

# *ataluren*

OVERVIEW

A New Approach to Genetic Disorders

# Ataluren Scientific Background

## WHAT IS ATALUREN?

*Ataluren* (formerly PTC124) is the first investigational therapy with the potential to enable the formation of a functioning protein in patients with genetic disorders due to a nonsense mutation.

A nonsense mutation is an interruption in the genetic code that prematurely halts the synthesis of an essential protein. *Ataluren* is currently being investigated for use in patients with nonsense mutation Duchenne muscular dystrophy (nmDMD) and nonsense mutation cystic fibrosis (nmCF).

## ATALUREN MECHANISM OF ACTION

In healthy individuals, ribosomes translate the informational code in the mRNA into protein until arriving at a stop signal in the mRNA, at which point the ribosome stops translation and a functioning protein results.

Nonsense mutations, however, create a premature stop signal in the mRNA causing the ribosome to terminate translation before a functioning protein is generated. This causes the protein to be short and non-functioning. The resulting disease is determined by which protein cannot be expressed in its entirety.

*Ataluren* allows the ribosome to continue translation of the mRNA, ignoring the premature stop signal until a fully functioning protein is formed.

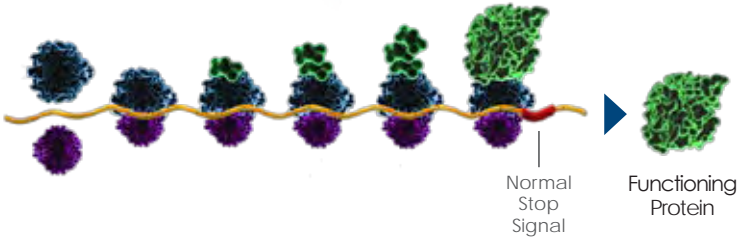
## ATALUREN COMPARED TO OTHER APPROACHES

Currently available therapies for nmDMD and nmCF focus on alleviation of symptoms, but do not address the protein synthesis interruption itself. *Ataluren*, taken orally, has the potential to address the underlying cause of the disease by overriding the premature stop signal to enable complete protein synthesis.

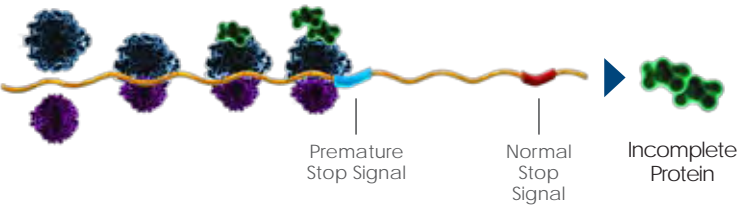
Unlike alternative approaches that rely on other gene and RNA therapeutic platforms, *ataluren* does not alter the patient's genetic code or introduce genetic materials into the body.

# Ataluren Mechanism of Action

## COMPLETE FUNCTIONING PROTEIN



## INCOMPLETE PROTEIN



## ATALUREN-FACILITATED FUNCTIONING PROTEIN

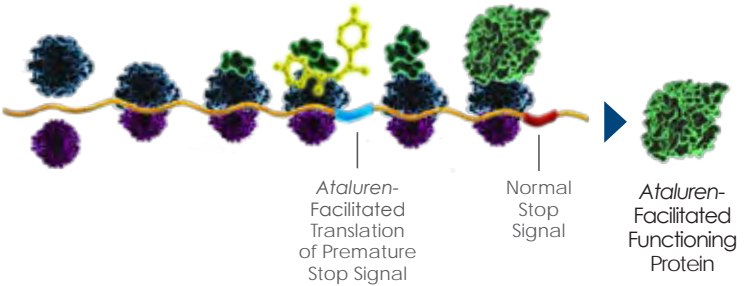


fig. 1 – Translation of an mRNA into protein: comparison of normal translation, premature termination of translation, and treatment with *ataluren* inducing synthesis of functioning protein.

# Nonsense Mutation Genetic Disorders

The National Institutes of Health (NIH) Office of Rare Diseases estimates that rare diseases afflict 25 million people in the US and that the majority of these cases are genetic disorders. In more than 2,400 genetic disorders, on average 5 to 15% of the patients have the disease due to a nonsense mutation. Besides nmDMD and nmCF, these genetic disorders include spinal muscular atrophy, hemophilia, lysosomal storage disorders, retinitis pigmentosa, familial hypercholesterolemia and some forms of cancer.

## Genetic Testing

*Ataluren* has the potential to treat any genetic disorder caused by a nonsense mutation.

To determine if a genetic disorder is caused by a nonsense mutation, patients require genetic testing. Genetic testing is done by a simple blood test that is ordered by a physician working in concert with a genetic lab.

Laboratories performing genetic testing vary by disorder and location. The website, Gene tests, [www.genetests.org](http://www.genetests.org) provides a listing of laboratories and contact information.

## Ongoing Clinical Trials

*Ataluren* has demonstrated proof of concept in Phase 2a clinical trials. PTC has initiated registration-directed clinical studies to understand whether *ataluren* can improve how patients with nmDMD and nmCF feel, function and whether the drug can be given safely over a long period.

### nmDMD

PTC has fully enrolled a Phase 2b clinical study of *ataluren* in nmDMD/BMD. The trial is a multi-center, randomized, double-blind, placebo-controlled study to determine whether *ataluren* can improve walking, activity, muscle function, and muscle strength. It is being conducted at more than 35 centers around the world with approximately 165 patients.

### nmCF

PTC is planning to initiate a longer-term, clinical study of nmCF in 2009. The trial will be a multi-center, randomized, double-blind, placebo-controlled study.

Additional trial details are available at [www.ptcbio.com](http://www.ptcbio.com).

## Completed Clinical Trials

### Phase 2a DATA nmDMD

Data from Phase 2a clinical trials of *ataluren* in pediatric patients with nmDMD show that administration of *ataluren* is associated with production of full-length dystrophin. *ataluren* treatment also resulted in statistically significant reductions in the leakage of muscle-derived creatine kinase into the blood.

### Phase 2a DATA nmCF

Data from Phase 2a clinical trials of *ataluren* in pediatric and adult patients with nmCF show that administration of *ataluren* results in production of full-length CFTR and statistically significant improvements in CFTR chloride channel function in the airways. *Ataluren* treatment was also associated with reductions in cough frequency and improvements in pulmonary function tests.

### ADVERSE EVENTS AND SAFETY PROFILE

Across all clinical studies to date, including Phase 1 healthy-volunteer studies, *ataluren* has been generally well tolerated. In Phase 2a studies, adverse events have been largely consistent with background symptoms and have usually been mild.

No concerning adverse findings have been identified based on physical examinations, vital sign measurements, ECGs, or laboratory studies. Consistent with this safety profile, mean compliance has been >90% in all studies.

## PUBLICATIONS

Eitan Kerem et al (2008) *Effectiveness of PTC124 treatment of cystic fibrosis caused by nonsense mutations: a prospective phase II trial. The Lancet* 372:719-27

Ming Du, Xiaoli Liu, Ellen M. Welch, Samit Hirawat, Stuart W. Peltz, and David M. Bedwell (2008) *PTC124 is an orally bioavailable compound that promotes suppression of the human CFTR-G542X nonsense allele in a CF mouse model. Proceedings of the National Academy of Sciences* 105(6):2064-2069

Ellen M. Welch et al (2007) *PTC124 targets genetic disorders caused by nonsense mutations Nature* 447:87-91

Samit Hirawat et al (2007) *Safety, Tolerability, and Pharmacokinetics of PTC124, a Nonaminoglycoside Nonsense Mutation Suppressor, Following Single- and Multiple-Dose Administration to Healthy Male and Female Adult Volunteers Journal of Clinical Pharmacology* 47(4):430-444

## GRANTS

The development of *ataluren* has also been supported by grants from:

- Cystic Fibrosis Foundation
- Muscular Dystrophy Association
- Parent Project Muscular Dystrophy
- FDA's Office of Orphan Products Development
- National Center for Research Resources

*Ataluren* has been granted orphan drug status by the FDA and the European Commission for nmDMD and nmCF.

## PARTNERSHIP WITH GENZYME

PTC Therapeutics, Inc. and Genzyme Corporation have an exclusive collaboration to develop and commercialize *ataluren*. PTC will commercialize *ataluren* in the United States and Canada and Genzyme will commercialize *ataluren* in all other countries.

## CONTACT US

PTC sends updates via email about our trials and other news about PTC. To join the mailing list, visit the Contact Us portion of our website and be sure to check "receive PTC updates." You may also send inquiries to [info@ptcbio.com](mailto:info@ptcbio.com).

