may establish a new precedent for future clinical trials in people with T1D and CKD for whom new therapies are highly needed.

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Disclosures

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