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Translational read-through of CFTR nonsense mutations and inducement of cystic fibrosis transmembrane conductance regulator (CFTR) function by ELX-02 treatment

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Cystic fibrosis is an autosomal recessive hereditary disease. Approximately 10% of the mutations are nonsense mutations. A strategy that addresses the defect caused by nonsense mutations is to induce readthrough of the premature termination, leading to translation of a full-length CFTR protein. Translational Readthrough Inducing Drugs (TRID’s) have been shown in vitro, in vivo, and in human subjects to improve CFTR activity and sweat chloride. Elixir is developing ELX-02, a TRID that enables the translation of full-length functional proteins. The effect of ELX-02 on CFTR activity was tested in Fisher Rat Thyroid (FRT) epithelial cells stably transfected with human CFTR542X or CFTRR117H, primary CF-patient derived bronchial epithelial (HBE) cultures (CFTR542X: Patient 50%); and a CF mouse model, expressing human CFTR542X. ELX-02 treatment increased the forskolin-induced transepithelial conductance in FRT cultures in a dose-dependent fashion, approaching that observed with G418 positive control; this was further augmented with the CFTR potentiator ivacaftor (VX-770). In HBE primary cells, ELX-02 induced a dose-dependent increase in short circuit current to 270% of non-treatment control, after 48-h incubation. Efficacy was again further enhanced (~2.5-fold) by addition of the CFTR potentiator, ivacaftor. Incubation of ELX-02 with or without VX-770 for up to 4 days resulted in a more pronounced effect on forskolin dependent CFTR activity. ELX-02 effect on CFTR activity was not affected by co-treatment with tobramycin, amikacin, neomycin or gentamicin. Lastly, repeated bi-weekly administration of ELX-02 to G542X transgenic mice for 4-week resulted in 4.6-fold increased CFTR current measurements compared to control; reflecting 12.6% of CFTR activity observed in wild type mice. Taken together, ELX-02 treatment restored ion transport activity and it rescued CFTR function in a CF mouse model; thus, providing a potential approach for life-long treatment of this genetic disease.