**ABSTRACT**

**Early therapy with ELX-03 to prevent progressive Fanconi Syndrome in *CtnsW138X* nonsense mutant mice. F Tohkmafshan, LL Chu M Akpa, A Hariri\* and PR Goodyer. Research Institute of the McGill University Health Centre; \* Eloxx Pharmaceuticals Inc.**

In previous studies, we observed that Eloxx aminoglycosides allow translational readthrough of the CTNSW138X nonsense mutation in cystinosis cells; this mutation arose in Ireland and was identified in regions across North America. In a preliminary clinical trial, we identified the threshold dose of subcutaneous ELX-02 (>1mg/kd), above which leukocyte cystine could be reduced. Unfortunately, this trial was prematurely curtailed by the COVID pandemic after the first 3 subjects. Based on preliminary data, we hypothesized that early treatment with doses of Eloxx compounds >1mg/kg might prevent progressive renal Fanconi Syndrome. We generated a new homozygous *CtnsW138X/W138X* mouse model using CRISPR technology and chose a founder line with the highest levels of kidney cystine. These mice develop increased excretion of retinol binding protein after 14 weeks of age. Dose-dependent increase in kidney *Ctns* transcript level and reduction of kidney cystine was evident 24 hours after s/c injection of 20-60 mg/kg ELX-03 (equivalent to 1.7-5.0 mg/kg in humans). The effect fell off significantly by 48 hours. Based on these data we are now studying the effects of early (>14weeks of age) treatment of ELX-03 (60mg/kg s/c q4days) on progressive low molecular weight proteinuria in *CtnsW138X/W138X* mice.