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.

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”.

ELX-02 Plasma Pharmacokinetics

ELX-02 PK is presented in Table 2.

Following single or twice weekly SC doses, ELX-02 was rapidly absorbed, with a t\text{max} of approximately 1 hour, independent of dose. ELX-02 was widely distributed and rapidly eliminated with a dose-dependent T\text{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.

ELX-02 Urine Pharmacokinetics

Following single or twice weekly SC doses, 0-2% of the ELX-02 dose was excreted unchanged as parent compound in urine within 12 hours, Figure 4.

Conclusions

ELX-02 shows linear and dose proportional PK following subcutaneous administration twice weekly. There were consistent and dose proportional increases in C\text{max}, AUC, and AUC\text{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 Phases 2 and 3 trials with nonselected CF patients.