

Phase I Renal Impairment Trial Results Supports Targeted Individualized Dosing of ELX-02 in Patients With Nephropathic Cystinosis

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Abstract

The aim of this study was to assess the pharmacokinetics (PK) and safety of ELX-02 in a renally impaired population and apply these findings to the individualized dosing of patients with nephropathic cystinosis. This phase I renal impairment (RI; mild, moderate, or severe), single-dose, PK, and safety evaluation included 6 participants assigned to each RI group. Six healthy controls with normal renal function were matched to participants with renal impairment. All received a single subcutaneous dose of 1-mg/kg ELX-02 on day 1 and were monitored for 72 hours after dosing with serial blood and urine samples. An estimated glomerular filtration rate (eGFR)-PK model of ELX-02 was developed from the RI study data and used to implement individualized dosing in a phase 2a study in patients with nephropathic cystinosis to achieve a weekly targeted exposure (area under the plasma concentration–time curve [AUC]). In participants with RI, ELX-02 clearance decreased, and exposure increased with severity of RI. ELX-02 plasma exposure was similar to healthy controls in participants with mild RI, but increasing severity of RI resulted in significantly decreased clearance, increased maximum plasma concentration, AUC from time zero to infinity, and half-life compared to controls. ELX-02 urinary clearance showed a similar pattern. Relationships between eGFR and exposure were defined supporting individualized dose determination for prediction of dose and AUC in patients with nephropathic cystinosis, achieving overall mean \pm 10.7% of AUC targets. ELX-02 was well tolerated by RI and nephropathic cystinosis populations. ELX-02 exhibits a consistent PK profile across increasing degrees of RI with reduced clearance, increased exposure, and prolonged renal elimination proportional to reductions in eGFR. The defined relationship between eGFR and plasma exposure enabled individualized dose adjustment in patients with nephropathic cystinosis.

Keywords

eGFR, ELX-02, nonsense mutations, pharmacokinetics, renal impairment

ELX-02, an investigational drug, is a novel eukaryotic ribosomal-specific glycoside that exhibits high selectivity toward the eukaryotic ribosome and decreased binding to mitochondrial and prokaryotic ribosomes compared to other agents that permit premature stop codon (nonsense mutation) read-through.^{1,2} This selectivity enables ELX-02 dosing sufficient to induce high levels of read-through and the synthesis of functional proteins in various nonsense mutation models of disease, including nephropathic cystinosis and cystic fibrosis.^{3,4}

CTNS^{W138X} is a mutant allele on the *CTNS* gene that is a nonsense mutation in cystinosis. The translational read-through capabilities of ELX-02 have been demonstrated in multiple in vitro cell models (organoid, human bronchial epithelia cells, Fischer rat thyroid cells, plasmids) and in multiple in vivo animal mouse models. These in vivo studies indicated that repeated subcutaneous (SC) dosing of 5 to 60 mg/kg of ELX-02 for 2 to 4 weeks resulted in the dose-dependent read-through of nonsense mutations to produce full-length,

functional proteins⁴ and induces read-through of an exogenous *CTNS*^{W138X} construct and of the endogenous *CTNS*^{W138X} in patient fibroblasts.³ The enhanced selectivity of ELX-02 is also reflected in a favorable safety profile compared to other read-through agents

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without appreciable toxicity.⁵ Collectively, these results support the further evaluation of ELX-02 efficacy and safety in patients with nephropathic cystinosis and cystic fibrosis.

The human pharmacokinetics (PK) and safety of ELX-02 have been studied in 2 phase 1a studies, which were combined for analysis in a total of 60 healthy subjects that evaluated single SC doses of ELX-02 between 0.3 and 7.5 mg/kg. ELX-02 demonstrated dose linearity and proportionality in plasma PK with rapid absorption (median time to maximum concentration ranged from 0.5 to 1 hour), widespread distribution, a short half-life (\approx 2-4 hours), and 98% bioavailability. Consistent with preclinical models, excretion of ELX-02 was rapid; the primary route of excretion was in urine, with the mean percentage of ELX-02 recovered ranging from 81.1% to 99.2% for SC doses; and the mean renal clearance for SC dosing ranged between 4.6 and 6.1 L/h. ELX-02 was essentially 100% eliminated in the urine as unchanged parent compound.⁶

Since ELX-02 is being developed for patient populations with renal impairment, such as nephropathic cystinosis and cystic fibrosis, it is important to understand the effects of renal function on ELX-02 PK. Nephropathic cystinosis is a rare autosomal recessive inborn error of metabolism that leads to early end-stage renal disease and progressive multiorgan failure. Biallelic loss of the *CTNS* gene compromises cystine efflux from the lysosome, with resultant accumulation of cystine crystals in every tissue of the body; renal proximal tubular cells are particularly susceptible.⁷ ELX-02 is also under development for patients with cystic fibrosis. Patients with cystic fibrosis may demonstrate renal impairment: In a cross-sectional, observational, single-center study of 226 adult patients with cystic fibrosis in Rome, 28.8% had a reduced estimated glomerular filtration rate (eGFR) of <90 mL/min/1.73 m². In a subset of patients who had undergone lung transplants, the eGFR was significantly lower than in nontransplanted patients ($P < .001$).⁸

Dose adjustment for renally eliminated drugs is common practice for patients with renal impairment, with antibiotics, beta blockers, and diuretics being several examples.⁹ Individualized dose adjustment targets optimal exposure that achieves therapeutic goals while avoiding potential safety risks associated with drug accumulation in renal impairment (RI). To appropriately dose-adjust in patients with renal insufficiency, it is necessary to understand the relationship between renal function and exposure.

To determine the effects of mild, moderate, or severe RI on the PK and safety of single SC doses of ELX-02, we conducted a phase 1 RI study. From these data, a PK model was developed based on the relationship between degree of RI (expressed as eGFR) and ELX-

02 exposure to support targeted individualized dosing of patients with nephropathic cystinosis in a phase 2a study.

Methods

For the studies noted herein, the clinical study protocol, any relevant associated documents, and informed consent forms were reviewed and approved by the appropriate independent ethics committee or institutional review board before performing any associated study procedures. All clinical trials are listed on www.clinicaltrials.gov.

Phase I RI Study

This study was conducted in the United States between January 2019 and August 2019. This study (ClinicalTrials.gov identifier: NCT03776539) was approved by the appropriate institutional review board and was performed in accordance with the principles embodied in the Declaration of Helsinki and of the International Council on Harmonization Good Clinical Practice.

The design and conduct of this study follows the recommendation of the US Food and Drug Administration Guidance for Industry in assessing PK in patients with impaired renal function.¹⁰⁻¹²

Study Design and Treatment. This clinical investigation was a 2-center, phase 1, open-label, single-dose PK study in healthy volunteers and subjects with mild, moderate, or severe RI. The primary objective of the study was to measure the effect of RI on the PK of ELX-02. The secondary objective was to assess the safety and tolerability of ELX-02 in subjects with normal renal function and subjects with RI.

Subjects enrolled in this study were categorized into 4 groups according to their renal function (Table 1). eGFR values were calculated using the Modification of Diet in Renal Disease 4-variable equation. The study was composed of a total of 24 subjects aged 51 to 77 years with mild (n = 6), moderate (n = 6), or severe renal impairment (n = 6) and 6 healthy control subjects with normal renal function.

Subjects were screened during a 35-day screening period to establish eligibility before study drug administration. Each qualified subject received a single SC dose of ELX-02 1 mg/kg (50 mg/mL) on day 1. They remained inpatient at the clinical site under close surveillance by the site staff for 72 hours after dosing and returned for a follow-up visit on day 8 (\pm 1 day). Serial blood and urine samples were collected to evaluate ELX-02 PK. The safety and tolerability of ELX-02 was assessed based on adverse events, local reactions at the injection site, physical examination, vital signs, electrocardiogram (ECG), and clinical

Table 1. Group Classification by Renal Function

Group	Targeted Number of Subjects	Description	eGFR, mL/min/1.73 m ²
1	6	Mild decrease in GFR	60-89
2	6	Moderate decrease in GFR	30-59
3	6	Severe decrease in GFR, not requiring dialysis	<30, not requiring dialysis
4	6	Control (normal) GFR	≥90

eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate.

laboratory parameters. The subjects with mild (group 1) and moderate (group 2) RI were dosed in parallel. Groups 3 (severe RI) and 4 (normal renal function) sequentially received the study drug.

Study Participation. To be eligible for study participation, men or nonpregnant women were required to be aged 18 to 80 years and have a body mass index between 18 and 40 kg/m² and body weight of at least 50 kg for men and 45 kg for women.

We recruited subjects with RI with stable underlying diseases including diabetes, hypertension, or cardiovascular disease. Subjects with RI had to have no other conditions that might significantly impact study drug absorption or metabolism, as determined by the investigator.

We recruited healthy subjects with normal renal function who had no clinically significant history of hematologic, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, and immunologic disease.

Sample Collection for PK Analysis. The quantification of ELX-02 in human plasma and urine has been previously described.⁶ ELX-02 was quantitated using a validated high-performance liquid chromatography method with tandem mass spectrometric detection (HPLC-MS/MS) at Aptuit (Verona, Italy) using [2H₃13C]-ELX-02 as the internal standard. Chromatographic separation was performed using a Waters (Milford, Massachusetts) Acquity UPLC HSS T3, 1.8 μm 2.1 × 50 mm analytical column. Mobile phase A consisted of 5 mM ammonium format + 0.1% (v/v) heptafluorobutyric acid; mobile phase B was methanol, the flow rate was 0.4 mL/min, and temperature was set at 25°C. The run time was ≈ 1.5 minutes. An API-4000 mass spectrometer (Applied Biosystems/MDS Sciex, Foster City, California) was used for detection, with TurboIonSpray interface and multiple reaction monitoring.

A total of 13 blood samples were drawn from each subject for PK analyses at 0.25, 0.5, 0.75, 1, 2, 4, 6, 12, 24, 36, 48, 72, and 168 hours after dosing. Plasma was harvested and analyzed for ELX-02 concentration using a validated HPLC/MS-MS method. While

predose blood samples for PK were not collected in this study, the HPLC-MS/MS assay for ELX-02 quantification is validated and specific; there are no known compounds, endogenous or otherwise, that would be expected to interfere with the assay, and there has been no evidence of interference in predose samples analyzed in other clinical trials of ELX-02. Urine samples were collected for quantitation of unchanged ELX-02 at the following time intervals: before dosing and 0 to 3, 3 to 6, 6 to 9, 9 to 12, 12 to 18, 18 to 24, 24 to 36, 36 to 48, and 48 to 72 hours after dosing.

Statistical Methods. Plasma and urine ELX-02 concentration data were used to calculate PK parameters using Phoenix WinNonlin software, version 8 or higher (Certara, Princeton, New Jersey). PK and safety data were summarized descriptively by renal group. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina).

Estimated Glomerular Filtration Rate Exposure PK Model. The relationship between eGFR and PK was assessed graphically. For treatment period 1, individual subject eGFR at screening was plotted against plasma ELX-02 exposure parameters (maximum plasma concentration [C_{max}] and area under the plasma concentration–time curve from time zero to infinity [AUC_{0-inf}]). The best fit regression line was achieved by a power model. The regression equation was then used to construct a dose assignment instrument used in the study of patients with nephropathic cystinosis to calculate recommended doses for treatment periods 2 and 3, based on the prior dosing period PK (if available), and target weekly AUC.

Phase 2a Study in Patients With Nephropathic Cystinosis
This study was conducted at the McGill University Health Centre, Montreal, Quebec, Canada, between August 2019 and December 2019. This study (www.ClinicalTrials.gov identifier: NCT03776539) was approved by the appropriate institutional review board and performed in accordance with Health Canada and US Food and Drug Administration regulations, and was performed in accordance with the principles embodied in the Declaration of Helsinki and of the

Table 2. Summary of Demographic and Baseline Characteristics

Category	Renal Function Group				Overall (N = 24)
	Group 1 (Mild, N = 6)	Group 2 (Moderate, N = 6)	Group 3 (Severe, N = 6)	Group 4 (Control, N = 6)	
Age, y, mean (SD)	66.8 (5.9)	65.0 (10.4)	61.8 (8.2)	57.7 (2.1)	62.8 (7.7)
Sex, n (%)					
Female	2 (33.3)	3 (50.0)	1 (16.7)	2 (33.3)	8 (33.3)
Male	4 (66.7)	3 (50.0)	5 (83.3)	4 (66.7)	16 (66.7)
Ethnicity, n (%)					
Hispanic or Latino	5 (83.3)	6 (100)	6 (100)	5 (83.3)	22 (91.7)
Not Hispanic or Latino	1 (16.7)	0	0	1 (16.7)	2 (8.3)
Race, n (%)					
White	5 (83.3)	5 (83.3)	6 (100)	6 (100)	22 (91.7)
Black	1 (16.7)	1 (16.7)	0	0	2 (8.3)
Height, cm, mean (SD)	166.82 (8.43)	162.37 (5.30)	165.47 (8.09)	164.00 (13.28)	164.66 (8.77)
Weight, kg, mean (SD)	74.72 (7.71)	82.13 (11.16)	78.67 (16.05)	76.88 (17.88)	78.10 (13.16)
BMI, kg/m ² , mean (SD)	26.9 (2.3)	31.3 (5.5)	28.6 (4.4)	28.2 (2.3)	28.7 (4.0)
eGFR, mL/min/1.73 m ² , mean (SD)	74.7 (9.3)	40.1 (4.5)	16.9 (9.8)	100.3 (15.7)	58.0 (34.1)

BMI, body mass index; eGFR, estimated glomerular filtration rate; SD, standard deviation.

Last results (scheduled or unscheduled) obtained before drug administration were used to generate this table.

Group 1: mild impairment group (eGFR, 60-89 mL/min/1.73 m²); group 2: moderate impairment group (eGFR, 30-59 mL/min/1.73 m²); group 3: severe impairment group (eGFR, <30 mL/min/1.73 m²); group 4: control group (eGFR, ≥90 mL/min/1.73 m²). Overall: included results from all function groups.

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Study Design and Treatment. This Phase 2a inpatient dose escalation safety, PK and pharmacodynamic study was conducted in 3 patients with nephropathic cystinosis with moderate RI. The patients were homozygous for the *W138X CTNS* allele. All patients had previously undergone kidney transplants, and their baseline eGFRs ranged from 44 to 49 mL/min/1.73 m².

Study objectives included assessment of the safety, tolerability, PK, and pharmacodynamics of escalating, repeated doses of ELX-02 administered SC in patients with cystinosis carrying at least 1 nonsense mutation *CTNS* allele.

This proof-of-concept trial used individualized dose adjustment to achieve target weekly AUC values. Screening-assessed eGFR values were input to the dose assignment instrument, developed based on the eGFR-exposure PK model, to determine recommended starting dose. Subjects were administered individualized SC doses of ELX-02 once daily for 7 days in treatment period 1 (target AUC, 47.5 µg · h/mL), 7 days in treatment period 2 (target AUC, 95 µg · h/mL), and 14 days in treatment period 3 (target AUC, 190 µg · h/mL). Interim PK evaluations were performed to evaluate projected versus actual patient exposures and adjust dose escalation recommendations accordingly.

Sample Collection for PK Analysis. A total of 13 blood samples were drawn from each subject for PK analyses

at 0.25, 0.5, 0.75, 1, 2, 4, 6, 12, 24, 36, 48, 72 and 168 (Day 8) hours post-dose. Plasma was harvested and analyzed for ELX-02 concentration using a validated HPLC/MS-MS method. Urine samples were collected for quantitation of unchanged ELX-02 on day 1 of each treatment period at the following time intervals: predose (first void in the morning of day 1), 0-3, 3-6, 6-9, 9-12, 12-18, 18-24, 24-36, 36-48, and 48-72 hours postdose.

Statistical Methods. Plasma and urine ELX-02 concentration data were used to calculate PK parameters using Phoenix WinNonlin software, version 8 or higher. PK and safety data were summarized descriptively by renal group. All statistical analyses were performed using SAS version 9.3.

Results

Phase I Renal Impairment Study

Demographics and Baseline Characteristics. A total of 24 subjects were enrolled in the study, and each subject received a single SC dose (1 mg/kg) of ELX-02. A summary of demographic and baseline characteristics for all subjects is provided in Table 2. The mean (standard deviation) age overall was 62.8 (7.7) years. All subjects were aged >50 years, with most being White (91.7%) and male (66.7%). The mean (standard deviation) BMI was 26.865 (2.253) kg/m².

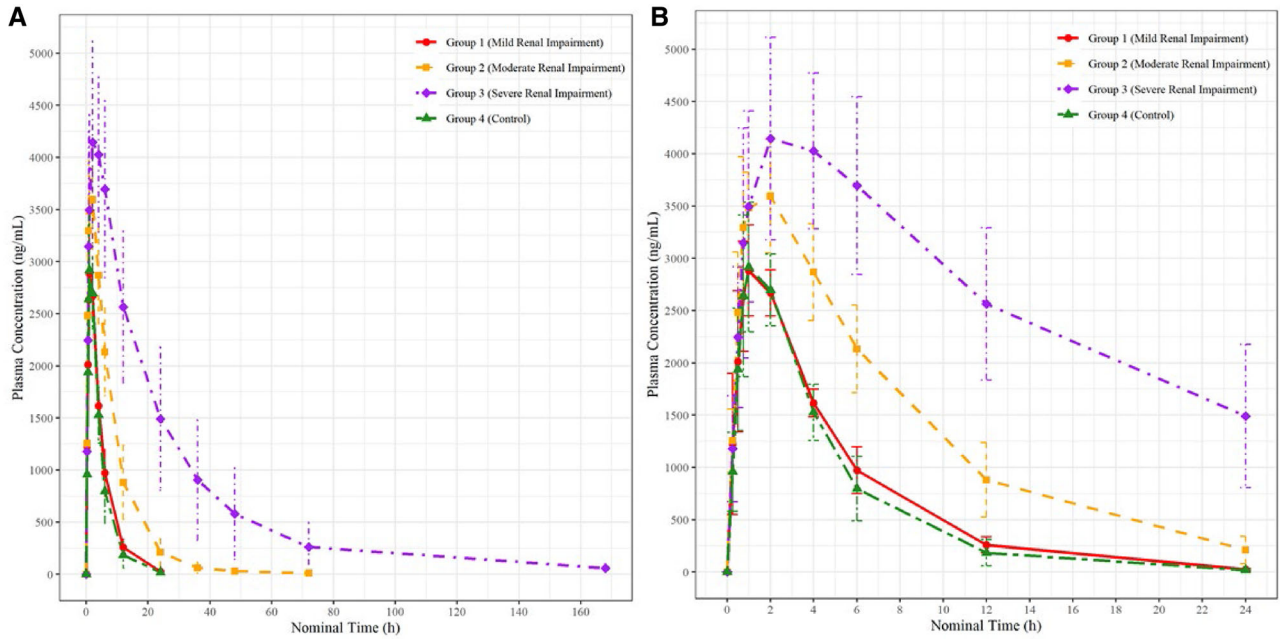


Figure 1. Mean (\pm standard deviation) plasma concentrations of ELX-02 by renal function group-linear scale (A) and with sampling truncated to 24 hours (B).

Table 3. Summary of Plasma ELX-02 PK Parameters by Renal Function Group (PK Population)

Parameter (Unit)	Group 1 (Mild, N = 6)		Group 2 (Moderate, N = 6)		Group 3 (Severe, N = 6)		Group 4 (Control, N = 6)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
AUC ₀₋₂₄ , ng • h/mL	16877.94	1714.57	32787.41	7410.46	64895.29	16967.68	15506.68	3444.66
AUC _{0-inf} , ng • h/mL	16997.41	1776.84	35179.57	9198.37	110925.53	49098.37	15214.30	2913.01
C _{max} , ng/mL	2993.33	280.33	3688.33	525.56	4273.33	947.49	2995.00	568.99
t _{1/2} , h	3.3	0.4	6.4	1.7	21.2	7.2	2.8	0.5
Cl/F, L/h	4.40	0.25	2.42	0.47	0.90	0.64	5.05	0.69
V _d /F, L	20.80	2.18	21.52	2.03	23.32	6.26	20.79	5.82

Parameter (Unit)	Group 1 (Mild Impairment, N = 6)			Group 2 (Moderate Impairment, N = 6)			Group 3 (Severe Impairment, N = 6)			Group 4 (Control, N = 6)		
	Median	Min	Max	Median	Min	Max	Median	Min	Max	Median	Min	Max
t _{max} , h	1.000	0.750	2.000	1.000	0.750	2.000	2.000	1.000	6.000	1.500	0.733	2.000

AUC₀₋₂₄, area under the plasma concentration–time curve from time zero to 24 hours; AUC_{0-inf}, area under the plasma concentration–time curve from time zero to infinity; C_{max}, maximum ELX-02 concentration; Cl/F, apparent clearance; eGFR, estimated glomerular filtration rate; PK, pharmacokinetic; SD, standard deviation; t_{1/2}, elimination half-life; t_{max}, time to maximum concentration; V_d/F, apparent volume of distribution.

Group 1: mild impairment group (eGFR, 60-89 mL/min/1.73 m²); group 2: moderate impairment group (eGFR, 30-59 mL/min/1.73 m²); group 3: severe impairment group (eGFR, <30 mL/min/1.73 m²); group 4: control group (eGFR, \geq 90 mL/min/1.73 m²).

Residual area (%) = $100 \times (1 - AUC_{0-t} / AUC_{0-inf})$.

Pharmacokinetics. The mean plasma concentration profiles for group 1 (mild impairment) and group 4 (normal) were nearly identical. The mean plasma ELX-02 C_{max} was higher in group 2 (moderate impairment) and group 3 (severe impairment) versus group 4 (normal). Likewise, the decline in plasma ELX-02 concentrations were prolonged in group 2 (moderate impairment) and group 3 (severe impairment) (Figure 1).

The mean plasma ELX-02 C_{max}, AUC, and half-life values were similar between group 1 (mild) and group 4 (normal), while they progressively increased with increasing severity of renal function in groups 2 (moderate) and 3 (severe), consistent with similar decreases in total clearance as severity of RI increased (Tables 3 and 4).

The urinary ELX-02 PK profiles were consistent with plasma, showing decreasing ELX-02 clearance

Table 4. Summary of Urine ELX-02 PK Parameters by Renal Function Group (PK Population)

Parameter (Unit)	Group 1 (Mild, N = 6)		Group 2 (Moderate, N = 6)		Group 3 (Severe, N = 6)		Group 4 (Control, N = 6)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Ae ₀₋₃ , mg	27.03	8.94	21.25	19.55	4.23	2.74	22.84	11.27
Ae ₃₋₆ , mg	13.63	7.64	15.36	5.30	9.25	5.45	30.51	14.07
Ae ₆₋₉ , mg	6.63	2.37	10.69	5.24	5.79	3.00	7.06	4.97
Ae ₉₋₁₂ , mg	2.70	0.75	7.80	4.09	5.10	1.51	3.86	2.16
Ae ₁₂₋₁₈ , mg	3.31	2.03	9.02	6.37	6.76	1.88	3.45	2.49
Ae ₁₈₋₂₄ , mg	7.56	10.47	4.06	4.21	7.57	1.65	0.75	0.63
Ae ₂₄₋₃₆ , mg	0.30	0.27	2.29	1.00	7.56	2.45	0.43	0.32
Ae ₃₆₋₄₈ , mg	0.19	0.08	0.96	0.71	4.46	1.48	0.15	0.05
Ae ₄₈₋₇₂ , mg	0.15	0.04	0.67	0.56	4.15	2.54	0.17	0.09
Ae _{0-t} , mg	61.50	19.37	72.10	26.45	54.86	8.74	69.22	17.70
R _{max} , mg/h	9.18	2.91	8.06	5.91	3.11	1.81	12.09	2.82
Fe _{0-t} , %	81.88	21.35	88.78	32.46	70.40	8.79	90.86	14.28
CL _R , L/h	3.19	0.98	1.96	0.52	0.66	0.40	4.15	0.64

Parameter (Unit)	Group 1 (Mild Impairment, N = 6)			Group 2 (Moderate Impairment, N = 6)			Group 3 (Severe Impairment, N = 6)			Group 4 (Control, N = 6)		
	Median	Min	Max	Median	Min	Max	Median	Min	Max	Median	Min	Max
T _{Rmax} , h	1.500	1.500	4.500	3.000	1.500	10.500	4.500	4.500	7.500	2.900	1.417	4.375

Ae, amount of ELX-02 excreted; CL_R, renal clearance; eGFR, estimated glomerular filtration rate; Fe, fraction of the dose excreted; PK, pharmacokinetic; R_{max}, maximum rate of excretion; SD, standard deviation; T_{Rmax}, time of the maximum excretion rate.

Group 1: mild impairment group (eGFR, 60-89 mL/min/1.73 m²); group 2: moderate impairment group (eGFR, 30-59 mL/min/1.73 m²); group 3: severe impairment group (eGFR, <30 mL/min/1.73 m²); group 4: control group (eGFR, ≥90 mL/min/1.73 m²).

with increased severity of RI. The mean values for amount of ELX-02 excreted from time zero to time of the last observation, maximum rate of excretion, and renal clearance decreased with increasing severity of RI. The median time of the maximum excretion rate was highest in group 3 (Tables 3 and 4), and there was a marked decrease in renal excretion for groups 2 and 3 compared to groups 1 and 4 (Table 4).

Estimated Glomerular Filtration Rate–PK Relationship. eGFR at screening was predictive of subject exposure, with higher C_{max} and AUC_{0-inf} values observed in subjects with lower eGFR values (Figure 2). The relationship between eGFR and AUC was generally linear at eGFR values of ≥40 mL/min/1.73 m²; however, increased variability was observed at eGFR values of ≤30 mL/min/1.73 m², corresponding to more uncertainty in the model in subjects with severe RI. A power regression yielded the best fit, with AUC_{0-inf} values exhibiting good fit (R² = 0.9245), while C_{max} exhibited higher intersubject variability and poor fit (R² = 0.4838). The relationship between eGFR and AUC was used to develop a dose assignment instrument for use in future RI patient populations.

Safety Evaluation. A summary of study drug-related treatment-emergent adverse events (TEAEs) is provided in Table 5. Most TEAEs (9/11; 82%) occurred in the control group. All TEAEs were classified as

mild in severity. There were no serious TEAEs, and no TEAEs leading to death or study discontinuation. Five healthy control subjects experienced 9 TEAEs, with the most common being injection site erythema (4; 66.7%) followed by injection site pruritus, injection site induration, decreased blood pressure, back pain, and dizziness (1 each; 16.7%). Of the 18 subjects with renal impairment, 1 subject with severe renal impairment (group 3) experienced 2 TEAEs (injection site erythema and injection site pruritus). There were no TEAEs in subjects with mild or moderate RI groups 1 and 2). There were no clinically important changes from baseline for hematology, biochemistry, coagulation, or urinalysis. There were no notable findings for ECGs or vital signs.

Phase 2a PK Evaluation in Patients With Nephropathic Cystinosis

Using the relationship described in Figure 2, a study-specific dose assignment instrument was implemented, and individualized dose adjustments were calculated to provide targeted ELX-02 exposure for each patient and each treatment period. Specifically, the initial dose was determined using each patient's screening eGFR. The higher doses in 2 subsequent treatment periods were determined based on the 24-hour PK results from the prior period to individualize doses and achieve anticipated target exposures. The dose levels, target exposures, actual day 1 exposure, estimated weekly

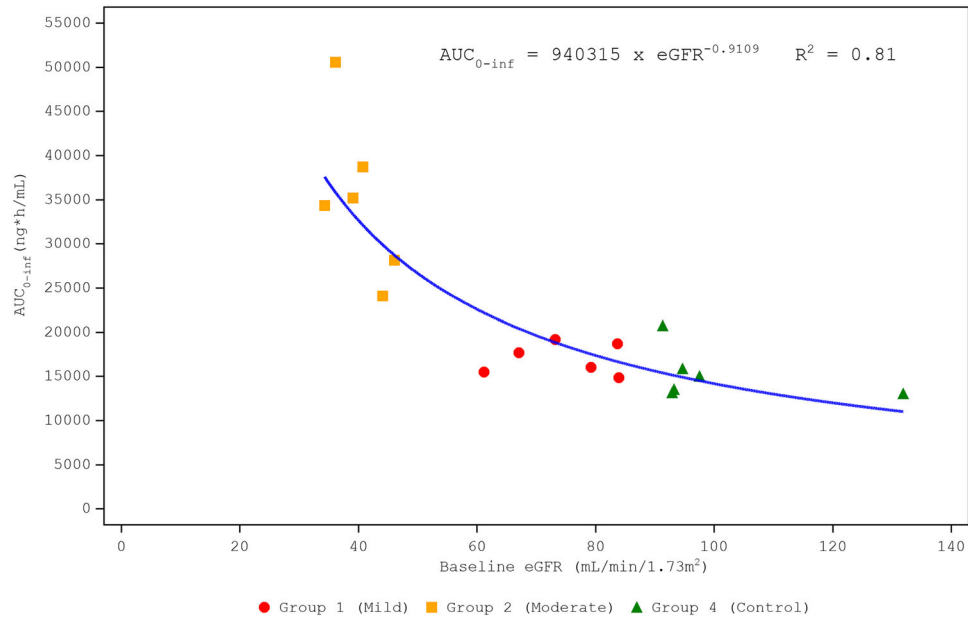


Figure 2. Individual AUC_{0-inf} vs baseline $eGFR \geq 30$ by renal function group. AUC_{0-inf} , area under the plasma concentration–time curve from time zero to infinity; $eGFR$, estimated glomerular filtration rate

Table 5. Frequency of Subjects Experiencing TEAEs and Number of Events Summarized for Each Renal Impairment Function Group

System Organ Class Preferred Term	Renal Function Group				Overall (N = 24) n (%) E
	Group 1 (Mild) (N = 6)	Group 2 (Moderate) (N = 6)	Group 3 (Severe) (N = 6)	Group 4 (Control) (N = 6)	
	n (%) E	n (%) E	n (%) E	n (%) E	
Any TEAE	0	0	1 (16.7) 2	5 (83.3) 9	6 (25.0) 11
General disorders and administration site conditions	0	0	1 (16.7) 2	5 (83.3) 6	6 (25.0) 8
Injection site erythema	0	0	1 (16.7) 1	4 (66.7) 4	5 (20.8) 5
Injection site pruritus	0	0	1 (16.7) 1	1 (16.7) 1	2 (8.3) 2
Injection site induration	0	0	0	1 (16.7) 1	1 (4.2) 1
Investigations	0	0	0	1 (16.7) 1	1 (4.2) 1
Decreased blood pressure	0	0	0	1 (16.7) 1	1 (4.2) 1
Musculoskeletal and connective tissue disorders	0	0	0	1 (16.7) 1	1 (4.2) 1
Back pain	0	0	0	1 (16.7) 1	1 (4.2) 1
Nervous system disorders	0	0	0	1 (16.7) 1	1 (4.2) 1
Dizziness	0	0	0	1 (16.7) 1	1 (4.2) 1

E, number of TEAEs; $eGFR$, estimated glomerular filtration rate; TEAEs, treatment-emergent adverse events.

Each subject could contribute only once to each of the incidence rates, regardless of the number of occurrences.

Group 1: mild impairment group ($eGFR$, 60-89 mL/min/1.73 m²); group 2: moderate impairment group ($eGFR$, 30-59 mL/min/1.73 m²); group 3: severe impairment group ($eGFR$, <30 mL/min/1.73 m²); group 4: control group ($eGFR$, ≥ 90 mL/min/1.73 m²); Overall: Included results from all function groups.

exposures, and estimated extent of reaching target exposures are shown in Table 6.

The dose assignment instrument allowed for more accurate exposure targeting based on screening $eGFR$ alone in treatment period 1: the administered doses (0.22-0.25 mg/kg) were approximately half the nominal dose originally planned. These dose levels, however, still produced AUC values that were high of target (122%). The addition of interim PK results allowed further refinement of the dose calculations, resulting in overall

mean percentage of target AUC of 104% in treatment period 2 and 98% in treatment period 3.

ELX-02 was well tolerated in these patients, with no study drug-related TEAEs or serious AEs reported.

Discussion

ELX-02, a renally eliminated investigational eukaryotic ribosomal-specific glycoside, is being developed to treat genetic diseases caused by nonsense mutations, and

Table 6. Comparison of Targeted and Actual Individual Exposures (AUC_{0-inf}) in Patients With Nephropathic Cystinosis

Subject ID	Screening eGFR	Treatment Period	Nominal/Actual Dose Level (mg/kg)	Day 1 AUC_{0-inf} (ng • h/mL)	Estimated Weekly AUC ($\mu\text{g} \cdot \text{h/mL}$)	Target Weekly AUC ($\mu\text{g} \cdot \text{h/mL}$)	Estimated % Target		
							% Target	Mean	SD
101-001	44	1	0.5/0.22	10 405	72.8	47.5	153%	122%	28%
101-005	45		0.5/0.23	7752	54.3	47.5	114%		
101-006	49		0.5/0.25	6731	47.1	47.5	99%		
101-001	44	2	1.0/0.28	14 013	98.1	95.0	103%	104%	18%
101-005	45		1.0/0.39	11 767	82.4	95.0	87%		
101-006	49		1.0/0.51	16 762	117.3	95.0	124%		
101-001	44	3	2.0/0.52	26 622	186.4	190.0	98%	98%	1%
101-005	45		2.0/0.90	26 684	186.8	190.0	98%		
101-006	49		2.0/0.79	26 332	184.3	190.0	97%		

AUC, area under the plasma concentration–time curve; AUC_{0-inf} , area under the plasma concentration–time curve from time zero to infinity; eGFR, estimated glomerular filtration rate; SD, standard deviation.

many of these patients may have some degree of RI. Recognizing the importance of dose adjustment for renally eliminated drugs in patients with RI, a phase 1 study was conducted to determine the effects of increasing severities of RI on the PK and safety of single SC doses of ELX-02. A PK model of eGFR and plasma ELX-02 exposure was prepared from the renal study data and used to assign individual dose levels to reach targeted exposures in a phase 2a PK evaluation in patients with nephropathic cystinosis.

The phase 1 RI study described herein was a standard design. Its conduct was facilitated by running the first 2 cohorts (mild and moderate RI) in parallel, followed by an exposure analysis to ensure patient safety in the severe group, and then followed by the third (severe RI) and fourth (matched normal renal function) cohorts. The mean plasma concentration profiles for group 1 (mild impairment) and group 4 (normal) were nearly identical. Mean C_{max} was higher in group 2 (moderate) and group 3 (severe) vs group 4 (normal). Likewise, the decline in plasma ELX-02 concentrations was more prolonged in group 2 (moderate) and group 3 (severe). Overall, AUC increased by about 2-fold going from normal and mild impairment to moderate impairment, and increased another 2- to 3-fold going from moderate to severe impairment. In contrast, mean C_{max} increased by only $\approx 40\%$ from the normal to severe impairment group. The normal group AUC_{0-inf} ($15.2 \mu\text{g} \cdot \text{h/mL}$) and C_{max} ($3.0 \mu\text{g/mL}$) results were consistent with those previously published (AUC_{0-inf} , $13.4 \mu\text{g} \cdot \text{h/mL}$ and C_{max} , $3.6 \mu\text{g/mL}$).⁶ Urinary clearance was consistent with plasma clearance, and the mean values for amount of ELX-02 excreted from time zero to time of the last observation and maximum rate of excretion decreased with increasing degree of RI. The differences observed across increasing degrees of RI are consistent with those expected for renally eliminated drugs.^{9,13}

The phase 2a PK evaluation applied the relationship between degree of RI (expressed as eGFR) and ELX-02 exposure to the individualized dosing of patients with nephropathic cystinosis. The results showed that not only were the initial assigned doses in treatment period 1 adjusted only based on individual eGFR values obtained at screening, much more accurate to achieve the target AUC than nominal (nearly double that of the assigned doses), but the dose assignment became more precise with the addition of interim PK results between treatment periods. These near-target projections were, in part, related to the weight-based dosing (mg/kg) used in this study. The actual exposures achieved in these patients by treatment period 3 were right on target (98%), illustrating that this approach can be applied to patient populations with RI to achieve optimal exposures.

ELX-02 was well tolerated in the phase 1 RI trial and the phase 2a nephropathic cystinosis trial. In the phase 1 RI trial, 6 of 24 subjects had 11 TEAEs, and all were classified as mild in intensity. The incidence of injection site reactions was lower than seen in previous studies.⁶ There were no serious AEs, and no TEAEs leading to death or study drug discontinuation. There were no clinically important changes from baseline for hematology, biochemistry, coagulation, or urinalysis. There were no notable findings for ECGs or vital signs. The mean AUC in subjects with severe RI was about $110 \mu\text{g} \cdot \text{h/mL}$, somewhat higher than the 7.5 mg/kg single ascending high-dose exposure of $86.9 \mu\text{g} \cdot \text{h/mL}$ observed in prior studies⁶ and was still well tolerated. Consistent with this trial, there were no study drug–related TEAEs or serious AEs reported in the phase 2a nephropathic cystinosis trial, supporting the continued development of ELX-02. Overall, the emerging safety profile of ELX-02 compares favorably to other read-through agents that cannot be used for chronic administration.⁹

Conclusions

ELX-02 shows a consistent PK profile across increasing degrees of RI with reduced clearance, increased exposure, and prolonged renal elimination time proportional to reductions in eGFR. As illustrated in patients with nephropathic cystinosis, the defined relationship between eGFR and plasma exposure enables individualized dose adjustment in patients with RI. ELX-02 was well tolerated in the phase 1 RI study and in the phase 2a nephropathic cystinosis study.

Conflicts of Interest

T.H., A.L., K.B. and M.-Y.H. are employees of Eloxx Pharmaceuticals. D.J.W. served as principal investigator for this study. K.M.P. and P.G. serve as paid consultants to Eloxx Pharmaceuticals.

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Data Availability Statement

Data presented in this article cannot be shared. For any other questions, please contact the corresponding author.

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