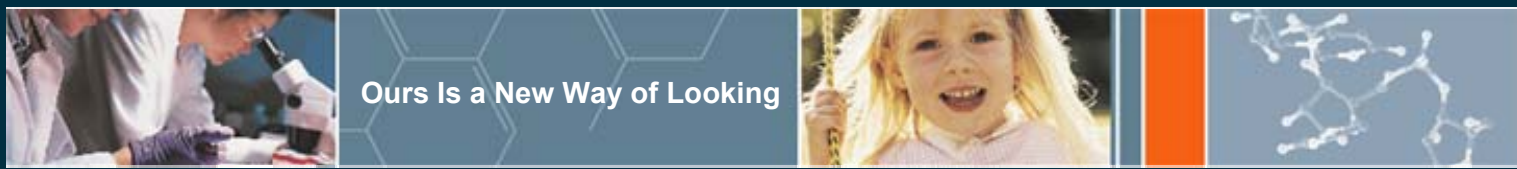


Ataluren: a new paradigm for the treatment of Duchenne muscular dystrophy and other genetic disorders

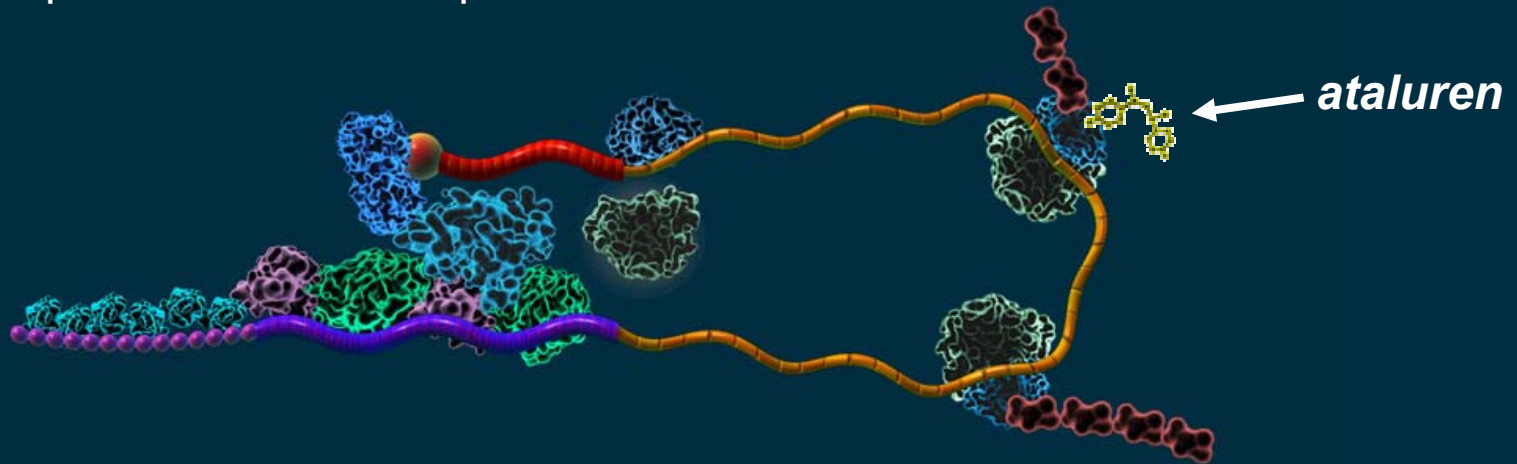


Julie Parsons M.D.
Assistant Professor of Pediatrics
Child Neurology Residency Program Director
University of Colorado School of Medicine

Nonsense mutation suppression technology identified *ataluren*: a single molecule for multiple indications

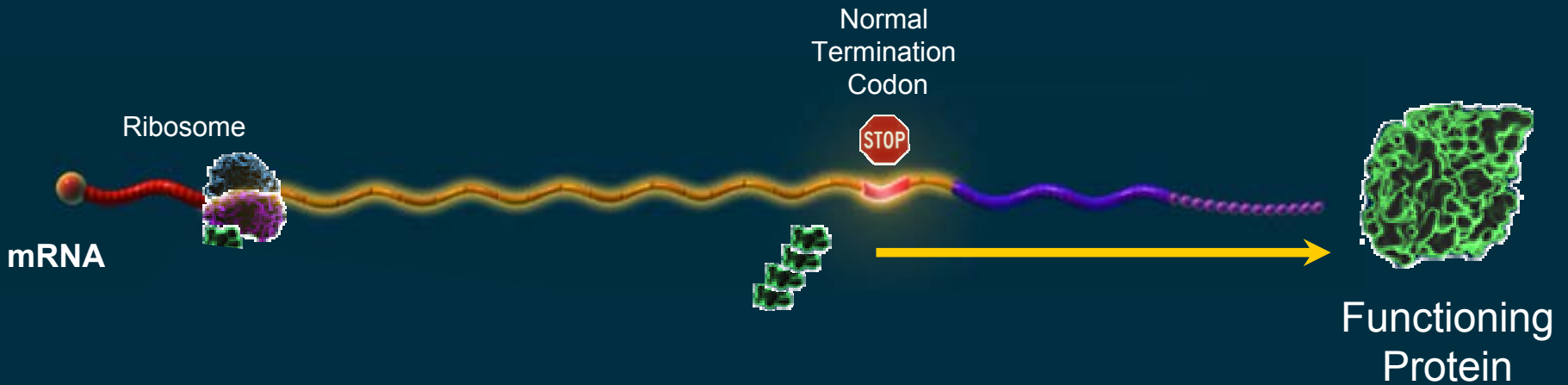
Nonsense suppression technology

- Targets the ribosome
- Single molecule is a potential treatment in >2400 genetic disorders
- Exemplifies the notion of personal medicine



Ataluren is a protein synthesis potentiator

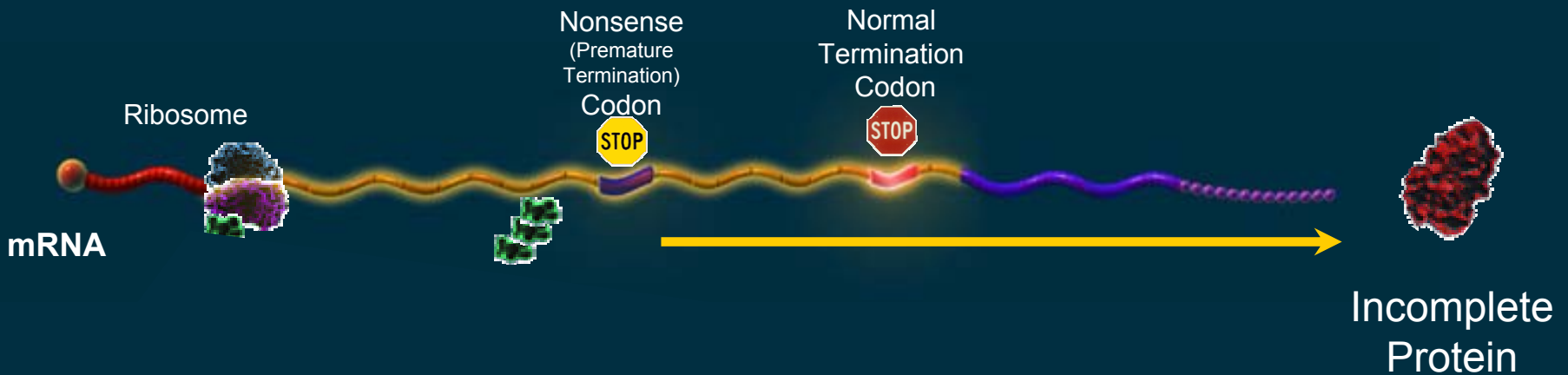
Normal Protein Synthesis



In healthy individuals, ribosomes translate the informational code in the messenger RNA (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 mutation interrupts synthesis of essential protein

Incomplete Protein Synthesis

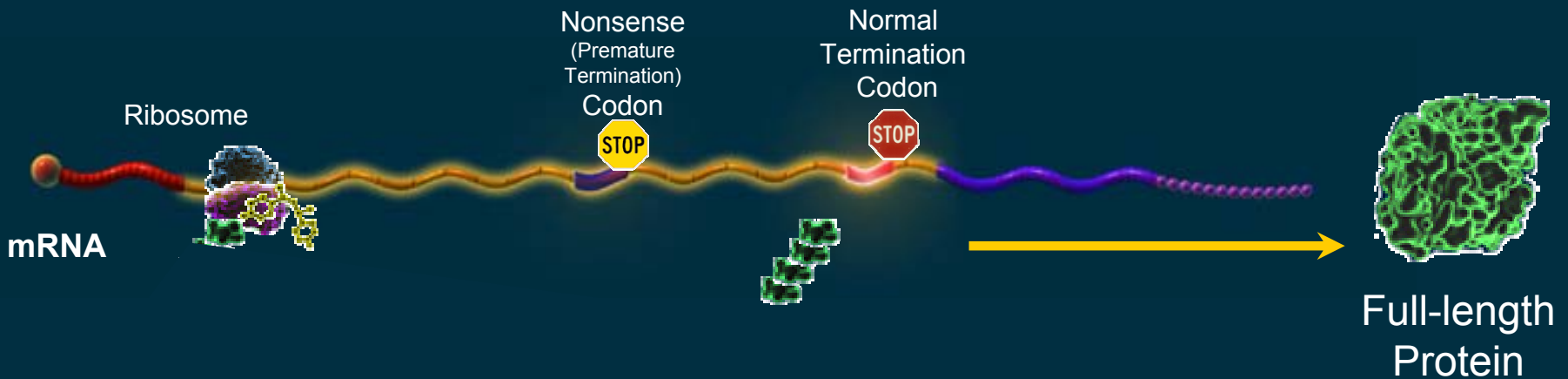


A nonsense mutation, an interruption in the genetic code, creates a premature stop signal in the mRNA causing the ribosome to terminate translation before a functioning protein is generated.

This causes the protein to be incompletely produced and non-functioning.

Ataluren allows ribosome to continue translation and the production of functioning protein

Ataluren Facilitated Protein Synthesis



Ataluren enables synthesis by allowing the ribosome to continue translation of the mRNA, ignoring the premature stop signal until a functioning protein is formed.

Duchenne muscular dystrophy (DMD)

- Cause
 - X-linked mutation in gene for dystrophin, a structural protein critical for muscle integrity
- Disease manifestations
 - Fragile muscles with high levels of muscle enzyme (eg, creatine kinase [CK]) in serum
 - Obvious muscle weakness by age 3-7 years
 - Need for wheelchair by 10-12 years
 - Diaphragmatic and cardiac weakness by 12-14 years
 - Respiratory or cardiac failure (median survival ~ 22 years)
- Treatments
 - Mechanical (braces, wheelchair, ventilator)
 - Tendon-release surgery
 - Corticosteroids

Cystic fibrosis (CF)

- Cause
 - Autosomal mutation in gene for cystic fibrosis transmembrane conductance regulator (CFTR), a chloride channel
- Disease manifestations
 - Viscous secretions in respiratory tract, pancreas, biliary tract
 - Chronic neutrophilic inflammation and recurrent *Pseudomonas aeruginosa* pneumonias
 - Progressive lung destruction, pancreatic enzyme insufficiency, liver inflammation
 - Respiratory failure and death (median survival ~ 35 years)
- Treatments
 - Pancreatic enzyme replacement
 - Dornase alfa (Pulmozyme®) mucolytic
 - Inhaled tobramycin (TOBI®) antibiotic

Ataluren is an investigational oral treatment for nmDMD/nmBMD and nmCF

- Potential to treat patients with genetic disorders due to **nonsense mutations**
 - Nonsense mutation Duchenne Muscular Dystrophy: **nmDMD**
 - Nonsense mutation Becker Muscular Dystrophy: **nmBMD**
 - Nonsense mutation Cystic Fibrosis: **nmCF**
- Nonsense mutations are the underlying cause of disease in a subset of patients across more than **2,400 genetic disorders**
- **Full length gene sequencing** is required to identify a nonsense mutation

- ***~13% of patients with DMD and ~10% of patients with CF have these disorders due to a nonsense mutation***

Clinical Development Update

Ataluren Preclinical and Phase 1 Clinical Characterization

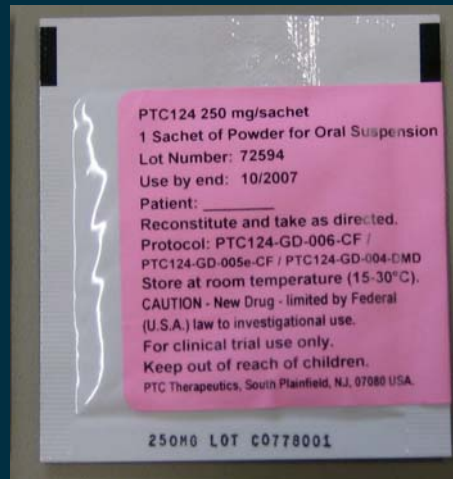


Ours Is a New Way of Looking



Ataluren has been manufactured under current good manufacturing practice (cGMP) guidelines

- Drug substance
 - Manufactured through 4-step chemical synthesis to predefined specifications of purity and stability



- Drug product (formulation)
 - Combined with excipients and vanilla flavoring to create a suitable formulation for use in both children and adults
 - Supplied as white crystalline powder in a sachet for mixing with water, juice, or milk

Ataluren induces production of full-length dystrophin in mdx mouse cells grown in culture

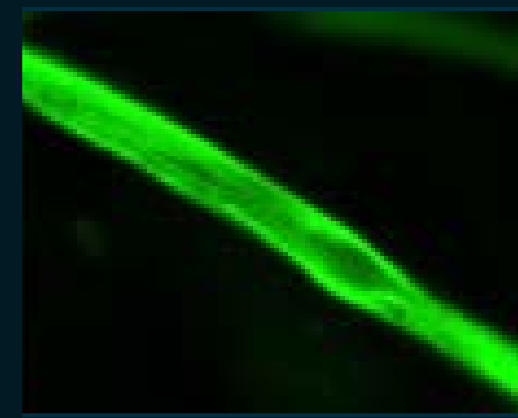
Control

*ataluren**

Dystrophin

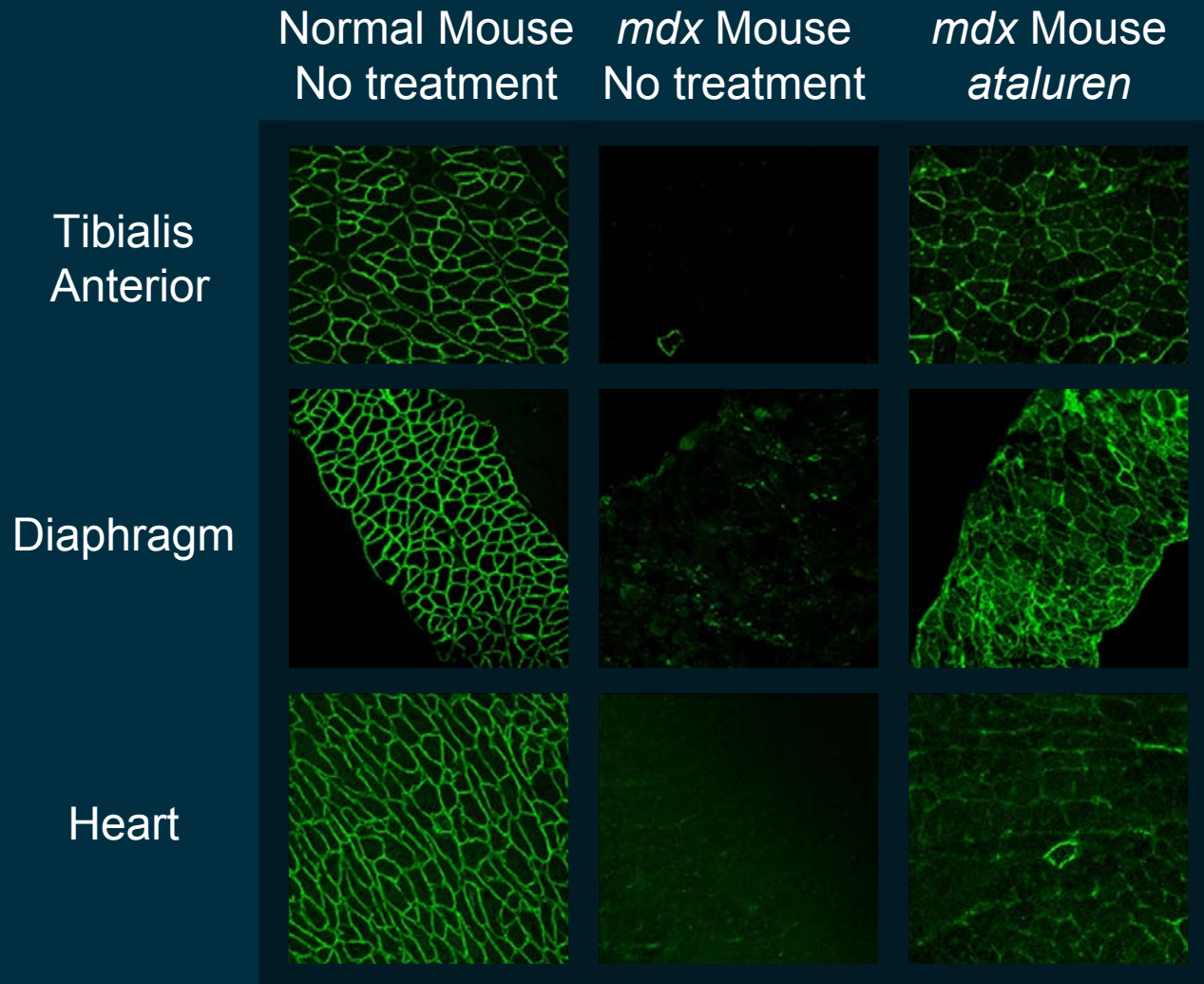


Myosin
Standard



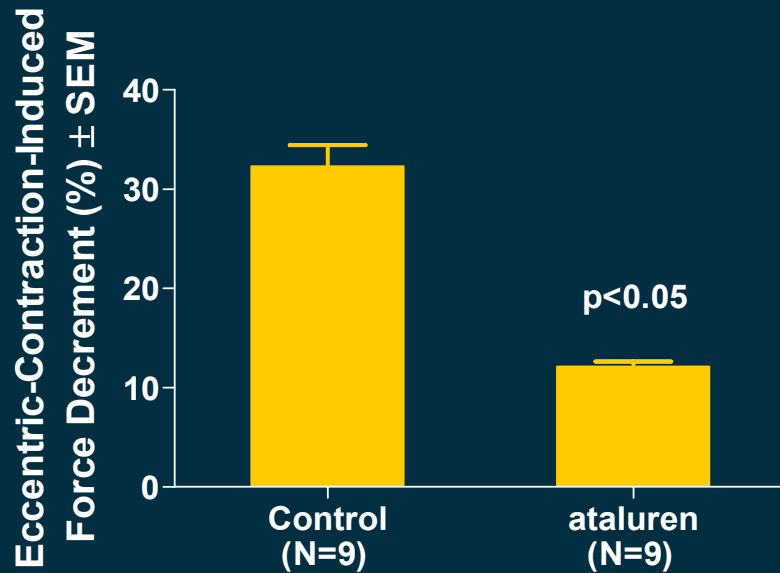
*10 μ g/mL for 12 days

Ataluren induces full-length dystrophin production in skeletal, diaphragm and heart muscles of mdx mice

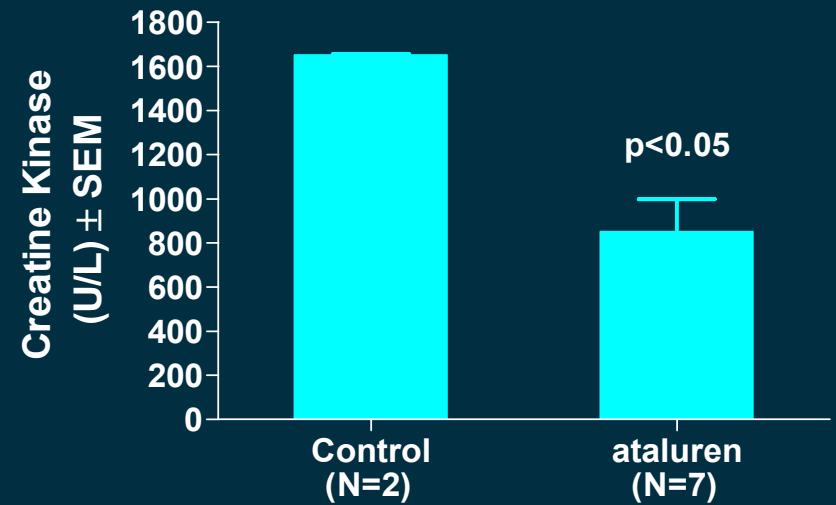


Ataluren induces dystrophin production and decreases muscle fragility in the *mdx* mouse

Reduced Muscle Injury

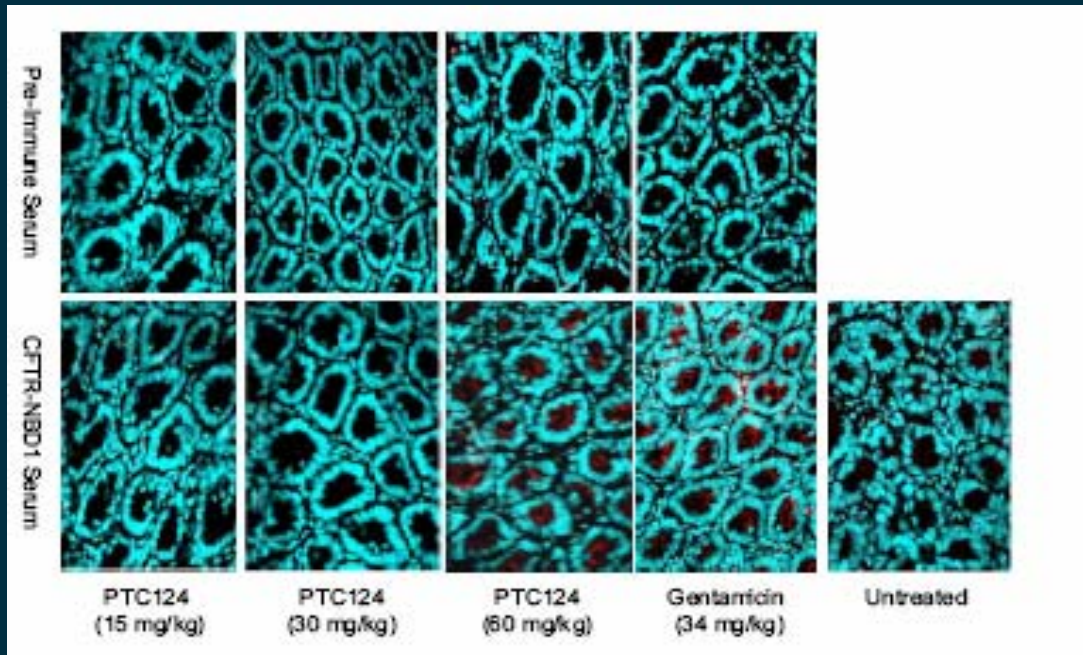


Reduced Serum Creatine Kinase



ataluren at trough plasma concentration of ~10 $\mu\text{g/mL}$ for 2 weeks

Human CFTR Immunofluorescence in the CF Mouse Model



Du, et al., *PNAS*, Feb 2008

Animal safety pharmacology/toxicology shows generally good tolerability and provides information for monitoring

- No neurological, pulmonary, or cardiovascular effects
- No genotoxicity (Ames, CHO cell, and rat micronucleus assays)
- Drug has been generally well tolerated at high doses/exposures in mice, rats, and dogs
- Species-specific findings help guide the safety monitor plan which includes renal and adrenal monitoring, as well as long-term follow-up of general health problems
- To date, no overt evidence of related effects in humans
- Future clinical studies will continue to monitor for these types of changes

Ataluren phase 1 clinical studies in healthy volunteers show *ataluren* to be tolerated in relevant dose range

- Two studies performed in 61 healthy young adults (ages: 18-30 years)
- Volunteers received *ataluren* for up to 2 weeks
- Results showed:
 - Drug powder was tasteless and odorless
 - Oral bioavailability was excellent, achieving desired blood levels when given with or without food
 - Nausea, diarrhea, and headache were seen at high doses (≥ 150 mg/kg)
 - Grade 1 increases in serum transaminase levels occurred
 - *ataluren* was well tolerated at doses through 100 mg/kg/day (a higher dose level than is proposed in trials in patients)

Clinical Development Update

Ataluren Phase 2 Studies



Ours Is a New Way of Looking



Phase 2a proof-of-concept studies in nmDMD and nmCF are complete

Pharmacodynamic, Safety, and Pharmacokinetic Studies

nmDMD

Study 004

nmCF

Study 003
Study 005

Study 006
Study 005e

Investigational Sites

US – 3 centers

Investigational Sites

Israel – 1 center, EU – 3 centers
US – 5 centers

Status

Accrual completed
Initial analyses completed

Status

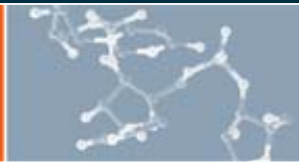
Accrual completed
Initial analyses completed

Clinical Development Update

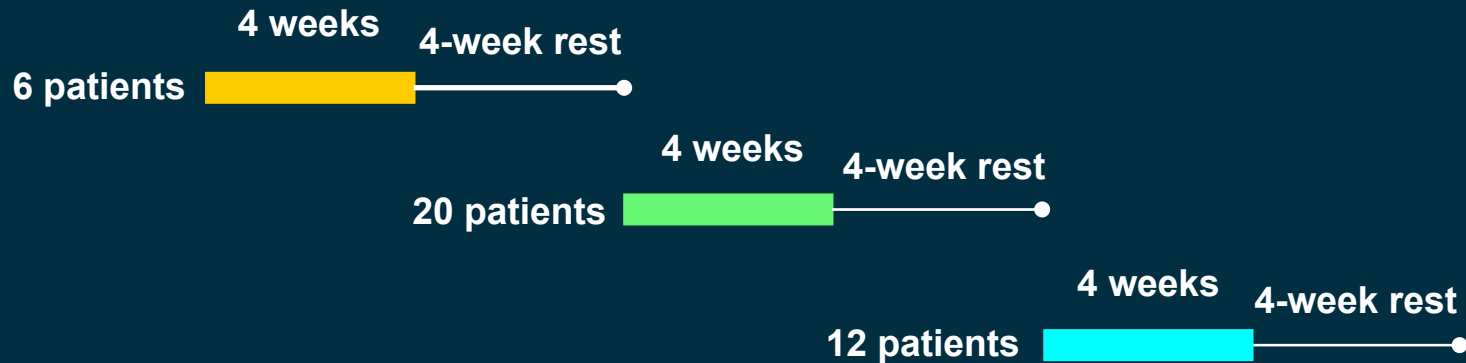
Ataluren Phase 2 Studies in nmDMD



Ours Is a New Way of Looking



Ataluren activity and safety have been evaluated across three dose levels in patients with nmDMD

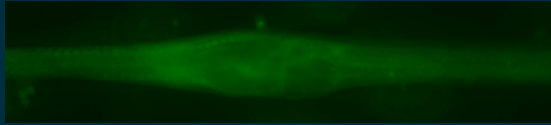


Ataluren Dose Level (mg/kg/dose)



Availability of patient assessment tools has offered methods to establish clinical proof of concept and benefit

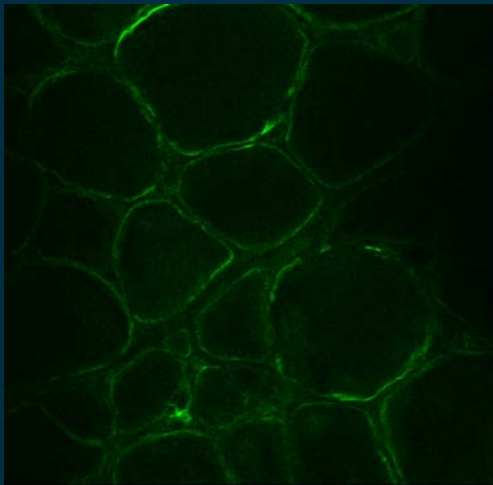
In Vitro Myotube



In Vitro Myotube Assay

- Staining confirms the potential for *ataluren*-induced stop codon readthrough

In Vivo Myofibers



In Vivo Myocyte Biopsy

- Staining indicates increased production of full-length muscle dystrophin in patient

Serum



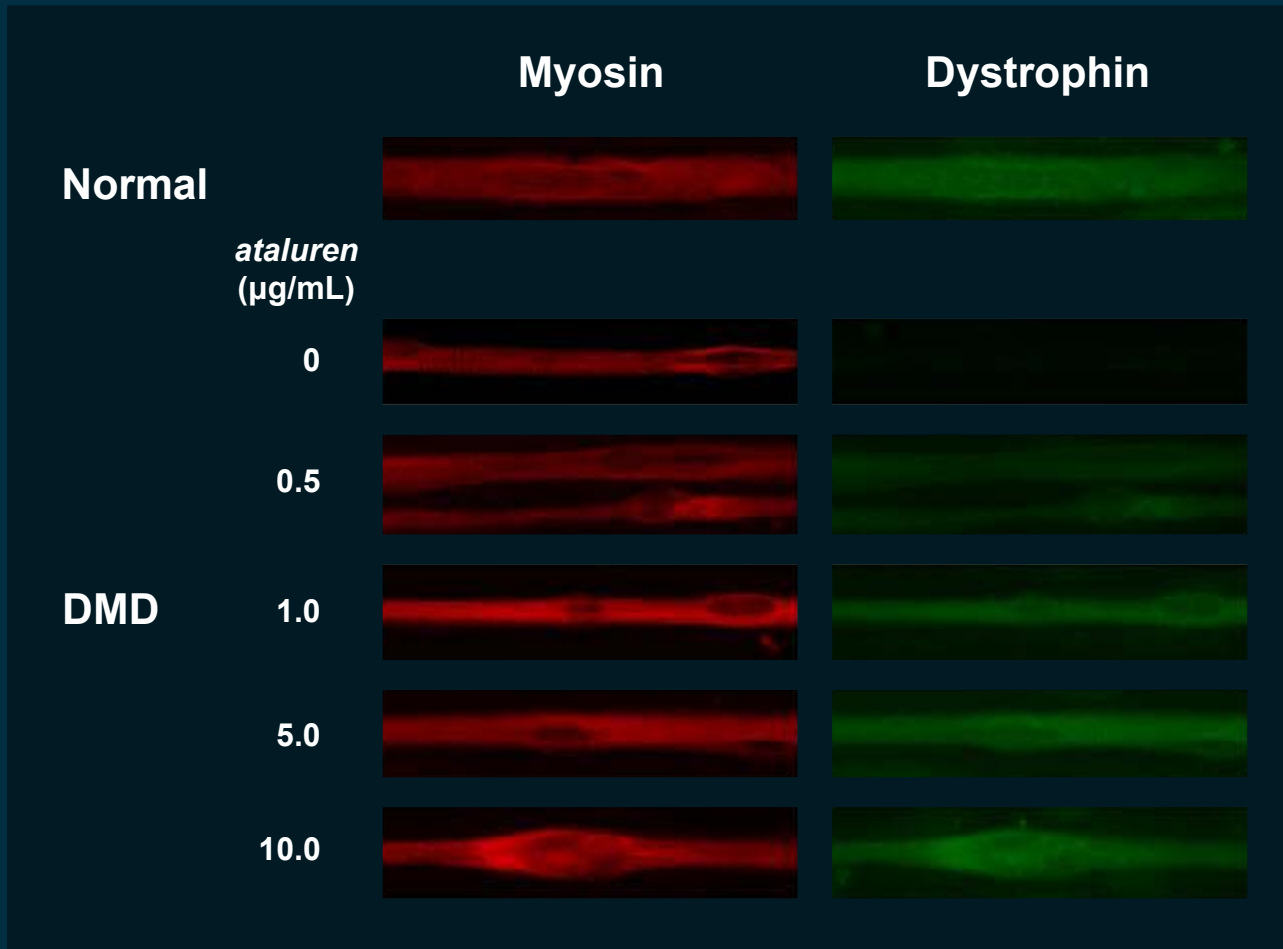
Serum Muscle Enzymes

- Decreases in serum CK indicated whole-body reductions in muscle fragility

Patients enrolled were boys with characteristic clinical and genetic features

Characteristic	Lowest Dose (N=6)	Middle Dose (N=20)	Highest Dose (N=12)
Age, median in yrs [range]	10 [5-11]	9 [6-13]	9 [5-17]
Ambulatory, n (%)	6 (100%)	19 (95%)	8 (67%)
CK [range] Normal<230 U/L	12,120 [8,645->16,000]	12,426 [6,556-49,500]	12,017 [2,931-39,000]
Steroid use, n (%)	6 (100%)	13 (65%)	8 (67%)
Stop mutation types	4 UGA 2 UAG	15 UGA 3 UAG 2 UAA	7 UGA 1 UAG 4 UAA
Location of mutations, range of exons	24 to 70	6 to 70	6 to 61

Ataluren treatment induced dose-dependent readthrough of stop codons in cultured myotubes from patients



Dose-dependent in vitro readthrough confirmed the potential for activity in 100% (35/35) of evaluable patients

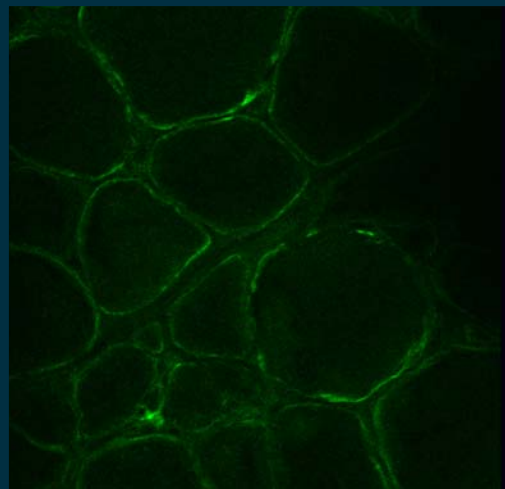
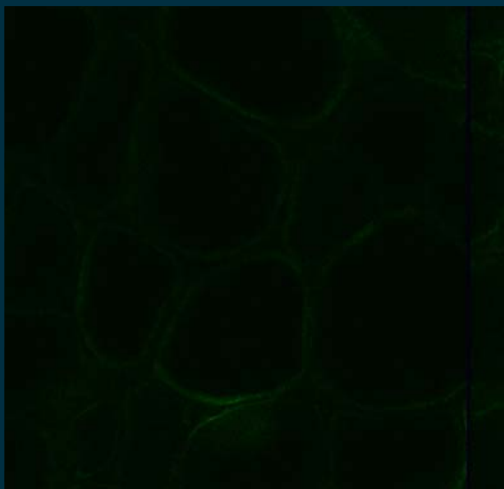
Pretreatment myocytes cultured in vitro with *ataluren* for 12 days

Positive immunofluorescence change in dystrophin expression in extensor digitorum brevis muscle

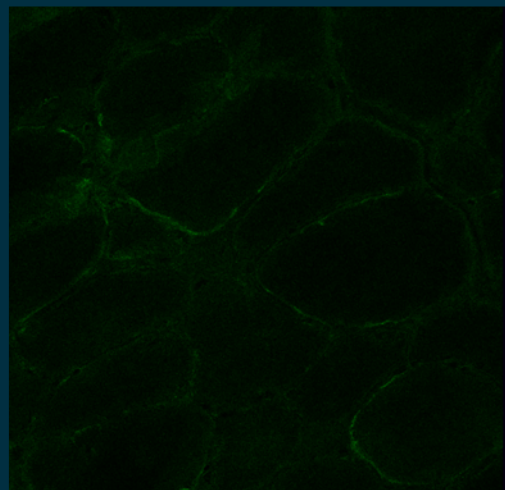
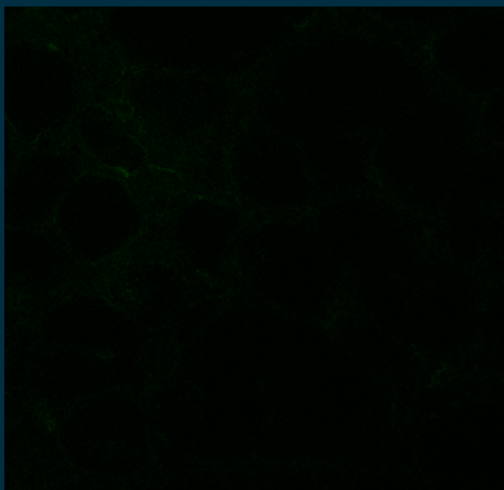
Pretreatment

End of Treatment (Day 28)

Patient A



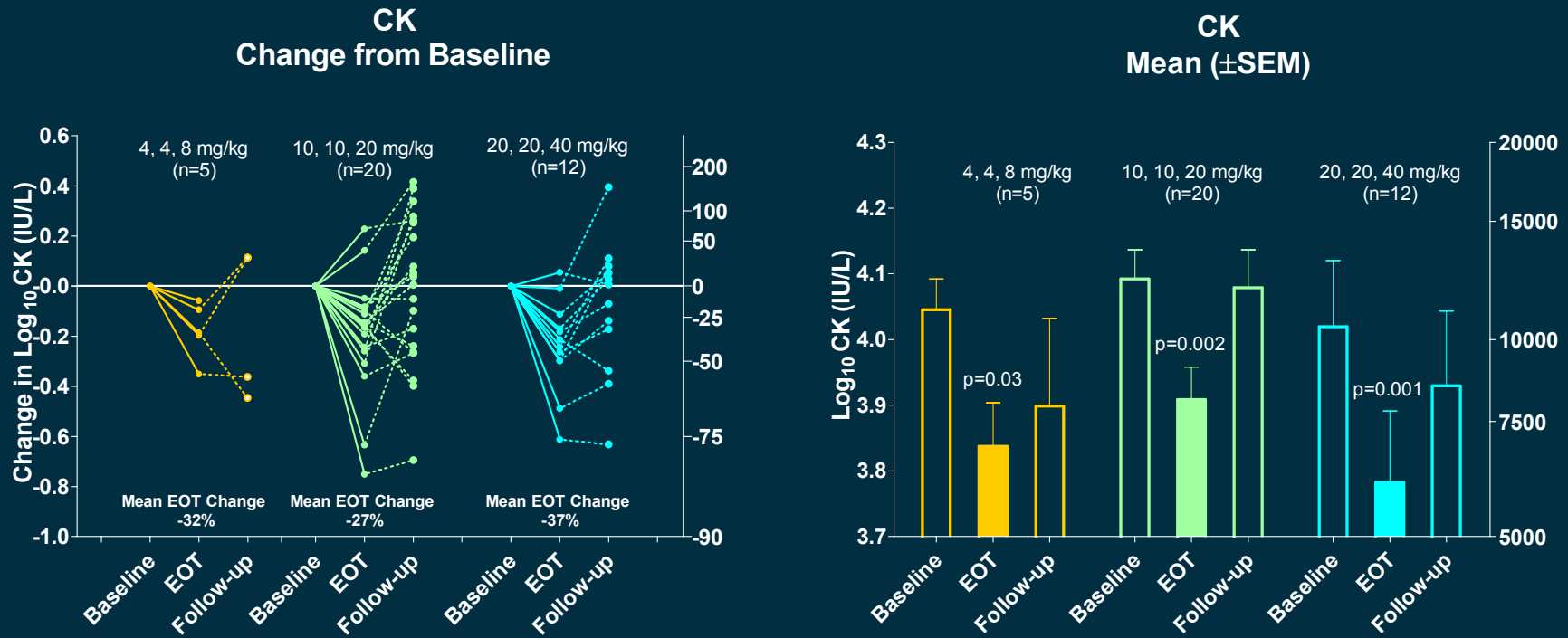
Patient B



- Qualitative increases in dystrophin staining in 50% (19/38) of biopsy pairs document in vivo activity*
- Similar in vivo response rates were seen across all *ataluren* dose levels

*Based on assessment of images by 4 external reviewers

Significant serum creatine kinase reductions suggested decreases in muscle fragility



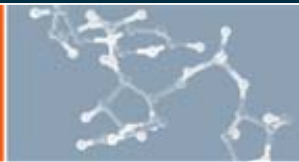
- *Ataluren*-related serum CK reductions were observed in most patients individually
- *Ataluren*-associated decreases were statistically significant at each dose level
- With cessation of *ataluren* treatment, mean serum CK concentrations reverted toward baseline, consistent with pharmacological activity

Clinical Development Update

Ataluren Safety Profile



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Analysis of adverse events and compliance indicates a generally well-tolerated safety profile (all studies)

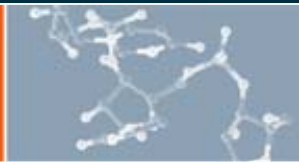
- Exposures up to 3 months have been tested
- Across all studies, adverse events have been largely consistent with background symptoms and have usually been mild (Grade 1)
- Frequency and severity of adverse events have not been obviously dose dependent
- Mild dysuria (Grade 1) without urinary abnormalities has been observed episodically in a minority of patients (primarily in patients with CF)
- No worrisome findings have been identified based on physical examinations, vital sign measurements, ECGs, or laboratory studies
- Mean compliance has been >90% in all studies

Clinical Development Update

Ataluren Phase 2a Conclusions



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Ataluren Phase 2a Conclusions

- *Ataluren* nonsense-suppression therapy in DMD and CF shows evidence of pharmacodynamic activity as indicated by:
 - In vitro and in vivo increases in dystrophin expression and treatment-associated reductions in serum creatinine kinase concentrations
- *Ataluren* has been generally well-tolerated; adverse events and laboratory abnormalities have been infrequent, usually mild, and not usually considered drug-related
- Compliance with therapy has been excellent
- The target plasma concentration range has been achieved

The Phase 2a profile supported registration-directed trials in DMD and CF

Clinical Development Update

Ataluren in nmDMD/nmBMD – Phase 2b Pivotal Study



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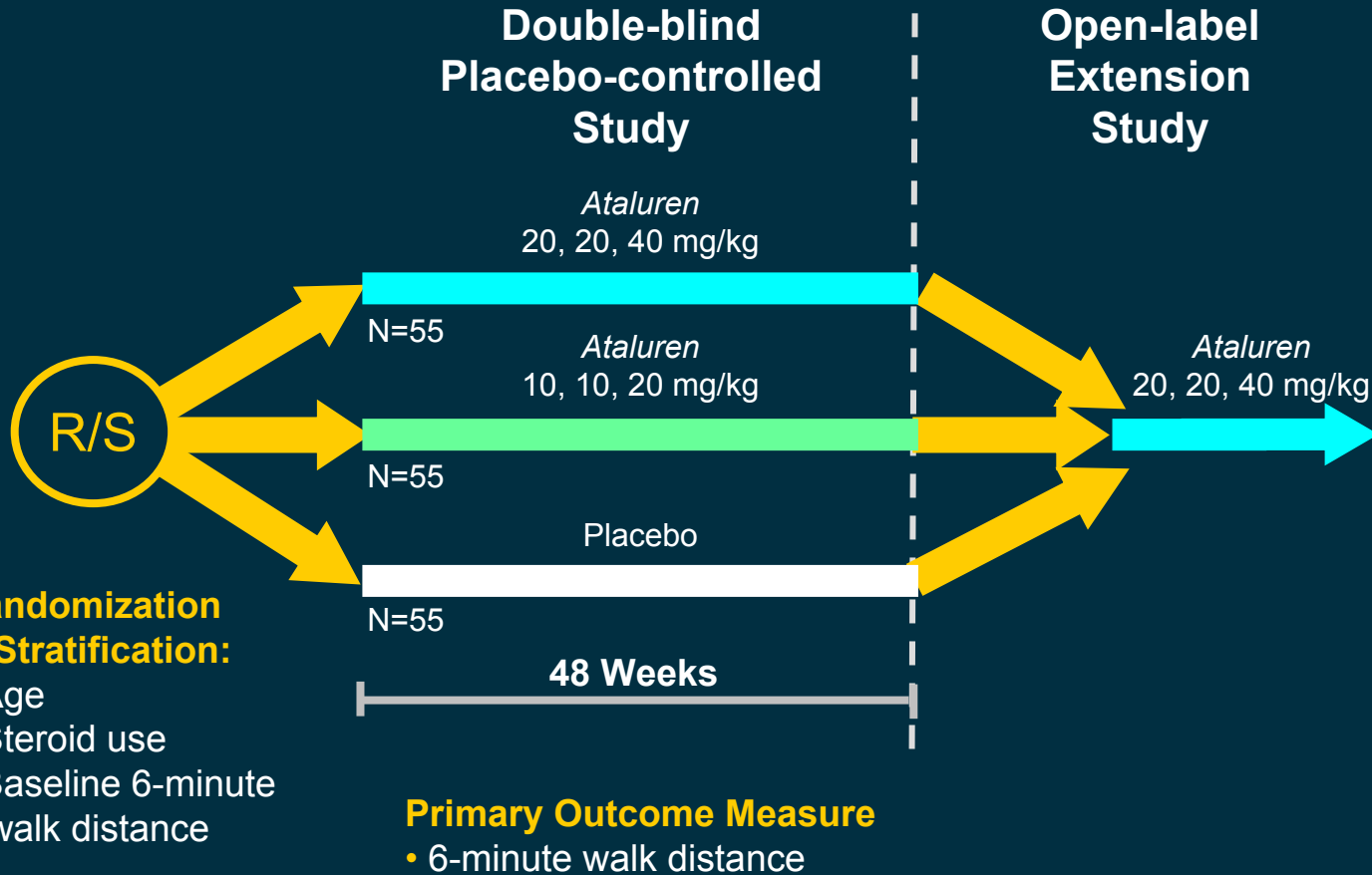
nmDMD pivotal study design

Eligibility Criteria:

- Nonsense-mediated DMD
- Males, ≥ 5 years
- Ambulatory (can walk ≥ 75 meters)

Randomization & Stratification:

- Age
- Steroid use
- Baseline 6-minute walk distance



Primary Outcome Measure

- 6-minute walk distance

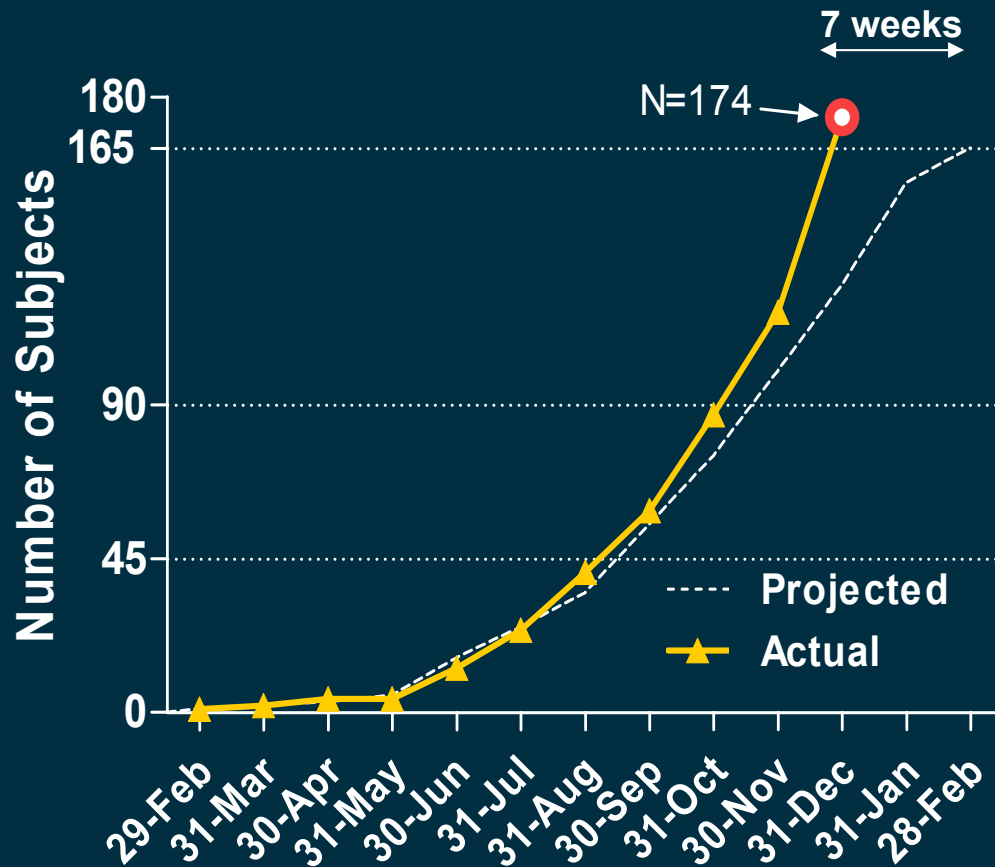
nmDMD phase 2b study outcome measures

- Primary Efficacy
 - 6-minute walk distance (primary)
- Secondary Efficacy
 - Activity (StepWatch® pedometry)
 - Timed function tests (supine to standing)
 - Serum CK values
 - Cognitive function (digit span test)
 - PedQL™ Physical Functioning score
- Tertiary Efficacy
 - Timed function tests (running, stair climbing)
 - Muscle strength (knee and elbow flexion and extension)
 - Heart rate at rest and during 6MWT
 - Accidental fall frequency
 - Other PedsQL™ scores and treatment satisfaction (TSQM)
 - Biceps muscle dystrophin expression
- Safety and exposure
 - Safety profile (adverse events and laboratory abnormalities)
 - Study drug compliance (daily diary and sachet counts)
 - *Ataluren* plasma concentrations (0 and 2 hours relative to AM dose)

Rationale for 6MWT as a primary clinical endpoint in DMD

- Evaluation of ambulation with the 6MWT has a logical connection to the manifestations of DMD
 - Ambulation is the major physical activity of human beings
 - Progressive loss of ambulation, as in DMD, is a critical functional concern for boys with the disease and their families
 - Boys with DMD walk less, walk more slowly, and fall more frequently than normal boys [McDonald 2005]
- Changes in duration of walking on the 6MWT assess how a boy with DMD functions
 - 6MWD constitutes a true (non-surrogate) clinical endpoint [Temple 1999]
 - An improvement would represent a clinically meaningful outcome of direct value to a boy with DMD
- 6MWT endurance may best match *ataluren* effects to reduce eccentric contraction injury of muscle in the *mdx* mouse

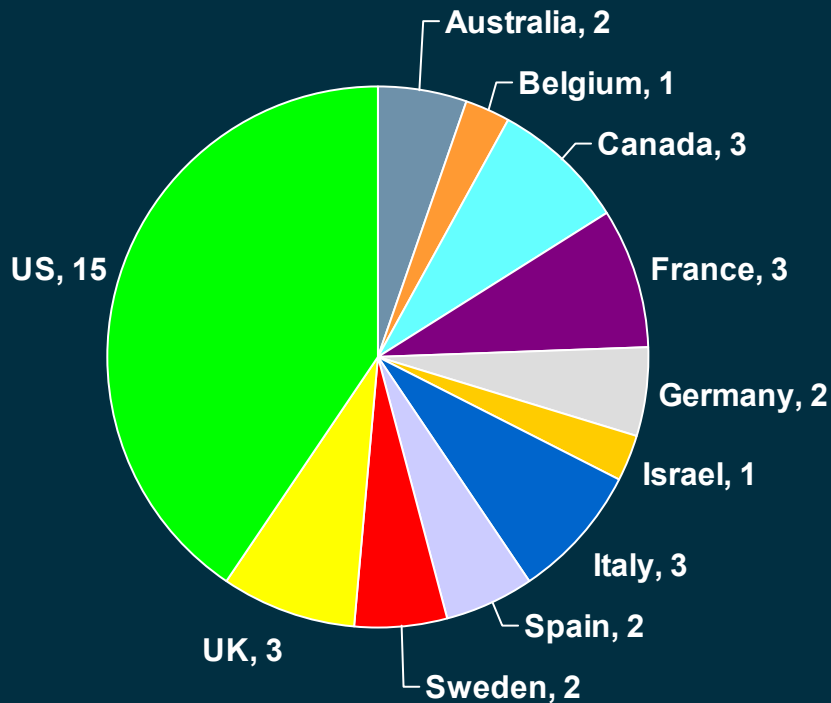
The Accrual Rate for Study 007 Exceeded Expectations



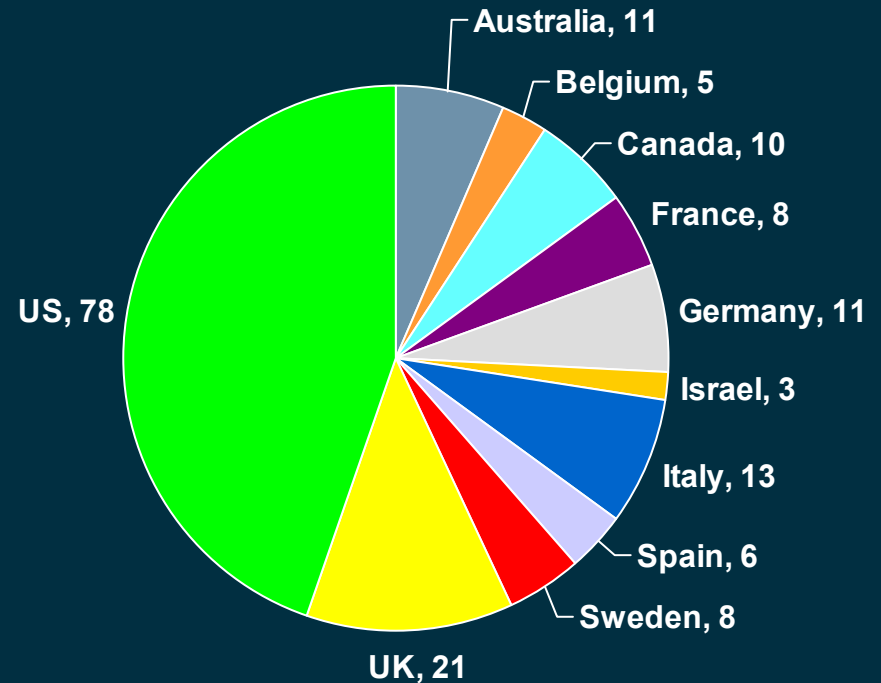
- Study completed accrual ahead of schedule in Jan 2009

Distribution of Sites and Subjects Shows Good Participation from Multiple Countries

Study Site Distribution



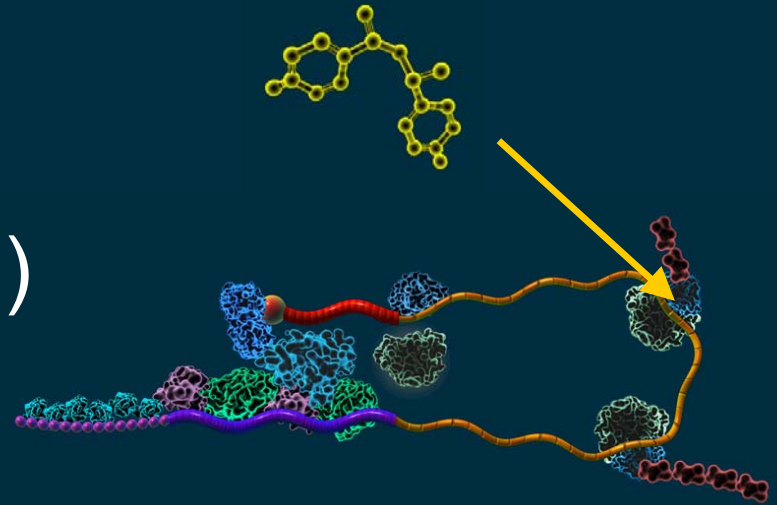
Enrolled Subjects Per Country



Positive Implication

- ***Multicenter participation enhances regulatory acceptance of trial results***

Ataluren (PTC124™) nmCF clinical results

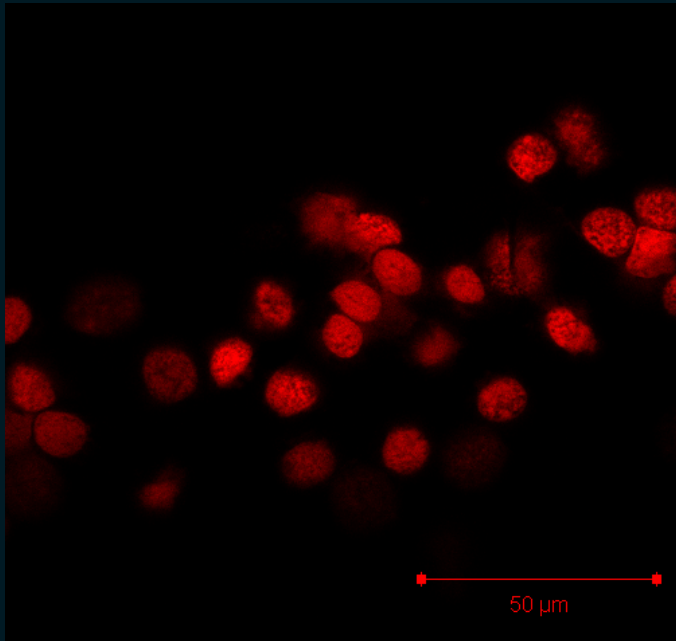


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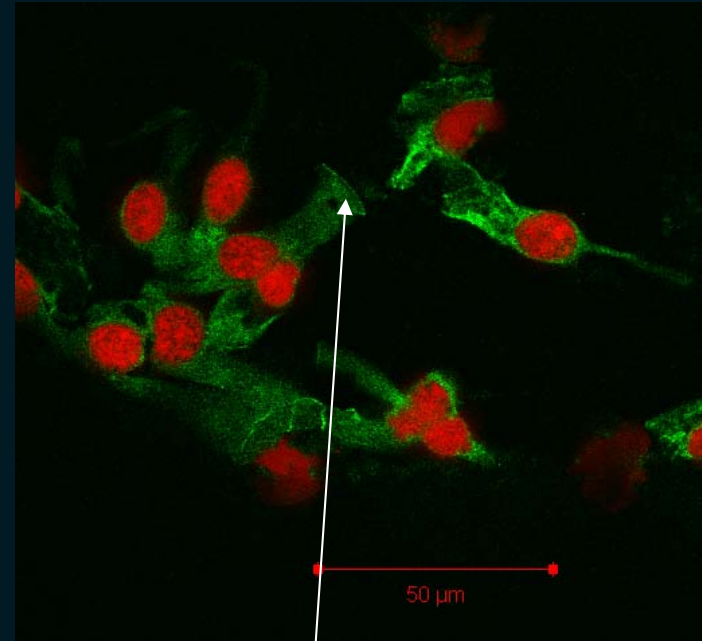


Immunostaining has provided evidence of *ataluren*-mediated increases in epithelial cell-surface CFTR

**Pre-treatment
(Day 0)**



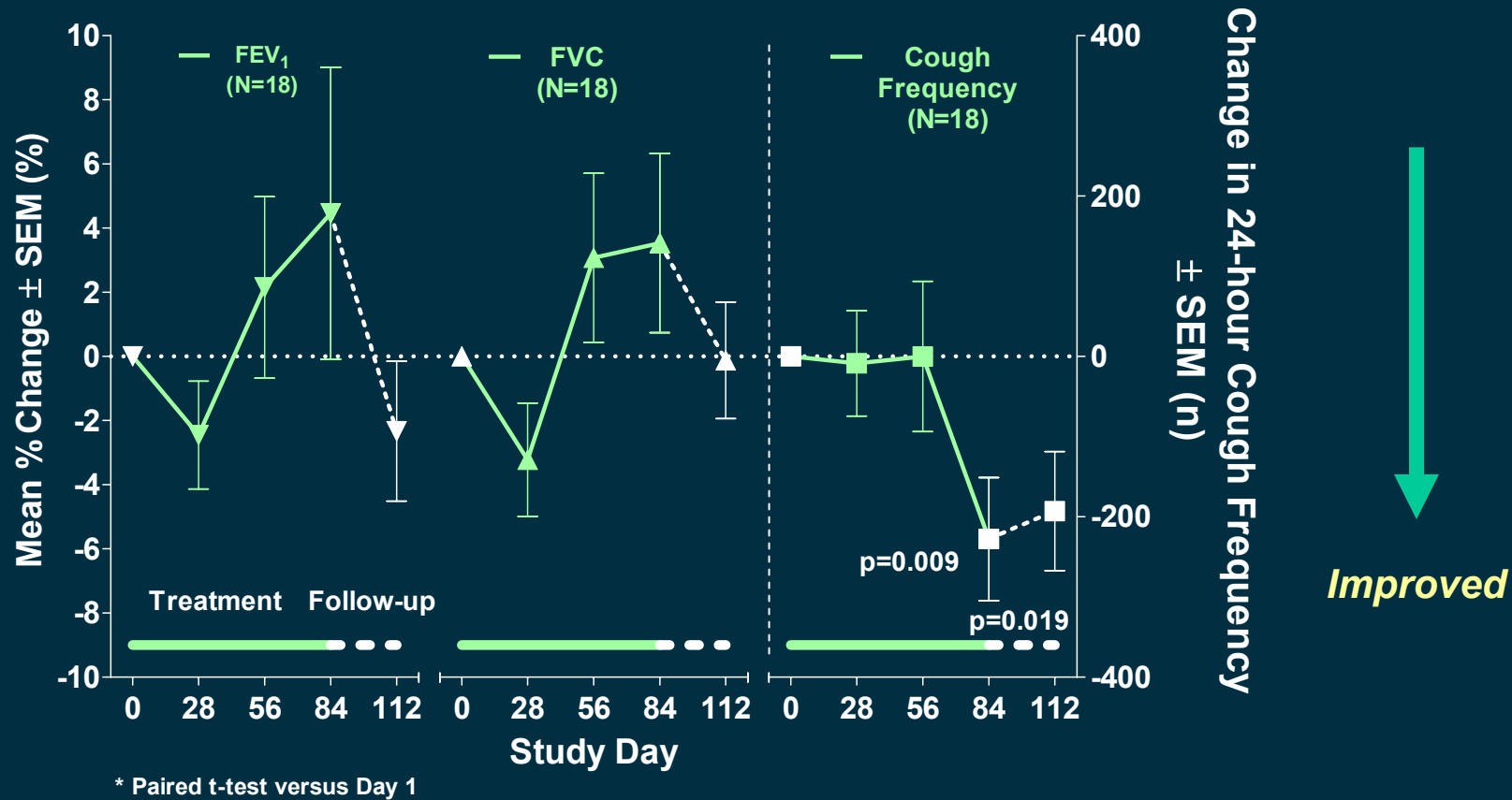
**End of *ataluren*
10-, 10-, 20-mg/kg Dose Level (Day 45)**



Full-length Apical CFTR

**Age = 17 years
Genotype = W882X/ΔF508
Stop codon type = UAG**

Increases in FEV₁ and FVC, and decreases in cough frequency indicate clinical benefit potential



An international phase 2b registration-directed study in patients with nmCF is being initiated

Randomization & Stratification:

- Age
- Inhaled antibiotic use
- Baseline FEV₁

Eligibility Criteria:

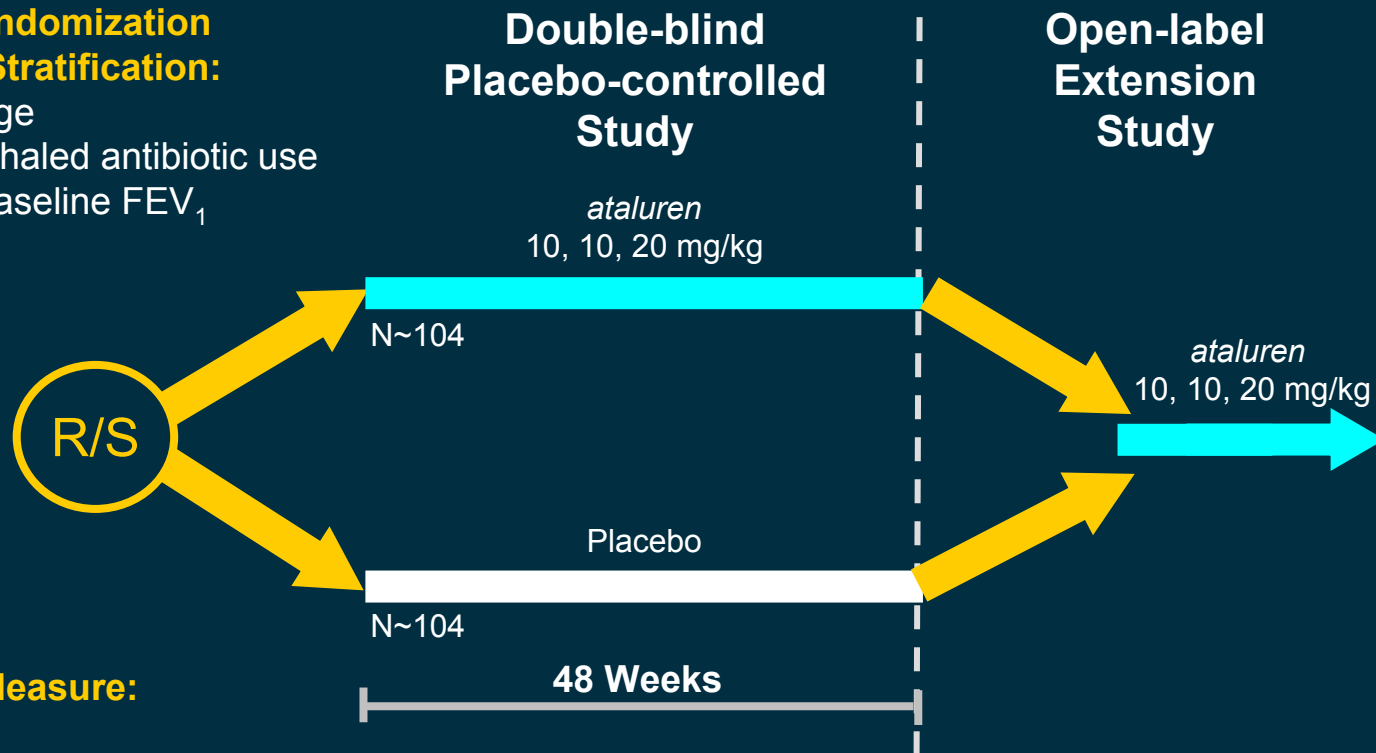
- Nonsense mutation CF
- Age ≥6 years
- FEV₁ ≥40% and ≤90% predicted

Primary Outcome Measure:

- FEV₁

Proposed Countries:

- Belgium, Canada, France, Germany, Israel, Italy, Poland, UK, US



Visits:

- Every 8 weeks

Summary of the *ataluren* (PTC124™) program

- *Ataluren* – A breakthrough investigational oral small molecule disease-modifying agent for the treatment of nonsense mutation genetic disorders (nmGD) addressing significant unmet medical need
 - Completed proof of concept in nmCF and nmDMD
 - Phase 2b pivotal study ongoing in nmDMD/BMD
 - Phase 2b pivotal extension study ongoing in nmDMD/BMD
 - Phase 2a nmDMD extension study is ongoing
 - Phase 3 pivotal nmCF study is being initiated
 - Partnered ex-US/CAN with GENZYME

Genetic Counseling in a New Era of Medicine: Mutation-Based Treatment

CEU Course co-sponsored by NSGC and PTC
Therapeutics



Ours Is a New Way of Looking



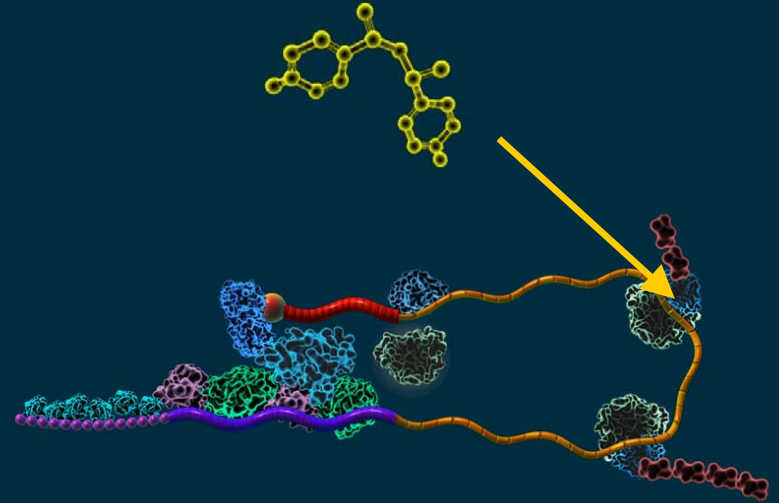
Genetic Counseling in a New Era of Medicine: Mutation-Based Treatment

- 11-session webinar co-sponsored by the National Society of Genetic Counselors and PTC Therapeutics
- Topics presented by genetic counselors, researchers and clinicians include:
 - Drug discovery and development
 - Clinical trial design
 - Ataluren discovery and mechanism of action
 - Role of genetic counselors in clinical trials
 - Patient registries as a tool to facilitate research and clinical trials
 - Therapeutic relevance of genotyping
 - Treating the multi-systemic effects of a single gene disorder
 - Patient perspectives of cystic fibrosis and Duchenne/Becker muscular dystrophy

CEU Course Logistics

- Registration opens June 15th at www.nsgc.org
- Recorded sessions released on NSGC website beginning June 22nd
- New sessions posted every three weeks through December
- Available 24/7 through June 2010.
- Overall learning objectives for course include:
 - Recognize the availability of current and future clinical trials for treatment of genetic diseases based on mutation type, and the necessity of genotyping for all patients.
 - Describe MOA and primary clinical aspects of ataluren.
 - Discuss clinical utility, appropriate testing methodologies, and patient impact of current mutation-specific treatment trials as well as ongoing research for future therapies.
- Has been submitted to the National Society for Genetic Counselors (NSGC) for approval of 1.55 Category 1 CEUs (15.5 contact hours)
- More information on www.nsgc.org or from dgoetz@ptcbio.com

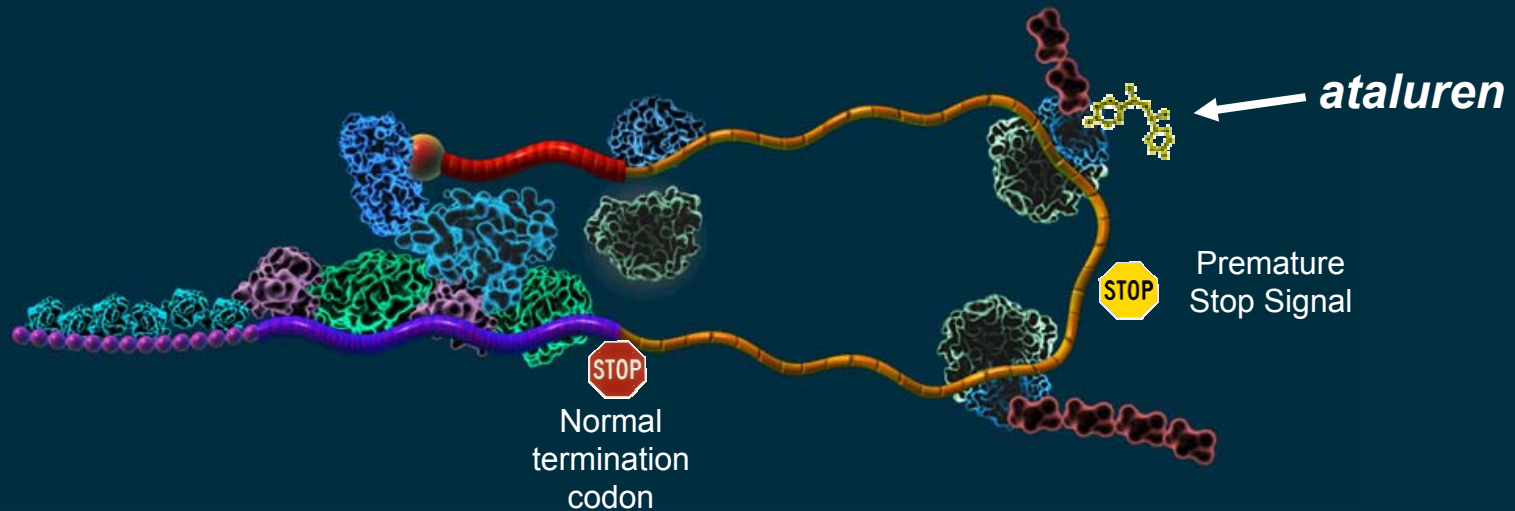
Appendix



Ours Is a New Way of Looking

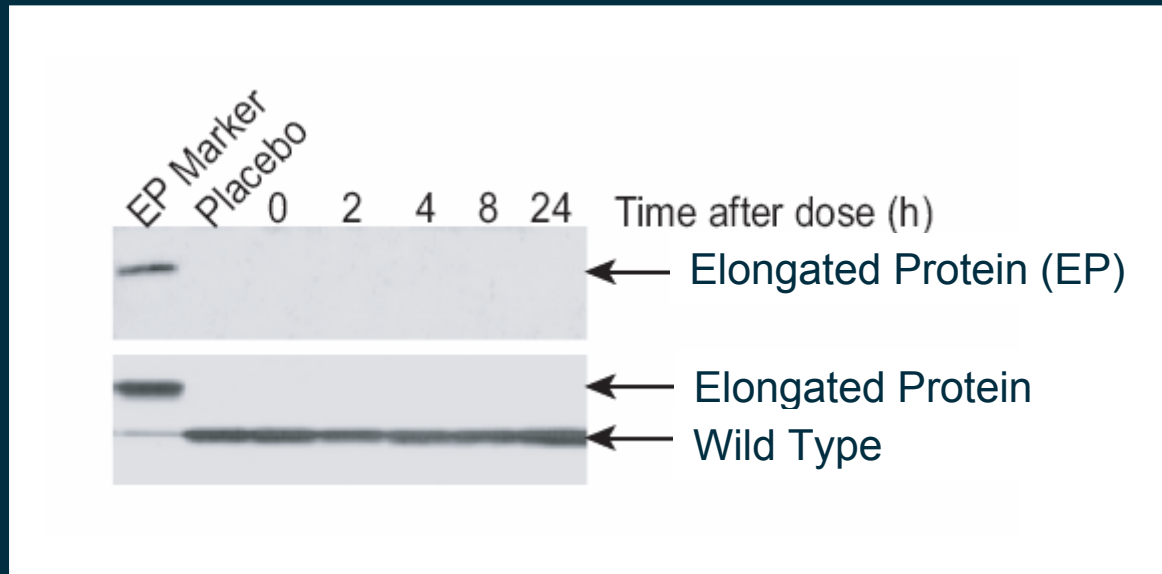


Ataluren does not read through normal termination codons



- In normal translation mRNA is in a closed loop structure, where the normal termination codon is at the end of the protein coding region.
- In the presence of a nonsense mutation, a premature stop codon exists in the protein coding region in a distinctly different context than the normal termination codon

Western Blot Analysis Reveals No Nonspecific Readthrough of Normal Stop Codons



Welch, et al, *Nature*, April 2007