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).

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/m².
- 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, 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.

Male
Female

Figure 2 – Subject Disposition
Demographic data and baseline characteristics were similar across treatment groups, Table 1.

Table 1 – Demographics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Male (N=28)</th>
<th>Female (N=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25±4</td>
<td>25±4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75±16</td>
<td>72±18</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>180±10</td>
<td>170±12</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25±3</td>
<td>26±3</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ELX-02 SC Dose (mg/kg)</th>
<th>Elux-02 IV 0.3 mg/kg SC</th>
<th>Elux-02 IV 1 mg/kg SC</th>
<th>Elux-02 IV 2.5 mg/kg SC</th>
<th>Elux-02 IV 5.0 mg/kg SC</th>
<th>Elux-02 IV 7.5 mg/kg SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>1144±142</td>
<td>357±62</td>
<td>675±120</td>
<td>1150±165</td>
<td>1905±333</td>
<td></td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>0.50±0.10</td>
<td>0.50±0.10</td>
<td>0.50±0.10</td>
<td>0.50±0.10</td>
<td>0.50±0.10</td>
<td>0.50±0.10</td>
</tr>
<tr>
<td>AUC∞ (ng•h/mL)</td>
<td>3891±123</td>
<td>1331±127</td>
<td>2574±230</td>
<td>5294±307</td>
<td>8991±1024</td>
<td></td>
</tr>
<tr>
<td>CL/F (L/h)</td>
<td>3.83±0.72</td>
<td>5.76±0.67</td>
<td>7.05±0.67</td>
<td>6.72±0.67</td>
<td>5.45±0.46</td>
<td>4.92±0.32</td>
</tr>
<tr>
<td>tmax (h)</td>
<td>3.62±0.36</td>
<td>16.92±3.25</td>
<td>23.36±3.19</td>
<td>30.14±0.77</td>
<td>70.53±3.8</td>
<td></td>
</tr>
</tbody>
</table>

Absorption of ELX-02 following a single SC dose was rapid and independent of dose, with a median tmax 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 constant 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.

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.