**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.

**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.

**Methods**

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.

Serum 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>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>Number of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild decrease on GFR</td>
<td>60.89</td>
</tr>
<tr>
<td>2</td>
<td>Moderate decrease in GFR</td>
<td>30.59</td>
</tr>
<tr>
<td>3</td>
<td>Severe decrease in GFR, not requiring dialysis</td>
<td>&lt;30, not requiring dialysis</td>
</tr>
<tr>
<td>4</td>
<td>Control (normal GFR)</td>
<td>≥90</td>
</tr>
</tbody>
</table>

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

**Table 3 – Demographics**

<table>
<thead>
<tr>
<th>Group</th>
<th>Statistic</th>
<th>Group 1 (mild)</th>
<th>Group 2 (moderate)</th>
<th>Group 3 (severe)</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Age</td>
<td>30.7 (6.3)</td>
<td>30.8 (6.9)</td>
<td>30.7 (7.0)</td>
<td>30.7 (6.5)</td>
<td>30.7 (6.5)</td>
</tr>
<tr>
<td>Sex</td>
<td>1.1 (1.0)</td>
<td>1.1 (1.0)</td>
<td>1.1 (1.0)</td>
<td>1.1 (1.0)</td>
<td>1.1 (1.0)</td>
</tr>
<tr>
<td>BMI</td>
<td>30.7 (7.0)</td>
<td>30.7 (7.0)</td>
<td>30.7 (7.0)</td>
<td>30.7 (7.0)</td>
<td>30.7 (7.0)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.1 (1.0)</td>
<td>1.1 (1.0)</td>
<td>1.1 (1.0)</td>
<td>1.1 (1.0)</td>
<td>1.1 (1.0)</td>
</tr>
<tr>
<td>Glucose</td>
<td>1.1 (1.0)</td>
<td>1.1 (1.0)</td>
<td>1.1 (1.0)</td>
<td>1.1 (1.0)</td>
<td>1.1 (1.0)</td>
</tr>
</tbody>
</table>

**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.

**Table 4 – ELX-02 PK Parameters**

**Figure 1** shows the mean ±SD plasma ELX-02 concentrations by renal function.

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

**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. AUC0-24 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.