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DRUG EVALUATION

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ELX-02: an investigational read-through agent for the treatment of nonsense mutation-related genetic disease

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ABSTRACT

Introduction: ELX-02, an investigational compound that is structurally an aminoglycoside analog, induces read-through of nonsense mutations through interaction with the ribosome, through which full-length functional proteins can be produced. It is being developed as a therapy for genetic diseases caused by nonsense mutations such as cystic fibrosis (CF) and nephropathic cystinosis. In Phase 1 clinical trials, 105 volunteers were exposed to ELX-02. To date, ELX-02 is well tolerated and there has been no reported treatment-related serious adverse events or deaths.

Areas Covered: The development of this molecule, from its pharmacology to the ongoing Phase 2 clinical trials is discussed.

Expert Opinion: Globally, nonsense mutations account for ~11% of all described gene lesions causing inherited monogenetic diseases. In CF and nephropathic cystinosis, they comprise from 10% to 12% of the disease-causative alleles. ELX-02 is in development as a therapeutic for patients with these alleles as *in vitro* and *in vivo* data demonstrated dose-dependent read-through of nonsense mutations to produce full-length, functional proteins. Since read-through efficiency varies between alleles and mRNA context, careful consideration of target patient populations is required. The results to date support the ongoing Phase 2 clinical evaluations of ELX-02 as a read-through agent.

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KEYWORDS
Cystic fibrosis; cystinosis; nonsense mutations; cf transmembrane conductance regulator (CFTR) gene; read-through

1. Overview of the market

Nonsense mutations are single nucleotide changes in the coding region of a DNA sequence that introduces an early (or premature) stop codon [1]. During mRNA translation, the ribosome pauses upon reaching the stop codon introduced by the nonsense mutation, which then allows termination factors to bind and signal the premature end of protein synthesis Figure 1 [2]. The resulting truncated protein products may be unstable or lack critical domains such as localization signals, which in either case results in a loss of protein function [3]. In addition to interrupting protein translation, a proof-reading mechanism known as nonsense-mediated mRNA decay (NMD) targets transcripts bearing some nonsense mutations for degradation [4]. The reduced mRNA stability resulting from NMD may reduce the steady-state expression level. Therefore, single nucleotide changes can reduce both mRNA and protein levels of essential genes. Globally, nonsense mutations account for ~11% of all described gene lesions causing inherited monogenetic diseases [1], most of which have few or no available disease-modifying therapies.

1.1. Cystic fibrosis

CF is a prevalent, monogenic, hereditary, life-shortening disorder with nearly 10% of the patient population bearing an allele carrying a nonsense mutation []. From a phenotypic standpoint, CF is a chronic, progressive, multisystem disease of secretory glands, causing severe damage primarily in the lungs and digestive systems. The disease characteristics include salty-tasting skin, poor growth, poor weight gain despite normal food intake, frequent chest infections, and coughing or shortness of breath [5–8]. CF is caused by mutations in the *cystic fibrosis transmembrane conductance regulator* (*CFTR*) gene that result in disease-causative alleles which are hereditary in transmission in an autosomal recessive pattern [9,10]. The CFTR protein functions as an adenosine triphosphate-gated anion channel that primarily transports chloride and bicarbonate ions according to their electrochemical gradients [11]. Disease severity and rate of progression in CF correlates with the amount of CFTR activity in the apical membrane of the respiratory epithelia cells [12]. Nonsense mutations generally yield no functional CFTR, and individuals carrying these alleles are typically among those with the most severe form of disease [12]. Despite great progress in the clinical availability of CFTR-directed small molecules that improve protein trafficking or channel potentiation, these CFTR protein-directed therapies are ineffective against *CFTR* nonsense alleles.

1.2. Cystinosis

Cystinosis is an ultra-rare autosomal recessive lysosomal storage disorder caused by mutations in the *cystinosin* gene (*CTNS*) which encodes the cystinosin lysosomal transporter

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Article Highlights

- ELX-02 has demonstrated dose-dependent read-through of nonsense mutations to generate full-length functional proteins in both in vitro and in vivo model systems.
- ELX-02 displays pharmacokinetics (PK) similar to that of aminoglycoside antibiotics such as gentamicin and is observed to be primarily excreted, via the kidneys, in urine as parent compound.
- To date, ELX-02 has been generally well tolerated in clinical studies, with more than 100 volunteers exposed and no reported drug-related serious adverse events.
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Box 1. Drug summary box

Drug name (generic)	ELX-02
Phase (for indication under discussion)	Phase 2
Indication (specific to discussion)	Cystic Fibrosis, Cystinosis
Pharmacology description/ mechanism of action	ELX-02 binds preferentially to the eukaryotic ribosome (improving read-through activity). Lower affinity of ELX-02 for the prokaryotic ribosome decouples the antibacterial activity from read-through activity.
Route of administration	Subcutaneous injection
Chemical structure	X H_2SO_4
Pivotal trial(s)	Phase 2 trials are ongoing

[13,14]. When left untreated, cystinosis is characterized by the pediatric onset of progressive renal insufficiency requiring dialysis or kidney transplantation by 10–12 years of age [14]. Approximately 12% of cases of cystinosis are caused by nonsense mutations [15]. Cystinosin is ubiquitously expressed and functions as a cystine-proton co-transporter, an activity required to remove cystine released from protein degradation in the lysosome [13]. Defects in cystinosin may lead to cystine accumulation and the formation of intra-lysosomal crystals. The tissues impacted, severity and age of onset are dependent upon the patient's *CTNS* genotype [16]. Mutations that result in a loss of cystine transport are associated with severe infantile presentation of the disease. Identification of mutations that inhibit transport activity can also be observed in individuals with later, juvenile onset disease suggesting that there may be additional cystinosin functions outside of cystine transport which contribute to some aspects of the disease [16]. Cystine accumulation within lysosomes can be reduced through cysteamine-mediated conversion of cystine to cysteine, which can then be removed from the lysosome [17]. The approval of cysteamine in the early 1990s and subsequent approval of extended release formulations has provided a therapeutic option for individuals with the disease. Early treatment with cysteamine bitartrate depletes intra-lysosomal cystine, helps manage the disease, and improves the outcome of cystinosis complications; however, it does not halt disease progression or kidney manifestations [18,19].

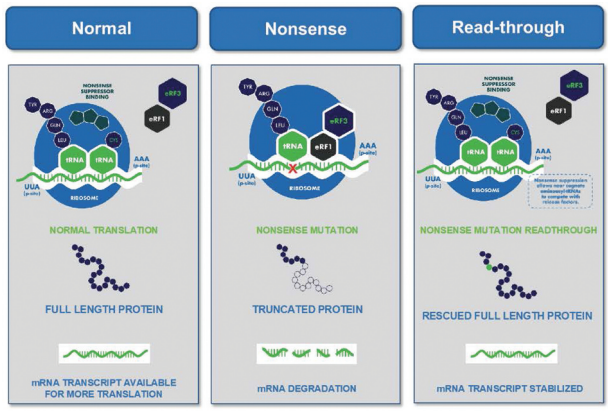

Figure 1. ELX-02 mechanism of action.

Normally, ribosomes translate mRNA to produce full-length protein and that mRNA transcript is then still available for additional rounds of translation. When a nonsense mutation is present in mRNA, the ribosome pauses upon reaching the stop codon, which then allows termination factors to bind and signal the premature end of protein synthesis. Nonsense mutations may also reduce mRNA stability by triggering NMD. ELX-02 can induce translational read-through by binding to the decoding site in the small subunit of the ribosome. This change reduces the ability of the ribosome to discriminate between cognate and near-cognate aminoacyl-transfer RNAs and increases the probability full-length protein will be produced. Read-through by ELX-02 also decreases NMD and increases the steady-state pool of transcript available to produce more protein.

2. Introduction to the compound

All studies noted herein, both in animals and in humans, have been approved by appropriate ethic committees, and all clinical trials have been listed on www.clinicaltrials.gov.

2.1. Chemistry

ELX-02 [6′-(R)-Methyl-5-O-(5-amino-5,6-dideoxy-α-L-talofuranosyl) -paromamine sulfate] Figure 2, previously referred to as NB-124 [20], is a novel small molecule, non-antibiotic aminoglycoside analog being developed for the treatment of genetic diseases caused by nonsense mutations. The drug substance is ELX-02 Sulfate, which is a white to off-white amorphous powder (Box 1).

Based on hypotheses regarding the off-target toxicities of traditional aminoglycoside antibiotics like gentamicin and G418, ELX-02 was initially synthesized in a campaign aimed at reducing affinity toward ribosomes from either prokaryotes or from eukaryotic mitochondria while maintaining or increasing affinity toward eukaryotic ribosomes in the cytosol [20–22]. This selectivity profile Figure 3 was hypothesized to improve nonsense mutation read-through while mitigating drug-induced tolerability attributed to binding to the mitochondrial ribosome. Optimization led to ELX-02 and other similar molecules showing greater read-through activity in a plasmid-based dual-luciferase assay and restoration of full length, functional protein by ELX-02 in cellular assays while simultaneously demonstrating improved cellular tolerability [20,23,24].

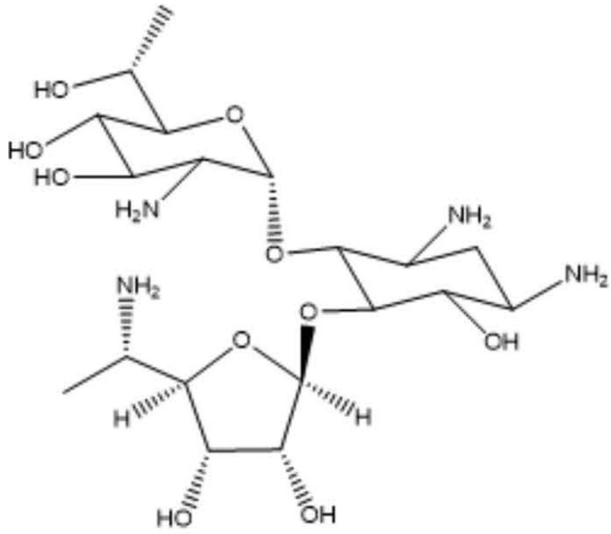

Figure 2. Structure of ELX-02.

The free base structure is illustrated. The compound has 16 chiral centers as detailed in the IUPAC name and illustrated in structural formula. The drug substance is a sulfate salt of the free base.

2.2. Pharmacodynamics

In an exemplar nonsense mutation model system, ELX-02 produced significant read-through of the premature stop codon found in *TP53* mRNA in DMS-114 cells, resulting in increased p53 protein expression and an increased mRNA content that is consistent with decreased NMD [24]. Native stop codon read-through protein products were not observed in either DMS-114 cells or in clinical samples from subjects dosed with ELX-02 in studies EL-001 or EL-006 (as described in Section 3 below). The number of native stop codon read-through proteins identified using proteomic analysis was lower than estimated and none of the read-through products identified with >2 peptides showed dose-dependent responses to ELX-02. Together, these results demonstrate significant premature stop codon read-through by ELX-02 with maintained native stop codon fidelity.

ELX-02 evaluation in multiple *in vitro* CF preclinical models (human bronchial epithelia cells, Fischer rat thyroid cells, dual-luciferase assay) demonstrated consistent read-through activity and efficacy [25]. The translational read-through capabilities and efficacy of ELX-02 have also been evaluated *in vivo*. ELX-02, administered at 30 mg/kg daily for 14 days to a CF mouse model expressing a human $CFTR^{G542X}$ transgene, achieved CFTR functional rescue superior to gentamicin and exhibited favorable pharmacodynamic (PD) properties [25].

ELX-02 read-through capabilities in cystinosis were initially demonstrated using a dual-luciferase reporter system and followed with studies in human and mouse cystinosis fibroblasts [26]. In fibroblasts from cystinosis patients homozygous for the *W138X* allele, administration of ELX-02 resulted in translational read-through of the *CTNS W138X* nonsense allele. This resultant increased protein expression reduced half-cystine levels and significantly increased *CTNS* mRNA levels. In the *CTNS Y226X* nonsense mutant mouse, 10 mg/kg ELX-02, given in 7 injections over a 3-week period, reduced kidney cell cystine levels by 30% compared with untreated animals, with no overt signs of renal toxicity [26].

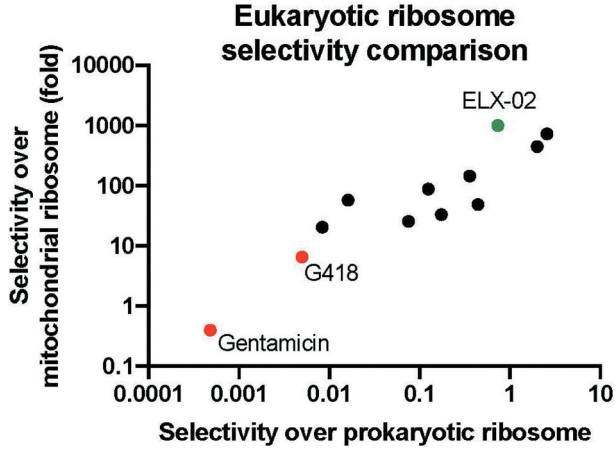

Figure 3. Comparison of eukaryotic ribosome selectivity for Gentamicin, G418, and ELX compounds.

Data were adapted with permission from Kandasamy et al., J Med Chem 13 December 2012;55(23):10,630–43. Copyright 2012 American chemical society. The upper right quadrant represents the target selectivity profile for compounds to induce read-through activity while not eliciting off-target activity. ELX-02 is shown as a green dot, other ELX molecules shown as black dots, and the reference compounds Gentamicin and G418, with their unfavorable toxicity profile, indicated using red dots.

2.3. Preclinical pharmacokinetics, metabolism and toxicology

Nonclinical studies demonstrate that ELX-02 does not undergo hepatic metabolism and is not a cytochrome p450 (CYP) substrate, inducer, or inhibitor. Single and repeated subcutaneous administration of ELX-02 display PK similar to that of aminoglycoside antibiotics such as gentamicin, and is similarly observed to be primarily excreted, via the kidney, in urine as parent compound [25–27]. However, in contrast to traditional aminoglycoside antibiotics, preclinical toxicology assessments demonstrated a reduced potential for nephrotoxicity and ototoxicity with chronic use of ELX-02 in accordance with the observations published in preclinical pharmacology studies [25,26].

3. Clinical studies

To date, ELX-02 has been evaluated in multiple Phase 1 clinical trials and has progressed to Phase 2 evaluation in cystinosis and CF Table 1.

3.1. Phase 1 studies study EL-001/006: 'Two phase 1a, randomized, double-blinded, placebo-controlled, single dose escalation studies to evaluate the safety, tolerability, and pharmacokinetics of ELX-02 in healthy adult subjects'

Studies EL-001 (NCT02807961) and EL-006 (NCT03292302) were Phase 1, randomized, double-blind, placebo-controlled, single-dose, dose escalating studies in healthy adult males and females [28]. In these studies, five ELX-02 doses were assessed: 0.3, 1.0, 2.5, 5.0, and 7.5 mg/kg. The 0.3 mg/kg dose was assessed as intravenous (IV) and subcutaneous (SC)

Table 1. ELX-02 doses and concentrations administered in phase 1 and 2 clinical studies.

Study No.	Population	Phase	Cohort	Dose	Number of Doses	Number Enrolled	Route of Administration
EL-001/EL-006	Healthy Adult Volunteers	1	1	0.3 mg/kg	1	7	IV
			2	0.3 mg/kg	1	7	SC
			3	1.0 mg/kg	1	6	SC
			4	2.5 mg/kg	1	6	SC
			5	5.0 mg/kg	1	8	SC
			6	7.5 mg/kg	1	6	SC
EL-002*	Healthy Adult Volunteers	1	1	0.1 mg/kg	9	6	SC
			2	0.3 mg/kg	9	5	SC
			3	1.0 mg/kg	9	6	SC
			4	2.5 mg/kg	9	6	SC
			5	1.0 mg/kg	9	6	SC
			6	2.5 mg.kg	9	6	SC
			7	5.0 mg/kg	9	6	SC
EL-008	Adults with Various Degrees of Renal Failure/ Healthy Adult Volunteers	1	N/A	1.0 mg/kg	1	24	SC
EL-003**	Patients with Nephropathic Cystinosis with One or More CTNS Nonsense Mutation	2	1	0.5 mg/kg	7	3	SC
			2	1.0 mg/kg	7		
			3	2.0 mg/kg	14		
EL-004	Patients with Cystic Fibrosis with at Least One G542X Allele	2	1	0.3 mg/kg	7	Up to 16	SC
			2	0.75 mg/kg	7		SC
			3	1.5 mg/kg	7		SC
			4	Individualized up to 3.0 mg/kg	14		SC
EL-012	Patients with Cystic Fibrosis with at Least One G542X Allele	2	1	0.3 mg/kg	7	Up to 16	SC
			2	0.75 mg/kg	7		SC
			3	1.5 mg/kg	7		SC
			4	Individualized up to 3.0 mg/kg	14		SC

*Subsequent to the 2.5 mg/kg dose, the diluted injection solution concentration was modified from 100 mg/mL to 50 mg/mL in order to mitigate the potential for injection site reactions

**Nominal doses to achieve individualized exposures.

formulation to determine absolute bioavailability. The placebo control consisted of either IV infusion or SC injection of normal saline at matching appearance and volumes. In total, 86 subjects were screened, of which 40 were randomized to receive ELX-02 and 20 were randomized to receive placebo. Single administration of ELX-02 either as an IV infusion over 30 minutes (dose of 0.3 mg/kg) or SC injection (doses of 0.3 to 7.5 mg/kg) resulted in a rapid maximum plasma concentration with a median t_{max} of 0.5–1 h. Using non-compartmental models, the mean terminal plasma half-lives ($t_{1/2}$) were about 2 h for IV treatment and the two lowest SC doses (0.3 and 1.0 mg/kg), 3–4 h for 2.5 and 5.0 mg/kg SC and 8 h for 7.5 mg/kg SC. The estimated absolute bioavailability was 0.98. After IV infusion the mean percent of ELX-02 recovered in urine during the first 12-hours post-start of infusion was 83.3% increasing to 85.2% at the 48 h time point. Similarly, for SC administration mean percent of ELX-02 recovered in urine within the first 12 h ranged from 78.5% to 93.8%, increasing to 81.1% and 99.2% at 48-h post-dose. The relatively short plasma half-life ($t_{1/2}$) and rapid renal excretion profile are supportive of a daily dosing paradigm.

3.2. Study EL-002: 'A phase 1, randomized, double-blinded, placebo-controlled, third party open, multiple dose escalation study to evaluate the safety, tolerability and pharmacokinetics of subcutaneously administered ELX-02 in independent consecutive cohorts of healthy subjects'

Study EL-002 (NCT03309605) was a Phase 1, randomized, double-blind, placebo-controlled, study during which sequential cohorts of healthy male and female adult volunteers received multiple doses of ELX-02 or placebo administered SC twice weekly (BIW) for 29 days to evaluate the safety, tolerability, and PK of ELX-02. In this multiple ascending dose study, five ELX-02 doses (0.1, 0.3, 1.0, 2.5, and 5.0 mg/kg) with two injection concentrations (50 mg/mL and 100 mg/mL) were assessed across seven cohorts. A total of 62 subjects were randomly assigned to ELX-02 treatment in the study. The results of this study were consistent with Study EL-001 and EL-006 and indicated dose proportional PK without evidence of accumulation. Elimination was reconfirmed as being primarily renal as parent compound and was essentially complete within 24 h post-dose. The results of this study were presented at the North American Cystic Fibrosis conference in 2019 [29] and are currently in preparation for publication.

3.3. Study EL-008: 'A phase 1, open-label, single-dose, parallel-group study to evaluate the effects of renal impairment on the pharmacokinetics of ELX-02'

Study EL-008 (NCT03776539) was a two-center, Phase 1, open-label, single-dose, four-parallel-group, PK study in subjects with mild (Group 1 [estimated glomerular filtration rate (eGFR) 60–89 mL/min/1.73 m^2]), moderate (Group 2 [eGFR 30–59 mL/min/1.73 m^2]), or severe (Group 3 [eGFR <30 mL/min/1.73 m^2, not requiring dialysis]) renal impairment, and matched healthy volunteers with normal renal function (Group 4 [eGFR ≥90 mL/min/1.73 m^2]) as the control. Overall, 108 subjects were screened. Twenty-four subjects were enrolled, six subjects in each group. All 24 subjects received a single SC dose of 1.0 mg/kg ELX-02 and

completed the study. In this study, as the degree of renal impairment increased, ELX-02 clearance decreased, and exposure increased. There were no significant differences in plasma ELX-02 concentrations between the control group and the mildly impaired renal group. The area under the plasma concentration–time curve over the last 24 h dosing interval (AUC_{0-24}) 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. These results were presented at the American Society of Nephrology Kidney Week in 2019 [30] and are in preparation for publication.

3.4. Phase 2 studies

Three Phase 2 clinical trials with ELX-02 have recently commenced: two in CF (EL-004 [NCT04126473] and EL-012 [NCT04135495]), and one in nephropathic cystinosis (EL-003, NCT04069260). Studies EL-004 and EL-012 are Phase 2 studies in CF patients with at least one *CFTR G542X* allele. In these studies, which are of a similar design, up to a total of 24 patients will receive four escalating doses of ELX-02 administered SC: 0.3 mg/kg for 7 days, 0.75 mg/kg for 7 days, 1.5 mg/kg for 7 days and then an individualized dose for 14 days. These studies are currently enrolling in Israel and Europe (EL-004) and the US (EL-012). Study EL-003 is a Phase 2 clinical trial in patients with nephropathic cystinosis bearing one or more *CTNS* gene nonsense mutations. This study was terminated early due to study design limitations which made it difficult to fully evaluate ELX-02-mediated white blood cell cystine reductions. The results are in preparation for publication and possible study design improvements to reduce confounding factors are under consideration.

4. Safety and tolerability

In the Phase 1 clinical trials, 105 volunteers have been exposed to ELX-02. To date, ELX-02 has been well tolerated with no reported treatment-related serious adverse events or deaths. The most frequently reported adverse events across studies were injection site reactions which were minimized with reduced injection solution concentration [29]. Other adverse events reported included headache, ear discomfort, nasopharyngitis, and diarrhea. In the multiple ascending dose study (EL-002), three subjects withdrew due to AEs of abnormal audiograms, which either had resolved or trended toward resolution upon follow-up [29]. Of the three, one subject out of twelve received ELX-02 at 2.5 mg/kg and two subjects out of six received ELX-02 at 5.0 mg/kg. In all cases, the hearing changes observed were not clinically significant. There were no notable trends observed in clinical safety laboratory tests, vital sign measurements, electrocardiograms, or physical examination findings among the different treatment groups compared to placebo. There have been no decreases in kidney function indicative of nephrotoxicity as measured by serum creatinine in any subject [28–30]. As ELX-02 is a non-antibiotic aminoglycoside analog, the reversibility of the limited auditory findings and lack of observed nephrotoxicity supports the central hypothesis of increased tolerability with improved ribosomal selectivity.

5. Conclusion

ELX-02 is a non-antibiotic, aminoglycoside analog developed for the treatment of genetic diseases caused by nonsense mutations. Preclinical studies demonstrated a dose-dependent read-through of nonsense mutations in either *CFTR* or *CTNS* to generate full-length, functional protein. To date, ELX-02 has been generally well tolerated in Phase 1 clinical studies, with more than 100 volunteers exposed, no reported drug-related serious adverse events or renal findings and limited, reversible, auditory findings. Collectively, these data support the ongoing evaluation of ELX-02 in Phase 2 trials with nonsense mutation-mediated diseases.

6. Expert opinion

Nonsense mutations account for ~11% of all described gene lesions causing inherited monogenetic diseases [1]. Consistent with this estimate, *CFTR* nonsense mutations comprise nearly 10% of the mutated alleles in individuals with CF worldwide []. Nonsense mutations may cause the production of a truncated protein and destabilize mRNA, resulting in no or minimal CFTR function. So far, no effective therapy is available for these nonsense mutations and it remains an area of high unmet clinical need. ELX-02, a novel, small molecule, non-antibiotic aminoglycoside analog, is being developed for the treatment of genetic diseases that are caused by nonsense mutations. ELX-02 induces read-through of nonsense mutations by interacting with the ribosome, through which full-length functional proteins can be produced. The fidelity of premature stops codon translation termination and ability to achieve compound-induced read-through are dependent on a variety of factors, including the identity of the stop codon and its surrounding mRNA context [31]. Since read-through efficiency varies between alleles, as well as mRNA context, the careful consideration of target patient populations is required.

Suppression of premature stop codons is mediated by the base pairing of a near-cognate aminoacyl-tRNA with the stop codon and subsequently, the amino acid becomes incorporated into the nascent polypeptide at this location. Local mRNA sequence context plays a key role in near-cognate aminoacyl-tRNA selection. Inducing read-through promotes insertion of amino acids that may differ from the natural amino acid [32], thus resulting in mutated proteins that may retain function and respond to CFTR modulators to further boost efficacy and treatment responsiveness.

Other translational read-through inducing drugs have previously been evaluated in the clinic in CF patients. Gentamicin, a relatively inefficient read-through agent, was delivered either systemically or via nasal drops and demonstrated read-through efficacy sufficient to correct CFTR electrophysiology [33–35]. However, traditional aminoglycoside antibiotics like gentamicin cannot be used as a systemic, long-term therapy due to nephrotoxicity and ototoxicity following uptake and accumulation in renal proximal tubules and cochlear hair cells, respectively [36,37]. Systemic administration of ELX-02

provides an opportunity to suppress the nonsense mutation found in *CFTR* and augment CFTR function in all affected organs to yield clinical benefit. To date, ELX-02 which is an aminoglycoside analog with no antibiotic properties, has shown an acceptable safety profile without severe or serious drug-related adverse events [28]. These potential TEAEs and interactions with nonsteroidal anti-inflammatory drugs or aminoglycoside antibiotics when co-administered, need to be closely monitored as clinical studies progress.

Ataluren (PTC124) is another investigational small molecule drug designed to overcome nonsense mutations by inducing selective ribosomal read-through. While early trials showed promise [38–40], ataluren failed to demonstrate efficacy in the primary pulmonary endpoints evaluated in a Phase 3 clinical trial in patients with CF [41,42]. A potential confounding effect in the initial Phase 3 patient population was observed as a subgroup analysis indicated a notable treatment effect in individuals not receiving inhaled tobramycin. Ultimately, inclusion criteria permitting enrollment of patients with any CF causative nonsense mutation despite the differences in read-through potential and NMD across alleles and individuals may have led to challenges in reaching the primary endpoint in the larger trials. Pairing a more potent read-through molecule in nonsense patient populations bearing responsive alleles provides an opportunity to meet the unmet need in this patient population.

Overall, the results to date support the ongoing clinical evaluation of ELX-02 as a read-through agent for CF, cystinosis, and other nonsense-mediated genetic diseases. Following completion of the Phase 2 clinical studies which are underway, confirmatory trials will need to be conducted to demonstrate treatment efficacy.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Declaration of interest

E. Kerem reports serving in an advisory role to Eloxx Pharmaceuticals as a Senior Consultant and receiving personal fees for those services in addition to serving as Global Lead Investigator for Phase 2 ELX-02 cystic fibrosis trials. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

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