Pharmacokinetics, Safety, and Tolerability of Single Ascending Doses of ELX-02 in Healthy Volunteers, A Potential Treatment for Cystic Fibrosis Caused by Nonsense Mutations*

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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, functional, full-length proteins.
- ELX-02 is being developed as a therapy for cystic fibrosis and nephropathic cystinosis caused by nonsense mutations.
- This first in human study was designed to evaluate the safety and PK of ELX-02 single doses in healthy volunteers.

Study Design

- Two Phase 1a, randomized, double-blind placebo controlled, single ascending dose clinical trials (EL-001 and EL-006) were conducted in healthy participants to evaluate the PK and safety of single doses of ELX-02.
- Subjects were randomly assigned to one of seven cohorts (Figure 1).

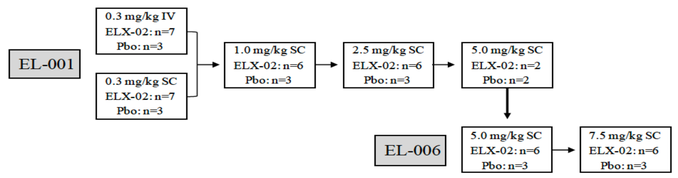

Figure 1 – Study Flowchart

- The decision to proceed to a higher dose was made based on recommendations from general and otological DSMBs based on predetermined stopping rules.
- Safety was assessed based on adverse event reporting, physical examinations, vital signs, laboratory safety data, ECGs, and auditory and vestibular assessments.

Primary Objectives

- To assess the safety and tolerability of single ascending SC administered doses of ELX-02 and of a single dose administered IV in healthy volunteers.
- To study the plasma and urine PK of single doses of ELX-02 administered either SC or IV in healthy volunteers.

Inclusion/Exclusion Criteria

Healthy female or male subjects who, at the time of screening:

- were between the ages of 18 and 45 years.
- had a BMI of 19 to 30 kg/m^2.
- had no personal (or current) history of hereditary hearing loss, persistent tinnitus, persistent imbalance, or persistent unsteadiness.
- had no evidence or history of clinically relevant diseases.
- had no presence of mitochondrial mutations predisposing the subject to aminoglycoside toxicity.

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Results

Subject disposition/demographics

In total, 86 subjects were screened. Of the 60 randomized, 40 were randomized to receive ELX-02 and 20 were randomized to receive placebo (Figure 2). Forty-two subjects were treated in Israel and 18 were treated in Belgium.

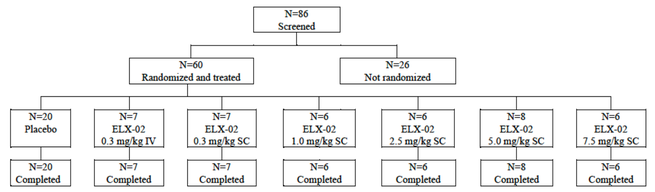

Figure 2 – Subject Disposition

Demographic data and baseline characteristics were similar across treatment groups, Table 1.

Table 1 – Demographics

Parameter	Placebo N=20	ELX-02 0.3 mg/kg IV N=7	ELX-02 0.3 mg/kg SC N=7	ELX-02 1.0 mg/kg SC N=6	ELX-02 2.5 mg/kg SC N=6	ELX-02 5.0 mg/kg SC N=8	ELX-02 7.5 mg/kg SC N=6	All ELX-02 Treatments N=40	All Subjects N=60
Gender, n (%)									
Female	7 (35.0%)	1 (14.3%)	1 (14.3%)	1 (16.7%)	0	3 (37.5%)	4 (66.7%)	10 (25.0%)	17 (28.3%)
Male	13 (65.0%)	6 (85.7%)	6 (85.7%)	5 (83.3%)	6 (100%)	5 (62.5%)	2 (33.3%)	30 (75.0%)	43 (71.7%)
Race, n (%)									
White	20 (100%)	7 (100%)	7 (100%)	6 (100%)	6 (100%)	8 (100%)	6 (100%)	40 (100%)	60 (100%)
Age, median (range) years	27.5 (20; 39)	27.0 (21; 29)	21.0 (19; 23)	22.0 (18; 27)	20.5 (19; 25)	31.0 (21; 40)	29.0 (26; 34)	24.5 (18; 40)	26.0 (18; 40)
BMI, median (range) kg/m^2	23.95 (20.1; 30.0)	23.60 (20.6; 26.6)	22.90 (20.9; 29.9)	24.15 (19.7; 26.5)	24.20 (20.5; 28.8)	24.35 (20.1; 27.5)	24.30 (21.0; 27.3)	23.75 (19.7; 29.9)	23.85 (19.7; 30.0)

N=number of subjects with available data, n=number of subjects with that observation.

ELX-02 Plasma Pharmacokinetics

PK parameters following the administration of a single dose are presented in Table 2.

Table 2 – Summary of ELX-02 Plasma PK Parameters Following Single SC Dose Administration

PK Parameter (unit)	ELX-02 0.3 mg/kg SC (N=7)	ELX-02 1.0 mg/kg SC (N=6)	ELX-02 2.5 mg/kg SC (N=6)	ELX-02 5.0 mg/kg SC (N=8)	ELX-02 7.5 mg/kg SC (N=6)
C_{max} (ng/mL)	1144±142	3576±502	8370±548	15030±1652	19605±3137
t_{max} (h)	0.50 (0.50-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
$AUC_{0\text{-}12h}$ (ng.h/mL)	3891±358	13131±1729	31153±2380	52946±6074	86891±10439
$AUC_{0\text{-}inf}$ (ng.h/mL)	3957±373	13434±1812	32546±2558	55521±7126$^{n=7}$	95177±17336$^{n=3}$
$t_{1/2}$ (h)	2.01±0.155	2.14±0.373	2.86±0.178	3.73±1.08$^{n=7}$	8.11±3.19$^{n=3}$
CL(/F)*(L/h)	5.83±0.752	5.50±0.672	5.70±0.607	6.23±0.715$^{n=7}$	5.94±1.22$^{n=3}$
Vd(/F)*(L)	16.9±2.50	16.9±3.36	23.5±2.19	33.1±8.77$^{n=7}$	70.5±33.8$^{n=3}$

Absorption of ELX-02 following a single SC dose was rapid and independent of dose, with a median t_{max} of 0.1 – 1 hour. Plasma ELX-02 exposure was dose proportional across the dose range (0.3 - 7.5 mg/kg). Elimination half-life increased with increasing dose, which was consistent with dose-dependent increases in volume of distribution, as apparent clearance remained consistent at approximately 6 L/h across the dose range.

As ELX-02 SC doses increased, ELX-02 plasma concentrations also increased in a dose proportional manner, Figure 3B.

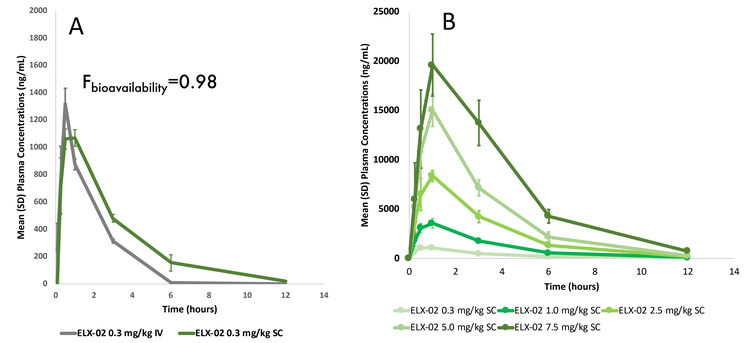

Figure 3 – Mean (±SD) ELX-02 Plasma Concentrations Vs. Time 0.3 mg/kg IV and 0.3 mg/kg SC (A) and 0.3 to 7.5 mg/kg SC (B)

ELX-02 administered SC showed linear and dose proportional AUC and C_{max} over the dose range studied.

ELX-02 Urine Pharmacokinetics

The primary route of ELX-02 elimination is renal as parent compound, Figure 4. The majority of the ELX-02 dose was excreted intact in the urine within 12 hours post-dose across the dose range.

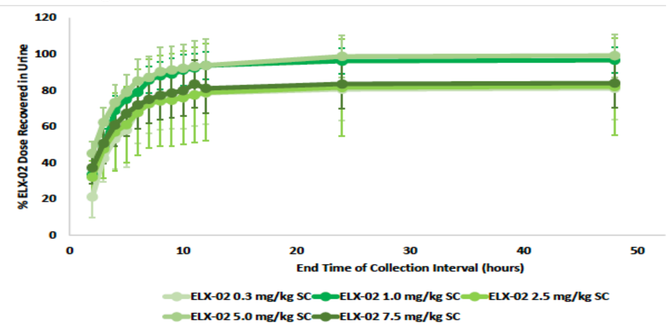

Figure 4 - Mean (±SD) Cumulative Amount Excreted in Urine vs. Time

Safety

ELX-02 was well tolerated. There were no serious adverse events, and there was no nephro- or oto- toxicity. In the ELX-02 group, 62.5% had at least one treatment emergent adverse event (TEAE), this rate was 45% in the placebo group. The most frequently reported TEAEs were injection site reactions (27.5% in ELX-02 and 10% in placebo). Additional AEs included headache, ear discomfort, and dizziness.

Conclusions

- ELX-02 shows rapid absorption, high bioavailability (98%) and linear and dose proportional PK following subcutaneous administration.
- Elimination is primarily renal as parent compound.
- To date, ELX-02 has been generally well tolerated in clinical studies, with 105 volunteers exposed, no reported SAEs or renal findings.
- The tolerability of the 7.5 mg/kg single dose supports the safety of the planned exposures and dose range being used in Phase 2.
- Collectively, these data support the future evaluation of ELX-02 in Phase 2 trials with nonsense mediated diseases.