Pharmacokinetics, Safety, and Tolerability of Multiple 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 study was designed to evaluate the safety and PK of multiple ascending doses of ELX-02 in healthy volunteers.

Study Design

- Phase 1, randomized, double-blinded, placebo controlled, multiple dose escalation study to evaluate the safety, tolerability and PK of subcutaneously (SC) administered ELX-02.
- Subjects were assigned to one of seven cohorts (Figure 1).

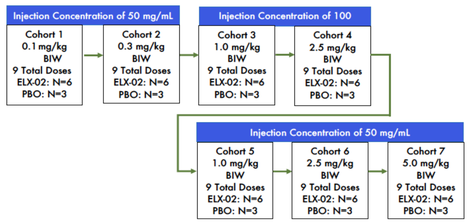

Figure 1 – Study Flowchart

- Subsequent to the 2.5 mg/kg dose, the injection solution concentration was modified from 100 mg/mL to 50 mg/mL in order to mitigate the potential for injection site reactions. Both the 50 or 100 mg/mL injection solution strengths gave similar plasma ELX-02 exposure, indicating no formulation-related differences in PK, therefore the results were combined in the analyses presented.
- The decision to proceed to a higher dose was made based on recommendations from a general and otological data safety monitoring board (DSMB) 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 multiple ascending SC administered doses of ELX-02.
- To study the plasma and urinary PK of ELX-02 administered as multiple SC doses.

Inclusion/Exclusion Criteria

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

- were between the ages of 18 and 55 years, inclusive.
- had a BMI of 19 to 32 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.

Results

Subject disposition/demographics

In total, 62 subjects were randomized, of which 41* were randomized to receive ELX-02 and 21 were randomized to receive placebo (Figure 2). Seven subjects withdrew prior to completion, 4 due to adverse events, 2 by voluntary withdrawal, and one at investigator discretion classified as “other”.

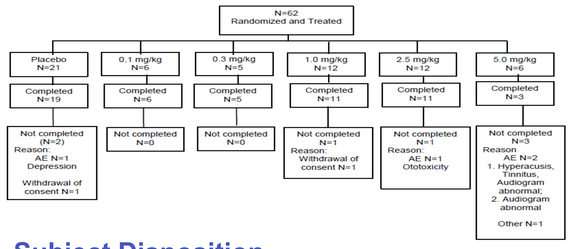

Figure 2 – Subject Disposition

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

Table 1 – Demographics

Parameter	All Placebo (N=21)	ELX-02 Dose: ELX-02 0.1 mg/kg (N=6)	ELX-02 0.3 mg/kg (N=5)	ELX-02 1.0 mg/kg (N=12)	ELX-02 2.5 mg/kg (N=12)	ELX-02 5.0 mg/kg (N=6)	All ELX-02 (N=41)
Sex, n (%)							
Male	7 (33.3)	5 (83.3)	0	4 (33.3)	2 (16.7)	3 (50)	14 (34.1)
Female	14 (66.7)	1 (16.7)	5 (100)	8 (66.7)	10 (83.3)	3 (50)	27 (65.9)
Race, n (%)							
White	19 (90.5)	6 (100)	5 (100)	12 (100)	12 (100)	0	35 (85.4)
Black	2 (9.5)	0	0	0	0	6 (100)	6 (14.6)
Age, median (range) years	40.0 (19-55)	42.5 (23-55)	32 (27-48)	37.5 (20-54)	46 (23-55)	33 (25-45)	39 (20-55)
BMI, median (range) kg/m^2	24.3 (20.3-30.3)	25.7 (21.5-27.4)	22 (19.7-27.2)	25.5 (20.7-30.4)	23.9 (19.3-30.1)	27.9 (22-29.6)	25 (19.3-30.4)

ELX-02 Plasma Pharmacokinetics

ELX-02 PK is presented in Table 2.

Table 2 – ELX-02 Plasma Pharmacokinetics

PK Parameter (unit)	Statistic	ELX-02 0.1 mg/kg SC (N=6)	ELX-02 0.3 mg/kg SC (N=5)	ELX-02 1.0 mg/kg SC (N=12)	ELX-02 2.5 mg/kg SC (N=12)	ELX-02 5.0 mg/kg SC (N=6)
Day 1						
C_{max} (ng/mL)	Mean (SD)	289.88 (60.01)	1004.60 (57.98)	2898.13 (338.44)	7736.03 (512.43)	16098.68 (2566.34)
t_{max} (h)	Mean (SD)	1.17 (0.93)	0.75 (0.18)	0.92 (0.12)	0.90 (0.13)	0.86 (0.14)
AUC_{0inf} (ng.h/mL)	Mean (SD)	1117.65 (171.03)	3152.66 (454.59)	11118.15 (1438.92)	28678.52 (4566.32)	63262.11 (13350.51)
$t_{1/2}$ (h)	Mean (SD)	2.31 (0.61)	2.06 (0.23)	2.32 (0.51)	2.87 (0.522)	2.96 (0.48)
Day 29						
C_{max} (ng/mL)	Mean (SD)	344.78 (42.2)	963.6 (72.53)	2839.64 (435.63)	7907.66 (1009.89)	15532.53 (2090.79)
t_{max} (h)	Mean (SD)	0.8 (0.27)	0.80 (0.11)	0.93 (0.12)	0.86 (0.13)	0.90 (0.14)
AUC_{0inf} (ng.h/mL)	Mean (SD)	1227.8 (183.27)	3150.02 (546.49)	10964.38 (1597.37)	30525.66 (7253.31)	55296.23 (7920)
$t_{1/2}$ (h)	Mean (SD)	2.09 (5.1)	2.39 (0.25)	2.29 (0.48)	3.00 (0.67)	3.12 (0.60)

Following single or twice weekly SC doses, ELX-02 was rapidly absorbed, with a t_{max} of approximately 1 hour, independent of dose. ELX-02 was widely distributed and rapidly eliminated with a dose-dependent $T_{1/2}$ of approximately 2-3 hours. Plasma ELX-02 exposure was dose proportional and Day 1 and Day 29 PK were similar, indicating no accumulation following the twice weekly regimen.

*Please note that based on preliminary data 42 patients randomized are listed in the abstract, however upon finalization of the database, the number was adjusted to 41.

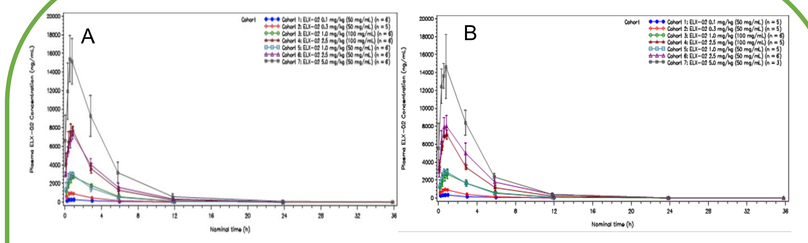

Figure 3 – Mean (±SD) ELX-02 Plasma Concentrations Vs. Time on Day 1 (A) and Day 29 (B)

Plasma concentration-time curves for Cohorts 3&5 and Cohorts 4&6, at equivalent dose levels but different injection solution strengths appear to overlap, suggesting no formulation-related differences in PK.

ELX-02 Urine Pharmacokinetics

Following Day 1 or Day 29 dosing approximately 76-94% of the ELX-02 dose was excreted unchanged as parent compound in urine within 12 hours, Figure 4.

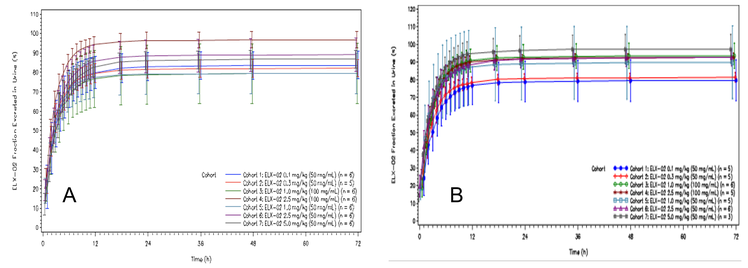

Figure 4 - Mean (±SD) Cumulative Amount Excreted in Urine vs. Time, Day 1 (A) and Day 29 (B)

Safety

ELX-02 was well tolerated. There were no SAEs or deaths. There were a total of 276 treatment emergent adverse events (TEAEs) reported across all cohorts, primarily mild in severity. Three subjects withdrew due to AEs of abnormal audiograms, which resolved or were trending toward resolution following study drug withdrawal. The most frequently reported adverse events in both the placebo and ELX-02 groups were injection site reactions; headache, ear discomfort and nasopharyngitis were also reported, Table 3.

Table 3– Adverse Events >5% in All ELX-02 Treated Subjects

Treatment-emergent Adverse Events System Organ Class Preferred Term, n (%)	All Placebo N=21	ELX-02 0.1 mg/kg SC N=6	ELX-02 0.3 mg/kg SC N=5	ELX-02 1.0 mg/kg SC N=12	ELX-02 2.5 mg/kg SC N=12	ELX-02 5.0 mg/kg SC N=6	All ELX-02 Treatments N=41
At least one TEAE	14 (66.7)	3 (50)	5 (100)	11 (91.7)	12 (100)	6 (100)	37 (90.2)
Ear discomfort	0	0	0	1 (8.3)	3 (25)	0	4 (9.8)
Diarrhea	0	0	0	2 (16.7)	1 (8.3)	0	3 (7.3)
Injection site reaction*	8 (38.1)	1 (16.7)	5 (100)	10 (83.3)	12 (100)	6 (100)	34 (82.9)
Nasopharyngitis	2 (9.5)	1 (16.7)	1 (20)	1 (8.3)	1 (8.3)	0	4 (9.8)
Headache	2 (9.5)	1 (16.7)	4 (80)	2 (16.7)	2 (16.7)	0	9 (22)

N=number of subjects with available data, n=number of subjects with that observation, TEAE=treatment-emergent adverse event
+Based on the high level preferred term

Conclusions

- ELX-02 shows linear and dose proportional PK following subcutaneous administration twice weekly.
- There were consistent and dose proportional increases in C_{max}, AUC_t, and AUC_{inf} across the dose range on Day 1 and Day 29, with no accumulation.
- Elimination is primarily renal as parent compound and is essentially complete within 24 hours postdose.
- 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 CF.
- Phase 2 trials will use the 50 mg/mL concentration with daily administration which achieves comparable exposure.