PTC124: SCIENTIFIC BACKGROUND

PTC124 is a first-in-class, orally delivered, investigational new drug for the treatment of genetic disorders resulting from nonsense mutations. Genetic disorders occur as a consequence of mutations in an individual's DNA. Nonsense mutations are single-point alterations in the DNA that prematurely halt the translation process, producing a truncated, nonfunctional protein. PTC124 is a unique drug that allows the cellular machinery to bypass the nonsense mutation and continue the translation process, restoring the production of full-length, functional protein.

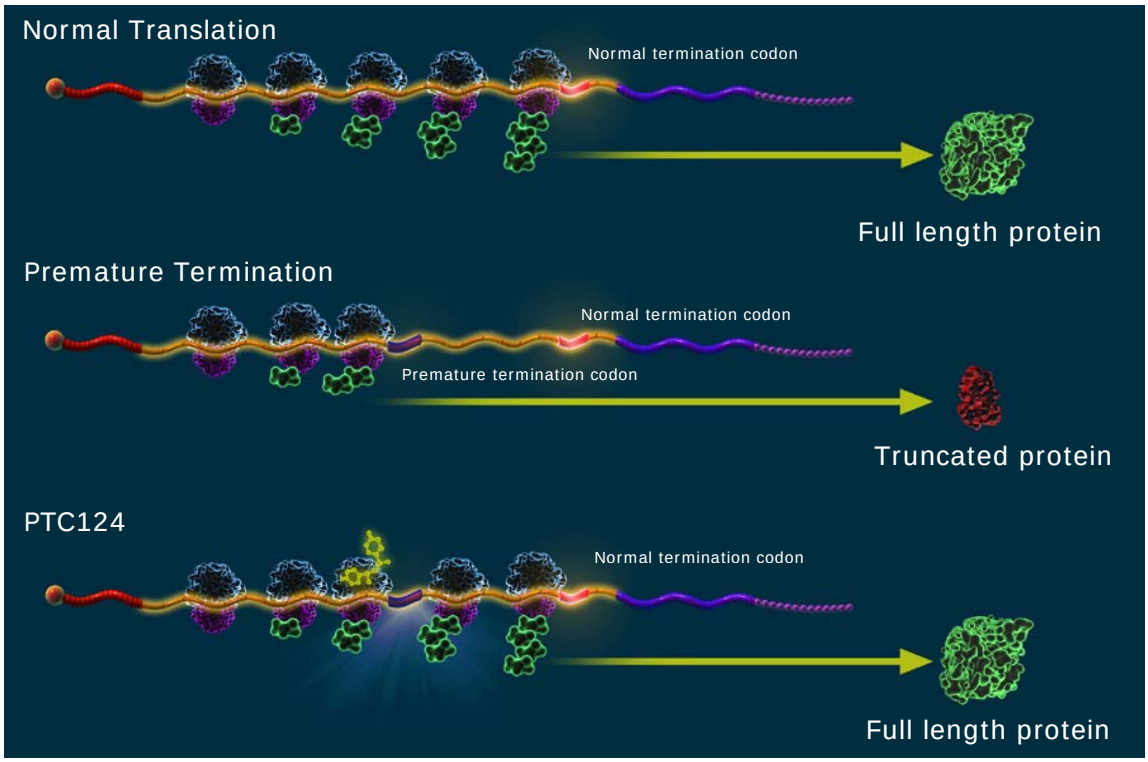

Figure 1. Comparison of normal translation, premature translation and treatment with PTC124 restoring full length protein synthesis

The National Institutes of Health (NIH) Office of Rare Diseases estimates that genetic disorders are responsible for the majority of rare diseases and that these diseases afflict 25 million people in the US. It is estimated that, on average, 5-15% of patients with any of at least 1,800 distinct genetic disorders have a nonsense mutation as an underlying cause of the disease.

The aminoglycoside antibiotic, gentamicin, has been shown to read through premature termination codons and has been evaluated as a potential treatment for genetic disorders caused by nonsense mutations. However, use of gentamicin for this purpose is limited by the need for intravenous administration and the potential for serious renal and otic toxicities. PTC124 is a new chemical entity unrelated to gentamicin and without antibacterial properties. It is an orally bioavailable drug which, in preclinical studies, is well tolerated even at dose levels much higher than those required to promote read-through of disease-causing nonsense mutations.

PTC124 induces up to 12-fold read-through of premature stop codons in cell culture studies, with activity observed at concentrations ranging from 0.1 to 3 μM. In similar experiments, gentamicin produces only a 2-fold maximal induction at concentrations a hundred times higher. PTC124 is active in the same muscular dystrophy and cystic fibrosis preclinical models that have provided the rationale for early clinical research with gentamicin.

In cell culture assays, the drug has demonstrated premature stop-codon read-through in primary cultured myotubes derived from the mdx muscular dystrophy mouse (Figure 2).

In in vivo experiments, oral administration of PTC124 to mdx mice has resulted in production of dystrophin protein in skeletal muscles, as measured by immunofluorescence. Similarly, in a mouse model of cystic fibrosis, treatment with PTC124 has generated full-length immunofluorescence evidence of CFTR in duodenal glands (Figure 3). This increase in CFTR resulted in chloride channel activity that is otherwise deficient in these animals (Figure 3).

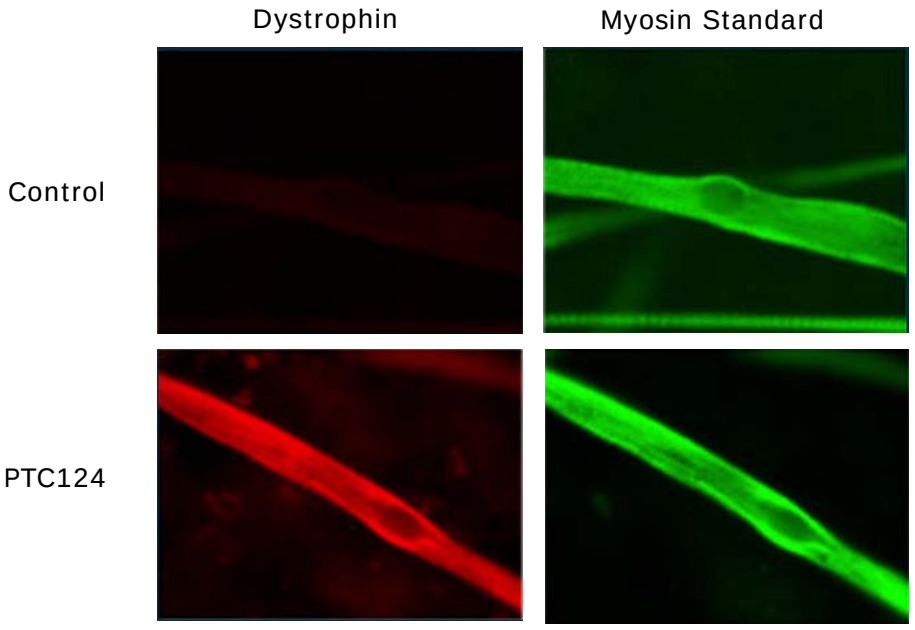

Figure 2. Immunofluorescence staining of dystrophin protein in myotube culture (left) and mdx mice (right).

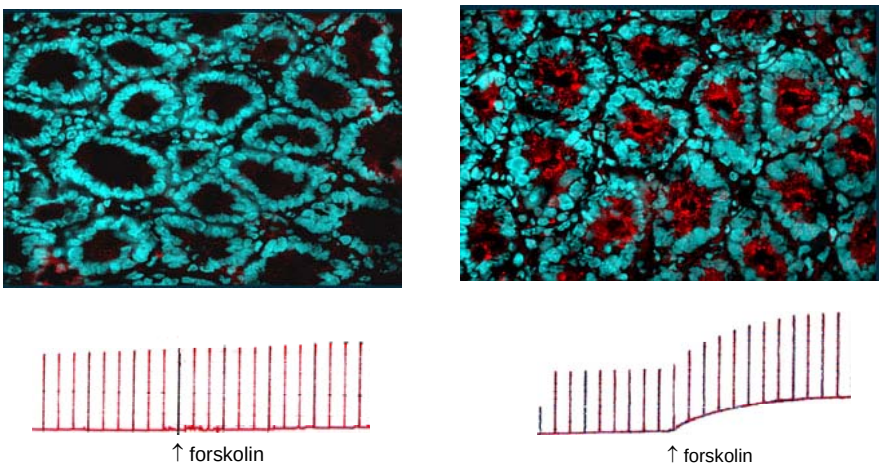

Figure 3. Immunofluorescence staining of CFTR in duodenal glands and forskolin-induced ion channel activity from homozygous CFTR-/- mice.

PTC124 has recently completed Phase 1 studies in healthy volunteers. Results have confirmed that the drug is orally bioavailable, generally well tolerated and safely achieves target plasma concentrations. Pharmacokinetic modeling of the Phase 1 results has allowed development of a dosing regimen for the planned Phase 2 studies in cystic fibrosis (CF) and Duchenne muscular dystrophy (DMD). Patients with these diseases who have gene-sequencing confirmation of a nonsense mutation as the basis for the disorder will be considered for study enrollment. Pending concurrence from regulatory authorities, Phase 2 studies in patients with CF and DMD are planned for the third quarter of 2005. In the Phase 2 studies, the activity of the drug in restoring full-length production of the missing disease-specific proteins will be assessed. PTC is working with patient advocacy groups and other organizations to develop studies of PTC124 in the US and in other regions of the world.

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