Cystinosis Research Foundation

Six-monthly Progress Report

(Mar 1st, 2026 – Aug 31st, 2026)

Project Title: Translational value of SGLT2 inhibitors in cystinosis

Principal Investigator: Olivier Devuyst

Co-Principal Investigator: Francesco Emma

Funding Period: September 1st, 2025 – August 31st, 2027

Specific aims (as proposed):

1. To characterize the protective effects of the SGLT2 inhibitor dapagliflozin on proximal tubular cellular pathways and to explore its potential off-target effects at the cellular and systemic levels.
2. To evaluate the species-dependent and long-term effects of SGLT2 inhibitor treatment in *Ctns*$^{-/-}$ mouse and rat models.
3. To design a first-in-human Phase II clinical trial protocol to determine the safety of the SGLT2 inhibitor dapagliflozin and its effects on proximal tubular dysfunction and renal Fanconi syndrome in young children with cystinosis and preserved renal function.

Progress toward Specific Aim 2

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This project builds on previous CRF-funded studies demonstrating that mTORC1 hyperactivation plays a key role in the pathogenesis of cystinosis-associated kidney

disease. While direct mTORC1 inhibitors have shown therapeutic potential, their clinical use is limited by significant adverse effects. Therefore, this study investigates whether the SGLT2 inhibitor dapagliflozin, which can indirectly modulate mTORC1 activity, may represent a safer therapeutic approach. The aim of the project is to evaluate the effects and underlying molecular mechanisms of dapagliflozin treatment in the *Ctns*$^{-/-}$ mouse model of cystinosis and to generate preclinical evidence supporting its future clinical translation.

As reported in the previous progress report, the initial phase of the study focused on the establishment of the experimental cohorts, the initiation of dapagliflozin treatment, and the monitoring of general health parameters, including food and water intake. Preliminary observations indicated normal feeding, supporting the good tolerability of the treatment.

Building on these initial findings, the study progressed as planned, with most experimental groups completing three months of dapagliflozin treatment. Data collected during this reporting period further confirmed the maintenance of normal food consumption.

Animals treated with dapagliflozin showed no signs of adverse effects or toxicity. Moreover, they exhibited a steady physiological increase in both body weight and body length throughout the treatment period (Figure 1A-D). Female body weight and body length are presented in Figures 1A and 1B, respectively, while male body weight and body length are shown in Figures 1C and 1D. We observed ha reduction in grooving of untreated cystinotic mice compeered to wild type, suggesting that the choice of selecting animals derived from our original breeding colony can ensure the robustness of the study.

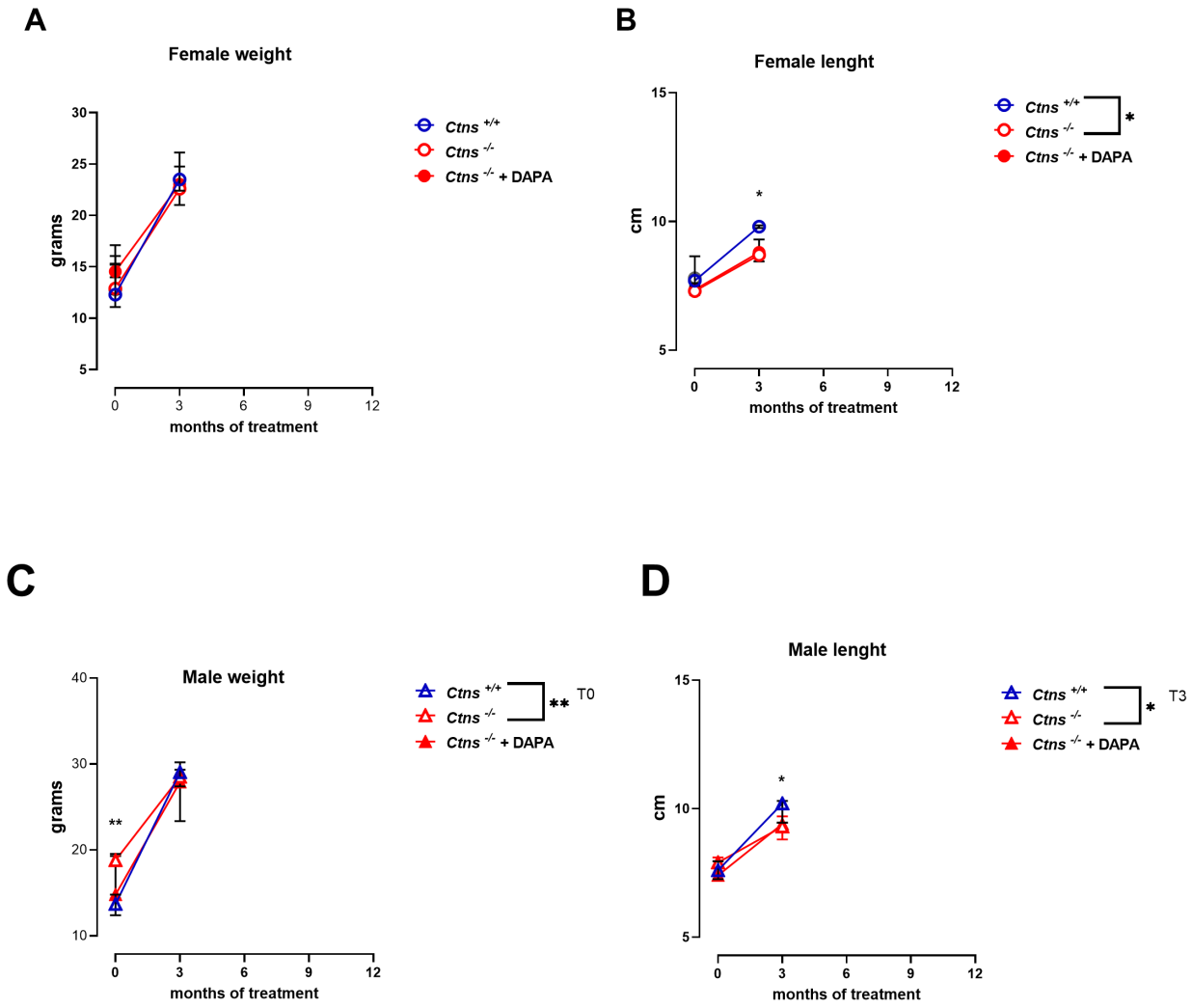


Figure 1. Body weight and length in female (A, B), and male (C, D) mice were monitored at baseline, and after three months of treatment, in *Ctns*$^{+/+}$, *Ctns*$^{-/-}$, and dapagliflozin-treated *Ctns*$^{-/-}$ mice. Data are presented as median values with interquartile range. Statistical differences among groups were analyzed using the Kruskal–Wallis test followed, when significant, by the uncorrected Dunn's test. Abbreviations: ns, non-significant; *p < 0.05; **p < 0.01.

The completion of three months of treatment represents the first major study endpoint. At this time point, urine samples were collected from all experimental groups and are currently being analyzed for markers of Fanconi syndrome. Preliminary measurements of urine output are presented in Figure 2A for females and Figure 2B for males.

SGLT2 inhibitors are known to induce polyuria. Consistent with this known effect, a mild increase in polyuria was observed after three months of dapagliflozin treatment compared with untreated animals (Figure. 2A,B).

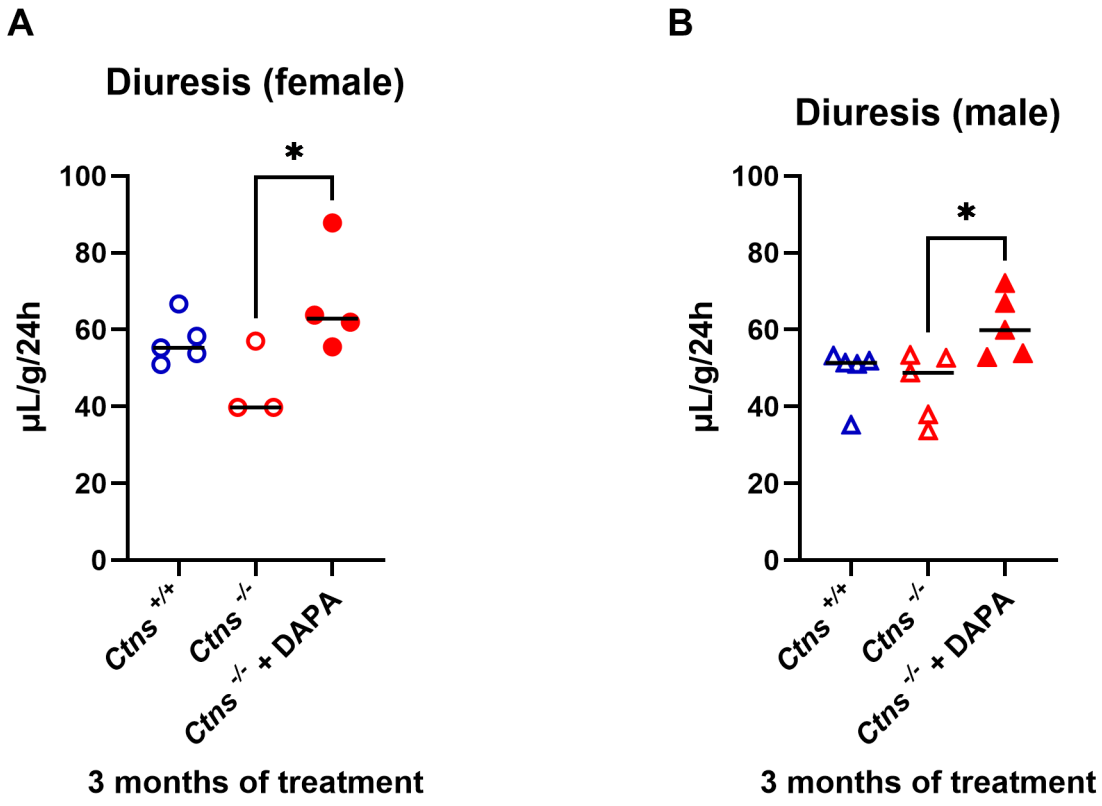


Figure 2. Levels of 24 h diuresis (A, B) normalized to body weight. Graphs showing mice individual values and line represented median value. Statistical analysis was performed using the Kruskal–Wallis test followed, when significant, by the uncorrected Dunn's test. $p < 0.05$.

The analyses currently underway will allow us to assess the impact of dapagliflozin treatment on disease progression and kidney-related outcomes. The results generated from these investigations will be reported in the next reporting period and will provide further insight into the therapeutic potential of dapagliflozin in this experimental model.