An Open, Single Dose, Parallel-Group Study to Evaluate the Effects of Renal Impairment on the Pharmacokinetics of ELX-02

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Background/Purpose

- ELX-02 is an investigational synthetic eukaryotic ribosomal selective glycoside (ERSG) which is optimized for translational read-through of nonsense mutations to restore production of normally localized, full-length, functional proteins.
- ELX-02 is being developed as a therapy for cystic fibrosis and nephropathic cystinosis caused by nonsense mutations.
- This study was designed to evaluate the safety and PK of ELX-02 in otherwise healthy participants with varying degrees of renal impairment.

Study Design

- Two center, Phase 1, open-label, single-dose, one-period, four parallel-group PK study in subjects with various severities of renal impairment and healthy volunteers.
- Subjects enrolled in the study were categorized into one of four groups based on their renal function (eGFR calculated using the MDRD4 equation), Table 1.

Table 1 – Subject Groups According to Renal Function

Group	Description	eGFR (mL/min/1.73m^2)	Number of Subjects
1	Mild decrease on GFR	60-89	6
2	Moderate decrease in GFR	30-59	6
3	Severe decrease in GFR, not requiring dialysis	<30; not requiring dialysis	6
4	Control (normal) GFR	≥90	6-8

- Each subject received a single SC dose of ELX-02 1 mg/kg on Day 1. They remained at the clinical site for 72 hrs post-dose and returned for a follow-up visit on Day 8.
- Serial blood and urine samples were collected to quantify ELX-02.
- The study also evaluated AEs, local reactions at the injection site, physical examinations, vital signs, ECG, markers of renal injury and clinical labs.
- Healthy subjects were matched with the renal impairment subjects by mean age (±10 years), mean BMI (±15%), and sex.

Primary Objectives

- To determine the effect of various severities of renal impairment on the plasma and urine PK of ELX-02 following a single SC dose in subjects with normal renal function, and mild, moderate and severe renal impairment.
- To assess the safety and tolerability of a single SC dose of ELX-02 in subjects with normal renal function and mild, moderate and severe renal impairment.

Results

Subject disposition/demographics

In total, 108 subjects were screened, of whom 24 were enrolled and assigned to one of four renal function groups. All enrolled subjects completed the study, Table 2.

Table 2 – Subject Disposition

Category	Statistic	Renal Function Group: Group 4 (Control)	Group 1 (Mild Impairment)	Group 2 (Moderate Impairment)	Group 3 (Severe Impairment)	Overall
Screened	N	81	9	8	10	108
Screening Failures	n (%)	75 (92.6)	3 (33)	2 (25)	4 (40)	84 (77.8)
Not Enrolled	n (%)	0	0	0	0	0
Enrolled	n (%)	6 (7.4)	6 (66.7%)	6 (75)	6 (60)	24 (22.2)
Safety Population	N	6	6	6	6	24
PK Population	n (%)	6 (100)	6 (100)	6 (100)	6 (100)	24 (100)
Completed the Study	n (%)	6 (100)	6 (100)	6 (100)	6 (100)	24 (100)

Demographic data and baseline characteristics were similar across renal function groups, Table 3.

Table 3 – Demographics

Category	Statistic	Renal Function Group: Group 4 (Control) N=6	Group 1 (Mild Impairment) N=6	Group 2 (Moderate Impairment) N=6	Group 3 (Severe Impairment) N=6	Overall N=24
Age	Mean (SD)	57.7 (2.1)	66.8 (5.9)	65 (10.4)	61.8 (8.2)	62.8 (7.7)
Sex						
Female	n (%)	2 (33.3)	2 (33.3)	3 (50)	1 (16.7)	8 (33.3)
Male	n (%)	4 (66.7)	4 (66.7)	3 (50)	5 (83.3)	16 (66.7)
Race						
White	n (%)	6 (100)	5 (83.3)	5 (83.3)	6 (100)	22 (91.7)
Black	n (%)	0	1 (16.7)	1 (16.7)	0	2 (8.3)
BMI (kg/m^2)	Mean (SD)	28.2 (2.37)	26.87 (2.25)	31.34 (5.50)	28.57 (4.46)	28.75 (3.99)
eGFR (mL/min/1.73m^2)	Mean (SD)	100.25 (15.65)	74.72 (9.25)	40.07 (4.54)	16.92 (9.77)	57.99 (34.06)
Serum Creatinine (mg/dL)	Mean (SD)	0.78 (0.15)	0.99 (0.18)	1.53 (0.35)	4.83 (2.18)	2.03 (1.97)

ELX-02 Plasma Pharmacokinetics

ELX-02 was rapidly absorbed following SC administration in all subjects, independent of renal function. Plasma ELX-02 exposure increased, and apparent clearance decreased with increasing severity of renal impairment. Decreased clearance was consistent with an increase in elimination half-life as severity of renal clearance as severity of renal impairment increased. Volume of distribution was widespread and independent of renal impairment status, Table 4 and Figure 1.

Table 4 – ELX-02 PK Parameters

	Group 4 (Control) N=6 Mean (SD)	Group 1 (Mild Impairment) N=6 Mean (SD)	Group 2 (Moderate Impairment) N=6 Mean (SD)	Group 3 (Severe Impairment) Mean (SD)
$AUC_{0\text{-}24}$ (h*mg/mL)	15150.65 (2863.42)	16877.94 (1714.57)	32787.41 (7410.46)	64895.29 (16967.68)
$AUC_{0\text{-}inf}$ (h*mg/mL)	15214.30 (2913.01)	16997.41 (1776.84)	35179.57 (9198.37)	110925.53 (49098.37)
C_{max} (ng/mL)	2995 (568.99)	2993.33 (280.33)	3688.33 (525.56)	4273.33 (947.49)
t_{max} (h)	1.45 (0.61)	1.13 (0.44)	1.29 (0.56)	2.83 (1.84)
$t_{1/2}$ (h)	2.81 (0.53)	3.28 (0.35)	6.41 (1.65)	21.82 (7.52)
Cl/F (L/hr)	5.05 (0.69)	4.4 (0.25)	2.42 (0.47)	0.90 (0.64)
V_d/F (L)	20.79 (5.82)	20.8 (2.18)	21.52 (2.03)	23.32 (6.26)

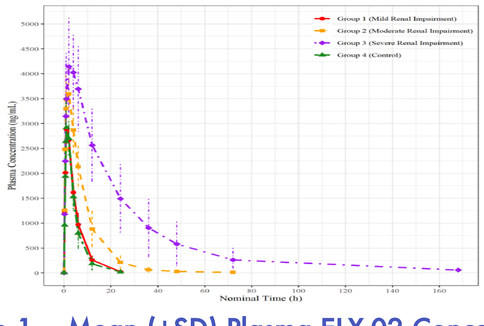

Figure 1 – Mean (±SD) Plasma ELX-02 Concentrations by Renal Function

Figure 2 shows that as degree of renal impairment increases, exposure increases and clearance decreases.

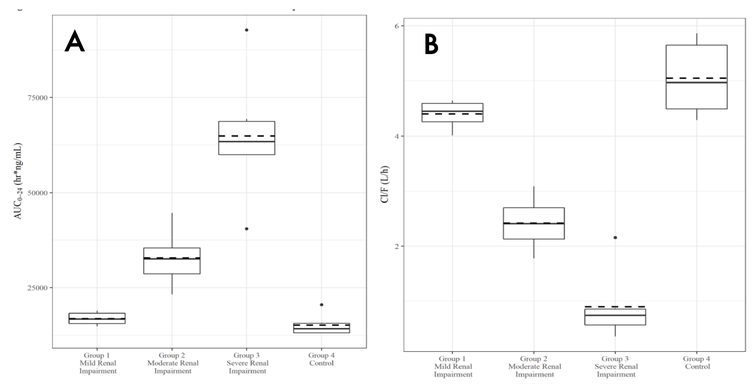

Figure 2 – Box and Whisker Plot of $AUC_{0\text{-}24}$ (A) and CI/F (B) for ELX-02 by Renal Function Group

ELX-02 Urine Pharmacokinetics

Renal clearance of ELX-02 showed similar trends as plasma, with decreasing clearance as the severity of renal impairment increased. Mean renal clearance values were 4.15 L/h in healthy subjects, compared to 3.19, 1.96 and 0.66 L/h in mild, moderate and severe renal impairment, respectively.

Safety

ELX-02 was well tolerated. There were no treatment emergent adverse events reported in Group 1 (mild) or Group 2 (moderate). One subject in Group 3 (severe) reported injection site reactions, five subjects in Group 4 (control) reported injection site reactions, blood pressure decreased, back pain and dizziness.

Conclusions

- As degree of renal impairment increased, the exposure to ELX-02 increased and its clearance decreased.
- There were no significant differences in plasma ELX-02 concentrations between the control group and the mildly impaired renal groups. $AUC_{0\text{-}24}$ was higher in the moderate and severe groups relative to the control group.
- The observed changes in plasma concentrations enable dose adjustment based on eGFR/renal function.
- Urinary ELX-02 clearance was similar to plasma clearance, with decreased rate in subjects with more severe renal impairment.
- To date, ELX-02 has been generally well tolerated in clinical studies, with 105 volunteers exposed, no reported SAEs or renal findings.
- Collectively, these data support the future evaluation of ELX-02 in Phase 2 trials with nonsense mediated diseases.