Use of Finerenone in Children with Chronic Kidney Disease and Proteinuria: Design of the FIONA and Open-Label Extension Studies

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Introduction

- The most common causes of chronic kidney disease (CKD) in children include congenital anomalies of the kidneys and urinary tract followed by glomerular and systemic immunological diseases.[1]
- Due to clinical studies predominantly being conducted in the adult population, there are few treatment options for children with CKD.
- Despite treatment with recommended renin-angiotensin-aldosterone system blockade therapy, patients with CKD continue to have proteinuria and progression of kidney disease.[2]
  - Therefore, novel treatment options are required that target modifiable risk factors, complement current therapies, and improve outcomes in children with CKD.
- Finerenone, a selective, non-steroidal mineralocorticoid receptor antagonist, is approved for the treatment of adults with CKD associated with type 2 diabetes mellitus (T2DM) to reduce the risk of adverse kidney and cardiovascular outcomes in the US,[3] EU,[4] and several countries following positive results from the phase 3 FIDELIO-DKD study (NCT02540993) and later from the FIGARO-DKD (NCT02545049) study.[5–7]
  - In a pooled analysis of FIDELIO-DKD and FIGARO-DKD (FIDELITY, N=13 026), finerenone was safe and efficacious in reducing albuminuria and decreasing the risk of adverse kidney and cardiovascular events.[7,8]
- Based on results in adults with CKD and T2DM, it is anticipated that combining finerenone with an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) will exert comparable beneficial effects on urinary protein excretion and kidney function in children with CKD and proteinuria, potentially providing a novel therapeutic strategy for this patient population.

Objective

- The FIONA study (NCT05196035) and the associated open-label extension study (FIONA OLE; NCT05457283) aim to demonstrate that combining finerenone with an ACEi or ARB is safe, well tolerated and efficacious in sustainably reducing urinary protein excretion in children with CKD and proteinuria.

Design

FIONA

- FIONA is a 6-month, multicenter, randomized, double-blind, placebo-controlled phase 3 study.
- FIONA is being conducted in approximately 25 countries, in collaboration with pediatric clinical trial networks connect4children, ESCAPE (Europe), NAPRTCS (US and Canada), and KNOW-Ped CKD (South Korea; **Figure 1**). Screening patients for participation began in March 2022, and the estimated completion date is March 2027. Approximately 219 participants will be randomly assigned to the study interventions.
- Eligible participants are aged 6 months to <18 years, with a clinical diagnosis of CKD and clinically relevant proteinuria, despite ACEi or ARB usage at screening. The list of key inclusion and exclusion criteria are detailed in **Table 1**.
- Participants will be randomized 2:1 to finerenone plus standard of care (ACEi or ARB) or placebo plus standard of care (**Figure 2**). Randomization is stratified according to CKD etiology (glomerular vs non-glomerular disease, defined by the investigator) and urinary protein-to-creatinine ratio (UPCR) category (average screening UPCR <1.0 g/g vs ≥1.0 g/g).
- The primary objective of the study is to demonstrate that finerenone, in addition to an ACEi or ARB, is superior to placebo in reducing urinary protein excretion. There are two alternative primary endpoints to address this objective:
  - UPCR reduction of ≥30% from baseline to day 180.
  - Percent change in UPCR from baseline to day 180.
- Secondary objectives are detailed in **Table 2**.

FIONA OLE

- The FIONA OLE study is an 18-month, multicenter, single-arm open-label study (**Figure 1**).
- Participants who are willing and likely eligible to transition from FIONA to FIONA OLE will enter an interim period of 7 days (**Figure 3**). The FIONA OLE trial starts with visit 1.
  - The key inclusion and exclusion criteria are detailed in **Table 1**.
- The primary objective of the FIONA OLE study is to provide long-term safety data for the use of finerenone in addition to an ACEi or ARB. The primary and secondary objectives are detailed in **Table 2**.

Figure 1. Countries participating in the study

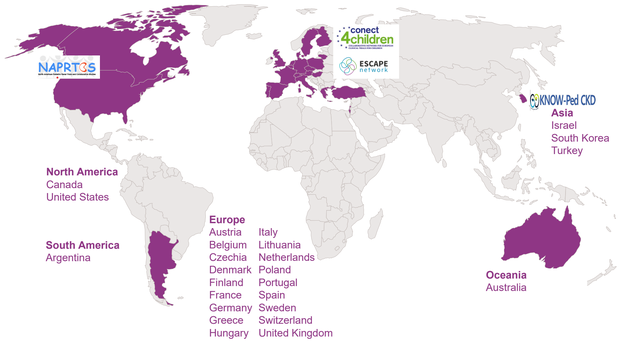
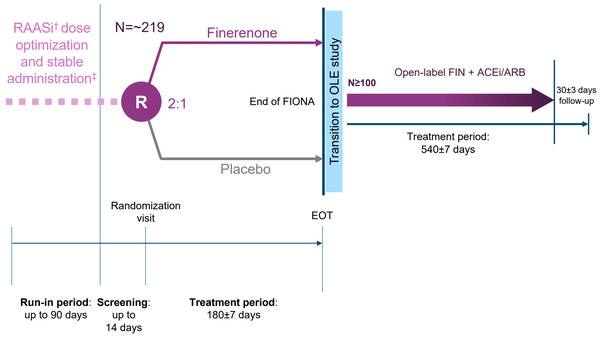


Table 1. FIONA and FIONA OLE key eligibility criteria

FIONA	
Inclusion criteria	**Exclusion criteria**
• Aged 6 months to <18 years	• Planned urological surgery expected to influence kidney function or scheduled kidney transplant within the study time frame
• CKD stages I–III (eGFR ≥30 mL/min/1.73 m^2) for children aged ≥1 year to <18 years, or serum creatinine ≤0.40 mg/dL for infants aged 6 months to <1 year	• Systemic hypertension (stage II as defined by the institutional guidelines on BP management) or systemic hypotension
• Proteinuria defined as UPCR of ≥0.50 g/g in patients aged ≥2 years with CKD stage II or III, or UPCR ≥1.0 g/g for patients aged <2 years or ≥2 years with CKD stage I	• Children with hemolytic uremic syndrome diagnosed ≤6 months prior to screening
• On a maximum tolerated dose of ACEi or ARB	• Patients with nephrotic syndrome receiving albumin infusions or with acute kidney injury requiring dialysis within the last 6 months prior to screening
• Serum [K$^+$] ≤5.0 mmol/L for children aged ≥2 years and ≤5.3 mmol/L for children aged <2 years	• Participants on IV glucocorticoids, cyclophosphamide, rituximab or abatacept within the last 6 months prior to screening
	• Concomitant therapy with an MRA, renin inhibitor, SGLT2i, ARNI or potassium sparing diuretic
	• Concomitant therapy with both ACEi and ARBs together
FIONA OLE	
Inclusion criteria	**Exclusion criteria**
• Aged ≥1 to <19 years	• Planned urological surgery expected to influence kidney function or scheduled kidney transplant within the study time frame
• Prior participation in FIONA study	• Systemic hypertension (stage II as defined by the institutional guidelines on BP management) or systemic hypotension
• CKD stages I–III (eGFR ≥30 mL/min/1.73 m^2) for children aged ≥1 year to <19 years	• Participants using rituximab, cyclophosphamide, abatacept, or IV glucocorticoids
• On a maximum tolerated dose of ACEi or ARB	• Concomitant therapy with an MRA, any renin inhibitor, any SGLT2i, ARNI, or potassium sparing diuretic
• Serum [K$^+$] ≤5.0 mmol/L for children aged ≥2 years and ≤5.3 mmol/L for children aged <2 years	• Concomitant therapy with both ACEi and ARBs together

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BP, blood pressure; CKD, chronic kidney disease; CYP3A4, cytochrome P450 3A4; eGFR, estimated glomerular filtration rate; IV, intravenous; [K$^+$], potassium concentration; MRA, mineralocorticoid receptor antagonist; OLE, open-label extension; SBP, systolic blood pressure; SGLT2i, sodium-glucose cotransporter-2 inhibitor; UPCR, urinary protein-to-creatinine ratio.

Figure 2. Study design



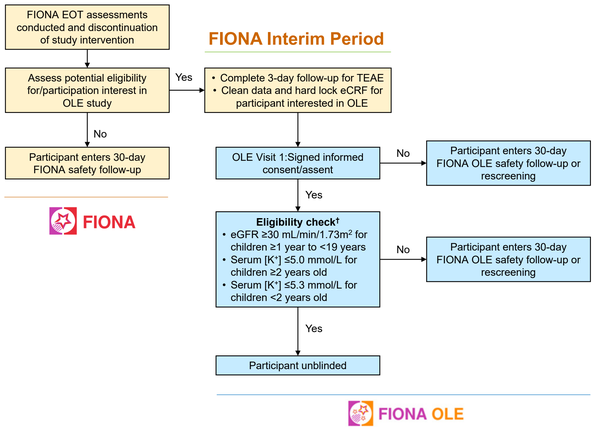
†RAASi = ACEi or ARB.
‡Mandatory for at least 30 days before screening.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; EOT, end of treatment; FIN, finerenone; OLE, open-label extension; R, randomization; RAASi, renin-angiotensin-aldosterone system inhibitor.

Table 2. FIONA and FIONA OLE study objectives and endpoints

Objectives	Endpoints
FIONA	
Primary	
• To demonstrate that finerenone in addition to an ACEi or ARB is superior to placebo in reducing urinary protein excretion	• UPCR reduction of ≥30% from baseline to day 180±7[†] • Percent change from baseline in UPCR to day 180±7[†]
Secondary	
• To assess the safety profile of finerenone in addition to SOC in children with CKD compared with placebo	• Number of participants with TEAEs • Change in serum [K$^+$], serum creatinine, eGFR, and SBP from baseline to day 180±7
• To further support the efficacy of finerenone in addition to SOC in children with CKD	• UPCR reduction of ≥30% from baseline to day 180±7 • Percent change in UPCR from baseline to day 180±7 • Change in UACR from baseline to day 180±7
• To confirm the dose and systemic exposure of finerenone in children with CKD	• PK (finerenone $C_{max,md}$, $AUC_{t,md}$) based on total concentrations in plasma
• To assess the acceptability and palatability of the age-appropriate pediatric formulation	• Taste and texture of the pediatric formulation
FIONA OLE	
Primary	
• To demonstrate that finerenone in addition to an ACEi or ARB is safe when given long term	• Number of participants with TEAEs • Change in serum [K$^+$] levels from baseline to day 540±7 • Change in SBP from baseline to day 540±7
Secondary	
• To assess the long-term treatment effects of finerenone in addition to SOC on proteinuria and kidney function	• Change in UPCR and UACR from baseline to day 540±7 • Change in eGFR from baseline to day 540±7

†These two primary endpoints are not considered as co-primary endpoints and the respective other endpoint is considered as a secondary endpoint. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; $AUC_{t,md}$, area under the curve for time after multiple doses; CKD, chronic kidney disease; $C_{max,md}$, maximum observed drug concentration after multiple doses; eGFR, estimated glomerular filtration rate; [K$^+$], potassium concentration; PK, pharmacokinetics; OLE, open-label extension; SBP, systolic blood pressure; SOC, standard of care; TEAE, treatment-emergent adverse event; UACR, urinary albumin-to-creatinine ratio; UPCR, urinary protein-to-creatinine ratio.

Figure 3. Transition from FIONA to FIONA OLE study



†The list of key inclusion and exclusion criteria that must be fulfilled can be found in **Table 1**.
eCRF, electronic case report form; eGFR, estimated glomerular filtration rate; EOT, end of treatment; [K$^+$], potassium concentration; OLE, open-label extension; TEAE, treatment-emergent adverse event.

Conclusions

- FIONA is the first randomized controlled trial to investigate the efficacy and safety of finerenone combined with standard of care in children with CKD and proteinuria.
- Should a reduction in urinary protein excretion be established, it can be inferred from the adult dataset that early intervention with finerenone may reduce proteinuria and slow kidney disease progression in this population.
- Eighteen months of additional follow-up in the OLE study will provide additional information on the safety profile of finerenone; this should contribute to the understanding of the benefit-to-risk profile of using finerenone in children with CKD.

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